DRUG EFFECTS ON THE EEG: A REFERENCE GUIDE

June 2023

Cynthia Kerson, 2(PhD), QEEGD, BCN, BCB, BCB-HRV
Phoebe Manalang, ND, MSFT, CNC, MH
Nicholas Kenneth Keahinuimakahahaikalani Smythe, BS

DRUG EFFECTS ON THE EEG: A REFERENCE GUIDE

June 2023

Cynthia Kerson, 2(PhD), QEEGD, BCN, BCB, BCB-HRV[1,2]
Phoebe Manalang, ND, MSFT, CNC, MH[1,3]
Nicholas Kenneth Keahinuimakahahaikalani Smythe, BS[1]

[1] Saybrook University, Dept. of Applied Psychophysiology
[2] APEd (Applied Psychophysiology Education), Napa, CA USA
[3] Daywaneti

This guide was created to consolidate our reference resources for drug effects on the electroencephalogram (EEG). It was developed in early 2023, and as we all know, this is a never-ending process. While there are thousands of studies looking at the effects of drugs, many look at behavioral, metabolic, and/or neurotransmitter, hormone, and other chemical changes. This reference guide is specific to effects on the EEG, in the waking and/or sleep state. It is sectioned by drug class. It includes a synopsis of each class and drug as well as highlights the points in the abstracts that are meaningful to this mission.
Each drug class chapter includes a synopsis of the overall effects on the EEG and each drug within the class includes articles informing of the research findings of the drug. There is a synopsis heading each paper and the most salient discussion within the abstract is highlighted. While many of the papers we reviewed are available in open access, there are many that are not and while we were able to access them through our university library system (Saybrook University), some may only be available for a fee.

VERY IMPORTANTLY: These studies of changes in the EEG report with a variable level of confidence. Reviewing the methodology of each study is imperative since the reported findings may have been observed by a single electrode, a variable dosage, individual dose effect, under-controlled behavioral effects, an inconsistency of frequency band ranges, or by using a statistical evaluation that heightens the meaningfulness of the findings. Many report of sleep changes and again, the variables are, well – variable. As well, mechanisms of action cannot be ascertained by EEG. **Caveat Emptor!**

Please use this as it seems fit to you and your practice and let us know if there are any additions to keep it updated. You can send your reference and abstract to dr.crkerson@gmail.com.

TABLE OF CONTENTS

RECENT SYSTEMATIC REVIEWS OF MEDICATION EFFECTS ON THE EEG

Rohit Aiyer, Vladan Novakovic & Robert L. Barkin (2016). A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry, Postgraduate Medicine, 128:7, 656-664, DOI: 10.1080/00325481.2016.1218261

----- ALCOHOL | ETHANOL -----

CLASS FACTS

SYNOPSIS: There are four types of alcohol: methyl alcohol, ethyl alcohol, propyl alcohol and butyl alcohol. Ethyl Alcohol, or ethanol (C2H5OH), is the type used in the production of alcoholic beverages. The other three types, methyl, propyl and butyl alcohol, if consumed can result in blindness and death, even in relatively small doses.

Neurophysiological correlates of alcohol-specific inhibition in alcohol use disorder and its association with craving and relapse.

Batschelet HM, Tschuemperlin RM, Moggi F, Soravia LM, Koenig T, Pfeifer P, Roesner S, Keller A, Stein M. Clin Neurophysiol. 2021 Jun;132(6):1290-1301. doi: 10.1016/j.clinph.2021.02.389. Epub 2021 Mar 26. PMID: 33867254.

Objective: This study investigates neurophysiological correlates of general and alcohol-specific inhibitory control in patients with Alcohol Use Disorder (AUD), focusing on its association with individual craving levels and with relapse at three-month follow-up. **Methods:** 59 abstinent AUD patients and 20 healthy controls performed a Go/NoGo task incorporating alcohol-related and neutral stimuli ***during 64-channel electroencephalography (EEG) recording, yielding four event-related potentials (ERP) per participant (NoGo-Alcohol, Go-Alcohol, NoGo-Neutral, Go-Neutral). Whole-scalp randomization-based statistics assessed effects of the factors group (patients/controls or relapsers/abstainers), craving level, response type (NoGo/Go) and picture type (alcohol/neutral) on topography and signal strength of the ERP components N2 and P3***. **Results:** No differences on group level were observed between patients and controls. However, ***analyses incorporating individual craving indicated that the topographic difference between alcohol-related and neutral NoGo-N2 components increased with craving. Moreover, topographic differences in the alcohol-related and neutral NoGo-P3 component allowed for differentiation between relapsers and abstainers***. ***Conclusions:*** *In alcohol-related contexts****, the response inhibition conflict reflected in the NoGo-N2 seems enhanced in patients with high craving. The inhibition-sensitive NoGo-P3 varies in relapsers but not in abstainers between neutral and alcohol-related contexts. Significance:*** *In AUD patients,* ***neurophysiological correlates of inhibition vary with alcohol-related contexts and craving, and might be indicative of relapse risk.***

Alcohol and Neural Dynamics: A Meta-analysis of Acute Alcohol Effects on Event-Related Brain Potentials.

Fairbairn CE, Kang D, Federmeier KD. Biol Psychiatry. 2021 May 15;89(10):990-1000. doi: 10.1016/j.biopsych.2020.11.024. Epub 2020 Dec 11. PMID: 33579536; PMCID: PMC8106628.

Background: An understanding of alcohol's acute neural effects could augment our knowledge of mechanisms underlying alcohol-related cognitive/motor impairment and inform interventions for addiction. Focusing on studies employing event-related brain potential methods, which offer a direct measurement of neural activity in functionally well-characterized brain networks, we present the first meta-analysis to explore acute effects of alcohol on the human brain. **Methods:** Databases were searched for randomized laboratory alcohol-administration trials assessing brain activity using event-related potentials. Hedges' g coefficients were pooled using 3-level random-effects meta-regression. **Results:** Sixty independent randomized controlled trials met inclusion (total N = 2149). ***Alcohol's effects varied significantly across neural systems, with alcohol leading to reductions in event-related potential components linked with attention (P3b), g = -0.40, 95% CI (-0.50, -0.29), automatic auditory processing (mismatch negativity), g = -0.44, 95% CI (-0.66, -0.22), and performance monitoring (error-***

related negativity), g = -0.56, 95% CI (-0.79, -0.33). These effects were moderated by alcohol dose**,** emerging as significant at doses as low as 0.026% blood alcohol concentration and increasing to moderate/large at 0.12%. In contrast, irrespective of dose, relatively small or nonsignificant alcohol effects emerged in other processing domains, including those linked to executive control (N2b responses) and stimulus classification (N2c responses). **Conclusions:** Contrary to traditional conceptualizations of alcohol as a "dirty drug" with broad central nervous system depressant effects, results instead support accounts positing targeted alcohol effects in specific processing domains. ***By identifying alcohol effects on brain systems involved in performance monitoring and attention, results move toward the identification of mechanisms underlying alcohol-related impairment as well as factors reinforcing addiction.***

Effects of Age and Acute Moderate Alcohol Consumption on Electrophysiological Indices of Attention. Garcia CC, Lewis B, Boissoneault J, Nixon SJ. J Stud Alcohol Drugs. 2020 May;81(3):372-383. doi: 10.15288/jsad.2020.81.372. PMID: 32527389; PMCID: PMC7299192.

Objective: Despite increased attention to risks and benefits associated with moderate drinking lifestyles among aging adults, relatively few empirical studies focus on acute alcohol effects in older drinkers. Using electroencephalographic indices of early attention modulation (P1 and N1) and later stimulus processing (P3), we investigated whether acute alcohol consumption at socially relevant doses differentially influences neurocognitive performance in older, relative to younger, moderate drinkers. **Method:** Younger (25-35 years; n = 97) and older (55-70 years; n = 87) healthy drinkers were randomly assigned to receive one of three alcohol doses (placebo, .04 g/dl, or .065 g/dl target breath alcohol concentrations). ***Repeated-measures analysis of variance examined the effects of age, alcohol dose concentration, and their potential interaction on P1/P3 amplitudes and N1 latency during completion of a directed attend/ignore task. Results: Age-specific effects on P1 amplitudes varied by instruction set, with alcohol-associated decreases in amplitude among older drinkers in response to task-relevant stimuli and increases to irrelevant stimuli, F(2, 141) = 2.70, p = .07, ηp2 = .04. In contrast, N1 analyses demonstrated alcohol-related latency reductions among older, relative to younger, adults, F(2, 83) = 3.42, p = .04. Although no Age × Alcohol interactions were detected for P3, main effects indicated dose-dependent amplitude reductions for relevant stimuli, F(2, 144) = 5.73, p < .01, ηp2 = .08. Conclusions: Our results underscore the impact of acute moderate alcohol consumption on attentional functioning, highlighting age-dependent sensitivity in electrophysiological indices of early attentional processing.*** Given the import of attentional functioning to quality of life and increases in drinking among a rapidly expanding aging population, these findings have broad public health relevance.

Parietal P3 and midfrontal theta prospectively predict the development of adolescent alcohol use. Harper J, Malone SM, Iacono WG. Psychol Med. 2021 Feb;51(3):416-425. doi: 10.1017/S0033291719003258. Epub 2019 Nov 18. PMID: 31736455; PMCID: PMC7231637.

Background: Subclinical adolescent alcohol use is highly prevalent and may have deleterious effects on important psychosocial and brain outcomes. Prior research has focused on identifying endophenotypes of pathological drinking, and the predictors of normative drinking remain understudied. ***This study investigated the incremental predictive value of two potential psychophysiological endophenotypes, P3 amplitude (an index of decision making) and midfrontal theta power (a correlate of attentional control), for prospectively predicting the expression and initiation of alcohol use emerging in adolescence*****. Methods:** A large (N = 594) epidemiological sample was prospectively assessed at ages 11/14/17. Alcohol/substance use was assessed at all ages via a computerized self-report inventory. EEG was recorded at age-14 during a visual oddball task to elicit P3 and theta. **Results:** ***Reduced target-related P3 and theta at age-14 prospectively predicted drinking at age-17 independent of one another. Among alcohol-naive individuals at age-14, attenuated P3 and theta*** increased the odds of new-onset

alcohol behaviors 3 years later. Importantly, the endophenotypes provided significant incremental predictive power of future non-clinical alcohol use beyond relevant risk factors (prior alcohol use; tobacco/illicit drug initiation; parental alcohol use disorder). **Conclusions:** The current report is ***the first of our knowledge to demonstrate that deviations in parietal P3 and midfrontal theta prospectively predict the emergence of normative/non-pathological drinking. P3 and theta provide modest yet significant explanatory variance beyond prominent self-report and familial risk measures. Findings offer strong evidence supporting the predictive utility of P3 and theta as candidate endophenotypes for adolescent drinking*.**

Preparing to approach or avoid alcohol: EEG correlates, and acute alcohol effects.
Korucuoglu O, Gladwin TE, Wiers RW. Neurosci Lett. 2014 Jan 24;559:199-204. doi: 10.1016/j.neulet.2013.12.003. Epub 2013 Dec 12. PMID: 24334167.
Recently an approach-bias for alcohol has been described as an important cognitive motivational process in the etiology of alcohol use problems. In the approach-bias, perception and action are inextricably linked and stimulus response associations are central to this bias: performance improves when task instructions are congruent with a pre-existing stimulus-response association. These pre-existing response associations could potentially allow advance response preparation and execution. ***The present study aimed at investigating the effect of the alcohol approach bias on response preparation by means of event-related desynchronization in the beta band (beta-ERD) of the EEG signal and the effect of acute alcohol in the approach bias in response to alcohol cues*.** Subjects (18 social drinkers) performed an adapted alcohol-Approach Avoidance Task, in which a preparatory period was provided between alcohol/soft drink cues and approach/avoid responses. Subjects were tested both in a placebo and in an alcohol condition (counterbalanced). ***Posterior beta-ERD was found to increase during preparation for alcohol-approach trials. The beta-ERD in the congruent block increased following alcohol administration. These results suggest that advance response preparation may play a role in the alcohol approach bias and that acute alcohol facilitates response preparatory processes for approach alcohol trials. Future EEG studies using the adapted AAT may help understanding approach biases in addiction***.

Resting-state EEG, Substance use and Abstinence After Chronic use: A Systematic Review.
Liu Y, Chen Y, Fraga-González G, Szpak V, Laverman J, Wiers RW, Richard Ridderinkhof K. Clin EEG Neurosci. 2022 Jul;53(4):344-366. doi: 10.1177/15500594221076347. Epub 2022 Feb 10. PMID: 35142589.
Resting-state EEG reflects intrinsic brain activity and its alteration represents changes in cognition that are related to neuropathology. Thereby, it provides a way of revealing the neurocognitive mechanisms underpinning chronic substance use. In addition, it is documented that some neurocognitive functions can recover following sustained abstinence. We present a systematic review to synthesize how chronic substance use is associated with resting-state EEG alterations and whether these spontaneously recover from abstinence. A literature search in Medline, PsycINFO, Embase, CINAHL, Web of Science, and Scopus resulted in 4088 articles, of which 57 were included for evaluation. It covered the ***substance of alcohol*** (18), tobacco (14), cannabis (8), cocaine (6), opioids (4), methamphetamine (4), and ecstasy (4). ***EEG analysis methods included spectral power, functional connectivity, and network analyses. It was found that long-term substance use with or without substance use disorder diagnosis was associated with broad intrinsic neural activity alterations, which were usually expressed as neural hyperactivation and decreased neural communication between brain regions. Some studies found the use of alcohol,*** tobacco, cocaine, cannabis, and methamphetamine ***was positively correlated with these changes*.** These alterations can partly recover from abstinence, which differed between drugs and may reflect their neurotoxic degree. Moderating factors that may explain results inconsistency are discussed. In

sum, ***resting-state EEG may act as a potential biomarker of neurotoxic effects of chronic substance use*.** Recovery effects awaits replication in larger samples with prolonged abstinence. Balanced sex ratio, enlarged sample size, advanced EEG analysis methods, and transparent reporting are recommended for future studies.

The neurophysiological and neurochemical effects of alcohol on the brain are inconsistent with current evidence based models of sleepwalking.

Pressman MR. Sleep Med Rev. 2019 Feb;43:92-95. doi: 10.1016/j.smrv.2018.10.003. Epub 2018 Nov 10. PMID: 30537569.

The DSM-5 and ICSD-3 have removed alcohol from the list of potential triggers for sleepwalking due to the lack of empirical evidence. ***Recent imaging and EEG based studies of sleepwalking and confusional arousals have provided a more data-based method of examining if alcohol is compatible with what is known about the neurophysiology and neurochemistry of sleepwalking. These studies have demonstrated a deactivation of the frontal areas of the brain, while the cingulate or motor cortex remains active and characterized activation in the form of beta EEG. This increase in activation is attributed to a decrease in the inhibitory activity the neurotransmitter GABAa.*** This cerebral excitability of the cingulate cortex of sleepwalkers is also present in the brains of sleepwalkers during wakefulness compared to normal controls. Alcohol is well established to have an inhibitory effect on the brain and specifically on the motor areas via the inhibitory effects of increased GABAA activity. Thus, the empirical data show sleepwalking is characterized by a decrease in the inhibitory activity of GABAA - permitting or facilitating motor activity while alcohol has the opposite effect of increasing GABAA and inhibiting motor activity. This is inconsistent with theories that alcohol is somehow a trigger or facilitator for sleepwalking.

Resting-state connectivity and network parameter analysis in alcohol-dependent males. A simultaneous EEG-MEG study.

Sion A, Bruña Fernández R, Martínez Maldonado A, Domínguez Centeno I, Torrado-Carvajal A, Rubio G, Pereda E, Jurado-Barba R. J Neurosci Res. 2020 Oct;98(10):1857-1876. doi: 10.1002/jnr.24673. Epub 2020 Jun 25. PMID: 32585750.

There is supporting evidence of alcohol negative effects on the brain: neuroimaging and psychophysiological studies finding anatomical and functional connectivity (FC) changes associated with the dependence process. Thus, the aim of this work was to evaluate brain FC and network characteristics of alcohol-dependent individuals in resting state. For this study, we included males diagnosed with alcohol dependence (N = 25) and a group of healthy individuals (N = 23). Simultaneous EEG-MEG (electroencephalographic and magnetoencephalographic) activity was recorded in 5 min of eyes-closed resting state. ***EEG-MEG activity was preprocessed and FC was computed through the leakage-corrected version of phase locking value (ciPLV). Additionally, local (degree, efficiency, clustering) and global (efficiency, characteristic path length) network parameters were computed. Connectivity analysis showed an increase in phase-lagged synchronization, mainly between frontal and frontotemporal regions, in high beta band, and a decrease in interhemispheric gamma, for alcohol-dependent individuals. Network analysis revealed intergroup differences at the local level for high beta, indicating higher degree, clustering, and efficiency, mostly at frontal nodes, together with a decrease in these measures at more posterior sites for patients' group. The hyper-synchronization in beta, next to the hypo-synchronization in gamma, could indicate an alteration in communication between hemispheres, but also a possible functional compensation mechanism in neural circuits*.** This could be also supported by network characteristic data, where local alterations in communication are observed.

Alcohol disrupts sleep homeostasis.

Thakkar MM, Sharma R, Sahota P. Alcohol disrupts sleep homeostasis. Alcohol. 2015 Jun;49(4):299-310. doi: 10.1016/j.alcohol.2014.07.019. Epub 2014 Nov 11. PMID: 25499829; PMCID: PMC4427543.

Alcohol is a potent somnogen and one of the most commonly used "over the counter" sleep aids. ***In healthy non-alcoholics, acute alcohol decreases sleep latency, consolidates and increases the quality (delta power) and quantity of NREM sleep during the first half of the night. However, sleep is disrupted during the second half.*** Alcoholics, both during drinking periods and during abstinences, suffer from a multitude of sleep disruptions manifested by profound insomnia, excessive daytime sleepiness, and altered sleep architecture. Furthermore, subjective and objective indicators of sleep disturbances are predictors of relapse. Finally, within the USA, it is estimated that societal costs of alcohol-related sleep disorders exceeds $18 billion. Thus, although alcohol-associated sleep problems have significant economic and clinical consequences, very little is known about how and where alcohol acts to affect sleep. In this review, we have described our attempts to unravel the mechanism of alcohol-induced sleep disruptions. We have conducted a series of experiments using two different species, rats and mice, as animal models. We performed microdialysis, immunohistochemical, pharmacological, sleep deprivation and lesion studies which suggest that the sleep-promoting effects of alcohol may be mediated via alcohol's action on the mediators of sleep homeostasis: adenosine (AD) and the wake-promoting cholinergic neurons of the basal forebrain (BF). Alcohol, via its action on AD uptake, increases extracellular AD resulting in the inhibition of BF wake-promoting neurons. Since binge alcohol consumption is a highly prevalent pattern of alcohol consumption and disrupts sleep, we examined the effects of binge drinking on sleep-wakefulness. Our ***results suggest that disrupted sleep homeostasis may be the primary cause of sleep disruption observed following binge drinking. Finally, we have also shown that sleep disruptions observed during acute withdrawal, are caused due to impaired sleep homeostasis. In conclusion, we suggest that alcohol may disrupt sleep homeostasis to cause sleep disruptions.***

ALPHA BLOCKERS

CLASS FACTS

SYNOPSIS: Used for reducing blood pressure, improve blood circulation, leg vein health, Reynaud's syndrome, and benign prostate hyperplasia by blocking alpha -1 and -2 adrenergic receptors.

----- PHENOXYBENZAMINE -----

DRUG FACTS

EEG spectral power increase in the prefrontal cortex of conscious rats elicited by drugs.
Sebban, C., Zhang, X. Q., Tesolin-Decros, B., Millan, M. J., & Spedding, M. (1999). *Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission.* British journal of pharmacology, 128(5), 1045–1054. https://doi.org/10.1038/sj.bjp.0702894

The electroencephalographic (EEG) effects of drugs interacting with dopaminergic and noradrenergic systems were studied in conscious rats. ***Power spectra (0 - 30 Hz) were recorded from electrodes implanted bilaterally in the prefrontal cortex. Drug effects on EEG power were calculated as the spectral power following drug administration divided by the spectral power after vehicle administration.*** Dopaminergic agonists at low doses, (apomorphine 0. 01 mg kg-1 s.c., quinpirole 0.01 mg kg-1 i.p.) and dopaminergic antagonists (haloperidol 1 mg kg-1 i.p., raclopride 2.5 mg kg-1 s.c.), which decrease dopaminergic transmission, ***induced an increase of EEG power***. Conversely, dopaminergic agonists at higher doses (apomorphine 0.5 mg kg-1 s.c., quinpirole 0.5 mg kg-1 i.p.) which increase activation of postsynaptic D2 and D3 receptors, induced a decrease of EEG power. The alpha1-adrenoceptor antagonists (phenoxybenzamine 0.64 mg kg-1 s.c., prazosin 0.32 mg kg-1 s.c.) and the alpha2-adrenoceptor agonists (UK 14304 0.05 mg kg-1 s.c., clonidine 0.025 mg kg-1 i.p.), which decrease noradrenergic transmission, induced an increase of EEG power. Conversely, the alpha1-adrenoceptor agonist, cirazoline (0.05 mg kg-1 s.c.), the adrenergic agent modafinil (250, 350 mg kg-1 i.p.) and alpha2-adrenoceptor antagonists (RX 821002 0.01 mg kg-1 s.c., yohimbine 0.5 mg kg-1 i.p.), which increase noradrenergic transmission, induced a decrease of EEG power. The effects of prazosin (0.64 mg kg-1 s.c.) were dose-dependently antagonized by co-administration with modafinil and cirazoline, but not by apomorphine. In conclusion, pharmacological modulation of dopaminergic and noradrenergic transmission may result in consistent EEG changes: decreased dopaminergic or noradrenergic activity induces an increase of EEG spectral power; while increased dopaminergic or noradrenergic activity decreases EEG spectral power.

----- PRAZOSIN -----
(Hypovase, Minipress, Pressin, Vasoflex)
DRUG FACTS

Prazosin shortens sleep and wake stages

Kleinlogel H. (1989). Effects of the selective alpha 1-adrenoceptor blocker prazosin on EEG sleep and waking stages in the rat. Neuropsychobiology, 21(2), 100–103. https://doi.org/10.1159/000118560

In order to gain a better understanding of the role of the noradrenergic system in the control of the EEG sleep-waking stages, the effects of the selective alpha 1-antagonist prazosin was investigated in the rat. Oral doses of prazosin (0.1-10 mg/kg) were administered that have been shown to enter the brain. EEG sleep and waking stages were recorded either during 8 h after drug administration at 8.00 in the morning or during 48 h after drug administration at 16.00 in the afternoon. ***It was found that prazosin at doses of 0.1-10 mg/kg shortened quiet waking. Starting at 1 mg/kg paradoxical sleep (PS) was shortened and, most interestingly, active waking and slow wave sleep (SWS) were prolonged***. PS spindles and dozing were shortened after a latency of some hours during the 48-hour experiment. However, during the 8-hour experiment PS spindles were prolonged at 0.32 and 1 mg/kg. These data suggest that in the rat alpha 1-adrenoceptor inhibition in the brain allows the occurrence of active waking and SWS and suppresses PS.

ANALEPTICS

CLASS FACTS

SYNOPSIS: Central nervous system stimulants that are often prescribed for depression, ADHD, apnea, recovery from anesthesia, and possibly as anti-convulsant.

----- AMPHETAMINE – DEXTROAMPHETAMINE - METHAMPHETAMINE ----- (Adderall, Dexedrine, Dextrostat, Desoxyn, Procentra, Vyvanse)

DRUG FACTS

SYNOPSIS: Some amphetamines are prescribed, while all methamphetamine is illicit. These drugs can alter the EEG to benefit cognitive functioning but abuse can decrease important EEG features.

Effects of stimulant medications on the EEG of girls with Attention-Deficit/Hyperactivity Disorder.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2007). Effects of stimulant medications on the EEG of girls with Attention-Deficit/Hyperactivity Disorder. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118(12), 2700–2708. https://doi.org/10.1016/j.clinph.2007.08.020

Objective: Stimulant medications are the most commonly used treatments for Attention-Deficit/Hyperactivity Disorder (AD/HD) in North America and Australia, although it is still not entirely known how these medications work. This study investigated the effects of stimulant medications on the EEG of girls with AD/HD. Methods: An initial EEG was recorded during an eyes-closed resting condition. Data from 19 electrode sites were Fourier transformed to provide absolute and relative power estimates for the delta, theta, alpha and beta bands. The data were then averaged into 9 regions and an analysis of both global and regional differences was performed. Subjects were placed on a six-month trial of a stimulant and a second EEG was recorded at the end of the trial. Results: The unmedicated girls had significantly greater total power, absolute delta and theta, more relative theta especially in the frontal regions, and reduced frontal relative delta and beta activity compared with controls. ***Medication resulted in normalisation of theta power, but after medication, increased relative beta was also apparent in the AD/HD group***. Conclusions: These results indicate that stimulant medications result in a normalisation of slow wave activity in the EEG. In line with published research on the effects of arousal on the EEG, these results suggest that stimulant medications may have their therapeutic effect by improving the EEG substrate of processing deficits in these children. However, this requires further testing during active processing tasks. Significance: This is the first study to investigate the effect of stimulant medications on the EEG of girls with AD/HD.

How to keep the brain awake? The complex molecular pharmacogenetics of wake promotion.

Hasan, S., Pradervand, S., Ahnaou, A., Drinkenburg, W., Tafti, M., & Franken, P. (2009). How

to keep the brain awake? The complex molecular pharmacogenetics of wake promotion. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 34(7), 1625–1640. https://doi.org/10.1038/npp.2009.3

Wake-promoting drugs are widely used to treat excessive daytime sleepiness. The neuronal pathways involved in wake promotion are multiple and often not well characterized. We tested d-amphetamine, modafinil, and YKP10A, a novel wake-promoting compound, in three inbred strains of mice. The wake duration induced by YKP10A and d-amphetamine depended similarly on genotype, whereas opposite strain differences were observed after modafinil. ***Electroencephalogram (EEG) analysis during drug-induced wakefulness revealed a transient approximately 2 Hz slowing of theta oscillations and an increase in beta-2 (20-35 Hz) activity only after YKP10A***. Gamma activity (35-60 Hz) was induced by all drugs in a drug- and genotype-dependent manner. Brain transcriptome and clustering analyses indicated that the three drugs have both common and specific molecular signatures. The correlation between specific EEG and gene-expression signatures suggests that the neuronal pathways activated to stay awake vary among drugs and genetic background.

Impairments in meth users

Kraiwattanapirom, N., Siripornpanich, V., Suwannapu, W., Unaharassamee, W., Chawang, O., Lomwong, N., Vittayatavornwong, L., & Chetsawang, B. (2022). *The quantitative analysis of EEG during resting and cognitive states related to neurological dysfunctions and cognitive impairments in methamphetamine abusers*. Neuroscience letters, 789, 136870. https://doi.org/10.1016/j.neulet.2022.136870

Several lines of evidence demonstrated the deleterious effect of methamphetamine (MA) on neurological and psychological functions. However, recent evidence on the neurological dysfunctions related to cognitive performance and psychosis in MA abusers needs to be elucidated. Therefore, the present study aimed to investigate the neurological functions using EEG measurement during cognitive tests in MA abusers with (MWP) or without (MWOP) psychosis compared to age-matched normal participants. The quantitative EEG (qEEG) was used to reveal the absolute power in 4 brain-wave frequencies including delta, theta, alpha, and beta waves. The results demonstrated poor attention in both groups of MA abusers. The deficit in mental flexibility was observed in MWP. The deficit in inhibition control and working memory were observed in MWOP. ***The greater delta, alpha and beta brain waves in multiple brain areas were observed in MWP during the resting (eyes-open) state. The greater alpha wave in multiple brain areas of MWP correlated with poor attention. The greater delta wave and lesser beta wave in the frontal brain correlated with poor inhibition and working memory in MWOP respectively. These findings demonstrated the applicability of EEG to determine neurological dysfunction related to cognitive impairments in MA abusers***.

Delta and theta, overall EEG differences

Newton, T. F., Cook, I. A., Kalechstein, A. D., Duran, S., Monroy, F., Ling, W., & Leuchter, A. F. (2003). Quantitative EEG abnormalities in recently abstinent methamphetamine dependent individuals. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 114(3), 410–415. https://doi.org/10.1016/s1388-2457(02)00409-1

Objective: Methamphetamine exposure is associated with long-lasting reductions in markers for dopaminergic neurons in preclinical models and probably in humans. Quantitative electroencephalography (EEG) has been used to characterize abnormalities in brain function in a number of disorders, including cocaine dependence, but this technique has not been used to characterize abnormalities associated with methamphetamine dependence. Methods: The sample included 11 methamphetamine dependent subjects and 11 non-drug using volunteers. Methamphetamine dependent subjects were hospitalized for 4 days to document abstinence; non-drug using volunteers were studied as outpatients. EEGs were recorded in the eyes-closed resting state, and absolute EEG power in each frequency band (0.5-4, 4-8, 8-12, and 12-20 Hz) was quantitated using a fast Fourier transform. EEG power was log-transformed prior to analysis. Conventional, EEG tracings were interpreted by a qualified electroencephalographer who was blinded to the subjects' identity. Results: ***Methamphetamine dependent volunteers with 4 days of abstinence had increased EEG power in the delta and theta bands. Power in the alpha and beta bands did not differ between the groups. Within the methamphetamine dependent group, a majority of the conventional EEGs were abnormal (64%), compared to 18% in the non-methamphetamine using group.*** Conclusions: Recently abstinent methamphetamine dependent subjects demonstrate QEEG abnormalities that are consistent with a generalized encephalopathy. Significance: Encephalopathic changes in brain electrical activity, as found here in methamphetamine dependence, are frequently associated with a range of cognitive and psychiatric abnormalities, suggesting further avenues of investigation.

Cz and Pz P300 amplitudes increase

Sawada, M., Iida, J., Ota, T., Negoro, H., Tanaka, S., Sadamatsu, M., & Kishimoto, T. (2010). Effects of osmotic-release methylphenidate in attention-deficit/hyperactivity disorder as measured by event-related potentials. Psychiatry and clinical neurosciences, 64(5), 491–498. https://doi.org/10.1111/j.1440-1819.2010.02134.x

Aim: Attention-deficit/hyperactivity disorder (ADHD) is a relatively common central nervous system disorder in school-age children, which may involve a specific disorder in cognition and/or information processing. Event-related potentials (ERP) are commonly used as physiological measures of cognitive function as they are easily measured and non-invasive. Thus, in the present study, we examined the effects of osmotic-release methylphenidate (MPH) (Concerta), a common treatment for childhood attention-deficit/hyperactivity disorder (ADHD), in ADHD children as measured by ERP. Methods: Ten ADHD children participated after giving consent. Based on the guidelines for evoked potential measurement, mismatch negativity (MMN) and P300 were obtained by auditory odd-ball tasks. We measured both MMN and P300 in the drug-naive condition and after intake of osmotic-release MPH. Results: The MMN amplitudes after intake of osmotic-release MPH were significantly greater than those in the drug-naive situation at Pz and C4. ***The P300 amplitudes after intake of osmotic-release MPH were significantly greater than those in the drug-naive situation at Cz and Pz***. Conclusion: MMN and P300 are sensitive tools for measuring the pharmacological effects of osmotic-release MPH in ADHD children.

Coherence and symmetry dysregulations

Chabot, R. J., Orgill, A. A., Crawford, G., Harris, M. J., & Serfontein, G. (1999). Behavioral and

electrophysiologic predictors of treatment response to stimulants in children with attention disorders. Journal of child neurology, 14(6), 343–351. https://doi.org/10.1177/088307389901400601

Behavioral and quantitative electroencephalography (EEG) techniques were used to evaluate treatment response to stimulant therapy in children with attention disorders. A sample of 130 children with attention disorders were evaluated with Conners and Diagnostic and Statistical Manual of Mental Disorders--III rating scales, and with neurometric quantitative EEG before and 6 to 14 months after treatment with stimulants. Significant quantitative EEG differences were found between the normal control population (N = 31) and the children with attention problems. ***Quantitative EEG abnormalities involved increased theta or alpha power, greatest in frontal regions, frontal theta/alpha hypercoherence, and posterior interhemispheric power asymmetry***. Behavioral improvement after stimulant treatment was seen in 81.5% of the children with attention-deficit hyperactivity disorder and 44.7% of the children with attention-deficit disorder, with the degree of correspondence between behavioral and quantitative EEG changes at 78.5%. Pretreatment clinical and quantitative EEG features could predict treatment response with a sensitivity of 83.1% and a specificity of 88.2%. A combined behavioral and quantitative EEG approach can be useful for following and predicting treatment response to stimulants in children with attention disorders.

Disruptions in EEG microstates

Chen, T., Su, H., Zhong, N., Tan, H., Li, X., Meng, Y., Duan, C., Zhang, C., Bao, J., Xu, D., Song, W., Zou, J., Liu, T., Zhan, Q., Jiang, H., & Zhao, M. (2020). *Disrupted brain network dynamics and cognitive functions in methamphetamine use disorder: insights from EEG microstates*. BMC psychiatry, 20(1), 334. https://doi.org/10.1186/s12888-020-02743-5

Background: Dysfunction in brain network dynamics has been found to correlate with many psychiatric disorders. However, there is limited research regarding resting electroencephalogram (EEG) brain network and its association with cognitive process for patients with methamphetamine use disorder (MUD). This study aimed at using EEG microstate analysis to determine whether brain network dynamics in patients with MUD differ from those of healthy controls (HC). Methods: A total of 55 MUD patients and 27 matched healthy controls were included for analysis. The resting brain activity was recorded by 64-channel electroencephalography. EEG microstate parameters and intracerebral current sources of each EEG microstate were compared between the two groups. Generalized linear regression model was used to explore the correlation between significant microstates with drug history and cognitive functions. Results: MUD patients showed lower mean durations of the microstate classes A and B, and a higher global explained variance of the microstate class C. Besides, MUD patients presented with different current density power in microstates A, B, and C relative to the HC. The generalized linear model showed that MA use frequency is negatively correlated with the MMD of class A. Further, the generalized linear model showed that MA use frequency, scores of Two-back task, and the error rate of MA word are correlated with the MMD and GEV of class B, respectively. Conclusions: ***Intracranial current source densities of resting EEG microstates are disrupted in MUD patients, hence causing temporal changes in microstate topographies, which are correlated with attention bias and history of drug use***.

Structural, not functional, dysfunction

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Johnstone, S. J., Abbott, I., Croft, R. J., Magee, C. A., Hsu, C. I., & Lawrence, C. A. (2005). Effects of methylphenidate on EEG coherence in attention-deficit/hyperactivity disorder. International journal of psychophysiology : official journal of the International Organization of Psychophysiology, 58(1), 4–11. https://doi.org/10.1016/j.ijpsycho.2005.03.004

This study investigated the effects of methylphenidate on intrahemispheric and interhemispheric EEG coherence in children with Attention-Deficit/Hyperactivity Disorder (AD/HD). Twenty boys with AD/HD Combined type and 20 age- and sex-matched control subjects, aged 8 to 13 years, participated in this study. EEG was recorded from 21 sites during an eyes-closed resting condition. Wave-shape coherence was calculated for eight intrahemispheric electrode pairs (four in each hemisphere), and eight interhemispheric electrode pairs, within each of the delta, theta, alpha and beta bands. AD/HD children were tested both off and, 6 months later, on a therapeutic dose of methylphenidate. In intrahemispheric comparisons, AD/HD children had lower theta coherences at long inter-electrode distances, and reduced lateralisation at both long and short-medium inter-electrode distances than controls. For interhemispheric comparisons, AD/HD children showed increased coherences in the frontal regions for the low frequency bands (delta and theta), and reduced coherences in the alpha bands in all other regions. These EEG coherences suggest reduced cortical differentiation and specialisation in AD/HD, particularly in the frontal regions. Methylphenidate did not produce any changes in coherence values. ***The lack of sensitivity of coherence measures to methylphenidate in the present study suggests that eyes-closed resting EEG coherence measures are associated with structural connectivity of the underlying regions of the brain rather than the degree of functionality of these regions. These results suggest the existence of structural as well as functional brain dysfunction in AD/HD***.

Slow wave EEG normalization

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2007). Effects of stimulant medications on the EEG of girls with Attention-Deficit/Hyperactivity Disorder. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118(12), 2700–2708. https://doi.org/10.1016/j.clinph.2007.08.020

Objective: Stimulant medications are the most commonly used treatments for Attention-Deficit/Hyperactivity Disorder (AD/HD) in North America and Australia, although it is still not entirely known how these medications work. This study investigated the effects of stimulant medications on the EEG of girls with AD/HD. Methods: An initial EEG was recorded during an eyes-closed resting condition. Data from 19 electrode sites were Fourier transformed to provide absolute and relative power estimates for the delta, theta, alpha and beta bands. The data were then averaged into 9 regions and an analysis of both global and regional differences was performed. Subjects were placed on a six-month trial of a stimulant and a second EEG was recorded at the end of the trial. Results: The unmedicated girls had significantly greater total power, absolute delta and theta, more relative theta especially in the frontal regions, and reduced frontal relative delta and beta activity compared with controls. Medication resulted in normalisation of theta power, but after medication, increased relative beta was also apparent in the AD/HD group. Conclusions: ***These results indicate that stimulant medications result in a***

normalisation of slow wave activity in the EEG. In line with published research on the effects of arousal on the EEG, these results suggest that stimulant medications may have their therapeutic effect by improving the EEG substrate of processing deficits in these children. However, this requires further testing during active processing tasks. Significance: This is the first study to investigate the effect of stimulant medications on the EEG of girls with AD/HD.

Ventrolateral prefrontal activation

Cubillo, A., Smith, A. B., Barrett, N., Giampietro, V., Brammer, M. J., Simmons, A., & Rubia, K. (2014). Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naive ADHD boys. Cerebral cortex (New York, N.Y. : 1991), 24(1), 174–185. https://doi.org/10.1093/cercor/bhs296

The stimulant methylphenidate (MPX) and the nonstimulant atomoxetine (ATX) are the most commonly prescribed medications for attention deficit hyperactivity disorder (ADHD). However, no functional magnetic resonance imaging (fMRI) study has as yet investigated the effects of ATX on inhibitory or any other brain function in ADHD patients or compared its effects with those of MPX. A randomized, double-blind, placebo-controlled, crossover pharmacological design was used to compare the neurofunctional effects of single doses of MPX, ATX, and placebo during a stop task, combined with fMRI within 19 medication-naive ADHD boys, and their potential normalization effects relative to 29 age-matched healthy boys. Compared with controls, ADHD boys under placebo showed bilateral ventrolateral prefrontal, middle temporal, and cerebellar underactivation. ***Within patients, MPX relative to ATX and placebo significantly upregulated right ventrolateral prefrontal activation, which correlated with enhanced inhibitory capacity.*** Relative to controls, both drugs significantly normalized the left ventrolateral prefrontal underactivation observed under placebo, while MPX had a drug-specific effect of normalizing right ventrolateral prefrontal and cerebellar underactivation observed under both placebo and ATX. The findings show shared and drug-specific effects of MPX and ATX on performance and brain activation during inhibitory control in ADHD patients with superior upregulation and normalization effects of MPX.

Reduced theta power compared to physical activity

Janssen, T. W., Bink, M., Geladé, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2016). A randomized controlled trial into the effects of neurofeedback, methylphenidate, and physical activity on EEG power spectra in children with ADHD. Journal of child psychology and psychiatry, and allied disciplines, 57(5), 633–644. https://doi.org/10.1111/jcpp.12517

Background: The clinical and neurophysiological effects of neurofeedback (NF) as treatment for children with ADHD are still unclear. This randomized controlled trial (RCT) examined electroencephalogram (EEG) power spectra before and after NF compared to methylphenidate (MPH) treatment and physical activity (PA) - as semi-active control group - during resting and active (effortful) task conditions to determine whether NF can induce sustained alterations in brain function. Methods: Using a multicentre three-way parallel group RCT design, 112 children with a DSM-IV diagnosis of ADHD, aged between 7 and 13 years, were initially included. NF training consisted of 30 sessions of theta/beta training at Cz over a 10-week period. PA training was a semi-active control group, matched in frequency and duration. Methylphenidate was

titrated using a double-blind placebo controlled procedure in 6 weeks, followed by a stable dose for 4 weeks. EEG power spectra measures during eyes open (EO), eyes closed (EC) and task (effortful) conditions were available for 81 children at pre- and postintervention (n = 29 NF, n = 25 MPH, n = 27 PA). Clinical trials registration: Train Your Brain? Exercise and Neurofeedback Intervention for ADHD, https://clinicaltrials.gov/show/;NCT01363544, Ref. No. NCT01363544. Results: ***Both NF and MPH resulted in comparable reductions in theta power from pre- to postintervention during the EO condition compared to PA (ηp (2) = .08 and .12). For NF, greater reductions in theta were related to greater reductions in ADHD symptoms.*** During the task condition, only MPH showed reductions in theta and alpha power compared to PA (ηp (2) = .10 and .12). Conclusions: This study provides evidence for specific neurophysiological effects after theta/beta NF and MPH treatment in children with ADHD. However, for NF these effects did not generalize to an active task condition, potentially explaining reduced behavioural effects of NF in the classroom.

Increased occipital alpha

Kerdar, M. S., Scheuerpflug, P., Srdinko, P., Wewetzer, C., Warnke, A., & Romanos, M. (2007). EEG-veränderungen unter Methylphenidat--eine Pilotstudie [*Quantitative effect of treatment with methylphenidate on EEG--a pilot study*]. Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie, 35(4), 247–256. https://doi.org/10.1024/1422-4917.35.4.247

Objective: As a presumptive side effect, a lowered seizure threshold due to medication with methylphenidate remains controversial. The pilot study at hand addresses the experimental verification of this claim. Furthermore, quantitative effects of methylphenidate treatment on EEG are measured. Method: The EEGs of 15 patients with ADHD aged 6 to 14 years were acquisitioned. Diagnosis was made according to multi-axial diagnostic procedures and in observance of all ICD-10 criteria. In order to evaluate the electrophysiological effects of methylphenidate, the EEG-data were analysed with regard to the composition of the frequency spectrum and the occurrence of pathological EEG-alterations. Results: ***The analysis of EEG data prior to and subsequent to medication with methylphenidate showed an increase of occipital alpha-activity, whereas of delta-theta-activity was reduced. Beta-activity increased in the central region and showed a trend towards a frontal increase. Neither before nor after treatment with methylphenidate could pathological potentials be detected. Conclusion: The results support the common view in the existing literature that methylphenidate does not lower the seizure threshold. Rather its effect on electrophysiological parameters can be described as a normalisation in terms of an acceleration of the occipital rhythm***.

Increased frontal beta

Loo, S. K., Hopfer, C., Teale, P. D., & Reite, M. L. (2004). EEG correlates of methylphenidate response in ADHD: association with cognitive and behavioral measures. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 21(6), 457–464. https://doi.org/10.1097/01.wnp.0000150890.14421.9a

The authors examined the association between EEG correlates of medication response and concomitant cognitive and behavioral changes among children with attention-deficit hyperactivity disorder (ADHD). Subjects were 36 children with ADHD, aged 8 to 12 years. EEG

activity was recorded from nine active electrodes during placebo and medication conditions. Medication administration resulted in increased alpha activity in central and parietal regions during both the baseline and cognitive activation conditions. Children who were medication responders exhibited increased frontal beta activity whereas nonresponders showed decreased beta activity in the same region. Increased frontal beta activity was significantly correlated with medication-related improvement in performance on Conners' Continuous Performance Test and parent behavior ratings in attention and hyperactivity. Decreased right frontal theta activity was associated with improvements in parent-rated attention, but not in CPT performance. ***Stimulant medication increases beta activity in children with ADHD, particularly in frontal regions.*** Increased cortical arousal and activation in the frontal cortex is strongly associated with sustained attention and response inhibition and with parent-rated attention and hyperactivity/impulsivity.

Decrease in alpha power right posterior

Paes, F., Machado, S., Arias-Carrión, O., Domingues, C. A., Teixeira, S., Velasques, B., Cunha, M., Minc, D., Basile, L. F., Budde, H., Cagy, M., Piedade, R., Kerick, S., Menéndez-González, M., Skaper, S. D., Norwood, B. A., Ribeiro, P., & Nardi, A. E. (2011). Effects of Methylphenidate on performance of a practical pistol shooting task: a quantitative electroencephalography (qEEG) study. International archives of medicine, 4(1), 6. https://doi.org/10.1186/1755-7682-4-6

Background: The present study examined absolute alpha power using quantitative electroencephalogram (qEEG) in bilateral temporal and parietal cortices in novice soldiers under the influence of methylphenidate (MPH) during the preparatory aiming period in a practical pistol-shooting task. We anticipated higher bi-hemispheric cortical activation in the preparatory period relative to pre-shot baseline in the methylphenidate group when compared with the control group because methylphenidate has been shown to enhance task-related cognitive functions. Methods: Twenty healthy, novice soldiers were equally distributed in control (CG; n = 10) and MPH groups 10 mg (MG; n = 10) using a randomized, double blind design. Subjects performed a pistol-shooting task while electroencephalographic activity was acquired. Results: We found main effects for group and practice blocks on behavioral measures, and interactions between group and phases on electroencephalographic measures for the electrodes T3, T4, P3 and P4. Regarding the behavioral measures, the MPH group demonstrated significantly poorer in shooting performance when compared with the control and, in addition, significant increases in the scores over practice blocks were found on both groups. In addition, regarding the electroencephalographic data, we observed a significant increase in alpha power over practice blocks, but alpha power was significantly lower for the MPH group when compared with the placebo group. Moreover, ***we observed a significant decrease in alpha power in electrodes T4 and P4 during PTM.*** Conclusion: Although we found no correlation between behavioral and EEG data, our findings show that MPH did not prevent the learning of the task in healthy subjects. However, during the practice blocks (PBs) it also did not favor the performance when compared with control group performance. It seems that the CNS effects of MPH demanded an initial readjustment period of integrated operations relative to the sensorimotor system. In other words, MPH seems to provoke a period of initial instability due to a possible modulation in neural activity, which can be explained by lower levels of alpha

power (i.e., higher cortical activity). However, after the end of the PB1 a new stabilization was established in neural circuits, due to repetition of the task, resulting higher cortical activity during the task. In conclusion, MPH group performance was not initially superior to that of the control group, but eventually exceeded it, albeit without achieving statistical significance.

Right insula activation

Rubia, K., Alegria, A. A., Cubillo, A. I., Smith, A. B., Brammer, M. J., & Radua, J. (2014). Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Biological psychiatry, 76(8), 616–628. https://doi.org/10.1016/j.biopsych.2013.10.016

Background: Psychostimulant medication, most commonly the catecholamine agonist methylphenidate, is the most effective treatment for attention-deficit/hyperactivity disorder (ADHD). However, relatively little is known on the mechanisms of action. Acute effects on brain function can elucidate underlying neurocognitive effects. We tested methylphenidate effects relative to placebo in functional magnetic resonance imaging (fMRI) during three disorder-relevant tasks in medication-naïve ADHD adolescents. In addition, we conducted a systematic review and meta-analysis of the fMRI findings of acute stimulant effects on ADHD brain function. Methods: The fMRI study compared 20 adolescents with ADHD under either placebo or methylphenidate in a randomized controlled trial while performing stop, working memory, and time discrimination tasks. The meta-analysis was conducted searching PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus databases. Peak coordinates of clusters of significant effects of stimulant medication relative to placebo or off medication were extracted for each study. Results: The fMRI analysis showed that methylphenidate significantly enhanced activation in bilateral inferior frontal cortex (IFC)/insula during inhibition and time discrimination but had no effect on working memory networks. The meta-analysis, including 14 fMRI datasets and 212 children with ADHD, showed that stimulants most consistently enhanced right IFC/insula activation, which also remained for a subgroup analysis of methylphenidate effects alone. A more lenient threshold also revealed increased putamen activation. Conclusions: ***Psychostimulants most consistently increase right IFC/insula activation, which are key areas of cognitive control and also the most replicated neurocognitive dysfunction in ADHD. These neurocognitive effects may underlie their positive clinical effects***.

Aid in emergence from general anesthesia.

Solt, K., Cotten, J. F., Cimenser, A., Wong, K. F., Chemali, J. J., & Brown, E. N. (2011). *Methylphenidate actively induces emergence from general anesthesia*. Anesthesiology, 115(4), 791–803. https://doi.org/10.1097/ALN.0b013e31822e92e5

Background: Although accumulating evidence suggests that arousal pathways in the brain play important roles in emergence from general anesthesia, the roles of monoaminergic arousal circuits are unclear. In this study, the authors tested the hypothesis that methylphenidate (an inhibitor of dopamine and norepinephrine transporters) induces emergence from isoflurane general anesthesia. Methods: Using adult rats, the authors tested the effect of intravenous methylphenidate on time to emergence from isoflurane general anesthesia. They then performed experiments to test separately for methylphenidate-induced changes in arousal and changes in minute ventilation. A dose-response study was performed to test for

methylphenidate-induced restoration of righting during continuous isoflurane general anesthesia. Surface electroencephalogram recordings were performed to observe neurophysiological changes. Plethysmography recordings and arterial blood gas analysis were performed to assess methylphenidate-induced changes in respiratory function. Intravenous droperidol was administered to test for inhibition of methylphenidate's actions. Results: Methylphenidate decreased median time to emergence from 280 to 91 s. The median difference in time to emergence without methylphenidate compared with administration of methylphenidate was 200 [155-331] s (median, [95% CI]). During continuous inhalation of isoflurane, methylphenidate induced return of righting in a dose-dependent manner, induced a shift in electroencephalogram power from delta (less than 4 Hz) to theta (4-8 Hz), and induced an increase in minute ventilation. Administration of intravenous droperidol (0.5 mg/kg) before intravenous methylphenidate (5 mg/kg) largely inhibited methylphenidate-induced emergence behavior, electroencephalogram changes, and changes in minute ventilation. Conclusions: Methylphenidate actively induces emergence from isoflurane general anesthesia by increasing arousal and respiratory drive, possibly through activation of dopaminergic and adrenergic arousal circuits. ***The authors' findings suggest that methylphenidate may be useful clinically as an agent to reverse general anesthetic-induced unconsciousness and respiratory depression at the end of surgery.***

Effects of methylphenidate on quantitative EEG of boys with attention-deficit hyperactivity disorder in continuous performance test.

Song, D. H., Shin, D. W., Jon, D. I., & Ha, E. H. (2005). Effects of methylphenidate on quantitative EEG of boys with attention-deficit hyperactivity disorder in continuous performance test. Yonsei medical journal, 46(1), 34–41. https://doi.org/10.3349/ymj.2005.46.1.34

The purpose of this study was to investigate the effects of methylphenidate, a psychostimulant, on quantitative electroencephalography (QEEG) during the continuous performance test (CPT) in boys with attention-deficit hyperactivity disorder (ADHD). The QEEG was obtained from 20 boys with ADHD. The amplitudes of 4 bands (alpha, beta, delta, and theta) in the QEEG, as well as the theta /beta ratio, before and after the administration of methylphenidate were compared during both the resting and CPT states. ***Methylphenidate induced a significant increase of alpha activities in both the right and left frontal and occipital areas, an increase of beta activities in almost all areas except for the temporal region, a decrease of theta activities in both the occipital and right temporo-parietal areas, a mild decrease of delta activities in the occipito-parietal areas, and an increase of the theta/beta ratio in the right frontal and parieto-occipital, and left temporal areas during the CPT state. No significant QEEG changes were induced by the administration of methylphenidate in the resting state. These data suggest that methylphenidate has greater electrophysiological influences on the cerebral topographical activities during the performance of attentional tasks, as compared to the resting state, in boys with ADHD***.

Alpha frequency as index for drug success

Sun, L., Wang, Y. F., He, H., & Chen, J. (2007). *Changes of the alpha competitive structure after administration of single dose methylphenidate in different subtypes of attention deficit hyperactivity disorder boys.* Beijing da xue xue bao. Yi xue ban. Journal of Peking University. Health sciences, 39(3), 289–292.

Objective: To investigate methylphenidate response to different subtypes of attention deficit hyperactivity disorder (ADHD) boys by measuring the changes of the alpha competitive structure after administration of single dose of methylphenidate, explore the neuropathological mechanism and search for the sensitive index to predict methylphenidate response in this disorder. Methods: The study involved 88 ADHD boys (40 ADHD-C boys,48 ADHD-I boys) who met the DSM-IV diagnostic criteria of ADHD, and their continuous Electroencephalogram (EEG) data collected before and 2 hours after taking methylphenidate (10 mg) were analyzed with EEG-encephaloflutuographic technology (EEG-ET). Results: After taking methylphenidate, (1) The main frequency of alpha band obviously increased in ADHD-C boys and ADHD-I boys (from 9.05+/-0.96 Hz up to 9.72+/-0.99 Hz, P=0.000; from 8.90+/- 0.93 Hz up to 9.25+/-0.86 Hz, P=0.002; separately) , especially in ADHD-C boy group (Z=-2.111, P=0.035). (2) The dominant probability of 8 Hz was significantly decreased in ADHD-C boys and ADHD-I boys (from 24.34%+/-12.70% down to 20.74%+/-12.46%, P=0.002; from 28.82%+/-12.51% down to 25.64%+/-12.176% ,P=0.003; separately). There was no significant difference in the changes of the dominant probability of 8 Hz between the two ADHD groups (Z=-0.494, P= 0.621).(3)The entropy value was significantly decreased in ADHD-I boys group(from 0.74+/-0.10 down to 0.70+/-0.13,t =3.579, P=0.001). There was no significant difference in the changes of the entropy value between the two ADHD groups (Z=-1.131 P=0.258). Conclusion: After administration of single dose of methylphenidate, slow alpha wave decreased in ADHD boys, especially in ADHD-C boy group; Single dose of methylphenidate can ameliorate the brain self-organization of ADHD-I boys. ***These findings suggest that the main frequency of alpha band may be the sensitive index to predict methylphenidate response in ADHD***.

Theta power lower based on MEG study

Wienbruch, C., Paul, I., Bauer, S., & Kivelitz, H. (2005). *The influence of methylphenidate on the power spectrum of ADHD children - an MEG study*. BMC psychiatry, 5, 29. https://doi.org/10.1186/1471-244X-5-29

Background: The present study was dedicated to investigate the influence of Methylphenidate (MPH) on cortical processing of children who were diagnosed with different subtypes of Attention Deficit Hyperactivity Disorder (ADHD). As all of the previous studies investigating power differences in different frequency bands have been using EEG, mostly with a relatively small number of electrodes our aim was to obtain new aspects using high density magnetoencephalography (MEG). Methods: 35 children (6 female, 29 male) participated in this study. Mean age was 11.7 years (+/- 1.92 years). 17 children were diagnosed of having an Attention-Deficit/Hyperactivity Disorder of the combined type (ADHDcom, DSM IV code 314.01); the other 18 were diagnosed for ADHD of the predominantly inattentive type (ADHDin, DSM IV code 314.0). We measured the MEG during a 5 minute resting period with a 148-channel magnetometer system (MAGNES 2500 WH, 4D Neuroimaging, San Diego, USA). Power values were averaged for 5 bands: Delta (D, 1.5-3.5 Hz), Theta (T, 3.5-7.5 Hz), Alpha (A, 7.5-12.5

Hz), Beta (B, 12.5-25 Hz) and Global (GL, 1.5-25 Hz).). Additionally, attention was measured behaviourally using the D2 test of attention with and without medication. Results: The global power of the frequency band from 1.5 to 25 Hz increased with MPH. Relative Theta was found to be higher in the left hemisphere after administration of MPH than before. A positive correlation was found between D2 test improvement and MPH-induced power changes in the Theta band over the left frontal region. A linear regression was computed and confirmed that the larger the improvement in D2 test performance, the larger the increase in Theta after MPH application. Conclusion: ***Main effects induced by medication were found in frontal regions. Theta band activity increased over the left hemisphere after MPH application. This finding contradicts EEG results of several groups who found lower levels of Theta power after MPH application. As relative Theta correlates with D2 test improvement we conclude that MEG provide complementary and therefore important new insights to ADHD***.

Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats.
Krause, M., Hoffmann, W. E., & Hajós, M. (2003). Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. Biological psychiatry, 53(3), 244–253. https://doi.org/10.1016/s0006-3223(02)01463-4

Background: Auditory gating is thought to reflect sensory information processing and is absent or diminished in schizophrenic patients. Although abnormal thalamic sensory processing has been proposed in schizophrenia, sensory gating of thalamic neurons has not been demonstrated experimentally. The aim of the present study was to establish whether auditory gating is present in the rat thalamus using a well-characterized animal model of auditory gating and schizophrenia. Methods: Hippocampal electroencephalogram and single-unit activity in the thalamic reticular nucleus (nRT) were recorded in anaesthetized rats. Evoked potentials in the hippocampus and neuronal activity in the nRT were monitored in response to bilateral auditory stimuli. ***The effects of the psychostimulant D-amphetamine and the antipsychotic haloperidol on auditory gating were evaluated. Results: Thalamic reticular nucleus neurons showed gated responses to paired-tone auditory stimuli, resembling hippocampal auditory gating. D-amphetamine disrupted auditory gating of nRT neurons and abolished their burst activity. D-amphetamine also disrupted hippocampal auditory gating and induced hippocampal theta activity***. The amphetamine-induced gating deficit was reversed by haloperidol in both regions. Conclusions: Our findings provide the first experimental evidence for auditory gating of nRT neurons. We demonstrated that amphetamine disrupts sensory processing of nRT neurons, indicating similarities between hippocampal and thalamic sensory gating. These findings support the presumed connection between dopamine hyperfunction and abnormal thalamic filtering in schizophrenia.

Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: a randomized pilot study
Ogrim, G., & Hestad, K. A. (2013). Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: a randomized pilot study. Journal of child and adolescent psychopharmacology, 23(7), 448–457. https://doi.org/10.1089/cap.2012.0090

Objective: The purpose of this pilot study was to compare the effects of 30 sessions of neurofeedback (NF) with stimulant medication on attention-deficit/hyperactivity disorder (ADHD) patients. Methods: Thirty-two medication-naïve ADHD patients, ages 7-16, from a neuropsychiatric clinic, were randomized to NF (n=16) or drug treatment (n=16). Other actions, such as parent management training, information, or support in school were given as needed, with no differences between the groups. All participants were assessed before treatment on two rating scales, each with parent and teacher forms. In addition, quantitative electroencephalogram (QEEG) and event-related potentials (ERPs), which included behavioral data from a go/no go test were administered. NF training took place in the clinic over a period of 7-11 months, and was followed by a repeat of the same assessment tools. The mean time interval between pre- and postassesment was not significantly different in the two groups. The 18 symptoms of ADHD (American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)) were used as the primary outcome measure. Results: Analysis of covariance revealed a significant difference between the groups at evaluation in favor of medication, with a large effect size. This picture was confirmed by other outcome measures. ***The QEEG spectral power in the theta and beta bands did not change in either group. In ERP, the P3 no go component increased significantly in 8 of 12 patients who had a clinically relevant medication effect, but did not increase in the medication nonresponders or the NF group. Conclusions: Our study supports effects for stimulants, but not for NF. Effects of NF may require thorough patient selection, frequent training sessions, a system for excluding nonresponders, and active transfer training. The P3 no go ERP component may be a marker for treatment response***.

Comparison of methods for the assessment of central nervous system stimulant response after dextroamphetamine administration to healthy male volunteers.

Slattum, P. W., Venitz, J., & Barr, W. H. (1996). Comparison of methods for the assessment of central nervous system stimulant response after dextroamphetamine administration to healthy male volunteers. Journal of clinical pharmacology, 36(11), 1039–1050. https://doi.org/10.1177/009127009603601108

The objective of this investigation was to evaluate a series of potential pharmacodynamic measures of central nervous system stimulation, including quantitative electroencephalography (EEG) and neuroendocrine, mood, and psychomotor performance measures. The reproducibility and sensitivity of the measures were compared. The study was conducted in two parts. The first part investigated the interindividual and intraindividual variability associated with a series of potential pharmacologic response measures under baseline (i.e., drug-free) conditions. It was an open-label, three-period pilot study in which healthy male volunteers underwent a series of tests (EEG, a visual continuous performance task, a finger tapping task, and self-rated mood scales) repeatedly during each study period. The second part evaluated the sensitivity of a series of potential response measures to detect the effects of dextroamphetamine, and was a double-blind, placebo-controlled, four-period crossover study in nine healthy male volunteers. Subjects received 5 mg, 10 mg, or 20 mg of dextroamphetamine or placebo orally and underwent the same series of tests as in Part I in addition to blood collection for determination of serum prolactin and dextroamphetamine levels. Peripheral response to dextroamphetamine was assessed by heart rate and blood

pressure measurement. The greatest variability among days, within days, and among participants was associated with the quantitative electroencephalographic parameters studied. First-session effects were apparent for several of the tests, including EEG. ***Consistent response on EEG (increased alpha power) to dextroamphetamine was observed only in the three subjects who had a baseline alpha activity greater than 35%***. Serum prolactin levels were inversely associated with the amount of dextroamphetamine administered, with the largest decrease in serum prolactin levels observed after the 5-mg dose, and this finding was statistically significant. Mood scales showed that three of nine participants experienced dysphoria after at least one dose level of dextroamphetamine. The effect on mood was generally greater as the dose increased. Doses could not be distinguished based on the results of the performance tests. Serum prolactin concentration was the most sensitive measure of central nervous system stimulation on EEG produced by dextroamphetamine under these study conditions. Cardiovascular measures were more sensitive measures of dextroamphetamine effects than the central nervous system measures.

Reduces anterior EEG power from alpha to gamma

Ding, X., Li, Y., Zhang, T., Li, D., Luo, S. X., Liu, X., & Hao, W. (2023). Electroencephalogram pattern association with drug-related cues in a long-duration virtual reality environment in patients with methamphetamine use disorder. Addiction biology, 28(1), e13248. https://doi.org/10.1111/adb.13248

The cognitive processing of drug-related cues and the subsequent dysregulation of behaviour play a central role in the pathophysiology of substance use disorders. Prior studies are limited by small sample sizes and a lack of immersion in stimulus presentation. In the present study, we recruited patients with methamphetamine use disorder (MUD; N = 1099) from four compulsory isolated detoxification centres and healthy control participants (N = 305). With a 12-min-long virtual reality (VR) protocol stimulus, we discovered that patients showed a ***decrease in electroencephalogram (EEG) power across alpha to gamma bands in anterior scalp regions under methamphetamine-related VR stimuli (e.g. a glass pipe and medical tubing) compared with the control stimuli (e.g. balls and cubes)***. Analysis of variance (ANOVA) showed that the interaction effects of stimuli type and group were significant in five EEG bands. Using generalised linear models, we classified the stimuli type (i.e. drug-related vs. drug-unrelated cues) in MUD patients with an f1 score of 90% on an out-of-sample testing set. The decreases of EEG between drug-related cues and drug-unrelated cues in delta, theta and alpha frequency bands are more frequently seen in patients than in healthy controls, perhaps reflecting general arousal and attenuated impulsive control. Our results suggest that EEG responses elicited by long-duration methamphetamine-related VR cues showed a specific signature, which may have future clinical implications.

Frontal deficits with abuse

Kraiwattanapirom, N., Siripornpanich, V., Suwannapu, W., Unaharassamee, W., Chawang, O., Lomwong, N., Vittayatavornwong, L., & Chetsawang, B. (2022). The quantitative analysis of EEG during resting and cognitive states related to neurological dysfunctions and cognitive impairments in methamphetamine abusers. Neuroscience letters, 789, 136870. https://doi.org/10.1016/j.neulet.2022.136870

Several lines of evidence demonstrated the deleterious effect of methamphetamine (MA) on neurological and psychological functions. However, recent evidence on the neurological dysfunctions related to cognitive performance and psychosis in MA abusers needs to be elucidated. Therefore, the present study aimed to investigate the neurological functions using EEG measurement during cognitive tests in MA abusers with (MWP) or without (MWOP) psychosis compared to age-matched normal participants. The quantitative EEG (qEEG) was used to reveal the absolute power in 4 brain-wave frequencies including delta, theta, alpha, and beta waves. The results demonstrated poor attention in both groups of MA abusers. The deficit in mental flexibility was observed in MWP. The deficit in inhibition control and working memory were observed in MWOP. **The greater delta, alpha and beta brain waves in multiple brain areas were observed in MWP during the resting (eyes-open) state. The greater alpha wave in multiple brain areas of MWP correlated with poor attention. The greater delta wave and lesser beta wave in the frontal brain correlated with poor inhibition and working memory in MWOP respectively.** These findings demonstrated the applicability of EEG to determine neurological dysfunction related to cognitive impairments in MA abusers.

Reward effects on frontal midline delta based upon ERPs

Cavanagh, J. F., Olguin, S. L., Talledo, J. A., Kotz, J. E., Roberts, B. Z., Nungaray, J. A., Sprock, J., Gregg, D., Bhakta, S. G., Light, G. A., Swerdlow, N. R., Young, J. W., & Brigman, J. L. (2022). Amphetamine alters an EEG marker of reward processing in humans and mice. Psychopharmacology, 239(3), 923–933. https://doi.org/10.1007/s00213-022-06082-z

The bench-to-bedside development of pro-cognitive therapeutics for psychiatric disorders has been mired by translational failures. This is, in part, due to the absence of pharmacologically sensitive cognitive biomarkers common to humans and rodents. Here, we describe a cross-species translational marker of reward processing that is sensitive to the aminergic agonist, d-amphetamine. ***Motivated by human electroencephalographic (EEG) findings, we recently reported that frontal midline delta-band power is an electrophysiological biomarker of reward surprise in humans and in mice. In the current series of experiments, we determined the impact of parametric doses of d-amphetamine on this reward-related EEG response from humans (n = 23) and mice (n = 28) performing a probabilistic learning task. In humans, d-amphetamine (placebo, 10 mg, 20 mg) boosted the Reward Positivity event-related potential (ERP) component as well as the spectral delta-band representations of this signal. In mice, d-amphetamine (placebo, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg) boosted both reward and punishment ERP features, yet there was no modulation of spectral activities. In sum, the present results confirm the role of dopamine in the generation of the Reward Positivity in humans, and pave the way toward a pharmacologically valid biomarker of reward sensitivity across species***.

Low- and high-demand tasks effect ERPs differently

Bhakta, S. G., Cavanagh, J. F., Talledo, J. A., Kotz, J. E., Benster, L., Roberts, B. Z., Nungaray, J. A., Brigman, J. L., Light, G. A., Swerdlow, N. R., & Young, J. W. (2022). EEG reveals that dextroamphetamine improves cognitive control through multiple processes in healthy participants. Neuropsychopharmacology : official publication of the American College of

Neuropsychopharmacology, 47(5), 1029–1036. https://doi.org/10.1038/s41386-021-01257-2

The poor translatability between preclinical and clinical drug trials has limited pro-cognitive therapeutic development. Future pro-cognitive drug trials should use translatable cross-species cognitive tasks with biomarkers (1) relevant to specific cognitive constructs, and (2) sensitive to drug treatment. Here, we used a difficulty-modulated variant of a cross-species cognitive control task with simultaneous electroencephalography (EEG) to identify neurophysiological biomarkers sensitive to the pro-cognitive effects of dextroamphetamine (d-amp) (10 or 20 mg) in healthy adults (n = 23), in a randomized, placebo-controlled, counterbalanced, double blind, within-subject study, conducted across three test days each separated by one week. D-amp boosted d-prime, sped reaction time, and increased frontal P3a amplitude to non-target correct rejections independent of task difficulty. Task difficulty did however, moderate d-amp effects on EEG during target performance. D-amp suppressed frontal theta power during easy target responses which negatively correlated with drug-induced improvement in hit rate while d-amp-induced changes in P3b amplitude during hard target trials strongly correlated with drug-induced improvement in hit rate. ***In summary, d-amp affected both behavioral and neurophysiological measures of cognitive control elements. Under low-demand, d-amp diminished cognitive control by suppressing theta, yet under high-demand it boosted control in concert with higher P3b amplitudes*.** These findings thus appear to reflect a gain-sharpening effect of d-amp: during high-demand processes were boosted while during low-demand processes were neglected. Future studies will use these neurophysiological measures of cognitive control as biomarkers to predict d-amp sensitivity in people with cognitive control deficits, including schizophrenia.

Drug can affect beta power and not theta power, altering TBR

Isiten, H. N., Cebi, M., Sutcubasi Kaya, B., Metin, B., & Tarhan, N. (2017). Medication Effects on EEG Biomarkers in Attention-Deficit/Hyperactivity Disorder. Clinical EEG and neuroscience, 48(4), 246–250. https://doi.org/10.1177/1550059416675232

EEG biomarkers have become increasingly used to aid in diagnosis of attention-deficit/hyperactivity disorder (ADHD). Despite several studies suggesting that EEG theta/beta ratio may help discriminating ADHD from other disorders, the effect of medications on theta/beta ratio is not known. Forty-three children with ADHD that were evaluated with quantitative EEG before and after methylphenidate were included in the study. Theta/beta ratio, theta and beta powers for whole brain, central, and frontal areas were calculated. ***Theta/beta power decreased significantly after treatment; however, this change was largely due to an increase in beta power, rather than a fall in theta power. The results suggest that beta power is sensitive to medication effects, while theta power remains as a trait biomarker unaffected by medication status*.** The value of EEG biomarkers for monitoring neuropsychological performance and clinical status should be explored by future studies.

Methamphetamine reduced EEG in alpha, beta, and gamma bands

Marvi, N., Haddadnia, J., & Fayyazi Bordbar, M. R. (2023). Evaluation of Drug Abuse on Brain Function using Power Spectrum Analysis of Electroencephalogram Signals in Methamphetamine, Opioid, Cannabis, and Multi-Drug Abuser Groups. Journal of

biomedical physics & engineering, 13(2), 181–192.
https://doi.org/10.31661/jbpe.v0i0.2210-1550

Background: The effect of different types of substances on brain function is still challenging; however, many studies have shown the functional and structural damage to the brain under influence of substance abuse.
Objective: This study aimed to quantitatively compare the effect of opioid (Op), methamphetamine (Meth), cannabis (Can), and simultaneous methamphetamine and opioid (Multi-Drug (MD)) abuse on brain function. Furthermore, the impacts of pure Op and Meth abuse were considered with simultaneous substance abuse.
Material and methods: In this descriptive study, the electroencephalogram (EEG) signal was recorded from 52 participants in the Meth, Op, Can, and MD abusers, and the Healthy Control (HC) groups at rest state. EEG data were analyzed on the frequency domain with electrode-based, cortex-based, and hemisphere-based approaches.
Results: However, ***the power spectrum in the delta band in the Op group, the gamma band in the Can group, and the gamma and beta bands in the MD group more significantly increased compared to the HC group, the power spectrum values in the Meth group reduced in the alpha, beta, and gamma bands. Moreover, the power spectrum values in the MD group more significantly higher than the Meth and Op groups in the beta and gamma bands*****.**
Conclusion: Since substance abuse in different types caused various changes in frequency components, the different power spectrum bands analysis in abusers can be reasonable to apply as a biomarker to detect the drug types.

----- ATOMOXETINE (Strattera) -----

DRUG FACTS

SYNOPSIS: While considered an antidepressant, this drug is usually prescribed to ADHD when traditional amphetamines are not indicated. This drug will increase global beta power but may cause temporal focal slowing. Decreased theta cordance may normalize upon drug ingestion. The frontal site differences with amphetamines may confirm medication choice.

Frontal site differences with amphetamines may confirm medication choice.

Aldemir, R., Demirci, E., Bayram, A., Canpolat, M., Ozmen, S., Per, H. & Tokmakci, M. (2018). Evaluation of two types of drug treatment with QEEG in children with ADHD. Translational Neuroscience, 9(1), 106-116. https://doi.org/10.1515/tnsci-2018-0017

Aims: The aim of this study is to evalute the effects of methylphenidate and atomoxetine treatments on electroencephalography (EEG) signals in volunteer children diagnosed with Attention Deficit and Hyperactivity Disorder (ADHD). Methods: The study contained 40 children all of whom were between the ages of 7 and 17. The participants were classified into two groups as ADHD (n=20), which was in itself divided into two groups as ADHD-MPH (ADHD-Methylphenidate treatment) (n=10) and as ADHD-ATX (ADHD-Atomoxetin treatment) (n=10), and one control group (n=20). Following the first EEG recordings of the ADHD group, long-acting methylphenidate dose was applied to one ADHD group and atomoxetine dose was applied to the other ADHD group. The effect of optimal dosage is about for 4-6 weeks in general. Therefore, the response or lack of response to the treatment was evaluated three

months after the beginning of the treatment. After methylphenidate and atomoxetine drug treatment, in order to obtain mean and maximum power values for delta, theta, alpha and beta band, the EEG data were analyzed. Results: ***The EEG power spectrum densities in all the bands yielded similar findings in both methylphenidate and atomoxetine. Although statistically significant frequency values of the electrodes were amplitude and maximally varied, in general, they appeared mostly at both frontal and temporal regions for methylphenidate and atomoxetine. Conclusion: Especially, after atomoxetine treatment, Quantitative Electroencephalography (QEEG) rates at frontal area electrodes were found statistically more significant than methylphenidate QEEG rates.*** What has been researched in this study is not only whether QEEG is likely to support the diagnosis, but whether changes on QEEG by treatment may be related to the severity of ADHD as well.

Increases global beta power

Barry, R. J., Clarke, A. R., Hajos, M., McCarthy, R., Selikowitz, M., & Bruggemann, J. M. (2009). Acute atomoxetine effects on the EEG of children with attention-deficit/hyperactivity disorder. Neuropharmacology, 57(7-8), 702–707. https://doi.org/10.1016/j.neuropharm.2009.08.003

Although stimulant medications are the most commonly-used treatments for Attention-Deficit/Hyperactivity Disorder (AD/HD), as many as 20% of treated children do not respond clinically to stimulants. This study investigated the effects of an acute dose of atomoxetine, a selective noradrenaline reuptake inhibitor (SNRI), on the electroencephalogram (EEG) and performance of children with AD/HD. An initial pre-medication EEG was recorded during an eyes-closed resting condition. Within two weeks, a second EEG was recorded 1 h after ingestion of 20 mg of atomoxetine. Data were Fourier transformed to provide absolute and relative power estimates for the delta, theta, alpha, beta and gamma bands. Compared to controls, the unmedicated AD/HD children had significantly elevated global absolute and relative delta, with reduced global relative alpha, and absolute and relative gamma, and many topographic differences. ***Atomoxetine produced significant global increases in absolute and relative beta, with several topographic changes in other bands, and a significant reduction in omission errors on a Continuous Performance Task.*** These results indicate that SNRIs can produce substantial normalisation of the AD/HD EEG profile, together with behavioural performance improvements. Although EEG changes induced by acute administration of psychostimulants (methylphenidate/dexamphetamine) and atomoxetine are not identical, both classes of AD/HD drugs produce similar EEG band changes. Further analysis of EEG responses to SNRIs and psychostimulants could reveal common neurophysiological processes closely linked to clinical improvement of AD/HD symptoms in response to pharmacotherapy, providing translational markers for clinical efficacy studies and potential translational biomarkers for AD/HD drug discovery.

Elevated alpha band may be a predictor of drug success

Chiarenza, G. A., Chabot, R., Isenhart, R., Montaldi, L., Chiarenza, M. P., Torto, M. G., & Prichep, L. S. (2016). The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders. International journal of psychophysiology : official journal of the International

Organization of Psychophysiology, 104, 44–52. https://doi.org/10.1016/j.ijpsycho.2016.04.004

Objective: The aim of our study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are responders and non-responders to long-term treatment with Atomoxetine at baseline and after 6 and 12months of treatment. Patients with attention deficit hyperactivity disorder (ADHD) received atomoxetine titrated, over 7days, from 0.5 to 1.2mg/kg/day. QEEG and Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy. Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked earlobes. ***Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values. Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values. Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine.*** Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta.

May cause temporal focal slowing

Finsterer, J., & Scorza, F. A. (2020). Atomoxetine-induced focal seizures with contralateral hypoperfusion and hyper-CKemia. Radiology case reports, 16(2), 369–371. https://doi.org/10.1016/j.radcr.2020.11.049

One of the drugs used to treat attention deficit hyperactivity syndrome is atomoxetine. Usually, the drug is well tolerated but in rare cases adverse advents may occur. An 18-year-old female under atomoxetine (60 mg/d) since 2 years for attention deficit hyperactivity syndrome since age 13 years, developed sudden onset headache, hemianopia to the right, hypoesthesia of the tongue and right arm, aphasia, and depersonalisation. Blood tests revealed hyper-CK-emia of 2860U/L, cerebral magnetic resonance imaging showed disturbed perfusion on the left temporo-parieto-occipital region, and ***electroencephalography (EEG) revealed focal slowing and spikes and sharp waves in the same projections. After discontinuation of atomoxetine, symptoms, EEG, and magnetic resonance imaging findings resolved spontaneously within 48 hours.*** In conclusion, atomoxetine may rarely cause severe side effects such as complex partial seizures with CK-elevation, transient hypoperfusion of the temporal, parietal and occipital lobes, and prolonged reorientation. Atomoxetine should be discontinued if such side effects occur.

Decreased theta cordance may normalize

Singh, G., Arun, P., Das, S., & Kaur, D. (2021). Can EEG Predict Response to Atomoxetine in attention deficit hyperactivity disorder at 1 Week? Journal of Attention Disorders, 25(5), 758–767. https://doi.org/10.1177/1087054719829574

Objective: The objective of the study is to predict the early changes in electroencephalography (EEG) at 1 week and its correlation to clinical response at 6 weeks after treatment with atomoxetine in children with ADHD. Method: In 50 children (6-14 years) with ADHD (Diagnostic and Statistical Manual of Mental Disorders [5th ed.; DSM-5]), Vanderbilt ADHD Parent Rating Scale (VADPRS) and Vanderbilt ADHD Teachers Rating Scale (VADTRS) were applied at baseline, 1, 4, and 6 weeks. EEG was recorded using International 10–20 System of electrode placement at baseline and at 1 week after atomoxetine treatment. EEG changes at 1 week after atomoxetine therapy was correlated to clinical response at 6 weeks. Results: Patients were classified as responders or nonresponders based on the VADPRS/VADTRS findings. ***After 1 week of treatment, responders' theta cordance values were decreased, whereas nonresponders' values didn't decrease significantly. Conclusion: Patients with decreased theta cordance values, especially in the left temporoparietal region, at 1 week were likely to respond to atomoxetine*** while those without any such change were likely to be nonresponders.

Event-related potentials reflect the efficacy of pharmaceutical treatments in children and adolescents with attention deficit/hyperactivity disorder

Yamamuro, K., Ota, T., Iida, J., Nakanishi, Y., Matsuura, H., Uratani, M., Okazaki, K., Kishimoto, N., Tanaka, S., & Kishimoto, T. (2016). Event-related potentials reflect the efficacy of pharmaceutical treatments in children and adolescents with attention deficit/hyperactivity disorder. Psychiatry research, 242, 288–294. https://doi.org/10.1016/j.psychres.2016.05.061

Few objective biological measures of pharmacological treatment efficacy exist for attention deficit/hyperactivity disorder (ADHD). Although we have previously demonstrated that event-related potentials (ERPs) reflect the effects of osmotic-release methylphenidate in treatment of naïve pediatric patients with ADHD, whether this is true for the therapeutic effects of atomoxetine (ATX) is unknown. Here, we used the Japanese version of the ADHD rating-scale IV to evaluate 14 patients with ADHD, and compared their ERP data with 14 age- and sex-matched controls. We measured P300 and mismatch negativity (MMN) components during an auditory oddball task before treatment (treatment naïve) and after 2 months of ATX treatment. ***Compared with controls, P300 components at baseline were attenuated and prolonged in the ADHD group at Fz (fronto-central), Cz (centro-parietal), Pz (parietal regions), C3 and C4 electrodes. ATX treatment reduced ADHD symptomology, and after 2 months of treatment, P300 latencies at Fz, Cz, Pz, C3, and C4 electrodes were significantly shorter than those at baseline. Moreover, MMN amplitudes at Cz and C3 electrodes were significantly greater than those at baseline. Thus, ERPs may be useful for evaluating the pharmacological effects of ATX in pediatric and adolescent patients with ADHD***.

----- CAFFEINE -----

DRUG FACTS

SYNOPSIS: Caffeine is a nonprescriptive drug and a CNS stimulant classified as methylxanthine. It is readily available in coffee, tea, chocolate, and soda and energy drinks. It combats fatigue and promotes wakefulness.

Reduced alpha in EC condition

Barry, R. J., Clarke, A. R., Johnstone, S. J., & Rushby, J. A. (2008). *Timing of caffeine's impact on autonomic and central nervous system measures: clarification of arousal effects*. Biological psychology, 77(3), 304–316. https://doi.org/10.1016/j.biopsycho.2007.11.002

The timing of caffeine effects on arousal levels was examined. From previous work in our laboratory, an increase in skin conductance level (SCL) was used as the marker of arousal increase, and we sought to identify the timing of this and related effects following caffeine ingestion. A single oral dose of caffeine (250 mg) was used in a randomised double-blind placebo-controlled repeated-measures cross-over study. Eyes-closed resting electroencephalogram (EEG) and autonomic data (SCL, heart rate, respiration rate, and systolic and diastolic blood pressure) during 2 min epochs that commenced every 4 min after ingestion, were analysed. The SCL placebo data were used to identify potential arousal measures prior to examining caffeine effects. Caffeine was associated with increased SCL, increased respiratory rate and a global reduction in alpha power. There were no significant cardiovascular effects of caffeine-induced arousal. These caffeine results are consistent with our recent electrodermal and EEG studies of arousal, and confirm the potential use of caffeine as a simple means of experimentally modifying arousal levels without task-related confounds.

From manuscript: A moderate dose of caffeine (approximately 200 mg) has been reported to reduce power in all frequency bands of the EEG during eyes-open resting conditions, between 30 min and 5 h post-caffeine administration (Bruce et al., 1986, Etevenon et al., 1986, Newman et al., 1992, Dimpfel et al., 1993, Kenemans and Lorist, 1995, Kaplan et al., 1997). However, from our perspective (Barry et al., 2005b), the eyes-open state involves not only an increase in arousal, but also some visual activation which results in changes in EEG power levels and topography (Barry et al., 2007a) relative to the eyes-closed resting state (the least activated state commonly accessible to laboratory investigation), our particular interest. Surprisingly, the effect of caffeine on resting eyes-closed EEG power is not commonly reported, but Clubley et al. (1979) found that 100 mg of caffeine increased delta power 2.8 h after administration, with no effect on other bands. No effect of caffeine on midline EEG was reported by Gevins et al. (2002), but their study was designed to test a variety of drugs and participants were led to believe that they were also consuming alcohol, so expectancy (Mikalsen et al., 2001) may have confounded caffeine effects in this null result. ***200 mg caffeine was administered to 10 participants in a randomised, placebo-controlled, double-blind cross-over design by Siepmann and Kirch (2002), who found no difference in alpha, but reductions in delta, theta, beta1 and beta2 power. Our finding of reduced alpha power with caffeine thus provided theoretically relevant new data which needs further support. Deslandes et al. (2005) have recently reported reduced alpha over the scalp in an eyes-closed condition, but used a large caffeine dose of 400 mg.***

Caffeine and EO state have additive effects on resting arousal measures.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2011). *Caffeine and opening the eyes have additive effects on resting arousal measures*. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 122(10), 2010–2015. https://doi.org/10.1016/j.clinph.2011.02.036

Objective: Studies indicate that the change from closed to open eyes in a resting condition results in an increase in skin conductance level (SCL) and a global decrease in EEG alpha activity, both indicative of increased arousal. Other studies show that ingestion of caffeine also produces SCL increase and alpha reduction. This study investigated the additivity of the effects of these two independent arousing variables. Method: EEG activity and SCL were recorded from 22 university students during both eyes-closed and eyes-open resting conditions, under the action of both caffeine and placebo, in a counterbalanced randomised double-blind study. Results: SCL increased significantly from eyes-closed to eyes-open conditions, and from placebo to caffeine, with no interaction. Global reductions in EEG alpha amplitude were apparent with opening of the eyes and caffeine ingestion; again, there was no interaction. Caffeine had a larger effect than opening the eyes on SCL, but their relative effect sizes were reversed in alpha. The two dependent measures showed the predicted negative correlation in both eyes-closed placebo and eyes-open caffeine conditions, with the latter substantially reduced relative to the former. Conclusions: ***Caffeine and opening the eyes have additive effects on two measures of arousal, increasing SCL and reducing global EEG alpha***. However, the independent variable effects are not equivalent, suggesting that one or both measures reflect additional non-arousal processes. Significance: As caffeine is widely used by both children and adults, knowledge of the additivity of arousal effects of caffeine and opening the eyes is important in controlling participant state in EEG studies. The current results confirm the use of mean global alpha amplitude as a measure of resting-state arousal, but also point to non-arousal effects of visual input.

Increase in P450 amplitude

Bruce, S. E., Werner, K. B., Preston, B. F., & Baker, L. M. (2014). *Improvements in concentration, working memory and sustained attention following consumption of a natural citicoline-caffeine beverage. International journal of food sciences and nutrition*, 65(8), 1003–1007. https://doi.org/10.3109/09637486.2014.940286

This study examined the neurocognitive and electrophysiological effects of a citicoline-caffeine-based beverage in 60 healthy adult participants enrolled in a randomized, double-blind, placebo-controlled trial. Measures of electrical brain activity using electroencephalogram (EEG) and neuropsychological measures examining attention, concentration and reaction time were administered. Compared to placebo, participants receiving the citicoline-caffeine beverage exhibited significantly faster maze learning times and reaction times on a continuous performance test, fewer errors in a go/no-go task and better accuracy on a measure of information processing speed. ***EEG results examining P450 event-related potentials revealed that participants receiving the citicoline-caffeine beverage exhibited higher P450 amplitudes than controls, suggesting an increase in sustained attention.*** Overall, these findings suggest that the beverage significantly improved sustained attention, cognitive effort and reaction

times in healthy adults. Evidence of improved P450 amplitude indicates a general improvement in the ability to accommodate new and relevant information within working memory and overall enhanced brain activation.

High theta activation during sleep deprivation alleviated by caffeine

Erblang, M., Sauvet, F., Drogou, C., Quiquempoix, M., Van Beers, P., Guillard, M., Rabat, A., Trignol, A., Bourrilhon, C., Erkel, M. C., Léger, D., Thomas, C., Gomez-Merino, D., & Chennaoui, M. (2021). *Genetic Determinants of Neurobehavioral Responses to Caffeine Administration during Sleep Deprivation: A Randomized, Cross Over Study* (NCT03859882). Genes, 12(4), 555. https://doi.org/10.3390/genes12040555

This study investigated whether four single nucleotide polymorphisms (SNPs) moderated caffeine effects on vigilance and performance in a double-blind and crossover total sleep deprivation (TSD) protocol in 37 subjects. In caffeine (2 × 2.5 mg/kg/24 h) or placebo-controlled condition, subjects performed a psychomotor vigilance test (PVT) and reported sleepiness every six hours (Karolinska sleepiness scale (KSS)) during TSD. EEG was also analyzed during the 09:15 PVT. Carriers of the TNF-α SNP A allele appear to be more sensitive than homozygote G/G genotype to an attenuating effect of caffeine on PVT lapses during sleep deprivation only because they seem more degraded, but they do not perform better as a result. The A allele carriers of COMT were also more degraded and sensitive to caffeine than G/G genotype after 20 h of sleep deprivation, but not after 26 and 32 h. Regarding PVT reaction time, ADORA2A influences the TSD effect but not caffeine, and PER3 modulates only the caffeine effect. ***Higher EEG theta activity related to sleep deprivation was observed in mutated TNF-α, PER3, and COMT carriers, in the placebo condition particularly. In conclusion, there are genetic influences on neurobehavioral impairments related to TSD that appear to be attenuated by caffeine administration.*** (NCT03859882).

Increase in mid-range power

Herrmann, W. M., & Kubicki, S. (1981). Beispiele für die Projektion von Substanzwirkungen typischer Psychopharmaka auf eine elektrophysiologische Messebene [*The use of electrophysiological techniques to project typical psychotropic drug effects: some examples* (author's transl)]. EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete, 12(1), 21–32.

A long existing hypothesis, i.e. that the EEG effects, in lead O2A2, of typical psychotropic drugs are substance class specific, when given as single oral dosages to healthy volunteers, is discussed. Using the technique of pharmacoelectroencephalograhpy, five typical representatives of neuroleptics, anxiolytics, antidepressives, psychostimulants (Fig. 2) as well as placebo were investigated in 75 volunteers, each receiving one representative of each substance class in a double blind 5-fach change over latin square design (Fig. 3). A five minute EEG record for lead O2A2 was obtained pre, 1 h and 3 hrs post drug intake under RR (Relaxed Recording) conditions. Typical samples of th EEG records are shown in Figs. 4--7. Parametrisation was done using power spectrum analysis. Then 3 x 7 target variables were formed--six relative power values in predetermined frequency bands and the total power between 1.5 and 30.0 Hz for 3 occasions of measurement (Fig. 4--7). Using a (five-group) linear discriminant analysis the substance effects on the EEG were transformed into 5 probability

measures for the five substance classes (Fig. 4--7). The present paper should provide a demonstration of some typical examples, using single subjects, of the projection of substance effects onto an electrophysiological level using a vector of 21 components (7 target variables for 3 occasions of measurement) as can be seen from Table 1. Furthermore, the transformation into probability measures of the five substance classes are shown in Table 2. Table 3 shows five examples of projections of substance effects, which do not fit into the classifications to which they belong. An attempt is made to explain, whether single target variables from the power spectrum can contribute differently to the discrimination between single substances of different substance classes. Within the accepted system of 4 psychotropic drug classes, the following variables seem to be of importance: a) The benzodiazepine anxiolytics show a marked increase in beta F1 (12.0--18.0 Hz) power and activity and, related to sedation, an increase in delta F-power and a decrease in alpha-power; b) ***The psychostimulants of the amphetamine type show an increase in total power and alpha-power, an increase in the power of the frequency ranges near to the alpha-band (slow beta, fast theta) and a decrease in delta F (1.5--5.5 Hz)-power, when delta F-power is high in the pre-values, indicating a stabilization in vigilance;*** c) The neuroleptics show a marked increase in theta F (5.5--8.5 Hz)-power, some increase in the delta F--and a decrease in the beta F1-and beta F3-power; d) Tricyclic antidepressants show an interaction between delta F-theta F-, alpha- and beta-power, in the sense of a dissociative shift in vigilance.

Effects on ERPs

Maciejewska, K., & Grabowska, K. (2020*). Acute effect of energy boost dietary supplement on P3 waveform: double blind, placebo-controlled study*. Acta neurobiologiae experimentalis, 80(4), 411–423.

Human cognition may be enhanced by energy drinks containing caffeine and/or other stimulants, which are thought to improve attentional as well as motor performance, and reduce reaction times. Due to the fact that literature shows that even low doses of caffeine may improve cognitive performance, we investigated an acute effect of a single dose of a caffeinated energy dietary supplement, on attention and motor responses by means of event related potentials. Healthy volunteers were examined in double blind, placebo controlled study. EEG recordings from 32 channels were performed in three sessions: before the supplementation (session 1), 30 min after the supplementation (session 2) and 90 min after the supplementation (session 3) in three tasks: visual P3, auditory P3, and motor task. ***Repeated measures ANOVA analysis showed reduced P3 amplitude increase after energy dietary supplementation (compared to placebo group) throughout all sessions (up to 90 min after consumption) in the visual task, and speeding the classification process observed as a decrease of P3 midpoint latency, but only 30 min after supplementation. The latter effect was present in both, but more pronounced in the visual task. Nonparametric cluster based permutation analysis showed one significant cluster in the placebo group from visual P3 task (approximately between 400 and 520 ms) over the centro-parietal area,*** which was absent in the study group. Our results suggest that caffeinated energy dietary supplement containing

only 55 mg of caffeine may enhance some attentional processes observed by changes in P3 features, but not in motor performance.

Caffeine may lessen slow wave sleep

Reichert, C. F., Veitz, S., Bühler, M., Gruber, G., Deuring, G., Rehm, S. S., Rentsch, K., Garbazza, C., Meyer, M., Slawik, H., Lin, Y. S., & Weibel, J. (2021). Wide awake at bedtime? Effects of caffeine on sleep and circadian timing in male adolescents - A randomized crossover trial. Biochemical pharmacology, 191, 114283. https://doi.org/10.1016/j.bcp.2020.114283

Adolescents often suffer from short and mistimed sleep. To counteract the resulting daytime sleepiness they frequently consume caffeine. However, caffeine intake may exaggerate sleep problems by disturbing sleep and circadian timing. In a 28-hour double-blind randomized crossover study, we investigated to what extent caffeine disturbs slow-wave sleep (SWS) and delays circadian timing in teenagers. Following a 6-day ambulatory phase of caffeine abstinence and fixed sleep-wake cycles, 18 male teenagers (14-17 years old) ingested 80 mg caffeine vs. placebo in the laboratory four hours prior to an electro-encephalographically (EEG) recorded nighttime sleep episode. Data were analyzed using both frequentist and Bayesian statistics. The analyses suggest that subjective sleepiness is reduced after caffeine compared to placebo. However, we did not observe a strong caffeine-induced reduction in subjective sleep quality or SWS, but rather a high inter-individual variability in caffeine-induced SWS changes. Exploratory analyses suggest that particularly those individuals with a higher level of SWS during placebo reduced SWS in response to caffeine. Regarding salivary melatonin onsets, caffeine-induced delays were not evident at group level, and only observed in participants exposed to a higher caffeine dose relative to individual bodyweight (i.e., a dose > 1.3 mg/kg). ***Together, the results suggest that 80 mg caffeine are sufficient to induce alertness at a subjective level. However, particularly teenagers with a strong need for deep sleep might pay for these subjective benefits by a loss of SWS during the night.*** Thus, caffeine-induced sleep-disruptions might change along with the maturation of sleep need.

Reduced low beta power during NREM

Weibel, J., Lin, Y. S., Landolt, H. P., Kistler, J., Rehm, S., Rentsch, K. M., Slawik, H., Borgwardt, S., Cajochen, C., & Reichert, C. F. (2021). *The impact of daily caffeine intake on nighttime sleep in young adult men*. Scientific reports, 11(1), 4668. https://doi.org/10.1038/s41598-021-84088-x

Acute caffeine intake can delay sleep initiation and reduce sleep intensity, particularly when consumed in the evening. However, it is not clear whether these sleep disturbances disappear when caffeine is continuously consumed during daytime, which is common for most coffee drinkers. To address this question, we investigated the sleep of twenty male young habitual caffeine consumers during a double-blind, randomized, crossover study including three 10-day conditions: caffeine (3 × 150 mg caffeine daily), withdrawal (3 × 150 mg caffeine for 8 days, then switch to placebo), and placebo (3 × placebo daily). After 9 days of continuous treatment, electroencephalographically (EEG)-derived sleep structure and intensity were recorded during a scheduled 8-h nighttime sleep episode starting 8 (caffeine condition) and 15 h (withdrawal condition) after the last caffeine intake. Upon scheduled wake-up time, subjective sleep quality

and caffeine withdrawal symptoms were assessed. Unexpectedly, neither polysomnography-derived total sleep time, sleep latency, sleep architecture nor subjective sleep quality differed among placebo, caffeine, and withdrawal conditions. ***Nevertheless, EEG power density in the sigma frequencies (12-16 Hz) during non-rapid eye movement sleep was reduced in both caffeine and withdrawal conditions when compared to placebo. These results indicate that daily caffeine intake in the morning and afternoon hours does not strongly impair nighttime sleep structure nor subjective sleep quality in healthy good sleepers who regularly consume caffeine. The reduced EEG power density in the sigma range might represent early signs of overnight withdrawal from the continuous presence of the stimulant during the day***.

----- COCAINE -----

DRUG FACTS

SYNOPSIS: Cocaine is a recreational drug, generally snorted, favored for its effects on dopamine pathways, leading to euphoria, reward experience, and alertness. This translated into higher power during a cue-driven ERP study and in another study, the possibility of delta-driven dopamine pathways. Blood perfusion and metabolism measures may provide insight into treatment success.

EEG cordance may be a value for treatment

Venneman, S., Leuchter, A., Bartzokis, G., Beckson, M., Simon, S. L., Schaefer, M., Rawson, R., Newton, T., Cook, I. A., Uijtdehaage, S., & Ling, W. (2006). *Variation in Neurophysiological Function and Evidence of Quantitative Electroencephalogram Discordance: Predicting Cocaine-Dependent Treatment Attrition.* The Journal of Neuropsychiatry and Clinical Neurosciences, 18(2), 208–216. https://doi.org/10.1176/jnp.2006.18.2.208

Cocaine treatment trials suffer from a high rate of attrition. We examined pretreatment neurophysiological factors to identify participants at greatest risk. Twenty-five participants were divided into concordant and discordant groups following electroencephalogram (EEG) measures recorded prior to a double-blind, placebo-controlled treatment trial. Three possible outcomes were examined: successful completion, dropout, and removal. Concordant (high perfusion correlate) participants had an 85% rate of successful completion, while discordant participants had a 15% rate of successful completion. Twenty-five percent of dropouts and 50% of participants removed were discordant (low perfusion correlate), while only 25% of those who completed were discordant. ***Failure to complete the trial was not explained by depression, craving, benzoylecgonine levels or quantitative electroencephalogram (QEEG) power; thus, cordance may help identify attrition risk. However, previous electroencephalogram (EEG) studies have not demonstrated an association between QEEG power measurements and treatment outcome. In this study, we examined cocaine-dependent participants using QEEG cordance, a measure that has moderately strong associations with cerebral perfusion and metabolism measured with positron emission tomography (PET) or single photon emission computed tomography (SPECT)*.**

Cocaine and ERPs

Moscon, J. A., Conti, C. L., & Nakamura-Palacios, E. M. (2016). Increased electroencephalographic activity in crack-cocaine users visualizing crack cues. Journal of Psychiatric Research, 83, 137–139. https://doi.org/10.1016/j.jpsychires.2016.08.016

Abstract: This study aimed to examine electrophysiologically the cerebral function under visual cue-reactivity paradigm in crack-cocaine users. This was an exploratory open trial in which young crack-cocaine-users and non-users were clinically examined. The participants' brain activity was analyzed by an event-related potentials procedure under a cue-reactivity paradigm with the random visual presentation of crack-related and neutral images. Nine young male crack-cocaine users and nine age-matched male healthy subjects from research center's neighborhood volunteered themselves to participate in this study. We demonstrated through electrophysiological tools that crack-cocaine users are more likely to show higher brain activity, notably in the frontal lobe region, when processing crack-related images. Though imaging studies have already showed increased brain activity in this paradigm, this data shows that event-related potentials can be an effective tool for brain evaluation in addiction.

From the manuscript: ***Moreover, cocaine addicts watching cocaine-cue videotapes had regional brain activations that were not present in healthy subjects watching the same tapes and that were not present in either cocaine addicts or healthy subjects when watching tapes that evoked happy or sad feelings, strengthening the idea that these activations are associated with the drug-taking experiences in drug-addicted subjects (Wexler et al., 2001). These results support the assumption that addiction is characterized and maintained through the sensitization of the mesolimbic dopaminergic system along with the incentive salience of drug and drug-related cues*** (Goldstein and Volkow, 2002, Dunning et al., 2011).

Delta generator for dopamine?

Alper K. R. (1999). *The EEG and cocaine sensitization: a hypothesis. The Journal of neuropsychiatry and clinical neurosciences*, 11(2), 209–221. https://doi.org/10.1176/jnp.11.2.209

The author presents the hypothesis that reduced delta EEG power observed in cocaine withdrawal is related to changes in dopamine (DA) transmission related to cocaine sensitization. Evidence for this hypothesis includes the topographic anatomical correspondence between the putative site of delta generation and the cortical terminal field of the mesotelencephalic DA system, as well as the laminar distribution and ultrastructural features of DA terminals in frontal cortex that appear to be adapted to the modulation of the delta rhythm, a global forebrain EEG mode. ***The effect of DA on membrane conductance of individual pyramidal neurons also suggests that DA exerts a significant influence on delta power by modulating the transition between global and local EEG modes***. Access to a neural correlate of sensitization via noninvasive EEG methodology could be useful in investigating the relationship of stimulant sensitization to the clinical syndrome of cocaine dependence.

Persistent QEEG abnormality in crack cocaine users at 6 months of drug abstinence.

Alper, K. R., Prichep, L. S., Kowalik, S., Rosenthal, M. S., & John, E. R. (1998). Persistent QEEG abnormality in crack cocaine users at 6 months of drug abstinence. Neuropsychopharmacology : official publication of the American College of

Neuropsychopharmacology, 19(1), 1–9. https://doi.org/10.1016/S0893-133X(97)00211-X

The major objective of this study was to examine the persistence of abnormal quantitative EEG (qEEG) measures over a six month time interval in subjects in strictly supervised drug free residential treatment for crack cocaine dependence. Seventeen subjects were assessed with qEEG at five to 10 days, one month and six months following their last use of cocaine. No ***significant changes were noted over time in abnormal qEEG measures, which included deficits of absolute and relative power in the delta band and increased relative alpha power. The persistence of qEEG abnormality in crack cocaine withdrawal suggests a persistent neurobiologic alteration resulting from chronic cocaine exposure. The specificity of the qEEG findings is discussed, and an interpretation is suggested with reference to the hypothesis of neural sensitization in cocaine dependence***.

Application of electrophysiological method to study interactions between ibogaine and cocaine.

Binienda, Z., Beaudoin, M. A., Thorn, B. T., Sadovova, N., Skinner, R. D., Slikker, W., Jr, & Ali, S. F. (2000). Application of electrophysiological method to study interactions between ibogaine and cocaine. Annals of the New York Academy of Sciences, 914, 387–393. https://doi.org/10.1111/j.1749-6632.2000.tb05212.x

The psychoactive indole alkaloid, ibogaine (IBO), has been investigated for over a decade concerning its reported anti-addictive properties for opioids as well as psychomotor stimulants. The mechanism for the anti-addictive action of IBO is still unclear. IBO interactions with opioid, NMDA, nicotinic, adrenergic, and serotonergic receptor sites have been suggested. The involvement of the dopaminergic system in IBO action is well documented. Increased or decreased levels of dopamine (DA) in specific brain regions following IBO pretreatment have been seen concomitantly with increased or decreased motor activity after subsequent amphetamine or cocaine administration. In this report, in vivo electrophysiological measures were monitored in awake adult male rats in order to investigate alterations of the electrocorticogram (ECoG) resulting from interactions between IBO and cocaine (COC). Rats were implanted bilaterally with bipolar ECoG electrodes. They were either injected with saline, COC alone (20 mg/kg, i.p.) or IBO (50 mg/kg, i.p.) and COC 1 hr later. The concentrations of DA, 5-HT, and their metabolites DOPAC, HVA, and 5-HIAA were assessed in the caudate nucleus in separate groups of saline-, COC-, and IBO/COC-treated rats. An alpha1 power increase was observed within 10 min after COC injection, which lasted for less than 20 min. ***A desynchronization over alpha2 and both beta power bands was observed throughout the recording. In IBO/COC-treated rats, a significant increase in delta, theta, and alpha1 power occurred within 20 min after COC injection ($p < 0.05$). This effect lasted for up to an hour***. DA levels significantly increased after COC only and decreased after IBO administration. A further decrease in levels of DA was observed in IBO/COC-treated rats. DA turnover increased significantly after IBO alone but was not observed after IBO/COC treatment. The alterations in ECoG and neurotransmitter levels suggest a decreased response to COC following IBO pretreatment.

rsfMRI effects of KB220Z™ on neural pathways in reward circuitry of abstinent genotyped heroin addicts

Blum, K., Liu, Y., Wang, W., Wang, Y., Zhang, Y., Oscar-Berman, M., Smolen, A., Febo, M., Han, D., Simpatico, T., Cronjé, F. J., Demetrovics, Z., & Gold, M. S. (2015). rsfMRI effects of KB220Z™ on neural pathways in reward circuitry of abstinent genotyped heroin addicts. Postgraduate medicine, 127(2), 232–241. https://doi.org/10.1080/00325481.2015.994879

Recently, Willuhn et al. reported that cocaine use and even non-substance-related addictive behavior increases as dopaminergic function is reduced. Chronic cocaine exposure has been associated with decreases in D2/D3 receptors and was also associated with lower activation of cues in occipital cortex and cerebellum, in a recent PET study by Volkow's et al. Therefore, treatment strategies, like dopamine agonist therapy, that might conserve dopamine function may be an interesting approach to relapse prevention in psychoactive drug and behavioral addictions. To this aim, we evaluated the effect of KB220Z™ on reward circuitry of 10 heroin addicts undergoing protracted abstinence (average 16.9 months). In a randomized placebo-controlled crossover study of KB220Z, five subjects completed a triple-blinded experiment in which the subject, the person administering the treatment, and the person evaluating the response to treatment were blinded to the treatment that any particular subject was receiving. In addition, nine subjects were genotyped utilizing the GARSDX™ test. We preliminarily report that KB220Z induced an increase in BOLD activation in caudate-accumbens-dopaminergic pathways compared to placebo following 1-hour acute administration. Furthermore, KB220Z also reduced resting-state activity in the putamen of abstinent heroin addicts. In the second phase of this pilot study of all 10 abstinent heroin-dependent subjects, we observed that three brain regions of interest were significantly activated from resting state by KB220Z compared to placebo ($p < 0.05$). ***Increased functional connectivity was observed in a putative network that included the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum. These results and other quantitative electroencephalogy (qEEG) study results suggest a putative anti-craving/anti-relapse role of KB220Z in addiction by direct or indirect dopaminergic interaction***. Due to small sample size, we caution definitive interpretation of these preliminary results, and confirmation with additional research and ongoing rodent and human studies of KB220Z is required.

Power spectral analysis of electroencephalographic desynchronization induced by cocaine in the rat.

Chang, A. Y., Kuo, T. B., & Chan, S. H. (1994). Power spectral analysis of electroencephalographic desynchronization induced by cocaine in the rat. Neuroscience letters, 170(1), 175–178. https://doi.org/10.1016/0304-3940(94)90267-4

Whereas it is well-known that cocaine induces EEG desynchronization and behavioral excitation in animals and human subjects, the detailed effect of cocaine on EEG activity remains to be fully elucidated. This communication reports our attempts in quantifying the effect of cocaine on EEG signals recorded from the somatosensory cortex of adult male Sprague-Dawley rats under chloral hydrate anesthesia (400 mg/kg i.p.). ***Continuous, on-line and real-time power spectral analysis revealed that i.v. administration of two doses of cocaine (1.5 or 3.0 mg/kg) dose-dependently induced EEG desynchronization, as indicated by a decrease in the root mean***

square and an increase in the mean power frequency values. More interestingly, whereas both doses of cocaine promoted a reduction in the alpha (8-13 Hz), theta (4-8 Hz) and delta (1-4 Hz) spectral components, the beta band (13-32 Hz) underwent differential alterations. The lower dose of cocaine elicited a transient increase, followed by a decrease in the power of the beta band. A prolonged increase in the power of the beta band, on the other hand, was observed after the higher dose of cocaine. These results suggest that subtle changes in the individual EEG spectral components, which are dose-dependent, may underlie the EEG desynchronization induced by cocaine.

Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence.

Costa, L., & Bauer, L. (1997). Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence. Drug and alcohol dependence, 46(1-2), 87–93. https://doi.org/10.1016/s0376-8716(97)00058-6

Resting electroencephalographic (EEG) activity was evaluated in 88 drug-dependent inpatients, abstinent 1-6 months, and 14 non-drug-dependent controls. The patients were assigned to one of four groups using DSM-III-R criteria: alcohol-dependent (n = 12), cocaine-dependent (n = 21), heroin-dependent (n = 19), or dual alcohol- and cocaine-dependent (n = 36). ***The analysis revealed significant differences between the five subject groups in high- and low-frequency beta power, but not in other frequency bands. Beta power was significantly greater in the alcohol-dependent and cocaine-dependent groups relative to non-drug-dependent controls***. These group differences did not correlate with quantity/frequency measures of alcohol or cocaine use, family history, personality, mood, or demographic characteristics. The similar increases in EEG beta found in alcohol- and cocaine-dependent patients do not suggest a direct drug effect. Rather, they suggest the existence of a common premorbid variable or a complex interaction between alcohol/drug use and other variables.

Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments.

Herning, R. I., Jones, R. T., Hooker, W. D., Mendelson, J., & Blackwell, L. (1985). Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments. Electroencephalography and clinical neurophysiology, 60(6), 470–477. https://doi.org/10.1016/0013-4694(85)91106-x

The effects of cocaine by two routes of administration were studied on the resting, awake human EEG during a 2 min sequential subtraction task. Fifty subjects were given 1 of 3 intravenous cocaine doses (0.2, 0.4 and 0.6 mg/kg). Thirty-three subjects received 1 of 3 oral doses of cocaine (2, 3 and 4 mg/kg). ***The EEG was analyzed as spectral power for delta, theta, alpha and beta bands. At each dose for both routes of administration, cocaine increased beta power. The increase was observed at the 5 min post-drug test session for the subjects given intravenous cocaine and at both 45 and 75 min test sessions for subjects given oral doses. In addition, a decrease in delta power was found at the 5 min test for the intravenous group and theta power was decreased at the 45 min test session. The increase in beta power was correlated with the area under the cocaine plasma versus time curve, but not with the***

cardiovascular effects of cocaine. The increased beta activity observed with cocaine may be a consequence of the direct stimulation of a central noradrenergic arousal system.

Gender differences in the EEG of abstinent cocaine abusers.

King, D. E., Herning, R. I., Gorelick, D. A., & Cadet, J. L. (2000). Gender differences in the EEG of abstinent cocaine abusers. Neuropsychobiology, 42(2), 93–98. https://doi.org/10.1159/000026678

Gender differences in the EEG were explored in cocaine-abusing individuals not seeking treatment. Twenty currently abstinent cocaine-abusing females aged 21-41 were studied. Their cocaine use history was matched to 20 currently abstinent cocaine-abusing males. Twelve female and 20 male non-drug-abusing individuals served as a control group. Resting eyes closed EEG was recorded from 8 leads. ***The males who used cocaine had elevated EEG beta ($p<0.0125$) and reduced alpha ($p<0.0125$) when compared to the cocaine-abusing females and control subjects. These findings suggest that the EEG of cocaine-abusing women may be more normal than that of cocaine-abusing men. Such gender-specific differences for cocaine-abusing populations may require gender-specific treatment to improve outcome***.

Quantitative EEG characteristics of children exposed in utero to cocaine.

Prichep, L. S., Kowalik, S. C., Alper, K., & de Jesus, C. (1995). Quantitative EEG characteristics of children exposed in utero to cocaine. Clinical EEG (electroencephalography), 26(3), 166–172. https://doi.org/10.1177/155005949502600308

Quantitative EEGs (QEEGs) were evaluated in a group of 6 school age children with in utero cocaine exposure. Their QEEGs showed significant deviations from age expected normal values. ***Further, the QEEG profile of brain dysfunction seen in these children was extremely similar to that previously reported in a large population of crack cocaine dependent adults. These abnormalities were characterized by significant excess of relative power in the alpha frequency band, and deficits of absolute and relative power in the delta and theta bands. Characteristic disturbances in interhemispheric relationships were also present. The similarities between the QEEG profiles of those adults with chronic exposure and children with prenatal exposure suggests that the brain dysfunction reflected in the QEEG is not a result of a transient change in neurotransmission, but a more profound alteration which persists in these children at school age***. Further study is required to extend these findings to a larger group of children, and to investigate the potential relationship between these neurophysiological abnormalities and the developmental, behavioral and co-morbid features observed in such children.

Neurometric QEEG studies of crack cocaine dependence and treatment outcome.

Prichep, L. S., Alper, K., Kowalik, S. C., & Rosenthal, M. (1996). Neurometric QEEG studies of crack cocaine dependence and treatment outcome. Journal of addictive diseases, 15(4), 39–53. https://doi.org/10.1300/J069v15n04_03

This paper presents an overview of the quantitative electrophysiological (QEEC) research on cocaine dependence conducted at Brain Research Laboratories of New York University Medical Center. These studies have demonstrated that subjects with DSM-III-R cocaine dependence (without dependence on any other substance) evaluated in the withdrawal state, have

replicable abnormalities in brain function when evaluated at baseline (approximately 5 to 10 days after last crack cocaine use), which are still seen at one and six month follow-up evaluations. ***These abnormalities were characterized by significant excess of relative alpha power and deficit of absolute and relative delta and theta power. Abnormalities were greater in anterior than posterior regions, and disturbances in interhemispheric relationships were also observed. In addition, QEEG subtypes were identified within the population of cocaine dependent subjects at baseline, and these subtypes were found to be significantly related to subsequent length of stay in treatment. The relationship between these QEEG findings and the neuropharmacology of cocaine dependence is discussed***.

Topographic imaging of quantitative EEG in response to smoked cocaine self-administration in humans.

Reid, M. S., Flammino, F., Howard, B., Nilsen, D., & Prichep, L. S. (2006). Topographic imaging of quantitative EEG in response to smoked cocaine self-administration in humans. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 31(4), 872–884. https://doi.org/10.1038/sj.npp.1300888

Quantitative electroencephalographic (qEEG) profiles were studied in cocaine-dependent patients in response to an acute, single-blind, self-administered dose of smoked cocaine base (50 mg) vs placebo. qEEG data were averaged using neurometric analytical methods and the spectral power of each primary bandwidth was computed and topographically imaged. Additional measures included cocaine-induced high, craving, and related subjective ratings, heart rate, blood pressure, and plasma cortisol and homovanillic acid levels. In all, 13 crack cocaine-dependent subjects were tested. Cocaine produced a rapid increase in subjective ratings of cocaine high and good drug effect, and a more persistent increase in cocaine craving and nervousness. Cocaine also produced a rapid rise in heart rate and a prolonged increase in plasma cortisol. Placebo, administered in the context of cocaine cues and dosing expectations, had no cocaine-like subjective or physiological effects. ***Cocaine produced a rapid increase in absolute theta, alpha, and beta power over the prefrontal cortex (FP1, FP2), lasting up to 25 min after dosing. The increase in theta power was correlated with good drug effect, and the increase in alpha power was correlated with nervousness. Cocaine also produced a similar increase in delta coherence over the prefrontal cortex, which was positively correlated with plasma cortisol, and negatively correlated with nervousness. Placebo resulted in an increase in alpha power over the prefrontal cortex. These data demonstrate the involvement of prefrontal cortex in the qEEG response to acute cocaine. Evidence indicates slow wave qEEG, delta and theta activity, involvement in the rewarding properties of cocaine***.

----- MDMA (Ecstasy) -----

DRUG FACTS

SYNOPSYS: Ecstasy is a stimulant that targets the NMDA receptor for the excitatory neurotransmitter glutamate. It is a mood and metabolism enhancer. It will decrease coherence, and delta and theta power and increase beta power. There are conflicting findings regarding alpha power.

MDMA, THC, and alcohol interactions

Lansbergen, M. ., Dumont, G. J. ., Gerven, J. M. van, Buitelaar, J. ., & Verkes, R. . (2011). *Acute effects of MDMA (3,4-methylenedioxymethamphetamine) on EEG oscillations: alone and in combination with ethanol or THC (delta-9-tetrahydrocannabinol).* Psychopharmacologia, 213(4), 745–756. https://doi.org/10.1007/s00213-010-2031-4

RATIONALE: Typical users of 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") are polydrug users, combining MDMA with alcohol or cannabis [most active compound: delta-9-tetrahydrocannabinol (THC)]. OBJECTIVES: The aim of the present study was to investigate whether co-administration of alcohol or THC with MDMA differentially affects ongoing electroencephalogram (EEG) oscillations compared to the administration of each drug alone. METHODS: In two separate experiments, 16 volunteers received four different drug conditions: (1) MDMA (100 mg); (2) alcohol clamp (blood alcohol concentration = 0.6 per thousand) or THC (inhalation of 4, 6 and 6 mg, interval of 1.5 h); (3) MDMA in combination with alcohol or THC; and (4) placebo. Before and after drug administration, electroencephalography was recorded during an eyes closed resting state. RESULTS: Theta and alpha power increased after alcohol intake compared to placebo and reduced after MDMA intake. No interaction between alcohol and MDMA was found. Significant MDMA x THC effects for theta and lower-1-alpha power indicated that the power attenuation after the combined intake of MDMA and THC was less than the sum of each drug alone. For the lower-2-alpha band, the intake of MDMA or THC alone did not significantly affect power, but the intake of combined MDMA and THC significantly decreased lower-2-alpha power. CONCLUSIONS: ***The present findings indicate that the combined intake of MDMA and THC, but not of MDMA and alcohol, affects ongoing EEG oscillations differently than the sum of either one drug alone. Changes in ongoing EEG oscillations may be related to the impaired task performance that has often been reported after drug intake.***

MDMA, power, and coherence

Dafters, R. I., Duffy, F., O'donnell, P. J., & Bouquet, C. (1999). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacologia, 145(1), 82–90. https://doi.org/10.1007/s002130051035

Despite animal studies implicating 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in serotonergic neurotoxicity, there is little direct evidence of changes in neural function in humans who use MDMA as a recreational drug. The present study investigated whether there is a correlation between quantitative EEG variables (spectral power and coherence) and cognitive/mood variables, and level of prior use of MDMA. Twenty-three recreational MDMA users were studied. Resting EEG was recorded with eyes closed, using a 128-electrode geodesic net system, from which spectral power, peak frequency and coherence levels were calculated. Tests of intelligence (NART), immediate and delayed memory, frontal function (card sort task), and mood (BDI and PANAS scales) were also administered. Pearson correlation analyses were used to examine the relationship between these measures and the subject's consumption of MDMA during the previous 12-month period. Partial correlation was used to control for the use of other recreational drugs. ***MDMA use was positively correlated with absolute power in the alpha (8-12 Hz) and beta (12-20 Hz) frequency bands, but not with the delta (1-3 Hz) or theta***

(4-7 Hz) bands. MDMA use was negatively correlated with EEG coherence, a measure of synchrony between paired cortical locations, in posterior brain sites thought to overly the main visual association pathways of the occipito-parietal region. MDMA use did not correlate significantly with any of the mood/cognitive measures except the card sort task, with which it was weakly negatively correlated. ***Alpha power has been shown to be inversely related to mental function and has been used as an indirect measure of brain activation in both normal and abnormal states. Reduced coherence levels have been associated with dysfunctional connectivity in the brain in disorders such as dementia, white-matter disease, and normal aging.*** Our results may indicate altered brain function correlated with prior MDMA use and show that electroencephalography may be a cheap and effective tool for examining neurotoxic effects of MDMA and other drugs.

MDMA LORETA analysis

Frei, E., Gamma, A., Pascual-Marqui, R., Lehmann, D., Hell, D., & Vollenweider, F. X. (2001). Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA). Human Brain Mapping, 14(3), 152–165. https://doi.org/10.1002/hbm.1049

3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy') is a psychostimulant drug producing heightened mood and facilitated social communication. In animal studies, MDMA effects are primarily mediated by serotonin (5-HT), but also by dopamine (DA) and possibly noradrenaline (NA). In humans, however, the neurochemical and neurophysiological basis of acute MDMA effects remains unknown. The distribution of active neuronal populations after administration of a single dose of MDMA (1.7 mg/kg) or placebo was studied in 16 healthy, MDMA-naïve volunteers. Thirty-one-channel scalp EEGs during resting with open and closed eyes was analyzed in the different EEG frequency bands. Scalp maps of power showed significant, global differences between MDMA and placebo in both eye conditions and all frequency bands. ***Low resolution brain electromagnetic tomography (LORETA) was used to compute 3D, functional images of electric neuronal activity from the scalp EEG data. MDMA produced a widespread decrease of slow and medium frequency activity and an increase of fast frequency activity in the anterior temporal and posterior orbital cortex, concomitant with a marked enhancement of mood, emotional arousal and increased extraversion.*** This activation of frontotemporal areas indicates that the observed enhancement of mood and possibly the increased extroversion rely on modulation of limbic orbitofrontal and anterotemporal structures known to be involved in emotional processes. Comparison of the MDMA-specific EEG pattern with that of various 5-HT, DA, and NA agonists indicates that serotonin, noradrenaline, and, to a lesser degree, dopamine, contribute to the effects of MDMA on EEG, and possibly also on mood and behavior.

Delta and alpha2 power increase

Herning, R. I., Better, W., Tate, K., & Cadet, J. L. (2005). *Neuropsychiatric alterations in MDMA users: preliminary findings.* Annals of the New York Academy of Sciences, 1053, 20–27. https://doi.org/10.1196/annals.1344.003

The use of marijuana is rampant among 3,4-methylenedioxymethamphetamine (MDMA) users. The co-occurrence of abuse of these two drugs has made it difficult to assess the specific

residual effects of MDMA alone. As a first step toward identifying the effects of long-term MDMA use, we studied 8 MDMA abusers, 8 marijuana/MDMA abusers, 15 marijuana abusers (matched in marijuana use without MDMA use), and 17 control subjects. EEG, cerebral blood velocity by pulsed transcranial Doppler (TCD), and psychological measures were collected. Three-minute resting eyes-closed EEG recordings were obtained from 16 electrodes. The EEG was converted to 6 frequency bands (delta, theta, alpha-1, alpha-2, beta-1, and beta-2) using a fast Fourier transformation. Blood flow velocity was determined using a temporal window for the right and left middle cerebral arteries using TCD. ***Absolute log delta power in the EEG of MDMA abusers at central electrode sites was significantly higher than that of the MDMA/marijuana, marijuana abusers, and control subjects. There were also increases in alpha-2 EEG power observed only in marijuana abusers.*** The blood flow measure, diastolic velocity, was increased in MDMA abusers whether they used marijuana or not. Because increases in delta power and perfusion deficits are associated with some chronic disorders, our findings in these ecstasy abusers suggest that MDMA use may be associated with a drug-induced neuropathological state. More research is necessary to test these ideas.

----- MODAFINIL -----

(Alertec, Carim, Modavigil, Modalert, Modiodal, Modafinilo, Provigil, Vigia)

DRUG FACTS

SYNOPSIS: Treatment for excessive sleeping/narcolepsy, it's effects on the EEG differ depending on the baseline EEG.

Slowing of theta and/or high beta increase depending on drug

Hasan, S., Pradervand, S., Ahnaou, A., Drinkenburg, W., Tafti, M., & Franken, P. (2009). How to keep the brain awake? The complex molecular pharmacogenetics of wake promotion. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 34(7), 1625–1640. https://doi.org/10.1038/npp.2009.3

Wake-promoting drugs are widely used to treat excessive daytime sleepiness. The neuronal pathways involved in wake promotion are multiple and often not well characterized. We tested d-amphetamine, modafinil, and YKP10A, a novel wake-promoting compound, in three inbred strains of mice. The wake duration induced by YKP10A and d-amphetamine depended similarly on genotype, whereas opposite strain differences were observed after modafinil. ***Electroencephalogram (EEG) analysis during drug-induced wakefulness revealed a transient approximately 2 Hz slowing of theta oscillations and an increase in beta-2 (20-35 Hz) activity only after YKP10A. Gamma activity (35-60 Hz) was induced by all drugs in a drug- and genotype-dependent manner.*** Brain transcriptome and clustering analyses indicated that the three drugs have both common and specific molecular signatures. The correlation between specific EEG and gene-expression signatures suggests that the neuronal pathways activated to stay awake vary among drugs and genetic background.

Mid-range frequencies power increases

Minzenberg, M. J., Yoon, J. H., Cheng, Y., & Carter, C. S. (2014). *Modafinil effects on middle-*

frequency oscillatory power during rule selection in schizophrenia. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 39(13), 3018–3026. https://doi.org/10.1038/npp.2014.155

Control-related cognitive processes such as rule selection are associated with cortical oscillations in the theta, alpha and, beta ranges, and modulated by catecholamine neurotransmission. Thus, a potential strategy for improving cognitive control deficits in schizophrenia would be to use pro-catecholamine pharmacological agents to augment these control-related oscillations. In a double-blind, placebo-controlled (within-subjects) study, we tested the effects of adjunctive single-dose modafinil 200 mg on rule-related 4-30 Hz oscillations in 23 stable schizophrenia patients, using EEG during cognitive control task performance. EEG data underwent time-frequency decomposition with Morlet wavelets to determine the power of 4-30 Hz oscillations. ***Modafinil (relative to placebo) enhanced oscillatory power associated with high-control rule selection in theta, alpha, and beta ranges, with modest effects during rule maintenance.*** Modafinil treatment in schizophrenia augments middle-frequency cortical oscillatory power associated with rule selection, and may subserve diverse subcomponent processes in proactive cognitive control.

Effects in gamma frequency

Minzenberg, M. J., Yoon, J. H., Cheng, Y., & Carter, C. S. (2016). Sustained Modafinil Treatment Effects on Control-Related Gamma Oscillatory Power in Schizophrenia. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 41(5), 1231–1240. https://doi.org/10.1038/npp.2015.271

Control-related cognitive processes such as rule selection and maintenance are associated with cortical oscillations in the gamma range, and modulated by catecholamine neurotransmission. Control-related gamma power is impaired in schizophrenia, and an understudied treatment target. It remains unknown whether pro-catecholamine pharmacological agents augment control-related gamma oscillations in schizophrenia. We tested the effects of 4-week fixed-dose daily adjunctive modafinil (MOD) 200 mg, in a randomized double-blind, placebo-controlled, parallel-groups design. Twenty-seven stable schizophrenia patients performed a cognitive control task during EEG, at baseline and after 4 weeks of treatment. EEG data underwent time-frequency decomposition with Morlet wavelets to determine power of 4-80 Hz oscillations. ***The modafinil group (n=14), relative to placebo group (n=13), exhibited enhanced oscillatory power associated with high-control rule selection in the gamma range after treatment, with additional effects during rule maintenance in gamma and sub-gamma ranges***. MOD-treated patients who exhibited improved task performance with treatment also showed greater treatment-related delay period gamma compared with MOD-treated patients without improved performance. This is the first evidence in schizophrenia of augmentation of cognition-related gamma oscillations by an FDA-approved agent with therapeutic potential. Gamma oscillations represent a novel treatment target in this disorder, and modulation of catecholamine signaling may represent a viable strategy at this target.

Theta, alpha, and beta power; alpha frequency shifts

Saletu, M. T., Anderer, P., Saletu-Zyhlarz, G. M., Mandl, M., Arnold, O., Nosiska, D.,

Zeitlhofer, J., & Saletu, B. (2005). EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil. European archives of psychiatry and clinical neuroscience, 255(1), 20–32. https://doi.org/10.1007/s00406-004-0530-1

The aim of the present study was to investigate the role of EEG mapping as an objective and quantitative measure of vigilance in untreated and modafinil-treated narcoleptics, and compare it with the conventional neurophysiological method of the Multiple Sleep Latency Test (MSLT) and the subjective Epworth Sleepiness Scale (ESS). In 16 drug-free narcoleptics and 16 normal controls a baseline 3-min vigilance-controlled EEG (V-EEG) and a 4-min resting EEG (R-EEG) were recorded during midmorning hours. Thereafter, in a double-blind, placebo-controlled crossover design, patients were treated with a 3-week fixed titration of modafinil (200, 300, 400 mg) and placebo. EEG-mapping, MSLT and ESS measures were obtained before and at the end of the third week of therapy. Statistical overall analysis by means of the omnibus significance test demonstrated significant EEG differences between untreated patients and controls in the resting condition only (R-EEG). ***Subsequent univariate analysis revealed an increase in absolute and relative theta power, a decrease in alpha-2 and beta power as well as a slowing of the dominant frequency and the centroids of the alpha, beta and total power spectrum and thus objectified a vigilance decrement in narcolepsy.*** Modafinil 400 mg/d significantly improved vigilance as compared with placebo ($p < or = 0.01$), inducing changes opposite to the aforementioned baseline differences (key-lock principle). The MSLT and the ESS also improved under modafinil as compared with placebo, but changes were less consistent. Spearman rank correlations revealed the highest correlations between EEG mapping and the ESS, followed by those between EEG mapping and the MSLT, while the lowest correlation was found between the MSLT and the ESS. In conclusion, EEG mapping is a valuable instrument for measuring vigilance decrements in narcolepsy and their improvement under psychostimulant treatment.

Theta augmentation in dentate gyrus

Tsanov, M., Lyons, D. G., Barlow, S., González Reyes, R. E., & O'Mara, S. M. (2010). The psychostimulant modafinil facilitates water maze performance and augments synaptic potentiation in dentate gyrus. Neuropharmacology, 59(1-2), 9–19. https://doi.org/10.1016/j.neuropharm.2010.03.010

Modafinil is a psychostimulant drug used widely for the treatment of narcolepsy, which also has additional positive effects on cognition. Here, we investigate the effects of modafinil on behavioural performance and synaptic plasticity in rats. Improved acquisition in the water maze task was observed in animals that underwent chronic treatment with modafinil. We found that the distance traveled and escape latency were reduced after the first day in chronically-treated rats, compared to controls. Importantly, swim velocity was similar for both groups, excluding pharmacological effects on motor skills. We also found that modafinil increases synaptic plasticity in the dentate gyrus of urethane-anaesthetized rats; modafinil induced a robust augmentation of the population spike, evident after application of 2 bursts of 200 Hz high-frequency stimulation. ***Furthermore, the modafinil-dependent enhancement of postsynaptic potentials correlated selectively with theta rhythm augmentation. We propose that modafinil may facilitate hippocampal-associated spatial representation via increased theta-related hippocampal plasticity***.

Awake EEG faster

Wang, D., Bai, X. X., Williams, S. C., Hua, S. C., Kim, J. W., Marshall, N. S., D'Rozario, A., & Grunstein, R. R. (2015). Modafinil Increases Awake EEG Activation and Improves Performance in Obstructive Sleep Apnea during Continuous Positive Airway Pressure Withdrawal. Sleep, 38(8), 1297–1303. https://doi.org/10.5665/sleep.4912

Objectives: We examined the changes in waking electroencephalography (EEG) biomarkers with modafinil during continuous positive airway pressure (CPAP) withdrawal in patients with obstructive sleep apnea (OSA) to investigate neurophysiological evidence for potential neurocognitive improvements. Design: Randomized double-blind placebo-controlled crossover study. CPAP was used for the first night and then withdrawn for 2 subsequent nights. Each morning after the 2 CPAP withdrawal nights, patients received either 200 mg modafinil or placebo. After a 5-w washout, the procedure repeated with the crossover drug. Settings: University teaching hospital. Participants: Stable CPAP users (n = 23 men with OSA). Measurement and results: Karolinska Drowsiness Test (KDT) (awake EEG measurement with eyes open and closed), Psychomotor Vigilance Task (PVT), and driving simulator Performance were assessed bihourly during the 3 testing days following CPAP treatment and CPAP withdrawal nights. ***Compared to placebo, modafinil significantly increased awake EEG activation (faster EEG frequency) with increased alpha/delta (A/D) ratio (P < 0.0001) and fast ratio = (alpha+beta)/(delta+theta) (P < 0.0001) across the 2 days of CPAP withdrawal***. The A/D ratio significantly correlated with the driving simulator response time (P = 0.015), steering variation (P = 0.002), and PVT reaction time (P = 0.006). In contrast, individual EEG band power of alpha, beta, theta, and delta did not correlate with any neurocognitive performance. Conclusions: Modafinil administration during continuous positive airway pressure (CPAP) withdrawal increased awake EEG activation, which correlated to improved performance. This study provides supporting neurophysiological evidence that modafinil is a potential short-term treatment option during acute CPAP withdrawal.

ANTICONVULSANTS

DRUG FACTS

SYNOPSIS: This class of drugs is primarily prescribed to control epilepsy. Each group can have very different effects depending on type of seizure and baseline EEG.

----- DIBENZAZEPINE ANTICONVULSANTS -----
(carbamazepine [Carbatrol, Epitol, Equetro, Tegretol]; eslicarbazepine [Aptiom]; oxcarbazine [Trileptal, Oxtellar])

DRUG FACTS

SYNOPSIS: Used to treat differing seizure types and certain neuralgias. They can also be prescribed for bipolar disorder and Lennox-Gastaut Syndrome. Their effects on the EEG differ significantly, and all affect alpha power and/or frequency. This is also true for the ERPs.

Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine:

Clemens, B., Ménes, A., Piros, P., Bessenyei, M., Altmann, A., Jerney, J., Kollár, K., Rosdy, B., Rózsavölgyi, M., Steinecker, K., & Hollódy, K. (2006). Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings. *Epilepsy research*, *70*(2-3), 190–199. https://doi.org/10.1016/j.eplepsyres.2006.05.003

Quantitative EEG (QEEG) effects of therapeutic doses ***of carbamazepine (CBZ), oxcarbazepine (OXC), valproate (VA) and lamotrigine (LA)*** monotherapy were investigated in patients with beginning epilepsy. Baseline waking EEG (EEG1) was recorded in the untreated state, the second EEG (EEG2) was done after 8 weeks of reaching the therapeutic dose. Left occipital data were used for analysis. QEEG target parameters were absolute band-power (delta: AD, theta: AT, alpha: AA, beta: AB), and ***alpha mean frequency (AMF).*** Group effects (untreated versus treated condition in the CBZ, VA, OXC, LA groups) were computed for each target parameter. One group with benign rolandic epilepsy remained untreated for clinical reasons and served to estimate the QEEG test-retest differences. In addition, the individual QEEG response to each drug was calculated as (EEG2-EEG1). **Results:** statistically significant ($p<0.05$) group differences indicated the QEEG domain systematically affected by the drugs. ***CBZ caused AT increase and AMF decrease. OXC caused AMF decrease. VA and LA did not decrease AMF (LA even increased it), but reduced broad-band power***. Individual power and AMF changes showed considerable variability in each group. >0.5 Hz AMF decrease (that was reported to predict cognitive impairment in prior studies) occurred in 10/41 patients in the CBZ group but never in the OXC, VA, LA groups. The results may be utilized in planning further studies addressing the relationship between antiepileptic drugs and their CNS effects. In addition, the relationship of AED-related cognitive impairment and AMF changes was discussed.

Efficacy of levetiracetam for reducing rolandic discharges in comparison with carbamazepine and valproate sodium in rolandic epilepsy

Kanemura, H., Sano, F., Ohyama, T., & Aihara, M. (2018). Efficacy of levetiracetam for reducing rolandic discharges in comparison with carbamazepine and valproate sodium in rolandic epilepsy. Seizure, 62, 79–83. https://doi.org/10.1016/j.seizure.2018.10.002

Purpose: The main purpose of this study was to compare the efficacy of levetiracetam (LEV) with the older antiepileptic drugs (AEDs) for preventing atypical evolution in children with Rolandic epilepsy (RE). Accordingly, the present study compared the efficacy of older AEDs (carbamazepine (CBZ) and valproate sodium (VPA)) with LEV in reducing rolandic discharges (RDs) on interictal electroencephalogram (EEG) in children with RE. Methods: Patients in this heterogenous study were subdivided into CBZ, VPA and LEV groups in accordance with the initial monotherapy. The CBZ and VPA groups were studied retrospectively, but the LEV group was studied prospectively. Appearances of discharges were counted and these rates were computed. In comparison with the baseline RD frequency, EEG response to AED treatment was classified such as complete disappearance and response (≥50% reduction in RD frequency). The time taken to attain complete disappearance or response in EEG responders was assessed for each AED treatment group. Results: **Responders comprised 10 (11.2%) of the 89 patients treated with CBZ, 41 (56.2%) of the 73 patients with VPA, and 25 (71.4%) of the 35 patients with LEV. Mean interval to achievement of EEG response in the CBZ, VPA, and LEV groups were 36.3, 23.1, and 14.7 months, respectively. EEG response was achieved significantly more rapidly with LEV than with CBZ ($p < 0.001$) or VPA ($p < 0.005$). Seizure control was not significantly different in all 3 investigated drugs.** Conclusions: LEV seems to be superior to CBZ and VPA in its ability to suppress RDs in children with RE.

Effects of Carbanazepine vs. Valproic Acid

Konishi, T., Naganuma, Y., Hongou, K., Murakami, M., Yamatani, M., & Okada, T. (1995). Effects of antiepileptic drugs on EEG background activity in children with epilepsy: initial phase of therapy. Clinical EEG (electroencephalography), 26(2), 113–119. https://doi.org/10.1177/155005949502600209.

In this study we evaluated the effects of antiepileptic drugs (AED) on EEG background activity in newly treated children with epilepsy. Table 2 EEG background activity before AED therapy compared with that in age-matched controls Control Group CBZ group p value EEG age 8.5 ± 3.0 8.4 ± 3.0 T.P. 1170 ± 610 1368 ± 828 — MF (Hz) 6.0 ± 1.1 5.2 ± 0.8 0.01 Delta (%) 39.0 ± 10.7 45.5 ± 8.8 0.05 Theta 18.4 ± 6.8 23.5 ± 11.3 0.1 Alpha 1 31.4 ± 10.9 21.1 ± 9.7 0.01 Alpha 2 11.4 ± 2.8 7.1 ± 6.9 0.02 Control group VPA group p value EEG age 10.8 ± 2.9 10.9 ± 3.1 T.P. 590 ± 345 836 ± 647 — MF (Hz) 6.9 ± 1.3 5.6 ± 1.3 0.02 Delta (%) 34.0 ± 9.2 46.1 ± 12.4 0.01 Theta 11.3 ± 6.4 15.3 ± 5.2 — Alpha 1 21.3 ± 13.2 21.4 ± 9.0 — Alpha 2 30.1 ± 175 14.3 ± 12.3 0.01 T.P. = total power MF = mean frequency In these EEG parameters there were no significant differences between the patients with different epileptic syndromes in each group, or in the frequency or severity of seizure attacks. 2) ***Changes in EEG background activity at the initiation of AED therapy (Figures 1 and 2) Total power was slightly elevated after 3 to 6 months of AED therapy in both the epileptic groups (not significant*)**. SUMMARY The effects of antiepileptic drugs (AED) on EEG background activity were evaluated in 37 newly treated children with epilepsy, compared with 46 age-matched healthy controls. Before AED therapy, the children with epilepsy, both partial (treated with carbamazepine, CBZ group) and generalized seizures

(treated with valproic acid, VPA group), already exhibited significant slowing of EEG with increased delta and decreased alpha power.

Effects of carbamazepine, oxcarbazepine, and levetiracetam:

Mecarelli, O., Vicenzini, E., Pulitano, P., Vanacore, N., Romolo, F. S., Di Piero, V., Lenzi, G. L., & Accornero, N. (2004). Clinical, cognitive, and neurophysiologic correlates of short-term treatment with carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers. *The Annals of pharmacotherapy*, *38*(11), 1816–1822. https://doi.org/10.1345/aph.1E136

Background: The adverse effects of the antiepileptic drugs (AEDs) originally developed are well known, while those of the newer AEDs remain unclear. **Objective:** To investigate clinical, cognitive, and neurophysiologic effects of carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers. **Methods:** A double-blind crossover study was conducted in 10 volunteers. Eight-day treatment with carbamazepine, oxcarbazepine, levetiracetam, or placebo was administered in random order. Drug doses were titrated gradually to the daily target doses on day 7: carbamazepine 800 mg, oxcarbazepine 1200 mg, and levetiracetam 1500 mg. At baseline and at the end of each treatment period, participants underwent cognitive and neurophysiologic assessment. A washout period of 14 days between treatment periods was conducted. **Results:** ***More adverse events were self-reported with carbamazepine*** (63%) than the other treatments (oxcarbazepine 12%, levetiracetam 20%, placebo 5%; $p < 0.001$ between the 4 groups). Carbamazepine induced the greatest motor slowing ($p = 0.002$), followed by oxcarbazepine ($p = 0.01$). Levetiracetam left baseline motor speed unchanged. All AEDs increased attention span from baseline values as shown on the Stroop test. Quantitative electroencephalogram (EEG) analysis showed that ***carbamazepine significantly increased the delta-theta power and reduced the frequency of alpha rhythm; oxcarbazepine induced smaller changes than carbamazepine. Levetiracetam did not change any EEG measurements. On color visually evoked potential (VEP) tests, carbamazepine induced a constant slowing of P1 latency***, while oxcarbazepine induced changes only after the blue-black pattern. All color VEP measures for volunteers receiving levetiracetam were almost unchanged. **Conclusions:** After short-term treatment in healthy volunteers, carbamazepine induced major clinical and neurophysiologic changes. Oxcarbazepine was better tolerated than carbamazepine. Levetiracetam interfered least with clinical and neurophysiologic test results.

The effects of levetiracetam, carbamazepine, and sodium valproate on P100 and P300 in epileptic patients

Tumay, Y., Altun, Y., Ekmekci, K., & Ozkul, Y. (2013). The effects of levetiracetam, carbamazepine, and sodium valproate on P100 and P300 in epileptic patients. Clinical neuropharmacology, 36(2), 55–58. https://doi.org/10.1097/WNF.0b013e318285f3da

Objective: Although the unfavorable effects of early antiepileptic drugs, valproic acid, and carbamazepine (CBZ) on cognitive functions and visual functions have been investigated, the unfavorable effects of levetiracetam (LEV) on cognitive and visual functions remain unknown. The aim of the present study is to investigate whether there is a difference between the adverse effects by comparing the P300 and P100 latencies of LEV with epileptic patients using CBZ or sodium valproate (VPA) and healthy subjects. Method: A control group of 20 healthy

subjects and 53 patients receiving monotherapy with CBZ (n = 15), VPA (n = 14), and LEV (n = 24) who admitted to neurology policlinic for investigation and treatment were enrolled in this study. Visual evoked potentials and event-related evoked potentials were studied according to these groups. Standard "oddball paradigm" (unpredictable stimuli series) was used to obtain P300. Results: ***The P300 latencies of epileptic patients receiving CBZ, VPA, and LEV were longer compared with the control group, and the differences were statistically significant (P = 0.001, 0.001, and 0.03, respectively). The P300 latency of patients receiving LEV was significantly shorter than the group receiving CBZ and VPA with statistically significant difference (P < 0.01 for both). The P300 amplitude was lower in the groups receiving CBZ, VPA, and LEV compared with the control group, and the difference was statistically significant (P < 0.05)*.** Conclusions: The present study shows that LEV disrupts P300 latency less than VPA and CBZ and does not prolong P100 as much as them.

----- DEPACOTE/DEPAKOTE -----

DRUG FACTS

Magnesium valproate in learning disabled children with interictal paroxysmal EEG patterns: Preliminary report.

Porras-Kattz, E., Harmony, T., Ricardo-Garcell, J., Galán, L., Fernández, T., Prado-Alcalá, R., Avecilla-Ramírez, G., Sánchez-Moreno, L., Barrera-Reséndiz, J., Corsi-Cabrera, M., & Valencia-Solís, E. (2011). Magnesium valproate in learning disabled children with interictal paroxysmal EEG patterns: Preliminary report. Neuroscience letters, 492(2), 99–104. https://doi.org/10.1016/j.neulet.2011.01.065

Previous studies have investigated whether routine use of antiepileptic drugs is adequate to improve cognitive abilities in children who are learning disabled not otherwise specified (LD NOS) and who display interictal paroxysmal patterns in the electroencephalogram (EEG) but do not have epilepsy, and the findings of these studies have been controversial. In the current study, 112 LD children without epilepsy were assessed; however, only 18 met the strict inclusion/exclusion criteria in order to obtain a homogeneous sample. These children showed interictal paroxysmal patterns in the EEG, and a randomized, double-blind trial was carried out on them. The children were treated with either magnesium valproate (MgV; 20mg/kg/day) or a placebo for six months, and differences in WISC subtests, in a computerized reading skills battery (BTL) and EEG recordings were evaluated between groups before and after the treatment period. Performance IQ score and several items of the BTL (rhymes and ordering of words) improved in children who received MgV, whereas no changes were observed in the placebo group. ***No changes in the number of interictal paroxysmal patterns were observed in any group; however increased EEG currents at 10.92 and 12.87Hz (alpha band) in posterior regions and decreased currents in frequencies within the theta band (3.90, 4.29 and 5.07Hz) in frontal regions and at 4.68 and 5.46Hz in the parietal cortex were observed, suggesting an improvement in EEG maturation***.

----- LAMOTRIGINE (Lamictal) -----

DRUG FACTS

A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry

Aiyer, R., Novakovic, V., & Barkin, R. L. (2016). A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry. Postgraduate medicine, 128(7), 656–664. https://doi.org/10.1080/00325481.2016.1218261

Objectives: It is known that psychotropic medications have an impact on the readings found in Electroencephalogram (EEG). In the field of psychiatry, there are several psychotropics utilized by clinicians. This review seeks to investigate all the available data for psychotropic drugs and their impact on EEG changes. **Methods**: A systematic review of all the published and ongoing literature was conducted via PubMed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used for each search. Key words for searches include 'EEG and Psychotropics', 'EEG and Mood Stabilizers', 'EEG and Clozapine', 'EEG and Bupropion', 'EEG and SSRI', 'EEG and Lamotrigine', 'EEG and Carbamazepine', 'EEG and Lithium' and 'EEG and Valproate', 'EEG and Haloperidol', 'EEG and Aripiprazole', 'EEG and Methylphenidate', 'EEG and Topiramate', 'EEG and Gabapentin' and 'EEG and Oxcarbamazepine'. After applying the inclusion criteria, 201 articles were eligible and reviewed. **Results**: ***Following an extensive review of selected studies from the 201 articles, the studies indicate that each of the psychotropic medications reviewed impact alpha, beta, delta and theta waves independently and differently from each other. Additionally, certain medications, particularly haloperidol and valproic acid, have dissimilar results exemplified in all waveforms***. Conclusions: This PRISMA systematic review illustrates that while there is available data on psychotropic medications and their proposed effect on EEG activity, further research is needed to confirm these findings to help allow clinical correlations to be made between the patient's response and the psychotropic agent.

Spontaneous and TMS-related EEG changes as new biomarkers to measure anti-epileptic drug effects.

Biondi, A., Rocchi, L., Santoro, V., Rossini, P. G., Beatch, G. N., Richardson, M. P., & Premoli, I. (2022). Spontaneous and TMS-related EEG changes as new biomarkers to measure anti-epileptic drug effects. Scientific reports, 12(1), 1919. https://doi.org/10.1038/s41598-022-05179-x

Robust biomarkers for anti-epileptic drugs (AEDs) activity in the human brain are essential to increase the probability of successful drug development. The frequency analysis of electroencephalographic (EEG) activity, either spontaneous or evoked by transcranial magnetic stimulation (TMS-EEG) can provide cortical readouts for AEDs. However, a systematic evaluation of the effect of AEDs on spontaneous oscillations and TMS-related spectral perturbation (TRSP) has not yet been provided. We studied the effects of Lamotrigine, Levetiracetam, and of a novel potassium channel opener (XEN1101) in two groups of healthy volunteers. **Levetiracetam suppressed TRSP theta, alpha and beta power, whereas Lamotrigine decreased delta and theta but increased the alpha power. Finally, XEN1101 decreased TRSP delta, theta, alpha and beta power. Resting-state EEG showed a decrease of**

theta band power after Lamotrigine intake. Levetiracetam increased theta, beta and gamma power, while XEN1101 produced an increase of delta, theta, beta and gamma power.
Spontaneous and TMS-related cortical oscillations represent a powerful tool to characterize the effect of AEDs on in vivo brain activity. Spectral fingerprints of specific AEDs should be further investigated to provide robust and objective biomarkers of biological effect in human clinical trials.

Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings.
Clemens, B., Ménes, A., Piros, P., Bessenyei, M., Altmann, A., Jerney, J., Kollár, K., Rosdy, B., Rózsavölgyi, M., Steinecker, K., & Hollódy, K. (2006). Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings. Epilepsy research, 70(2-3), 190–199. https://doi.org/10.1016/j.eplepsyres.2006.05.003
Quantitative EEG (QEEG) effects of therapeutic doses of carbamazepine (CBZ), oxcarbazepine (OXC), valproate (VA) and lamotrigine (LA) monotherapy were investigated in patients with beginning epilepsy. Baseline waking EEG (EEG1) was recorded in the untreated state, the second EEG (EEG2) was done after 8 weeks of reaching the therapeutic dose. Left occipital data were used for analysis. QEEG target parameters were absolute band-power (delta: AD, theta: AT, alpha: AA, beta: AB), and alpha mean frequency (AMF). Group effects (untreated versus treated condition in the CBZ, VA, OXC, LA groups) were computed for each target parameter. ***One group with benign rolandic epilepsy remained untreated for clinical reasons and served to estimate the QEEG test-retest differences. In addition, the individual QEEG response to each drug was calculated as (EEG2-EEG1). Results: statistically significant (p<0.05) group differences indicated the QEEG domain systematically affected by the drugs. CBZ caused AT increase and AMF decrease. OXC caused AMF decrease. VA and LA did not decrease AMF (LA even increased it), but reduced broad-band power. Individual power and AMF changes showed considerable variability in each group. >0.5 Hz AMF decrease*** (that was reported to predict cognitive impairment in prior studies) occurred in 10/41 patients in the CBZ group but never in the OXC, VA, LA groups. The results may be utilized in planning further studies addressing the relationship between antiepileptic drugs and their CNS effects. In addition, the relationship of AED-related cognitive impairment and AMF changes was discussed.

Lamotrigine decreases EEG synchronization in a use-dependent manner in patients with idiopathic generalized epilepsy.
Clemens, B., Piros, P., Bessenyei, M., & Hollódy, K. (2007). Lamotrigine decreases EEG synchronization in a use-dependent manner in patients with idiopathic generalized epilepsy. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118(4), 910–917. https://doi.org/10.1016/j.clinph.2006.11.016
Objective: To investigate the quantitative EEG effects of lamotrigine (LTG) monotherapy. **Hypothesis**: LTG was predicted to decrease thalamo-cortical neuronal synchronization in idiopathic generalized epilepsy (IGE). **Methods**: Waking EEG background activity of 19 IGE patients was investigated before treatment and in the course of LTG monotherapy. Raw

absolute power (RAP), raw percent power (RRP), and raw mean frequency (RMF) were computed for 19 electrodes and four frequency bands (delta=1.5-3.5Hz, theta=3.5-7.5Hz, alpha=7.5-12.5Hz, and beta=12.5-25.0Hz). Inter- and intrahemispheric coherence was computed for eight electrode pairs and the four frequency bands. In addition, scalp-averages were calculated for each variable. Group differences were computed by means of nonparametric statistics including correction for multiple comparisons. **Results**: Main results were decreased delta and theta RAP ($p<0.05$ for scalp-averages). LTG compressed the delta, theta, and alpha RAP datasets, reducing the upper limit of the scatter in particular. Spearman r-values indicated marked correlation between the starting values (RAPuntreated) and the LTG-related decrease (RAPtreated-RAPuntreated) in three bands: delta ($r=-0.72$; $p=0.0005$), theta ($r=-0.59$; $p=0.007$), and alpha ($r=-0.61$; $p=0.006$). ***Thus, the greater the baseline neuronal synchronization, the marked the dampening effect of LTG on it. The remaining findings were decreased theta RRP, theta RMF, and increased alpha RMF ($p<0.05$ for scalp-averages). The electrode-related changes were small but topographically consistent across the 19 electrode sites. LTG did not affect coherence***. **Conclusions**: 1. LTG partially normalized the spectral composition of EEG background activity. LTG decreased pathological thalamo-cortical synchronization in use-dependent manner. 2. LTG did not cause quantitative EEG alterations suggesting worsening of the physiological brain functions. Instead, its profile suggested a mild psychostimulant effect. Significance: The results contribute to the understanding of the effect of LTG at the network level.

Imaging the cortical effect of lamotrigine in patients with idiopathic generalized epilepsy: a low-resolution electromagnetic tomography (LORETA) study.

Clemens, B., Piros, P., Bessenyei, M., Tóth, M., Hollódy, K., & Kondákor, I. (2008). Imaging the cortical effect of lamotrigine in patients with idiopathic generalized epilepsy: a low-resolution electromagnetic tomography (LORETA) study. Epilepsy research, 81(2-3), 204–210. https://doi.org/10.1016/j.eplepsyres.2008.06.002

Purpose: Anatomical localization of the cortical effect of lamotrigine (LTG) in patients with idiopathic generalized epilepsy (IGE). **Methods**: 19 patients with untreated IGE were investigated. EEG was recorded in the untreated condition and 3 months later when LTG treatment abolished the seizures. 19-channel EEG was recorded, and a total of 2min artifact-free, waking EEG was processed to low-resolution electromagnetic tomography (LORETA) analysis. Activity (that is, current source density, A/m(2)) was computed in four frequency bands (delta, theta, alpha, and beta), for 2394 voxels that represented the cortical gray matter and the hippocampi. Group differences between the untreated and treated conditions were computed for the four bands and all voxels by multiple t-tests for interdependent datasets. The results were presented in terms of anatomical distribution and statistical significance. **Results**: $p<0.01$ (uncorrected) changes (decrease of activity) emerged in the theta and the alpha bands. Theta activity decreased in a large cluster of voxels including parts of the temporal, parietal, occipital cortex bilaterally, and in the transverse temporal gyri, insula, hippocampus, and uncus on the right side. ***Alpha activity decreased in a relatively smaller cortical area involving the right temporo-parietal junction and surrounding parts of the cortex, and part of the insula on the right side***. **Conclusions**: LTG decreased theta activity in several cortical areas where abnormally increased theta activity had been found in a prior study in another cohort of

untreated IGE patients [Clemens, B., Bessenyei, M., Piros, P., Tóth, M., Seress, L., Kondákor, I., 2007b. Characteristic distribution of interictal brain electrical activity in idiopathic generalized epilepsy. Epilepsia 48, 941-949]. These LTG-related changes might be related to the decrease of seizure propensity in IGE.

Influence of lamotrigine addition on computerized background EEG parameters in severe epileptogenic encephalopathies.

Foletti, G., & Volanschi, D. (1994). Influence of lamotrigine addition on computerized background EEG parameters in severe epileptogenic encephalopathies. European neurology, 34 Suppl 1, 87–89. https://doi.org/10.1159/000119518

In 12 adults with typical Lennox-Gastaut syndrome and partial epilepsies with secondary bilateral synchrony unsatisfactorily controlled by current antiepileptic drugs, ***the following computerized background EEG parameters were studied before and during beneficial antiepileptic effect of lamotrigine addition: absolute and relative spectral power density; alpha/theta index; dominant frequency of occipital alpha, theta and delta bands. The only significant influence of lamotrigine addition was a moderate decrease of the median and mean absolute delta power (p < 0.01)***. We concluded there was a poor influence of therapeutic doses of lamotrigine on the background diffuse slow dysrhythmias characteristic to severe early encephalopathies which engender both severe secondary epilepsies and different degrees of mental handicap.

Comparison of the effects of vigabatrin, lamotrigine, and topiramate on quantitative EEGs in patients with epilepsy.

Neufeld, M. Y., Kogan, E., Chistik, V., & Korczyn, A. D. (1999). Comparison of the effects of vigabatrin, lamotrigine, and topiramate on quantitative EEGs in patients with epilepsy. Clinical neuropharmacology, 22(2), 80–86. https://doi.org/10.1097/00002826-199903000-00003

Information on the effects of newer antiepileptic drug (AEDs) on the electroencephalogram (EEG) is sparse and contradictory. Quantitative EEG (qEEG) provides a method of estimating the effects of drugs on the central nervous system. Twenty-three adult patients with difficult-to-control complex partial seizures, with or without secondary generalization, participated in an add-on study with one of three newer AEDs: vigabatrin (n = 10), lamotrigine (n = 6), and topiramate (n = 7). Frequency analysis and topographic mapping of awake EEGs before and during treatment with the drug were compared. Statistical analysis was performed using 2-way analysis of variance (ANOVA) with repeated measures. ***Vigabatrin administration was followed by a diffuse decrease in the absolute alpha (p < 0.05) and beta (p < 0.02) activities and a decrease in the absolute theta in the frontal and parieto-occipital regions (p < 0.03). Lamotrigine caused a significant diffuse increase in the faster frequencies (relative alpha p < 0.04 and relative beta p < 0.02), and decrease in the slower activities (relative theta in the posterior head regions p < 0.03 and relative delta diffusely p < 0.05). Topiramate increased the absolute beta (p < 0.05) and theta (p < 0.02) activities diffusely and decreased the relative alpha activity over the left hemisphere (p < 0.03). The different effect profiles of the newer AEDs on the electrical brain activity may reflect their different mechanisms of action***.

----- LEVETIRACETAM (Keppra) -----

DRUG FACTS

Effects of Sodium Valproate, Levetiracetam and Phenytoin Therapy on Evoked Potentials in Children with Epilepsy

Behgal, J., Rana, R., Lather, T., Bala, K., & Kaushik, J. S. (2019). Effects of Sodium Valproate, Levetiracetam and Phenytoin Therapy on Evoked Potentials in Children with Epilepsy. Indian journal of pediatrics, 86(9), 860. https://doi.org/10.1007/s12098-019-02906-7

Visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) have been used to study the effects of antiepileptic drugs (AED) on visual and auditory pathways among adults, with limited studies on children [1,2,3,4]. This cross-sectional study included 36 children (aged 5–15 y) with epilepsy on AED for a duration, not less than 6 mo and 34 healthy controls. Antiepileptic drugs that were used included valproate (VPA) [14 (39%)], phenytoin (PHT) [11(31%)], and levetiracetam (LEV) (3(8%)]. Rest were on combination of VPA/ clobazam (CLB) [4 (11%)], VPA/LEV [2 (5.5%)] and VPA/LEV/CLB [2 (5.5%)]. Majority of the epilepsy was idiopathic [29 (81%)] followed by neurocysticercosis in the rest seven (19%) children. All children underwent flash VEP and BAEP as per the standard protocol. P-100 latency on both the sides were comparable among Children with epilepsy (CWE) and controls [right side: 99.8 (20.5) vs. 104.1 (15.7); p = 0.34; left side: 98.2 (25.8) vs. 104.5 (15.1); p = 0.25]. Similarly, P-100 amplitudes were comparable except for N75P100 amplitude being higher in CWE compared to controls [right side: 11.8 (6.94) vs. 8.71 (3.55); p = 0.02; left side: 11.3 (7.08) vs. 7.33 (4.03); p = 0.04]. ***Peak latencies of waves I, wave III, wave V and interpeak intervals I-III and I-V of BAEP were comparable between the two groups. AEDs decelerate central impulses and the transmission rate by increasing the effect of Gamma-aminobutyric acid (GABA) and causing sodium-channel blockade, resulting in prolonged latency of P100 as well as P300 [5]. Adult studies have demonstrated prolonged wave III/ V absolute latency and I-III/I-V inter-peak latency (IPL) on BAEP and prolonged P-100 latencies and decreased N75P100, P100N145 amplitudes on VEP among patients on PHT, VPA and LEV [1,2,3,4]. The present study revealed that most of the VEP and BAEP characteristics were comparable between children with epilepsy on VLP, LEV and PHT either alone or in combination when compared to healthy control***s. This study with a limited sample size shows that the use of conventional antiepileptic drugs for a duration of at least 6 mo in children with epilepsy are safe on the visual and auditory system.

Spontaneous and TMS-related EEG changes as new biomarkers to measure anti-epileptic drug effects.

Biondi, A., Rocchi, L., Santoro, V., Rossini, P. G., Beatch, G. N., Richardson, M. P., & Premoli, I. (2022). Spontaneous and TMS-related EEG changes as new biomarkers to measure anti-epileptic drug effects. Scientific reports, 12(1), 1919. https://doi.org/10.1038/s41598-022-05179-x

Robust biomarkers for anti-epileptic drugs (AEDs) activity in the human brain are essential to increase the probability of successful drug development. The frequency analysis of electroencephalographic (EEG) activity, either spontaneous or evoked by transcranial magnetic stimulation (TMS-EEG) can provide cortical readouts for AEDs. However, a systematic

evaluation of the effect of AEDs on spontaneous oscillations and TMS-related spectral perturbation (TRSP) has not yet been provided. We studied the effects of Lamotrigine, Levetiracetam, and of a novel potassium channel opener (XEN1101) in two groups of healthy volunteers. ***Levetiracetam suppressed TRSP theta, alpha and beta power, whereas Lamotrigine decreased delta and theta but increased the alpha power. Finally, XEN1101 decreased TRSP delta, theta, alpha and beta power. Resting-state EEG showed a decrease of theta band power after Lamotrigine intake. Levetiracetam increased theta, beta and gamma power, while XEN1101 produced an increase of delta, theta, beta and gamma power. Spontaneous and TMS-related cortical oscillations represent a powerful tool to characterize the effect of AEDs on in vivo brain activity***. Spectral fingerprints of specific AEDs should be further investigated to provide robust and objective biomarkers of biological effect in human clinical trials.

Anti-Seizure Medication Treatment of Benign Childhood Epilepsy With Centrotemporal Spikes: A Systematic Review and Meta-analysis

Cheng, W., Yang, Y., Chen, Y., Shan, S., Li, C., Fang, L., Zhang, W., Lan, S., & Zhang, X. (2022). Anti-Seizure Medication Treatment of Benign Childhood Epilepsy With Centrotemporal Spikes: A Systematic Review and Meta-analysis. Frontiers in pharmacology, 13, 821639. https://doi.org/10.3389/fphar.2022.821639

Background: This study aimed to evaluate the efficacy and tolerability of Anti-Seizure medication (ASM) treatment in patients with BECTS. Method: We searched PubMed, Cochrane Library, Embase, MEDLINE, Web of Science, China National Knowledge Infrastructure (CNKI), WANFANG DATA, and China Science and Technology Journal Database (VIP) between 1 Jan 1990, and 1 Sep 2021, for randomized controlled studies. Data on seizure freedom rate, rate of treatment withdrawal due to serious adverse events, rate of any adverse events and dropout, 50% remission rate, the proportion of patients whose EEG to be normalized, and improvement in cognitive function were extracted by two authors independently. The pooled data were meta-analyzed using a random effects model. Results: A total of 27 studies evaluating 9 ASMs were included, 19 of which were suitable for meta-analysis. ***Compared with sulthiame (STM), levetiracetam (LEV) was associated with a higher probability of treatment withdrawal due to serious adverse events [RR = 5.12, 95% CI (1.19, 22.01), I 2 = 0.0%], experiencing any adverse events [RR = 5.12, 95% CI (1.19, 22.01)], and dropping out for any reason [RR = 3.17, 95% CI (1.36, 10.11)], while it did not affect the seizure freedom rate [RR = 0.90, 95% CI (0.75, 1.06)]. LEV significantly improved cognitive performance relative to carbamazepine (CBZ) but had no effect on the proportion of any adverse events [RR = 0.62, 95% CI (0.25, 1.59)] and EEG to be normalized [RR = 1.27, 95% CI (0.94, 1.71)]. There was no higher probability of a 50% remission rate when comparing valproic acid (VPA) to LEV [RR = 0.96, 95% CI (0.57, 1.61)] and oxcarbazepine (OXC) [RR = 0.61, 95% CI (0.31, 1.20)]. In addition, STM was related to a higher probability of EEG normalization than placebo [RR = 4.61, 95% CI (2.12, 10.01)]. The included single studies also provided some evidence for the efficacy and/or tolerability of other ASMs in BECTS, including topiramate, lamotrigine, clobazam, and clonazepam***. The risk of bias of the included studies was frequently low or unclear. Conclusion: This study indicated some discrepancies in efficacy and tolerability among ASMs used in patients with BECTS. More

randomized controlled trials (RCTs) comparing ASMs with larger populations are required to ascertain the optimum antiepileptic drug treatment to guide clinicians.

Effect of levetiracetam monotherapy on background EEG activity and cognition in drug-naïve epilepsy patients.

Cho, J. R., Koo, D. L., Joo, E. Y., Yoon, S. M., Ju, E., Lee, J., Kim, D. Y., & Hong, S. B. (2012). Effect of levetiracetam monotherapy on background EEG activity and cognition in drug-naïve epilepsy patients. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 123(5), 883–891. https://doi.org/10.1016/j.clinph.2011.09.012

Objective: To investigate the cognitive effect of levetiracetam (LEV) monotherapy with quantitative electroencephalogram (EEG) analysis and neuropsychological (NP) tests. **Methods**: Twenty-two drug-naïve epilepsy patients were enrolled. EEG recordings were performed before and after LEV therapy. Relative power of discrete frequency bands was computed, as well as alpha peak frequency (APF) at occipital electrodes. Eighteen patients performed a battery of NP tests twice across LEV treatment. **Results:** ***LEV therapy decreased the power of delta (1-3 Hz, p<0.01) and theta (3-7 Hz, p<0.05) bands and increased that of alpha-2 (10-13 Hz, p<0.05) and beta-2 (19-24 Hz, p<0.05) bands. Region-specific spectral change was observed: delta power change was significant in fronto-polar region, theta in anterior region, alpha-2 in broad region, and beta-2 in left fronto-central region. APF change was not significant. Improvement in diverse NP tests requiring attention, working memory, language and executive function was observed. Change in theta, alpha-2, and beta-2 power was correlated with improvement in several NP tests***. **Conclusions**: Our data suggest LEV is associated with acceleration of background EEG frequencies and improved cognitive function. Change in frequency band power could predict improvement in several cognitive domains across LEV therapy. Significance: Combined study of quantitative EEG analysis and NP tests can be useful in identifying cognitive effect of antiepileptic drugs.

Efficacy of levetiracetam for reducing rolandic discharges in comparison with carbamazepine and valproate sodium in rolandic epilepsy

Kanemura, H., Sano, F., Ohyama, T., & Aihara, M. (2018). Efficacy of levetiracetam for reducing rolandic discharges in comparison with carbamazepine and valproate sodium in rolandic epilepsy. Seizure, 62, 79–83. https://doi.org/10.1016/j.seizure.2018.10.002

Purpose: The main purpose of this study was to compare the efficacy of levetiracetam (LEV) with the older antiepileptic drugs (AEDs) for preventing atypical evolution in children with Rolandic epilepsy (RE). Accordingly, the present study compared the efficacy of older AEDs (carbamazepine (CBZ) and valproate sodium (VPA)) with LEV in reducing rolandic discharges (RDs) on interictal electroencephalogram (EEG) in children with RE. **Methods**: Patients in this heterogenous study were subdivided into CBZ, VPA and LEV groups in accordance with the initial monotherapy. The CBZ and VPA groups were studied retrospectively, but the LEV group was studied prospectively. Appearances of discharges were counted and these rates were computed. In comparison with the baseline RD frequency, EEG response to AED treatment was classified such as complete disappearance and response (≥50% reduction in RD frequency). ***The time taken to attain complete disappearance or response in EEG responders was assessed for***

each AED treatment group. Results: Responders comprised 10 (11.2%) of the 89 patients treated with CBZ, 41 (56.2%) of the 73 patients with VPA, and 25 (71.4%) of the 35 patients with LEV. Mean interval to achievement of EEG response in the CBZ, VPA, and LEV groups were 36.3, 23.1, and 14.7 months, respectively. EEG response was achieved significantly more rapidly with LEV than with CBZ (p < 0.001) or VPA (p < 0.005). Seizure control was not significantly different in all 3 investigated drugs. **Conclusions**: LEV seems to be superior to CBZ and VPA in its ability to suppress RDs in children with RE.

Treatment for the Benign Childhood Epilepsy With Centrotemporal Spikes: A Monocentric Study

Kessi, M., Yan, F., Pan, L., Chen, B., Olatoutou, E., Li, D., He, F., Rugambwa, T., Yang, L., Peng, J., & Yin, F. (2021). Treatment for the Benign Childhood Epilepsy With Centrotemporal Spikes: A Monocentric Study. Frontiers in neurology, 12, 670958. https://doi.org/10.3389/fneur.2021.670958

Background and Purpose: To date, there is no specific treatment guideline for the benign childhood epilepsy with centrotemporal spikes (BECTS). Several countries recommend levetiracetam, carbamazepine, sodium valproate, oxcarbazepine, and lamotrigine as first-line drugs. Nevertheless, some of these drugs are associated with cognitive decline. Available studies that investigated the efficacy of levetiracetam and sodium valproate on BECTS involved small sample sizes. This study aimed to evaluate the efficacy of levetiracetam and sodium valproate on cognition, and to investigate the prognostic factors for BECTS as whole. **Methods**: Clinical data and treatment status of all patients with BECTS at Xiangya Hospital, Central South University followed from 2008 to 2013 were analyzed retrospectively. Since electrical status epilepticus in sleep (ESES) has been confirmed to play a role in cognitive deterioration, in order to evaluate the response to drugs and their cognitive effects, we created two groups of patients according to the levels of spike wave index (SWI): group 1; 0-50% SWI and group 2; >50% SWI at the last follow up. **Results**: A total of 195 cases were enrolled: 49.7% received monotherapies, 24.1% duotherapies and 27.2% polytherapies. Medications included; levetiracetam plus other drug (s) (75.9%), levetiracetam alone (32.8%), sodium valproate plus other drug (s) (31.3%), and sodium valproate alone (5.1%). After 2 years of treatment and follow up, 71% of the cases had a good seizure outcome, 15.9% had an improvement of SWI, and 91.7% had a normal DQ/IQ. ***Sodium valproate combined with levetiracetam, and sodium valproate alone correlated with good improvement of SWI, whereas, focal spikes were linked with poor improvement. For both groups (group 1 and group 2): monotherapy, levetiracetam alone, and a normal DQ/IQ at seizure onset correlated with good cognitive outcomes, in contrast, polytherapy, sodium valproate plus other drug (s), levetiracetam plus sodium valproate, an initial SWI of ≥85%, and multifocal spikes were linked to cognitive deterioration***. **Conclusions**: Monotherapy, particularly levetiracetam seems to be a good first-line therapy which can help in normalizing the electroencephalograph and preventing cognitive decline. Polytherapy, mostly the administration of sodium valproate seems to relate with poor cognition, therefore, it is recommended to avoid it.

Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children

Liu, M. J., Su, X. J., Md, X. S., Wu, G. F., Zhang, Y. Q., Gao, L., Wang, W., Liao, J. X., Wang, H., Mai, J. N., Gao, J. Y., Shu, X. M., Huang, S. P., Zhang, L., & Zou, L. P. (2017). Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children. Medicine, 96(4), e5623. https://doi.org/10.1097/MD.0000000000005623

This multicenter clinical trial was conducted to examine current practice of benign epilepsy with centrotemporal spikes and especially address the question that in what circumstances 1 antiepileptic drug (AED) should be preferred. Twenty-five medical centers participate in this clinical trial. The general information, clinical information, and treatment status were collected under the guidance of clinicians and then analyzed. Difference between different treatment groups was compared, and usefulness of the most commonly used AEDs was evaluated. A total of 1817 subjects were collected. The average age of the subject was 8.81 years. The average age of onset is 6.85 years (1-14 years). Male-to-female ratio is 1.13:1. A total of 62.9% of the patients are receiving monotherapies, and 10.6% are receiving multidrug therapy. Both age and course of disease of treated rolandic epilepsy (RE) patients are significantly different from those of untreated patients. ***Bilateral findings on electroencephalography (EEG) are less seen in patients with monotherapy compared with patients with multidrug therapy. Except for 25.4% patients not taking any AEDs, oxcarbazepine (OXC), sodium valproate (VPA), and levetiracetam (LEV) are the most commonly used 3 AEDs. VPA and LEV are commonly used in add-on therapy. OXC and LEV are more effective as monotherapy than VPA***. Age of onset of Chinese RE patients is 6.85 years. Bilateral findings on EEG could be a risk factor to require multidrug therapy. In Chinese patients, OXC, VPA, and LEV are most commonly used AEDs as monotherapy and OXC and LEV are more effective than VPA

Clinical, cognitive, and neurophysiologic correlates of short-term treatment with carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers.

Mecarelli, O., Vicenzini, E., Pulitano, P., Vanacore, N., Romolo, F. S., Di Piero, V., Lenzi, G. L., & Accornero, N. (2004). Clinical, cognitive, and neurophysiologic correlates of short-term treatment with carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers. The Annals of pharmacotherapy, 38(11), 1816–1822. https://doi.org/10.1345/aph.1E136

Background: The adverse effects of the antiepileptic drugs (AEDs) originally developed are well known, while those of the newer AEDs remain unclear. Objective: To investigate clinical, cognitive, and neurophysiologic effects of carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers.

Methods: A double-blind crossover study was conducted in 10 volunteers. Eight-day treatment with carbamazepine, oxcarbazepine, levetiracetam, or placebo was administered in random order. Drug doses were titrated gradually to the daily target doses on day 7: carbamazepine 800 mg, oxcarbazepine 1200 mg, and levetiracetam 1500 mg. At baseline and at the end of each treatment period, participants underwent cognitive and neurophysiologic assessment. A washout period of 14 days between treatment periods was conducted. Results: More adverse events were self-reported with carbamazepine (63%) than the other treatments (oxcarbazepine 12%, levetiracetam 20%, placebo 5%; $p < 0.001$ between the 4 groups). Carbamazepine induced

the greatest motor slowing (p = 0.002), followed by oxcarbazepine (p = 0.01). Levetiracetam left baseline motor speed unchanged. All AEDs increased attention span from baseline values as shown on the Stroop test. ***Quantitative electroencephalogram (EEG) analysis showed that carbamazepine significantly increased the delta-theta power and reduced the frequency of alpha rhythm; oxcarbazepine induced smaller changes than carbamazepine. Levetiracetam did not change any EEG measurements. On color visually evoked potential (VEP) tests, carbamazepine induced a constant slowing of P1 latency, while oxcarbazepine induced changes only after the blue-black pattern. All color VEP measures for volunteers receiving levetiracetam were almost unchanged. Conclusions: After short-term treatment in healthy volunteers, carbamazepine induced major clinical and neurophysiologic changes***. Oxcarbazepine was better tolerated than carbamazepine. Levetiracetam interfered least with clinical and neurophysiologic test results.

Increased EEG current-source density in the high Beta frequency band induced by levetiracetam adjunctive therapy in refractory partial epilepsy.

Park, S. P., & Kwon, O. Y. (2009). Increased EEG current-source density in the high Beta frequency band induced by levetiracetam adjunctive therapy in refractory partial epilepsy. Journal of clinical neurology (Seoul, Korea), 5(4), 178–185. https://doi.org/10.3988/jcn.2009.5.4.178

Background and purpose: Levetiracetam (LEV) is an antiepileptic drug (AED) that has favorable effects on cognition. Although neuropsychological studies have demonstrated these favorable outcomes on cognition, there are few electrophysiologic data describing the functional changes exerted by LEV. The purpose of this study was to determine the effects of LEV adjunctive therapy on the current-source density (CSD) in the high beta frequency band (22-30 Hz) of EEG background activity in refractory partial epilepsy (RPE). **Methods**: We conducted a 24-week, open-label, prospective study in 24 patients with RPE. Scalp electroencephalography and neuropsychological tests (NPTs) were conducted twice, once before the LEV trial and then again after 24 weeks of medication. **Results:** ***The CSD in the 22-30 Hz band of EEG background activity increased in the bilateral anterior cingulate gyri, left parahippocampal gyrus, and a small area of the right anterior parahippocampal gyrus after the LEV trial. Neither seizure freedom nor the dosage increment of LEV elicited meaningful CSD changes***. Verbal memory and executive function were improved after the 24-week LEV trial. **Conclusions:** To our knowledge, this is the first study to examine the changes in CSD induced by LEV adjunctive therapy in RPE patients. The CSD changes and NPT results suggest that LEV enhances the activities of the neuronal networks in the prefrontal cortex and left hippocampus.

Levetiracetam Modulates EEG Microstates in Temporal Lobe Epilepsy

Ricci, L., Croce, P., Pulitano, P., Boscarino, M., Zappasodi, F., Narducci, F., Lanzone, J., Sancetta, B., Mecarelli, O., Di Lazzaro, V., Tombini, M., & Assenza, G. (2022). Levetiracetam Modulates EEG Microstates in Temporal Lobe Epilepsy. Brain topography, 35(5-6), 680–691. https://doi.org/10.1007/s10548-022-00911-2

To determine the effects of Levetiracetam (LEV) therapy using EEG microstates analysis in a population of newly diagnosed Temporal Lobe Epilepsy (TLE) patients. We hypothesized that the impact of LEV therapy on the electrical activity of the brain can be globally explored using

EEG microstates. Twenty-seven patients with TLE were examined. We performed resting-state microstate EEG analysis and compared microstate metrics between the EEG performed at baseline (EEGpre) and after 3 months of LEV therapy (EEGpost). The microstates A, B, C and D emerged as the most stable. LEV induced a reduction of microstate B and D mean duration and occurrence per second ($p < 0.01$). Additionally, LEV treatment increased the directional predominance of microstate A to C and microstate B to D ($p = 0.01$). ***LEV treatment induces a modulation of resting-state EEG microstates in newly diagnosed TLE patients. Microstates analysis has the potential to identify a neurophysiological indicator of LEV therapeutic activity. This study of EEG microstates in people with epilepsy opens an interesting path to identify potential LEV activity biomarkers that may involve increased neuronal inhibition of the epileptic network***.

Measuring the effects of first antiepileptic medication in Temporal Lobe Epilepsy: Predictive value of quantitative-EEG analysis

Ricci, L., Assenza, G., Pulitano, P., Simonelli, V., Vollero, L., Lanzone, J., Mecarelli, O., Di Lazzaro, V., & Tombini, M. (2021). Measuring the effects of first antiepileptic medication in Temporal Lobe Epilepsy: Predictive value of quantitative-EEG analysis. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 132(1), 25–35. https://doi.org/10.1016/j.clinph.2020.10.020

Objective: To determine the quantitative EEG responses in a population of drug-naïve patients with Temporal Lobe Epilepsy (TLE) after Levetiracetam (LEV) initiation as first antiepileptic drug (AED). We hypothesized that the outcome of AED treatment can be predicted from EEG data in patients with TLE. **Methods:** Twenty-three patients with TLE and twenty-five healthy controls were examined. Clinical outcome was dichotomized into seizure-free (SF) and non-seizure-free (NSF) after two years of LEV. EEG parameters were compared between healthy controls and patients with TLE at baseline (EEGpre) and after three months of AED therapy (EEGpre-post) and between SF and NSF patients. Receiver Operating Characteristic curves models were built to test whether EEG parameters predicted outcome. **Results:** ***AED therapy induces an increase in EEG power for Alpha ($p = 0.06$) and a decrease in Theta ($p < 0.05$). Connectivity values were lower in SF compared to NSF patients ($p < 0.001$). Quantitative EEG predicted outcome after LEV treatment with an estimated accuracy varying from 65.2% to 91.3% (area under the curve [AUC] = 0.56-0.93) for EEGpre and from 69.9% to 86.9% (AUC = 0.69-0.94) for EEGpre-post***. **Conclusions:** AED therapy induces EEG modifications in TLE patients, and such modifications are predictive of clinical outcome. Significance: Quantitative EEG may help understanding the effect of AEDs in the central nervous system and offer new prognostic biomarkers for patients with epilepsy.

The effects of levetiracetam, carbamazepine, and sodium valproate on P100 and P300 in epileptic patients

Tumay, Y., Altun, Y., Ekmekci, K., & Ozkul, Y. (2013). The effects of levetiracetam, carbamazepine, and sodium valproate on P100 and P300 in epileptic patients. Clinical neuropharmacology, 36(2), 55–58. https://doi.org/10.1097/WNF.0b013e318285f3da

Objective: Although the unfavorable effects of early antiepileptic drugs, valproic acid, and carbamazepine (CBZ) on cognitive functions and visual functions have been investigated, the

unfavorable effects of levetiracetam (LEV) on cognitive and visual functions remain unknown. The aim of the present study is to investigate whether there is a difference between the adverse effects by comparing the P300 and P100 latencies of LEV with epileptic patients using CBZ or sodium valproate (VPA) and healthy subjects. **Method:** A control group of 20 healthy subjects and 53 patients receiving monotherapy with CBZ (n = 15), VPA (n = 14), and LEV (n = 24) who admitted to neurology policlinic for investigation and treatment were enrolled in this study. Visual evoked potentials and event-related evoked potentials were studied according to these groups. Standard "oddball paradigm" (unpredictable stimuli series) was used to obtain P300. **Results:** ***The P300 latencies of epileptic patients receiving CBZ, VPA, and LEV were longer compared with the control group, and the differences were statistically significant (P = 0.001, 0.001, and 0.03, respectively). The P300 latency of patients receiving LEV was significantly shorter than the group receiving CBZ and VPA with statistically significant difference (P < 0.01 for both). The P300 amplitude was lower in the groups receiving CBZ, VPA, and LEV compared with the control group, and the difference was statistically significant (P < 0.05)***. **Conclusions:** The present study shows that LEV disrupts P300 latency less than VPA and CBZ and does not prolong P100 as much as them.

Resting-state fMRI revealed different brain activities responding to valproic acid and levetiracetam in benign epilepsy with central-temporal spikes

Zhang, Q., Yang, F., Hu, Z., Zhang, Z., Xu, Q., Dante, M., Wu, H., Li, Z., Li, Q., Li, K., & Lu, G. (2017). Resting-state fMRI revealed different brain activities responding to valproic acid and levetiracetam in benign epilepsy with central-temporal spikes. European radiology, 27(5), 2137–2145. https://doi.org/10.1007/s00330-016-4531-z

Objectives: Our aim was to investigate regional difference in brain activities in response to antiepileptic drug (AED) medications in benign epilepsy with central-temporal spikes (BECTS) using resting-state functional magnetic resonance imaging (fMRI). **Methods:** Fifty-seven patients with BECTS underwent resting-state fMRI scans after receiving either valproic acid (VPA) (n = 15), levetiracetam (LEV) (n = 21), or no medication (n = 21). fMRI regional homogeneity (ReHo) parameter among the three groups of patients were compared and were correlated with total doses of AED in the two medicated groups. Results: Compared with patients on no-medication, patients receiving either VPA or LEV showed decreased ReHo in the central-temporal region, frontal cortex, and thalamus. In particular, the VPA group showed greater ReHo decrease in the thalamus and milder in cortices and caudate heads compared with the LEV group. In addition, the VPA group demonstrated a negative correlation between ReHo values in the central-temporal region and medication dose. **Conclusion:** Both VPA and LEV inhibit resting-state neural activity in the central-temporal region, which is the main epileptogenic focus of BECTS. VPA reduced brain activity in the cortical epileptogenic regions and thalamus evenly, whereas LEV reduced brain activity predominantly in the cortices. Interestingly, VPA showed a cumulative effect on inhibiting brain activity in the epileptogenic regions in BECTS. ***Key points: • Regional differences in brain activity in response to different AEDs in BECTS. • AEDs inhibit resting-state neural activity in epileptogenic and subcortical regions in BECTS. • Valproic acid effect on the cortical epileptogenic regions and thalamus evenly. • Levetiracetam effect seen predominantly in cortices. • Valproic acid has a cumulative effect on inhibiting brain activity in epileptogenic regions***.

Valproate but not levetiracetam slows the EEG alpha peak frequency – A pharmaco-EEG study

Zöllner, J. P., Strzelczyk, A., Rosenow, F., & Kienitz, R. (2021). Valproate but not levetiracetam slows the EEG alpha peak frequency - A pharmaco-EEG study. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 132(6), 1203–1208. https://doi.org/10.1016/j.clinph.2021.02.392

Objective: Studies of the effect of valproate (VPA) on the background EEG have shown varying results. Therefore, we compared the effect of VPA and levetiracetam (LEV) on the EEG alpha peak frequency (APF). **Methods:** We retrospectively examined the APF in resting-state EEG of patients undergoing inpatient video-EEG monitoring (VEM) during withdrawal of VPA or LEV. We assessed APF trends by computing linear fits across individual patients' APF as a function of consecutive days, and correlated the APF and daily antiseizure medication (ASM) doses on a single-patient and group level. **Results:** The APF in the VPA-group significantly increased over days with falling VPA doses ($p = 0.005$, $n = 13$), but did not change significantly in the LEV-group ($p = 0.47$, $n = 18$). APF correlated negatively with daily ASM doses in the VPA-group (average of $r = -0.74 \pm 0.12$ across patients, $p = 0.0039$), but not in the LEV-group (average of $r = -0.17 \pm 0.18$ across patients, $p = 0.4072$). **Conclusions:** ***Our results suggest that VPA treatment slows the APF. This APF reduction correlates with the daily dose of VPA and is not present in LEV treatment***.

----- LORAZEPAM (Ativan, Temesta) -----

DRUG FACTS

An association between resting state EEG parameters and the severity of topiramate-related cognitive impairment

Barkley, C. M., Hu, Z., Fieberg, A. M., Eberly, L. E., Birnbaum, A. K., Leppik, I. E., & Marino, S. E. (2021). An association between resting state EEG parameters and the severity of topiramate-related cognitive impairment. Epilepsy & behavior : E&B, 114(Pt A), 107598. https://doi.org/10.1016/j.yebeh.2020.107598

Introduction: Many commonly prescribed drugs cause cognitive deficits. We investigated whether parameters of the resting-state electroencephalogram (rsEEG) are related to the severity of cognitive impairments associated with administration of the antiseizure drug topiramate (TPM) and the benzodiazepine lorazepam (LZP). **Methods:** We conducted a double-blind, randomized, placebo-controlled crossover study. After a baseline visit, subjects completed three sessions at which they received either a single dose of TPM, LZP, or placebo. Four-hours after drug administration and at baseline, subjects completed a working memory (WM) task after their rsEEG was recorded. After quantifying drug-related behavioral (WM accuracy (ACC)/reaction time (RT)) and electrophysiological (alpha, theta, beta (1,2), gamma power) change for each subject, we constructed drug-specific mixed effects models of change for each WM and EEG measure. Regression models were constructed to characterize the relationship between baseline rsEEG measures and drug-related performance changes. **Results:** ***Linear mixed effects models showed theta power increases in response to TPM administration***. The results of the regression models revealed a number of robust relationships between baseline rsEEG parameters and TPM-related, but not LZP-related, WM impairment.

Conclusions: We showed for the first time that parameters of the rsEEG are associated with the severity of TPM-related WM deficits; this suggests that rsEEG measures may have novel clinical applications in the future.

Lorazapem and Methylphenidate on ERPs:

Berchou, R., Chayasirisobhon, S., Green, V., & Mason, K. (1986). The pharmacodynamic properties of lorazepam and methylphenidate drugs on event-related potentials and power spectral analysis in normal subjects. *Clinical EEG (electroencephalography)*, *17*(4), 176–180.

The effect of lorazepam and methylphenidate on the ERPs and power spectral analysis was studied. ***Lorazepam caused prolonged latency and decreased amplitude of N200 and P300***. This result suggests that lorazepam affects the neural processing of cognitive function. The drowsiness induced by lorazepam correlated inversely with alpha frequency power, but had no direct correlation with fast activity. On the contrary, when ***methylphenidate was given, there was no change in ERPs***. There was an ***increase in percent alpha frequency correlated with the alertness of the subjects***. An analysis of variance involving the factors of drug and time of rating showed that subjects showed a significant (p less than 0.0001) decrease in alertness over time while receiving lorazepam, and a significant (p less than 0.05) increase in alertness over time while receiving methylphenidate.

Benzodiazepine administration effect on EEG fractal dimension: results and causalities.

Michail, E., Chouvarda, I., & Maglaveras, N. (2010). Benzodiazepine administration effect on EEG fractal dimension: results and causalities. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference, 2010, 2350–2353. https://doi.org/10.1109/IEMBS.2010.5627851

This work aims at examining the influence of lorazepam, an anxiolytic drug with sedative effects, on brain activity and specifically on EEG Fractal Dimension (FD). The main objective is to clarify the reasons for FD increase after drug intake and to establish a relationship between FD and EEG energy bands. 14 healthy subjects that received either 2.5mg of lorazepam (verum case) or placebo (placebo case) participated in the experiment. 20 EEG channels have been used. ***One-way ANOVA test revealed that lorazepam increases significantly both FD (p = 0) and beta energy band (p = 1.18E-013 for beta1 band and p = 2.29E-011 for beta2 band) and decreases alpha energy band (p = 0.05 for alpha1 and p = 0.0036 for alpha2), whereas there was not any significant difference on placebo subjects before and after drug intake. Moreover, correlation results indicate that there is a strong correlation between FD and beta energy band (mean correlation coefficient = 0.4120 for beta1 and 0.5358 for beta2) and a negative correlation between FD and alpha1 energy band (mean correlation coefficient -0.4930)***. Additionally, the mean correlation coefficient between FD and a combination of the different energy bands (beta1+beta2-alpha1) is 0.6185 and reaches value 0.684 for channels F7, T6, P4. These results indicate that there is a relationship between EEG energy bands and FD and provide a link between the classic spectral analysis and the complexity analysis.

----- OXCABAZEPINE (Trileptal) -----

DRUG FACTS

Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children

Liu, M. J., Su, X. J., Md, X. S., Wu, G. F., Zhang, Y. Q., Gao, L., Wang, W., Liao, J. X., Wang, H., Mai, J. N., Gao, J. Y., Shu, X. M., Huang, S. P., Zhang, L., & Zou, L. P. (2017). Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children. Medicine, 96(4), e5623. https://doi.org/10.1097/MD.0000000000005623

This multicenter clinical trial was conducted to examine current practice of benign epilepsy with centrotemporal spikes and especially address the question that in what circumstances 1 antiepileptic drug (AED) should be preferred.Twenty-five medical centers participate in this clinical trial. The general information, clinical information, and treatment status were collected under the guidance of clinicians and then analyzed. Difference between different treatment groups was compared, and usefulness of the most commonly used AEDs was evaluated. A total of 1817 subjects were collected. The average age of the subject was 8.81 years. The average age of onset is 6.85 years (1-14 years). Male-to-female ratio is 1.13:1. A total of 62.9% of the patients are receiving monotherapies, and 10.6% are receiving multidrug therapy. Both age and course of disease of treated rolandic epilepsy (RE) patients are significantly different from those of untreated patients. ***Bilateral findings on electroencephalography (EEG) are less seen in patients with monotherapy compared with patients with multidrug therapy. Except for 25.4% patients not taking any AEDs, oxcarbazepine (OXC), sodium valproate (VPA), and levetiracetam (LEV) are the most commonly used 3 AEDs. VPA and LEV are commonly used in add-on therapy. OXC and LEV are more effective as monotherapy than VPA***. Age of onset of Chinese RE patients is 6.85 years. Bilateral findings on EEG could be a risk factor to require multidrug therapy. In Chinese patients, OXC, VPA, and LEV are most commonly used AEDs as monotherapy and OXC and LEV are more effective than VPA.

Clinical, cognitive, and neurophysiologic correlates of short-term treatment with carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers.

Mecarelli, O., Vicenzini, E., Pulitano, P., Vanacore, N., Romolo, F. S., Di Piero, V., Lenzi, G. L., & Accornero, N. (2004). Clinical, cognitive, and neurophysiologic correlates of short-term treatment with carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers. The Annals of pharmacotherapy, 38(11), 1816–1822. https://doi.org/10.1345/aph.1E136

Background: The adverse effects of the antiepileptic drugs (AEDs) originally developed are well known, while those of the newer AEDs remain unclear. Objective: To investigate clinical, cognitive, and neurophysiologic effects of carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers. **Methods:** A double-blind crossover study was conducted in 10 volunteers. Eight-day treatment with carbamazepine, oxcarbazepine, levetiracetam, or placebo was administered in random order. Drug doses were titrated gradually to the daily target doses on day 7: carbamazepine 800 mg, oxcarbazepine 1200 mg, and levetiracetam 1500 mg. At baseline and at the end of each treatment period, participants underwent cognitive and neurophysiologic assessment. A washout period of 14 days between treatment periods was

conducted. Results: More adverse events were self-reported with carbamazepine (63%) than the other treatments (oxcarbazepine 12%, levetiracetam 20%, placebo 5%; $p < 0.001$ between the 4 groups). Carbamazepine induced the greatest motor slowing ($p = 0.002$), followed by oxcarbazepine ($p = 0.01$). Levetiracetam left baseline motor speed unchanged. All AEDs increased attention span from baseline values as shown on the Stroop test. ***Quantitative electroencephalogram (EEG) analysis showed that carbamazepine significantly increased the delta-theta power and reduced the frequency of alpha rhythm; oxcarbazepine induced smaller changes than carbamazepine. Levetiracetam did not change any EEG measurements***. On color visually evoked potential (VEP) tests, carbamazepine induced a constant slowing of P1 latency, while oxcarbazepine induced changes only after the blue-black pattern. All color VEP measures for volunteers receiving levetiracetam were almost unchanged. **Conclusions**: After short-term treatment in healthy volunteers, carbamazepine induced major clinical and neurophysiologic changes. Oxcarbazepine was better tolerated than carbamazepine. Levetiracetam interfered least with clinical and neurophysiologic test results.

Effects of oxcarbazepine and phenytoin on the EEG and cognition in healthy volunteers.
Salinsky, M. C., Spencer, D. C., Oken, B. S., & Storzbach, D. (2004). Effects of oxcarbazepine and phenytoin on the EEG and cognition in healthy volunteers. Epilepsy & behavior : E&B, 5(6), 894–902. https://doi.org/10.1016/j.yebeh.2004.07.011
We studied the EEG and cognitive effects of oxcarbazepine (OXC) and phenytoin (PHT) using a double-blind, randomized, parallel-group design. Thirty-two healthy volunteers received a maximum of 1200 mg of OXC or 360 mg of PHT. ***EEG and cognitive testing were performed at baseline and after 12 weeks of treatment. For each subject and measure, test-retest Z scores were calculated from regression equations derived from 73 healthy controls. Twenty-six subjects completed the study. Both the OXC and PHT groups had significant slowing of the EEG peak frequency and increased relative theta and delta power. Differences between AEDs (antiepileptic drugs) were not significant.*** Significant cognitive effects were seen on 5 of 20 measures, primarily measures of motor speed and reaction time. Again, there were no significant differences between AEDs. The only significant difference between AEDs was for the POMS-Vigor scale, favoring OXC. The small sample size may have contributed to the lack of significant differences between AEDs.

----- PHENYTOIN -----
(Dilantin, Di-Phen, Epitoin, Epanutin, Oxcarbazepine, Phenytek)
DRUG FACTS

Effects of Sodium Valproate, Levetiracetam and Phenytoin Therapy on Evoked Potentials in Children with Epilepsy
Behgal, J., Rana, R., Lather, T., Bala, K., & Kaushik, J. S. (2019). Effects of Sodium Valproate, Levetiracetam and Phenytoin Therapy on Evoked Potentials in Children with Epilepsy. Indian journal of pediatrics, 86(9), 860. https://doi.org/10.1007/s12098-019-02906-7
Visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) have been used to study the effects of antiepileptic drugs (AED) on visual and auditory pathways among adults, with limited studies on children [1,2,3,4]. This cross-sectional study included 36 children (aged

5–15 y) with epilepsy on AED for a duration, not less than 6 mo and 34 healthy controls. Antiepileptic drugs that were used included valproate (VPA) [14 (39%)], phenytoin (PHT) [11(31%)], and levetiracetam (LEV) (3(8%)]. Rest were on combination of VPA/ clobazam (CLB) [4 (11%)], VPA/LEV [2 (5.5%)] and VPA/LEV/CLB [2 (5.5%)]. Majority of the epilepsy was idiopathic [29 (81%)] followed by neurocysticercosis in the rest seven (19%) children. All children underwent flash VEP and BAEP as per the standard protocol. P-100 latency on both the sides were comparable among Children with epilepsy (CWE) and controls [right side: 99.8 (20.5) vs. 104.1 (15.7); p = 0.34; left side: 98.2 (25.8) vs. 104.5 (15.1); p = 0.25]. Similarly, P-100 amplitudes were comparable except for N75P100 amplitude being higher in CWE compared to controls [right side: 11.8 (6.94) vs. 8.71 (3.55); p = 0.02; left side: 11.3 (7.08) vs. 7.33 (4.03); p = 0.04]. Peak latencies of waves I, wave III, wave V and interpeak intervals I-III and I-V of BAEP were comparable between the two groups. AEDs decelerate central impulses and the transmission rate by increasing the effect of Gamma-aminobutyric acid (GABA) and causing sodium-channel blockade, resulting in prolonged latency of P100 as well as P300 [5]. Adult studies have demonstrated prolonged wave III/ V absolute latency and I-III/I-V inter-peak latency (IPL) on BAEP and prolonged P-100 latencies and decreased N75P100, P100N145 amplitudes on VEP among patients on PHT, VPA and LEV [1,2,3,4]. The present study revealed that most of the VEP and BAEP characteristics were comparable between children with epilepsy on VLP, LEV and PHT either alone or in combination when compared to healthy controls. This study with a limited sample size shows that the use of conventional antiepileptic drugs for a duration of at least 6 mo in children with epilepsy are safe on the visual and auditory system.

Effects of antiepileptic drug treatment on the background frequency of EEGs in epileptic patients

Herkes, G. K., Lagerlund, T. D., Sharbrough, F. W., & Eadie, M. J. (1993). Effects of antiepileptic drug treatment on the background frequency of EEGs in epileptic patients. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 10(2), 210–216. https://doi.org/10.1097/00004691-199304000-00008

The effect of changing antiepileptic drug concentrations within the therapeutic range on the EEGs of epileptic subjects was studied by quantitative EEG analysis. Twenty-seven patients had administration of one or more drugs discontinued on admission to the hospital for prolonged video/EEG monitoring, and drug levels were correlated daily with the simultaneous EEG background. ***Phenytoin, alone or in combination with other drugs, led to significant changes in the mean EEG background frequency and increased the percentage of power in the theta and delta bands.*** In the plasma ranges studied, carbamazepine, phenobarbital, and valproic acid did not lead to significant change in the EEG background frequency; however, the number of subjects taking these medications was small.

The influence of antiepileptic drugs on the electroencephalogram: a review of controlled clinical studies.

Schmidt D. (1982). The influence of antiepileptic drugs on the electroencephalogram: a review of controlled clinical studies. Electroencephalography and clinical neurophysiology. Supplement, 36, 453–466

The effect of antiepileptic drugs on the EEG was studied in a review of 23 controlled trials with therapeutic drug monitoring and serial EEG observations. There is a good correlation of suppression of paroxysmal discharges and an increase in the plasma concentrations of diazepam, phenobarbital, phenytoin, alone or in combination with phenobarbital or primidone. The correlation is variable during treatment with carbamazepine and in patients with focal discharge receiving sodium valproate or a delayed response to sodium valproate treatment. An increase in beta activity is correlated with a raised plasma concentration of clonazepam, phenytoin and phenobarbital, but not in all patients receiving these drugs. ***The degree and the localization of cerebral impairment seem to influence the drug-induced fast EEG response. Slowing of background occurs with high plasma concentrations of diazepam, phenytoin, alone or in combination with phenobarbital or primidone. The correlation of paroxysmal discharges with clinical seizure frequency is good for phenobarbital, phenytoin, alone or in combination. The correlation is variable for carbamazepine and the delayed response to sodium valproate. A slowing of background activity is correlated with clinical drug toxicity due to carbamazepine, phenytoin, phenobarbital and primidone treatment in most patients.***

Effects of oxcarbazepine and phenytoin on the EEG and cognition in healthy volunteers.

Salinsky, M. C., Spencer, D. C., Oken, B. S., & Storzbach, D. (2004). Effects of oxcarbazepine and phenytoin on the EEG and cognition in healthy volunteers. Epilepsy & behavior : E&B, 5(6), 894–902. https://doi.org/10.1016/j.yebeh.2004.07.011

We studied the EEG and cognitive effects of oxcarbazepine (OXC) and phenytoin (PHT) using a double-blind, randomized, parallel-group design. Thirty-two healthy volunteers received a maximum of 1200 mg of OXC or 360 mg of PHT. EEG and cognitive testing were performed at baseline and after 12 weeks of treatment. For each subject and measure, test-retest Z scores were calculated from regression equations derived from 73 healthy controls. Twenty-six subjects completed the study. ***Both the OXC and PHT groups had significant slowing of the EEG peak frequency and increased relative theta and delta power. Differences between AEDs (antiepileptic drugs) were not significant***. Significant cognitive effects were seen on 5 of 20 measures, primarily measures of motor speed and reaction time. Again, there were no significant differences between AEDs. The only significant difference between AEDs was for the POMS-Vigor scale, favoring OXC. The small sample size may have contributed to the lack of significant differences between AEDs.

----- TIAGABINE (Gabatril) -----

DRUG FACTS

Effects of the GABA-uptake inhibitor tiagabine on electroencephalogram, spike-wave discharges and behaviour of rats.

Coenen, A. M., Blezer, E. H., & van Luijtelaar, E. L. (1995). Effects of the GABA-uptake inhibitor tiagabine on electroencephalogram, spike-wave discharges and behaviour of rats. Epilepsy research, 21(2), 89–94. https://doi.org/10.1016/0920-1211(95)00015-3

Effects of the anticonvulsant tiagabine in doses of 1, 3 and 10 mg/kg were investigated on electroencephalogram (EEG), spike-wave discharges and behaviour of WAG/Rij rats. These rats are considered as an animal model of generalized, non-convulsive, absence epilepsy. WAG/Rij

rats spontaneously show a considerable number of spike-wave discharges in their EEG. These discharges can be facilitated by GABA agonists. The facilitatory effects of these agonists are completely opposite to their effects on convulsive seizures, which are reduced by these drugs. Tiagabine enhances the effects on the GABA system, since it acts as a GABA re-uptake inhibitor. According to expectations, tiagabine enhanced in a dose-related way both the number and mean duration of spike-wave discharges. ***The low dose of 1 mg/kg had almost no effects, but doses of 3 and 10 mg/kg were effective. Furthermore, tiagabine in the latter two doses increased the power in the higher beta band of the background EEG, whereas no significant changes in behavioural parameters were found. An unexpected finding was the occurrence of a second type of spike-wave discharges. These were again seen with the two higher doses of tiagabine, while 1 mg/kg had no effect. An assumption is that this second type of discharges are forerunners of genuine spike-wave discharges. In general, this experiment supports that non-convulsive epilepsy is associated with a GABA hyperfunction.*** It also underlines the biochemical differences of convulsive and non-convulsive animal models of epilepsy. Tiagabine, with its GABA-mimetic properties, belongs to the category of drugs effective in convulsive animal models and not in non-convulsive models of epilepsy.

----- TOPIRAMATE (Topamax) -----

DRUG FACTS

An association between resting state EEG parameters and the severity of topiramate-related cognitive impairment

Barkley, C. M., Hu, Z., Fieberg, A. M., Eberly, L. E., Birnbaum, A. K., Leppik, I. E., & Marino, S. E. (2021). An association between resting state EEG parameters and the severity of topiramate-related cognitive impairment. Epilepsy & behavior : E&B, 114(Pt A), 107598. https://doi.org/10.1016/j.yebeh.2020.107598

Introduction: Many commonly prescribed drugs cause cognitive deficits. We investigated whether parameters of the resting-state electroencephalogram (rsEEG) are related to the severity of cognitive impairments associated with administration of the antiseizure drug topiramate (TPM) and the benzodiazepine lorazepam (LZP). **Methods:** We conducted a double-blind, randomized, placebo-controlled crossover study. After a baseline visit, subjects completed three sessions at which they received either a single dose of TPM, LZP, or placebo. Four-hours after drug administration and at baseline, subjects completed a working memory (WM) task after their rsEEG was recorded. ***After quantifying drug-related behavioral (WM accuracy (ACC)/reaction time (RT)) and electrophysiological (alpha, theta, beta (1,2), gamma power) change for each subject, we constructed drug-specific mixed effects models of change for each WM and EEG measure. Regression models were constructed to characterize the relationship between baseline rsEEG measures and drug-related performance changes***. **Results:** Linear mixed effects models showed theta power increases in response to TPM administration. The results of the regression models revealed a number of robust relationships between baseline rsEEG parameters and TPM-related, but not LZP-related, WM impairment. **Conclusions:** ***We showed for the first time that parameters of the rsEEG are associated with the severity of TPM-related WM deficits; this suggests that rsEEG measures may have novel clinical applications in the future***.

Clinical and electroencephalographic effects of topiramate in patients with epilepsy and healthy volunteers.

Mecarelli, O., Piacenti, A., Pulitano, P., Vicenzini, E., Rizzo, C., Rinalduzzi, S., de Feo, M. R., & Accornero, N. (2001). Clinical and electroencephalographic effects of topiramate in patients with epilepsy and healthy volunteers. Clinical neuropharmacology, 24(5), 284–289. https://doi.org/10.1097/00002826-200109000-00005

Although topiramate, one of the newer drugs used in treating epilepsy, is effective in reducing seizure frequency and has a wide spectrum of action, it often induces intolerable adverse effects, predominantly related to the central nervous system. Information that would help document adverse reactions early, thus allowing topiramate doses to be adjusted during the drug titration and maintenance phases, could be obtained from electroencephalogram (EEG) studies. We studied the clinical effects and EEG changes induced by topiramate in patients with refractory partial epilepsy receiving the drug as add-on therapy. To exclude effects related to the other drugs and to epilepsy itself, we compared data from patients and healthy volunteers. After receiving topiramate, 22.6% of patients became seizure free and 29% had their seizures reduced by 50% or more. Topiramate nevertheless induced noteworthy adverse reactions, the main problems being sedative and cognitive changes. Also, in healthy volunteers, a single 100-mg dose of topiramate induced mild adverse reactions, mainly affecting concentration and attention, with difficulties in speech and writing. In patients with epilepsy, the EEG changes induced by topiramate consisted of increased delta and theta activities and decreased activity in the rapid bands. This recognizable topiramate-induced EEG pattern was again evident in the healthy volunteers, in whom we also detected a significant reduction in the alpha frequency rhythm. ***Our results confirm that topiramate needs to be introduced gradually while patients undergo close neuropsychologic and neurophysiologic monitoring to detect adverse sedative and cognitive reactions early. The EEG correlate of these events seems to be increased activity in the slower frequency bands***.

Comparison of the effects of vigabatrin, lamotrigine, and topiramate on quantitative EEGs in patients with epilepsy.

Neufeld, M. Y., Kogan, E., Chistik, V., & Korczyn, A. D. (1999). Comparison of the effects of vigabatrin, lamotrigine, and topiramate on quantitative EEGs in patients with epilepsy. Clinical neuropharmacology, 22(2), 80–86. https://doi.org/10.1097/00002826-199903000-00003.

Abstract. Information on the effects of newer antiepileptic drug (AEDs) on the electroencephalogram (EEG) is sparse and contradictory. Quantitative EEG (qEEG) provides a method of estimating the effects of drugs on the central nervous system. Twenty-three adult patients with difficult-to-control complex partial seizures, with or without secondary generalization, participated in an add-on study with one of three newer AEDs: vigabatrin (n = 10), lamotrigine (n = 6), and topiramate (n = 7). Frequency analysis and topographic mapping of awake EEGs before and during treatment with the drug were compared. Statistical analysis was performed using 2-way analysis of variance (ANOVA) with repeated measures. Vigabatrin administration was followed by a diffuse decrease in the absolute alpha ($p < 0.05$) and beta ($p < 0.02$) activities and a decrease in the absolute theta in the frontal and parieto-occipital regions ($p < 0.03$). ***Lamotrigine caused a significant diffuse increase in the faster frequencies (relative***

alpha p < 0.04 and relative beta p < 0.02), and decrease in the slower activities (relative theta in the posterior head regions p < 0.03 and relative delta diffusely p < 0.05). Topiramate increased the absolute beta (p < 0.05) and theta (p < 0.02) activities diffusely and decreased the relative alpha activity over the left hemisphere (p < 0.03). The different effect profiles of the newer AEDs on the electrical brain activity may reflect their different mechanisms of action.

Topiramate effects on the EEG and alertness in healthy volunteers: a different profile of antiepileptic drug neurotoxicity.

Salinsky, M., Storzbach, D., Oken, B., & Spencer, D. (2007). Topiramate effects on the EEG and alertness in healthy volunteers: a different profile of antiepileptic drug neurotoxicity. Epilepsy & behavior : E&B, 10(3), 463–469. https://doi.org/10.1016/j.yebeh.2006.12.011

Objective: Previous quantitative EEG (QEEG) studies of carbamazepine (CBZ), oxcarbazepine (OXC), and phenytoin (PHT) revealed a pattern of EEG slowing and an increase in drowsiness on the awake maintenance task (AMT). EEG slowing has been shown to correlate with negative effects on cognitive tests. Topiramate (TPM) is a novel AED with relatively large negative effects on cognitive function. We tested the hypothesis that TPM would induce significant slowing of EEG background rhythms and an increase in AMT drowsiness. **Methods:** Forty healthy volunteers were randomized to TPM, gabapentin (GBP), or placebo. Doses were escalated as tolerated to a maximum of 400mg/day for TPM or 3600 mg/day for GBP, over a 10-week period, followed by a minimum 2-week plateau period. Volunteers underwent an EEG, cognitive tests, and the AMT prior to starting an AED and again 12 weeks later. The EEG was captured using a structured recording protocol and quantified using the fast Fourier transform. Four target measures were derived from the averaged occipital electrodes (peak frequency of the dominant posterior rhythm, median frequency, percentage theta, and percentage delta). Test-retest changes for all measures were scored against similar test-retest distributions previously obtained from untreated healthy volunteers. **Results:** ***TPM produced no significant change in any of the four target EEG measures or on the AMT, even though several target cognitive tests revealed moderate or greater negative effects. There were also no significant changes in the placebo group. GBP slowed the peak and median frequency EEG measures and increased the percentage of theta and delta activity. Neither TPM, GBP, nor placebo caused a significant increase in drowsiness on the AMT.*** **Conclusions:** TPM has a unique neurotoxicity profile. It has no effect on EEG background measures or on the AMT, but induces moderate to large negative changes in many cognitive test scores. This profile differs from those of CBZ, OXC, PHT, and GBP.

Quantitative EEG effects of topiramate.

Wang, W. W., Li, J. C., & Wu, X. (2003). Quantitative EEG effects of topiramate. Clinical EEG (electroencephalography), 34(2), 87–92. https://doi.org/10.1177/155005940303400208

Objective: The study is to invesigate the effect of topiramate (TPM) on EEG by means of quantitative pharmacoelectroencephalography (QPEEG). **Methods:** One dose of TPM was administrated to epileptics and healthy adults. The EEG samples were obtained prior to and at regular intervals within the 24 hours following the administration of TPM. The EEG activity was processed with power spectral analysis.

Results: ***The power of slow wave, alpha 1 bands and total power increased after the administration of TPM, the power or slow wave in both occipital areas, and the total power of all scalp areas also increased. The percent of power increased at the theta band and alpha 1 band (healthy adults) or delta band, theta band (patients).*** **Conclusion:** TPM can change the EEG background activity. These changes are different from other antiepileptic drugs.

----- VALPROATE -----
(Depacon, Depakote, Depakote CP, Depakote ER, Depakene, Divalproex, Epilim, Stavzor, Valproate sodium, Valproic acid)

DRUG FACTS

A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry

Aiyer, R., Novakovic, V., & Barkin, R. L. (2016). A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry. Postgraduate medicine, 128(7), 656–664. https://doi.org/10.1080/00325481.2016.1218261

Objectives: It is known that psychotropic medications have an impact on the readings found in Electroencephalogram (EEG). In the field of psychiatry, there are several psychotropics utilized by clinicians. This review seeks to investigate all the available data for psychotropic drugs and their impact on EEG changes. **Methods:** A systematic review of all the published and ongoing literature was conducted via PubMed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used for each search. Key words for searches include 'EEG and Psychotropics', 'EEG and Mood Stabilizers', 'EEG and Clozapine', 'EEG and Bupropion', 'EEG and SSRI', 'EEG and Lamotrigine', 'EEG and Carbamazepine', 'EEG and Lithium' and 'EEG and Valproate', 'EEG and Haloperidol', 'EEG and Aripiprazole', 'EEG and Methylphenidate', 'EEG and Topiramate', 'EEG and Gabapentin' and 'EEG and Oxcarbamazepine'. After applying the inclusion criteria, 201 articles were eligible and reviewed. **Results:** ***Following an extensive review of selected studies from the 201 articles, the studies indicate that each of the psychotropic medications reviewed impact alpha, beta, delta and theta waves independently and differently from each other. Additionally, certain medications, particularly haloperidol and valproic acid, have dissimilar results exemplified in all waveforms***. **Conclusions:** This PRISMA systematic review illustrates that while there is available data on psychotropic medications and their proposed effect on EEG activity, further research is needed to confirm these findings to help allow clinical correlations to be made between the patient's response and the psychotropic agent.

Effects of Sodium Valproate, Levetiracetam and Phenytoin Therapy on Evoked Potentials in Children with Epilepsy

Behgal, J., Rana, R., Lather, T., Bala, K., & Kaushik, J. S. (2019). Effects of Sodium Valproate, Levetiracetam and Phenytoin Therapy on Evoked Potentials in Children with Epilepsy. Indian journal of pediatrics, 86(9), 860. https://doi.org/10.1007/s12098-019-02906-7

Visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) have been used to study the effects of antiepileptic drugs (AED) on visual and auditory pathways among adults,

with limited studies on children [1,2,3,4]. This cross-sectional study included 36 children (aged 5–15 y) with epilepsy on AED for a duration, not less than 6 mo and 34 healthy controls. Antiepileptic drugs that were used included valproate (VPA) [14 (39%)], phenytoin (PHT) [11(31%)], and levetiracetam (LEV) (3(8%)]. Rest were on combination of VPA/ clobazam (CLB) [4 (11%)], VPA/LEV [2 (5.5%)] and VPA/LEV/CLB [2 (5.5%)]. Majority of the epilepsy was idiopathic [29 (81%)] followed by neurocysticercosis in the rest seven (19%) children. All children underwent flash VEP and BAEP as per the standard protocol. P-100 latency on both the sides were comparable among Children with epilepsy (CWE) and controls [right side: 99.8 (20.5) vs. 104.1 (15.7); p = 0.34; left side: 98.2 (25.8) vs. 104.5 (15.1); p = 0.25]. Similarly, P-100 amplitudes were comparable except for N75P100 amplitude being higher in CWE compared to controls [right side: 11.8 (6.94) vs. 8.71 (3.55); p = 0.02; left side: 11.3 (7.08) vs. 7.33 (4.03); p = 0.04]. Peak latencies of waves I, wave III, wave V and interpeak intervals I-III and I-V of BAEP were comparable between the two groups. ***AEDs decelerate central impulses and the transmission rate by increasing the effect of Gamma-aminobutyric acid (GABA) and causing sodium-channel blockade, resulting in prolonged latency of P100 as well as P300 [5]. Adult studies have demonstrated prolonged wave III/ V absolute latency and I-III/I-V inter-peak latency (IPL) on BAEP and prolonged P-100 latencies and decreased N75P100, P100N145 amplitudes on VEP among patients on PHT, VPA and LEV [1,2,3,4]. The present study revealed that most of the VEP and BAEP characteristics were comparable between children with epilepsy on VLP, LEV and PHT either alone or in combination when compared to healthy controls***. This study with a limited sample size shows that the use of conventional antiepileptic drugs for a duration of at least 6 mo in children with epilepsy are safe on the visual and auditory system.

Ethosuximide, sodium valproate or lamotrigine on EEG:

Brigo, F., Igwe, S. C., & Lattanzi, S. (2019). Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. *The Cochrane database of systematic reviews*, *2*(2), CD003032. https://doi.org/10.1002/14651858.CD003032.pub4

This is an updated version of the Cochrane Review previously published in 2017. Absence seizures (AS) are brief epileptic seizures which present in childhood and adolescence. Depending on clinical features and electroencephalogram (EEG) findings they are divided into typical, atypical absences, and absences with special features. Typical absences are characterised by sudden loss of awareness and an EEG typically shows generalised spike wave discharges at three cycles per second. Ethosuximide, valproate and lamotrigine are currently used to treat absence seizures. This review aims to determine the best choice of antiepileptic drug for children and adolescents with AS. **Objectives:** To review the evidence for the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures (AS), when compared with placebo or each other. **Selection criteria:** Randomised parallel group monotherapy or add-on trials which include a comparison of any of the following in children or adolescents with AS: ethosuximide, sodium valproate, lamotrigine, or placebo. **Data collection and analysis:** Outcome measures were: (1) proportion of individuals seizure free at one, three, six, 12 and 18 months post randomisation; (2) people with a 50% or greater reduction in seizure frequency; (3) normalisation of EEG and/or negative hyperventilation test; and (4) adverse effects. Data were independently extracted by two

review authors. Results are presented as risk ratios (RR) with 95% confidence intervals (95% CIs). We used GRADE quality assessment criteria to evaluate the certainty of evidence derived from all included studies. **Main results:** On the basis of our selection criteria, we included no new studies in the present review. Eight small trials (total number of participants: 691) were included from the earlier review. Six of them were of poor methodological quality (unclear or high risk of bias) and seven recruited less than 50 participants. There are no placebo-controlled trials for ethosuximide or valproate, and hence, no evidence from RCTs to support a specific effect on AS for either of these two drugs. ***Due to the differing methodologies used in the trials comparing ethosuximide, lamotrigine and valproate, we thought it inappropriate to undertake a meta-analysis. One large randomised, parallel double-blind controlled trial comparing ethosuximide, lamotrigine and sodium valproate in 453 children with newly diagnosed childhood absence epilepsy found that at 12 months, the freedom-from-failure rates for ethosuximide and valproic acid were similar and were higher than the rate for lamotrigine. The frequency of treatment failures due to lack of seizure control (P < 0.001) and intolerable adverse events (P < 0.037) was significantly different among the treatment groups, with the largest proportion of lack of seizure control in the lamotrigine cohort, and the largest proportion of adverse events in the valproic acid group. Overall, this large study demonstrates the superior effectiveness of ethosuximide and valproic acid compared to lamotrigine as initial monotherapy aimed to control seizures without intolerable adverse effects in children with childhood absence epilepsy.*** The risk of bias for this study was low. We rated the overall certainty of the evidence available from the included studies to be moderate or high. **Authors' conclusions:** Since the last version of this review was published, we have found no new studies. Hence, the conclusions remain the same as the previous update. With regards to both efficacy and tolerability, ethosuximide represents the optimal initial empirical monotherapy for children and adolescents with AS. However, if absence and generalised tonic-clonic seizures coexist, valproate should be preferred, as ethosuximide is probably inefficacious on tonic-clonic seizures.

Anti-Seizure Medication Meta Analysis on EEG:

Cheng, W., Yang, Y., Chen, Y., Shan, S., Li, C., Fang, L., Zhang, W., Lan, S., & Zhang, X. (2022). Anti-Seizure Medication Treatment of Benign Childhood Epilepsy With Centrotemporal Spikes: A Systematic Review and Meta-analysis. *Frontiers in pharmacology*, *13*, 821639. https://doi.org/10.3389/fphar.2022.821639

Objective: This study aimed to evaluate the efficacy and tolerability of Anti-Seizure medication (ASM) treatment in patients with BECTS. **Method:** We searched PubMed, Cochrane Library, Embase, MEDLINE, Web of Science, China National Knowledge Infrastructure (CNKI), WANFANG DATA, and China Science and Technology Journal Database (VIP) between 1 Jan 1990, and 1 Sep 2021, for randomized controlled studies. Data on seizure freedom rate, rate of treatment withdrawal due to serious adverse events, rate of any adverse events and dropout, 50% remission rate, the proportion of patients whose EEG to be normalized, and improvement in cognitive function were extracted by two authors independently. The pooled data were meta-analyzed using a random effects model. **Results:** A total of 27 studies evaluating 9 ASMs were included, 19 of which were suitable for meta-analysis. ***Compared with sulthiame (STM), levetiracetam (LEV) was associated with a higher probability of treatment withdrawal due to***

serious adverse events [RR = 5.12, 95% CI (1.19, 22.01), I^2 = 0.0%], experiencing any adverse events [RR = 5.12, 95% CI (1.19, 22.01)], and dropping out for any reason [RR = 3.17, 95% CI (1.36, 10.11)], while it did not affect the seizure freedom rate [RR = 0.90, 95% CI (0.75, 1.06)]. LEV significantly improved cognitive performance relative to carbamazepine (CBZ) but had no effect on the proportion of any adverse events [RR = 0.62, 95% CI (0.25, 1.59)] and EEG to be normalized [RR = 1.27, 95% CI (0.94, 1.71)]. There was no higher probability of a 50% remission rate when comparing valproic acid (VPA) to LEV [RR = 0.96, 95% CI (0.57, 1.61)] and oxcarbazepine (OXC) [RR = 0.61, 95% CI (0.31, 1.20)]. In addition, STM was related to a higher probability of EEG normalization than placebo [RR = 4.61, 95% CI (2.12, 10.01)]. The included single studies also provided some evidence for the efficacy and/or tolerability of other ASMs in BECTS, including topiramate, lamotrigine, clobazam, and clonazepam. The risk of bias of the included studies was frequently low or unclear. **Conclusion:** This study indicated some discrepancies in efficacy and tolerability among ASMs used in patients with BECTS. More randomized controlled trials (RCTs) comparing ASMs with larger populations are required to ascertain the optimum antiepileptic drug treatment to guide clinicians.

Role of gender and valproate use on EEG

Giuliano, L., Mainieri, G., Aguglia, U., Bilo, L., Durante, V., Ermio, C., Galimberti, C. A., La Neve, A., Monti, G., Ranzato, F., Zambrelli, E., & Mostacci, B. (2021). Long-term prognosis of juvenile myoclonic epilepsy: A systematic review searching for sex differences. Seizure, 86, 41–48. https://doi.org/10.1016/j.seizure.2021.01.005.

Purpose: Juvenile myoclonic epilepsy (JME), like other forms of idiopathic generalized epilepsy, shows a marked female predominance. However, few studies have specifically addressed the role of sex in its long-term prognosis. We performed a systematic review of the literature relevant to JME prognosis, focusing on sex-based differences in prognostic factors and outcome. **Methods:** A comprehensive literature search of the PubMed and Scopus databases was performed, considering all articles up to April 2020 in which long-term prognosis in JME had been explored and sex differences in outcome or prognostic factors were specified. **Results:** We included 25 articles published between 1984 and 2020. Sex differences in epilepsy outcome were explored by 21 of the 25 studies, but only three reported different outcomes in male vs female patients. ***All three found female sex to be associated with a later response to antiseizure medications, worse seizure control, and a higher risk of relapse in their entire study samples, which included JME patients. Eight studies found sex-based differences in possible predictors of long-term outcome: prolonged epileptiform EEG runs and the presence of eye closure sensitivity, both more frequent in women, were factors possibly linked to a poorer prognosis, as were praxis induction and generalized EEG asymmetric changes, which instead were more common in men. Valproate use, more frequent in men, was associated with a better outcome.*** **Conclusion:** Most studies do not highlight sex differences in JME prognosis. However, some sex specificities do emerge, especially with regard to particular reflex traits and EEG abnormalities. Finally, sex may condition therapeutic choices, and thus have a possible impact on long-term outcome.

Efficacy of levetiracetam for reducing rolandic discharges in comparison with carbamazepine and valproate sodium in rolandic epilepsy

Kanemura, H., Sano, F., Ohyama, T., & Aihara, M. (2018). Efficacy of levetiracetam for reducing rolandic discharges in comparison with carbamazepine and valproate sodium in rolandic epilepsy. Seizure, 62, 79–83. https://doi.org/10.1016/j.seizure.2018.10.002

Purpose: The main purpose of this study was to compare the efficacy of levetiracetam (LEV) with the older antiepileptic drugs (AEDs) for preventing atypical evolution in children with Rolandic epilepsy (RE). Accordingly, the present study compared the efficacy of older AEDs (carbamazepine (CBZ) and valproate sodium (VPA)) with LEV in reducing rolandic discharges (RDs) on interictal electroencephalogram (EEG) in children with RE. **Methods:** Patients in this heterogenous study were subdivided into CBZ, VPA and LEV groups in accordance with the initial monotherapy. The CBZ and VPA groups were studied retrospectively, but the LEV group was studied prospectively. Appearances of discharges were counted and these rates were computed. In comparison with the baseline RD frequency, EEG response to AED treatment was classified such as complete disappearance and response (≥50% reduction in RD frequency). The time taken to attain complete disappearance or response in EEG responders was assessed for each AED treatment group. **Results:** Responders comprised 10 (11.2%) of the 89 patients treated with CBZ, 41 (56.2%) of the 73 patients with VPA, and 25 (71.4%) of the 35 patients with LEV. ***Mean interval to achievement of EEG response in the CBZ, VPA, and LEV groups were 36.3, 23.1, and 14.7 months, respectively. EEG response was achieved significantly more rapidly with LEV than with CBZ ($p < 0.001$) or VPA ($p < 0.005$). Seizure control was not significantly different in all 3 investigated drugs***. **Conclusions:** LEV seems to be superior to CBZ and VPA in its ability to suppress RDs in children with RE.

Treatment for the Benign Childhood Epilepsy With Centrotemporal Spikes: A Monocentric Study

Kessi, M., Yan, F., Pan, L., Chen, B., Olatoutou, E., Li, D., He, F., Rugambwa, T., Yang, L., Peng, J., & Yin, F. (2021). Treatment for the Benign Childhood Epilepsy With Centrotemporal Spikes: A Monocentric Study. Frontiers in neurology, 12, 670958. https://doi.org/10.3389/fneur.2021.670958

Background and Purpose: To date, there is no specific treatment guideline for the benign childhood epilepsy with centrotemporal spikes (BECTS). Several countries recommend levetiracetam, carbamazepine, sodium valproate, oxcarbazepine, and lamotrigine as first-line drugs. Nevertheless, some of these drugs are associated with cognitive decline. Available studies that investigated the efficacy of levetiracetam and sodium valproate on BECTS involved small sample sizes. This study aimed to evaluate the efficacy of levetiracetam and sodium valproate on cognition, and to investigate the prognostic factors for BECTS as whole. **Methods:** Clinical data and treatment status of all patients with BECTS at Xiangya Hospital, Central South University followed from 2008 to 2013 were analyzed retrospectively. Since electrical status epilepticus in sleep (ESES) has been confirmed to play a role in cognitive deterioration, in order to evaluate the response to drugs and their cognitive effects, we created two groups of patients according to the levels of spike wave index (SWI): group 1; 0-50% SWI and group 2; >50% SWI at the last follow up. **Results:** A total of 195 cases were enrolled: 49.7% received monotherapies, 24.1% duotherapies and 27.2% polytherapies. Medications included; levetiracetam plus other

drug (s) (75.9%), levetiracetam alone (32.8%), sodium valproate plus other drug (s) (31.3%), and sodium valproate alone (5.1%). After 2 years of treatment and follow up, ***71% of the cases had a good seizure outcome, 15.9% had an improvement of SWI, and 91.7% had a normal DQ/IQ. Sodium valproate combined with levetiracetam, and sodium valproate alone correlated with good improvement of SWI, whereas, focal spikes were linked with poor improvement. For both groups (group 1 and group 2): monotherapy, levetiracetam alone, and a normal DQ/IQ at seizure onset correlated with good cognitive outcomes, in contrast, polytherapy, sodium valproate plus other drug (s), levetiracetam plus sodium valproate, an initial SWI of ≥85%, and multifocal spikes were linked to cognitive deterioration***. **Conclusions:** Monotherapy, particularly levetiracetam seems to be a good first-line therapy which can help in normalizing the electroencephalograph and preventing cognitive decline. Polytherapy, mostly the administration of sodium valproate seems to relate with poor cognition, therefore, it is recommended to avoid it.

Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children

Liu, M. J., Su, X. J., Md, X. S., Wu, G. F., Zhang, Y. Q., Gao, L., Wang, W., Liao, J. X., Wang, H., Mai, J. N., Gao, J. Y., Shu, X. M., Huang, S. P., Zhang, L., & Zou, L. P. (2017). Clinical features of benign epilepsy of childhood with centrotemporal spikes in chinese children. Medicine, 96(4), e5623. https://doi.org/10.1097/MD.0000000000005623

This multicenter clinical trial was conducted to examine current practice of benign epilepsy with centrotemporal spikes and especially address the question that in what circumstances 1 antiepileptic drug (AED) should be preferred.Twenty-five medical centers participate in this clinical trial. The general information, clinical information, and treatment status were collected under the guidance of clinicians and then analyzed. Difference between different treatment groups was compared, and usefulness of the most commonly used AEDs was evaluated. A total of 1817 subjects were collected. The average age of the subject was 8.81 years. The average age of onset is 6.85 years (1-14 years). Male-to-female ratio is 1.13:1. A total of 62.9% of the patients are receiving monotherapies, and 10.6% are receiving multidrug therapy. Both age and course of disease of treated rolandic epilepsy (RE) patients are significantly different from those of untreated patients. ***Bilateral findings on electroencephalography (EEG) are less seen in patients with monotherapy compared with patients with multidrug therapy. Except for 25.4% patients not taking any AEDs, oxcarbazepine (OXC), sodium valproate (VPA), and levetiracetam (LEV) are the most commonly used 3 AEDs. VPA and LEV are commonly used in add-on therapy. OXC and LEV are more effective as monotherapy than VPA***. Age of onset of Chinese RE patients is 6.85 years. Bilateral findings on EEG could be a risk factor to require multidrug therapy. In Chinese patients, OXC, VPA, and LEV are most commonly used AEDs as monotherapy and OXC and LEV are more effective than VPA

Magnesium valproate and interictal paroxysmal EEG

Porras-Kattz, E., Harmony, T., Ricardo-Garcell, J., Galán, L., Fernández, T., Prado-Alcalá, R., Avecilla-Ramírez, G., Sánchez-Moreno, L., Barrera-Reséndiz, J., Corsi-Cabrera, M., & Valencia-Solís, E. (2011). Magnesium valproate in learning disabled children with

interictal paroxysmal EEG patterns: Preliminary report. Neuroscience letters, 492(2), 99–104. https://doi.org/10.1016/j.neulet.2011.01.065.

Previous studies have investigated whether routine use of antiepileptic drugs is adequate to improve cognitive abilities in children who are learning disabled not otherwise specified (LD NOS) and who display interictal paroxysmal patterns in the electroencephalogram (EEG) but do not have epilepsy, and the findings of these studies have been controversial. In the current study, 112 LD children without epilepsy were assessed; however, only 18 met the strict inclusion/exclusion criteria in order to obtain a homogeneous sample. These children showed interictal paroxysmal patterns in the EEG, and a randomized, double-blind trial was carried out on them. ***The children were treated with either magnesium valproate (MgV; 20mg/kg/day) or a placebo for six months, and differences in WISC subtests, in a computerized reading skills battery (BTL) and EEG recordings were evaluated between groups before and after the treatment period. Performance IQ score and several items of the BTL (rhymes and ordering of words) improved in children who received MgV, whereas no changes were observed in the placebo group.*** No changes in the number of interictal paroxysmal patterns were observed in any group; however increased EEG currents at 10.92 and 12.87Hz (alpha band) in posterior regions and decreased currents in frequencies within the theta band (3.90, 4.29 and 5.07Hz) in frontal regions and at 4.68 and 5.46Hz in the parietal cortex were observed, suggesting an improvement in EEG maturation.

The effects of levetiracetam, carbamazepine, and sodium valproate on P100 and P300 in epileptic patients

Tumay, Y., Altun, Y., Ekmekci, K., & Ozkul, Y. (2013). The effects of levetiracetam, carbamazepine, and sodium valproate on P100 and P300 in epileptic patients. Clinical neuropharmacology, 36(2), 55–58. https://doi.org/10.1097/WNF.0b013e318285f3da

Objective: Although the unfavorable effects of early antiepileptic drugs, valproic acid, and carbamazepine (CBZ) on cognitive functions and visual functions have been investigated, the unfavorable effects of levetiracetam (LEV) on cognitive and visual functions remain unknown. The aim of the present study is to investigate whether there is a difference between the adverse effects by comparing the P300 and P100 latencies of LEV with epileptic patients using CBZ or sodium valproate (VPA) and healthy subjects. Method: A control group of 20 healthy subjects and 53 patients receiving monotherapy with CBZ (n = 15), VPA (n = 14), and LEV (n = 24) who admitted to neurology policlinic for investigation and treatment were enrolled in this study. ***Visual evoked potentials and event-related evoked potentials were studied according to these groups. Standard "oddball paradigm" (unpredictable stimuli series) was used to obtain P300. Results: The P300 latencies of epileptic patients receiving CBZ, VPA, and LEV were longer compared with the control group, and the differences were statistically significant (P = 0.001, 0.001, and 0.03, respectively). The P300 latency of patients receiving LEV was significantly shorter than the group receiving CBZ and VPA with statistically significant difference (P < 0.01 for both). The P300 amplitude was lower in the groups receiving CBZ, VPA, and LEV compared with the control group, and the difference was statistically significant (P < 0.05). Conclusions: The present study shows that LEV disrupts P300 latency less than VPA and CBZ and does not prolong P100 as much as them.***

Resting-state fMRI revealed different brain activities responding to valproic acid and levetiracetam in benign epilepsy with central-temporal spikes

Zhang, Q., Yang, F., Hu, Z., Zhang, Z., Xu, Q., Dante, M., Wu, H., Li, Z., Li, Q., Li, K., & Lu, G. (2017). Resting-state fMRI revealed different brain activities responding to valproic acid and levetiracetam in benign epilepsy with central-temporal spikes. European radiology, 27(5), 2137–2145. https://doi.org/10.1007/s00330-016-4531-z

Objectives: Our aim was to investigate regional difference in brain activities in response to antiepileptic drug (AED) medications in benign epilepsy with central-temporal spikes (BECTS) using resting-state functional magnetic resonance imaging (fMRI). Methods: Fifty-seven patients with BECTS underwent resting-state fMRI scans after receiving either valproic acid (VPA) (n = 15), levetiracetam (LEV) (n = 21), or no medication (n = 21). fMRI regional homogeneity (ReHo) parameter among the three groups of patients were compared and were correlated with total doses of AED in the two medicated groups. Results: Compared with patients on no-medication, patients receiving either VPA or LEV showed decreased ReHo in the central-temporal region, frontal cortex, and thalamus. In particular, the VPA group showed greater ReHo decrease in the thalamus and milder in cortices and caudate heads compared with the LEV group. In addition, the VPA group demonstrated a negative correlation between ReHo values in the central-temporal region and medication dose. Conclusion: Both VPA and LEV inhibit resting-state neural activity in the central-temporal region, which is the main epileptogenic focus of BECTS. VPA reduced brain activity in the cortical epileptogenic regions and thalamus evenly, whereas LEV reduced brain activity predominantly in the cortices. Interestingly, VPA showed a cumulative effect on inhibiting brain activity in the epileptogenic regions in BECTS. ***Key points: • Regional differences in brain activity in response to different AEDs in BECTS. • AEDs inhibit resting-state neural activity in epileptogenic and subcortical regions in BECTS. • Valproic acid effect on the cortical epileptogenic regions and thalamus evenly. • Levetiracetam effect seen predominantly in cortices. • Valproic acid has a cumulative effect on inhibiting brain activity in epileptogenic regions.***

Valproate but not levetiracetam slows the EEG alpha peak frequency – A pharmaco-EEG study

Zöllner, J. P., Strzelczyk, A., Rosenow, F., & Kienitz, R. (2021). Valproate but not levetiracetam slows the EEG alpha peak frequency - A pharmaco-EEG study. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 132(6), 1203–1208. https://doi.org/10.1016/j.clinph.2021.02.392

Objective: Studies of the effect of valproate (VPA) on the background EEG have shown varying results. Therefore, we compared the effect of VPA and levetiracetam (LEV) on the EEG alpha peak frequency (APF). **Methods:** We retrospectively examined the APF in resting-state EEG of patients undergoing inpatient video-EEG monitoring (VEM) during withdrawal of VPA or LEV. ***We assessed APF trends by computing linear fits across individual patients' APF as a function of consecutive days, and correlated the APF and daily antiseizure medication (ASM) doses on a single-patient and group level.*** **Results:** ***The APF in the VPA-group significantly increased over days with falling VPA doses (p = 0.005, n = 13), but did not change significantly in the LEV-group (p = 0.47, n = 18). APF correlated negatively with daily ASM doses in the VPA-group (average of r = −0.74 ± 0.12 across patients, p = 0.0039), but not in the LEV-group (average of r = −0.17 ± 0.18 across patients, p = 0.4072).*** **Conclusions:** Our results suggest that VPA

treatment slows the APF. This APF reduction correlates with the daily dose of VPA and is not present in LEV treatment.

VIGABATRIN

DRUG FACTS

Comparison of the effects of vigabatrin, lamotrigine, and topiramate on quantitative EEGs in patients with epilepsy.

Neufeld, M. Y., Kogan, E., Chistik, V., & Korczyn, A. D. (1999). Comparison of the effects of vigabatrin, lamotrigine, and topiramate on quantitative EEGs in patients with epilepsy. Clinical neuropharmacology, 22(2), 80–86. https://doi.org/10.1097/00002826-199903000-00003.

Abstract. Information on the effects of newer antiepileptic drug (AEDs) on the electroencephalogram (EEG) is sparse and contradictory. Quantitative EEG (qEEG) provides a method of estimating the effects of drugs on the central nervous system. Twenty-three adult patients with difficult-to-control complex partial seizures, with or without secondary generalization, participated in an add-on study with one of three newer AEDs: vigabatrin (n = 10), lamotrigine (n = 6), and topiramate (n = 7). Frequency analysis and topographic mapping of awake EEGs before and during treatment with the drug were compared. Statistical analysis was performed using 2-way analysis of variance (ANOVA) with repeated measures. ***Vigabatrin administration was followed by a diffuse decrease in the absolute alpha ($p < 0.05$) and beta ($p < 0.02$) activities and a decrease in the absolute theta in the frontal and parieto-occipital regions ($p < 0.03$). Lamotrigine caused a significant diffuse increase in the faster frequencies (relative alpha $p < 0.04$ and relative beta $p < 0.02$), and decrease in the slower activities (relative theta in the posterior head regions $p < 0.03$ and relative delta diffusely $p < 0.05$). Topiramate increased the absolute beta ($p < 0.05$) and theta ($p < 0.02$) activities diffusely and decreased the relative alpha activity over the left hemisphere ($p < 0.03$). The different effect profiles of the newer AEDs on the electrical brain activity may reflect their different mechanisms of action***.

ANTIDEPRESSANTS

CLASS FACTS

SYNOPSIS: This class of drugs is usually prescribed to alleviate the symptoms of clinical depression, and may be second line for pain, and anxiety and panic disorders. The EEG has been studied prognostically to see if a particular class of antidepressant will be optimal of toxic. Patterns such as theta cordance (a measure of cerebral metabolism) are used to affirm treatment considerations.

A systematic review on EEG

Aiyer, R., Novakovic, V., & Barkin, R. L. (2016). *A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry*. Postgraduate medicine, 128(7), 656–664. https://doi.org/10.1080/00325481.2016.1218261

Objectives: It is known that psychotropic medications have an impact on the readings found in Electroencephalogram (EEG). In the field of psychiatry, there are several psychotropics utilized by clinicians. This review seeks to investigate all the available data for psychotropic drugs and their impact on EEG changes. Methods: A systematic review of all the published and ongoing literature was conducted via PubMed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used for each search. Key words for searches include 'EEG and Psychotropics', 'EEG and Mood Stabilizers', 'EEG and Clozapine', 'EEG and Bupropion', 'EEG and SSRI', 'EEG and Lamotrigine', 'EEG and Carbamazepine', 'EEG and Lithium' and 'EEG and Valproate', 'EEG and Haloperidol', 'EEG and Aripiprazole', 'EEG and Methylphenidate', 'EEG and Topiramate', 'EEG and Gabapentin' and 'EEG and Oxcarbamazepine'. After applying the inclusion criteria, 201 articles were eligible and reviewed.
Results: Following an extensive review of selected studies from the 201 articles, the studies indicate that each of the psychotropic medications reviewed impact alpha, beta, delta and theta waves independently and differently from each other. Additionally, certain medications, particularly haloperidol and valproic acid, have dissimilar results exemplified in all waveforms.
Conclusions: This PRISMA systematic review illustrates that while there is available data on psychotropic medications and their proposed effect on EEG activity, further research is needed to confirm these findings to help allow clinical correlations to be made between the patient's response and the psychotropic agent.

----- ATYPICAL ANTIDEPRESSANTS -----

DRUG CLASS

SYNOPSIS: Prescribed to affect neurotransmitter levels to alleviate depression, effects on the EEG vary based upon drug, presentation, and baseline EEG. It includes NDRIs, NaSSAs, SARIs, serotonin modulators, and NRIs.

----- NDRIs (Dopamine Norepinephrine Reuptake Inhibitors) -----

DRUG FACTS

SYNOPSIS: These reuptake receptor inhibitors provide more dopamine and norepinephrine availability. Bupropion is the only NDRI on the market today.

----- BUPROPION (Wellbutrin) -----

DRUG FACTS

SYNOPSIS: In addition to its antidepressant qualities, this medication can be prescribed to help with smoking and appetite suppression, and ADHD. High and over-doses may lead to seizures and deadly EEG burst suppression. Frontal alpha and theta behaviors, as well as a novel EEG analysis (ATR) can predict successful antidepressant type.

Antidepressant Treatment Response (ATR) algorithm to predict best antidepressant outcome

Cook, I. A., Hunter, A. M., Caudill, M. M., Abrams, M. J., & Leuchter, A. F. (2020). *Prospective testing of a neurophysiologic biomarker for treatment decisions in major depressive disorde*r: The PRISE-MD trial. *Journal of psychiatric research*, *124*, 159–165. https://doi.org/10.1016/j.jpsychires.2020.02.028

Management of Major Depressive Disorder (MDD) might be improved by a biomarker to predict whether a selected medication is likely to lead to remission. We previously reported on a quantitative electroencephalogram-based biomarker, the Antidepressant Treatment Response (ATR) index, that integrated recordings at baseline and after one week of treatment. The present study prospectively tested whether treatment directed by the biomarker increased the likelihood of remission; we hypothesized that continued treatment with a drug predicted to lead to remission (i.e., high ATR values) would be associated with better outcomes than if the drug was predicted not to lead to remission (i.e., low ATR values). We enrolled 180 adult outpatients with unipolar MDD from the community. ***After one week of escitalopram treatment to determine the biomarker, stratified randomization (high vs. low ATR [antidepressant treatment response]) was used to assign subjects to either continued escitalopram or a switch to bupropion as a blinded control condition, for seven additional weeks.*** For the 73 evaluable subjects assigned to continued escitalopram treatment, the remission rate was significantly higher for those in whom ATR had predicted remission versus non-remission (60.4% vs. 30.0%, respectively, p = 0.01). Accuracy was enhanced by combining 1-week depressive symptom change with ATR (68.6% vs 28.9%). This prospective validation study supports further development of the ATR biomarker, alone or together with early symptom change, to improve care by identifying individuals unlikely to remit with their current

treatment and support the decision to change treatment after one week rather than after failing a full, prolonged course of medication.
[from manuscript]: ***The three qEEG features incorporated into ATR were relative combined theta and alpha power (3–12 Hz), alpha1 absolute power (8.5–12 Hz), and alpha2 absolute power (9–11.5 Hz). Relative combined theta and alpha power (3–12 Hz) was calculated as the ratio of absolute combined theta and alpha power, divided by total power (2–20 Hz). ATR (version 4.1) employed a weighted combination of relative theta and alpha power at week 1, and the difference between alpha1 power at baseline and alpha2 power at week 1, scaled to range from 0 (low probability of remission) to 100 (high probability)***. This is the same computation of the ATR values as was used in the earlier studies (the same software was used in both projects); the electrode locations have been shifted to reduce exclusion of subjects for ECG-contamination of the ear electrodes.

Treatment success based upon baseline theta2 and alpha2 symmetry in rACC

Jaworska, N., Blondeau, C., Tessier, P., Norris, S., Fusee, W., Blier, P., & Knott, V. (2014). *Examining relations between alpha power as well as anterior cingulate cortex-localized theta activity and response to single or dual antidepressant pharmacotherapies*. Journal of psychopharmacology (Oxford, England), 28(6), 587–595. https://doi.org/10.1177/0269881114523862

Electrocortical indices may be useful in predicting antidepressant response. Greater pretreatment alpha power and high rostral anterior cingulate cortex (rACC) theta activity tend to index a favorable outcome. The predictive utility of alpha power asymmetry has been under-explored. ***Baseline alpha2 (10.5-13.0 Hz) power/asymmetry, rACC theta2 (6.0-8.0 Hz) activity and early (one week) changes in these measures were assessed in relation to antidepressant response by week 12 to three treatment regimens (escitalopram (ESC) + bupropion (BUP), ESC or BUP) in patients with major depressive disorder (N=51). No treatment differences in response existed at week 12. Overall, treatment responders exhibited high, and non-responders low, frontal baseline alpha2 power. Frontal alpha2 power weakly discriminated responders/non-responders overall while posterior alpha2 power and BA25-localized theta2 activity strongly discriminated ESC responders/non-responders. No associations with alpha2 asymmetry and response emerged. BUP responders exhibited high, and BUP non-responders low, baseline rACC theta2 activity. Greater early decreases in rACC theta2 activity existed in ESC+BUP non-responders versus ESC+BUP responders. BUP responders exhibited greater rACC theta2 activity decreases than ESC responders. These preliminary results indicate that baseline and early changes in alpha2 and rACC theta2 activity associate with response and have implications for tailoring antidepressant treatments.***

Single case drug toxicity and burst suppression in EEG

Mundi, J. P., Betancourt, J., Ezziddin, O., Tremayne, B., Majic, T., & Mosenifar, Z. (2012). Dilated and Unreactive Pupils and Burst-Suppression on Electroencephalography due to Buproprion Overdose. Journal of Intensive Care Medicine, 27(6), 384–388. https://doi.org/10.1177/0885066611429661

Burst-suppression pattern on electroencephalography (EEG) occurs upon dissociation of the cortex from underlying brain structures. Unless the pattern is a physiologic consequence of

administered sedatives, this electroencephalographic pattern is indicative of a poor neurologic outcome and high mortality. We report a case of a 29-year-old female thought to be brain dead based on initial physical examination and EEG findings of burst-suppression, who was later found to have supratherapeutic serum levels of bupropion. This is the second documented case of burst-suppression pattern on EEG in a patient who overdosed on bupropion. We propose that burst-suppression in the setting of bupropion toxicity may revert with drug clearance.

Antidepressant Treatment Response (ATR) algorithm to predict best antidepressant outcome

Cook, I. A., Hunter, A. M., Caudill, M. M., Abrams, M. J., & Leuchter, A. F. (2020). *Prospective testing of a neurophysiologic biomarker for treatment decisions in major depressive disorde*r: The PRISE-MD trial. *Journal of psychiatric research*, *124*, 159–165. https://doi.org/10.1016/j.jpsychires.2020.02.028

Management of Major Depressive Disorder (MDD) might be improved by a biomarker to predict whether a selected medication is likely to lead to remission. We previously reported on a quantitative electroencephalogram-based biomarker, the Antidepressant Treatment Response (ATR) index, that integrated recordings at baseline and after one week of treatment. The present study prospectively tested whether treatment directed by the biomarker increased the likelihood of remission; we hypothesized that continued treatment with a drug predicted to lead to remission (i.e., high ATR values) would be associated with better outcomes than if the drug was predicted not to lead to remission (i.e., low ATR values). We enrolled 180 adult outpatients with unipolar MDD from the community. ***After one week of escitalopram treatment to determine the biomarker, stratified randomization (high vs. low ATR [antidepressant treatment response]) was used to assign subjects to either continued escitalopram or a switch to bupropion as a blinded control condition, for seven additional weeks.*** For the 73 evaluable subjects assigned to continued escitalopram treatment, the remission rate was significantly higher for those in whom ATR had predicted remission versus non-remission (60.4% vs. 30.0%, respectively, p = 0.01). Accuracy was enhanced by combining 1-week depressive symptom change with ATR (68.6% vs 28.9%). This prospective validation study supports further development of the ATR biomarker, alone or together with early symptom change, to improve care by identifying individuals unlikely to remit with their current treatment and support the decision to change treatment after one week rather than after failing a full, prolonged course of medication.

[from manuscript]: ***The three qEEG features incorporated into ATR were relative combined theta and alpha power (3–12 Hz), alpha1 absolute power (8.5–12 Hz), and alpha2 absolute power (9–11.5 Hz). Relative combined theta and alpha power (3–12 Hz) was calculated as the ratio of absolute combined theta and alpha power, divided by total power (2–20 Hz). ATR (version 4.1) employed a weighted combination of relative theta and alpha power at week 1, and the difference between alpha1 power at baseline and alpha2 power at week 1, scaled to range from 0 (low probability of remission) to 100 (high probability)***. This is the same computation of the ATR values as was used in the earlier studies (the same software was used in both projects); the electrode locations have been shifted to reduce exclusion of subjects for ECG-contamination of the ear electrodes.

----- NaSSAs (Noradrenergic & Specific Serotonin Antidepressant) -----

DRUG FACTS

---- MIRTAZAPINE (Remeron) ----

DRUG FACTS

SYNOPSIS: These alpha-2-adrenergic receptors increase serotonin and norepinephrine and are generally used for pain, anxiety, panic, headaches, and OCD, as well as appetite stimulation. It has a sedative effect, and this is present in the sleep EEG during slow wave sleep in delta, theta, and alpha.

Comparison of multiple antidepressants on the effects on slow wave sleep

Schmid, D. A., Wichniak, A., Uhr, M., Ising, M., Brunner, H., Held, K., Weikel, J. C., Sonntag, A., & Steiger, A. (2006). Changes of Sleep Architecture, Spectral Composition of Sleep EEG, the Nocturnal Secretion of Cortisol, ACTH, GH, Prolactin, Melatonin, Ghrelin, and Leptin, and the DEX-CRH Test in Depressed Patients during Treatment with Mirtazapine. Neuropsychopharmacology (New York, N.Y.), 31(4), 832–844. https://doi.org/10.1038/sj.npp.1300923

The noradrenergic and specific serotoninergic antidepressant mirtazapine improves sleep, modulates hormone secretion including blunting of hypothalamic-pituitary-adrenocortical (HPA) activity, and may prompt increased appetite and weight gain. The simultaneous investigation of sleep electroencephalogram (EEG) and hormone secretion during antidepressive treatment helps to further elucidate these effects. We examined sleep EEG (for later conventional and quantitative analyses) and the nocturnal concentrations of cortisol, adrenocorticotropin (ACTH), growth hormone (GH), prolactin, melatonin and the key factors of energy balance, ghrelin, and leptin before and after 28 days of treatment of depressed patients (seven women, three men, mean age 39.9+/-4.2 years) with mirtazapine. In addition, a sleep EEG was recorded at day 2 and the dexamethasone-corticotropin-releasing hormone (DEX-CRH) test was performed to assess HPA activity at days -3 and 26. Psychometry and mirtazapine plasma concentrations were measured weekly. ***Already at day 2, sleep continuity was improved. This effect persisted at day 28, when slow-wave sleep, low-delta, theta and alpha activity***, leptin and (0300-0700) melatonin increased, and cortisol and ghrelin decreased. ACTH and prolactin remained unchanged. The first two specimens of GH collected after the start of quantitative EEG analysis were reduced at day 28. The DEX-CRH test showed, at day 26, a blunting of the overshoot of ACTH and cortisol found at day -3. The Hamilton Depression score decreased from 32.1+/-7.3 to 15.5+/-6.7 between days -1 and 28. A weight gain of approximately 3 kg was observed. This unique profile of changes is compatible with the action of mirtazapine at 5-HT-2 receptors, at presynaptic adrenergic alpha 2 receptors, at the HPA system, and on ghrelin and leptin.

Some EEG abnormalities, but no epileptiform activity

Sterr, A., Padberg, F., Mergl, R., Amann, B., Mulert, C., Juckel, G., Grunze, H., Hegerl, U., & Pogarell, O. (2004). EEG abnormalities associated with antidepressant treatment: A

comparison of mirtazapine, citalopram, venlafaxine, reboxetine and amitriptyline. Pharmacopsychiatry. https://doi.org/10.1055/s-2003-825522

Objectives: Abnormalities in electroencephalography (EEG) recordings may occasionally occur during treatment with antipsychotics. In contrast, limited data are available regarding antidepressants. We investigated EEG changes in patients receiving a stable monotherapy with mirtazapine, citalopram, reboxetine, venlafaxine, amitriptyline. Methods: Digital EEG recordings of 255 patients (80-mirtazapine, 58-citalopram, 22-reboxetine, 50-venlafaxine, 45-amitriptyline) were retrieved from a database and visually interpreted by two independent raters. Results: There was no statistically significant difference between groups regarding the frequency of ***EEG-abnormalities, which were found in 6(7.5%) patients with mirtazapine***, 4(6.9%) with citalopram, none with reboxetine, 9(18%) with venlafaxine, and 5(11.1%) with amitriptyline. Epileptiform activity was not observed in any group. Conclusion: ***Mildly abnormal EEG patterns may occur but are generally rare during antidepressive monotherapy. However, a higher frequency of abnormalities may be observed with venlafaxine or amitriptyline. No epileptiform EEG activity was observed as previously reported for mirtazapine***.

----- SARIs (Serotonin Agonists and Reuptake Inhibitors) -----

DRUG FACTS

SYNOPSIS: This class of drug will encourage serotonin manufacture as well as availability while inhibiting receptor action.

----- NEFAZODONE (Desyrel) -----

DRUG FACTS

SYNOPSIS: This drug was removed from the US market in 2003 due to its high level of liver toxicity. It does not affect sleep EEG, which is negatively correlated with nightmare and other sleep patient reporting. As well, it has an opposite effect on the EEG to fluoxetine.

No effect on polysomnographic EEG recordings

Gillin, J. C., Smith-Vaniz, A., Schnierow, B., Rapaport, M. H., Kelsoe, J., Raimo, E., Marler, M. R., Goyette, L. M., Stein, M. B., & Zisook, S. (2001). An open-label, 12-week clinical and sleep EEG study of nefazodone in chronic combat-related posttraumatic stress disorder. The Journal of clinical psychiatry, 62(10), 789–796. https://doi.org/10.4088/jcp.v62n1007

Background: We examined the effects of nefazodone on polysomnographic sleep measures and subjective reports of sleep quality and nightmares. as well as other symptoms, in patients with chronic combat-related posttraumatic stress disorder (PTSD) during a 12-week, open-label clinical trial. To our knowledge, this is the first polysomnographic study of treatment in patients with PTSD. Method: The subjects were 12 male veterans (mean age = 54 years) who met DSM-IV diagnostic criteria for PTSD (mean duration = 30 years). All but I patient also met DSM-IV criteria for major depressive disorder. Patients were evaluated weekly with clinical ratings in an open-label clinical trial. Polysomnographic recordings for 2 consecutive nights were obtained before treatment and at 2, 4, 8, and 12 weeks. The dose of nefazodone was adjusted according

to individual clinical needs. Final mean daily dose was 441 mg. Results: ***The patients reported significantly fewer nightmares and sleep problems during treatment. Nevertheless, contrary to studies in depressed patients, nefazodone did not significantly affect polysomnographic sleep measures compared with baseline***. In addition, the patients showed significant improvement in the Clinical Global Impressions of PTSD symptoms (global score, hyperarousals and intrusions subscales), the Clinician-Administered PTSD Scale (global, hyperarousal, and intrusions subscales), the Hamilton Rating Scale for Depression (HAM-D). and the Beck Depression Inventory (BDI). Conclusion: These patients with chronic, treatment-resistant, combat-related PTSD showed significant improvement of subjective symptoms of nightmares and sleep disturbance, as well as depression and PTSD symptoms. in this 12-week open-label clinical trial. Nevertheless, objective polysomnographic sleep measures did not change. Further studies, including double-blind. placebo-controlled trials, are needed to extend these findings and to understand the relationships between the physiology of sleep and symptoms of poor sleep and nightmares.

Differing effects on sleep EEG than fluoxetine

Rush, A. J., Armitage, R., Gillin, J. C., Yonkers, K. A., Winokur, A., Moldofsky, H., Vogel, G. W., Kaplita, S. B., Fleming, J. B., Montplaisir, J., Erman, M. K., Albala, B. J., & McQuade, R. D. (1998). Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biological psychiatry, 44(1), 3–14. https://doi.org/10.1016/s0006-3223(98)00092-4

Background: Sleep disturbances are common in major depressive disorder. In previous open-label trials, nefazodone improved sleep continuity and increased rapid eye movement (REM) sleep, while not affecting stage 3/4 sleep or REM latency: in contrast, fluoxetine suppressed REM sleep. This study compared the objective and subjective effects of nefazodone and fluoxetine on sleep. Methods: This paper reports combined results of three identical, multisite, randomized, double-blind, 8-week, acute-phase trials comparing nefazodone (n = 64) with fluoxetine (n = 61) in outpatients with nonpsychotic major depressive disorder and insomnia. Sleep electroencephalographic (EEG) recordings were gathered at baseline and weeks 2, 4, and 8. Clinical ratings were obtained at weeks 1-4, 6, and 8. Results: ***Nefazodone and fluoxetine were equally effective in reducing depressive symptoms; however, nefazodone differentially and progressively increased (while fluoxetine reduced) sleep efficiency and reduced (while fluoxetine increased) the number of awakenings in a linear fashion over the 8-week trial. Fluoxetine, but not nefazodone, prolonged REM latency and suppressed REM sleep. Nefazodone significantly increased total REM sleep time.*** Clinical evaluations of sleep quality were significantly improved with nefazodone compared with fluoxetine. Conclusions: Nefazodone and fluoxetine were equally effective antidepressants. Nefazodone was associated with normal objective, and clinician- and patient-rated assessments of sleep when compared with fluoxetine. These differential sleep EEG effects are consistent with the notion that nefazodone and fluoxetine may have somewhat different modes and spectra of action.

----- TRAZODONE (Desyrel) -----

DRUG FACTS

SYNOPSIS: Widely prescribed as a sleep medication, it will increase slow wave sleep and has no effect on the REM cycle.

Effects on sleep

Suzuki, H., Yamadera, H., Nakamura, S., & Endo, S. (2002). Effects of Trazodone and Imipramine on the Biological Rhythm: An Analysis of Sleep EEG and Body Core Temperature. Journal of Nippon Medical School = Nippon Ika Daigaku Zasshi, 69(4), 333–341. https://doi.org/10.1272/jnms.69.333

Depression commonly involves abnormalities of the sleep-wake rhythm, the temperature rhythm, and other biological rhythms. The changes of these biological rhythms are caused in remission by medications. However, it has yet to be clarified whether the biological rhythms are changed as a result of recovery from depression or from the direct pharmacological effects of the antidepressants. Therefore, we have undertaken a study on the direct effects of the antidepressants trazodone and imipramine on the biological rhythms of healthy volunteers. The study involved 12 healthy male volunteers (ages 21～28 years, mean age 23.9±1.7 years) who had given written informed consent. Placebo, trazodone, and imipramine were each administered in a single blind manner four times a day, during the three-day study period. The total daily dosage of trazodone was 100 mg (50 mg in one subject), and of imipramine 40 mg (20 mg in one subject). Subjects were submitted to polysomnography (PSG) and body core temperature (rectal temperature) measurements during the study period. We compared the data concerning the antidepressants to those of the placebo. ***The results show that, with regard to the sleep rhythm, trazodone significantly increased slow wave sleep (SWS), but no changes were observed in REM (rapid eye movement) sleep.*** Imipramine significantly decreased REM sleep and prolonged the REM cycle. With regard to the temperature rhythm, trazodone showed a tendency to advance the appearance time of the minimal temperature. Imipramine significantly lowered the maximal temperature and decreased the difference between the maximal and the minimal temperature, but no changes in the phases were observed. Neither antidepressant had any effect on the temperature cycle. Trazodone and imipramine showed different effects on PSG. Furthermore, they had different effects on the temperature rhythm. The changes of the sleep-wake rhythm were greater than those of the temperature rhythm. Although the two antidepressants had different mechanisms of action, it is worthy of note that both directly influenced the biological rhythms of healthy volunteers.

----- SEROTONIN MODULATORS -----

DRUG FACTS

SYNOPSIS: This drug class can treat depression, anxiety, eating disorders, fibromyalgia and PMS.

----- VILAZODONE (Viibryd)-----

DRUG FACTS

SYNOPSIS: A 5-HT_{1A} partial agonist prescribed for MDD. It is not commonly prescribed due to a high rate of side effects. According to Biomarkers of Psychiatric Disorders (Turck, C), REM sleep was essentially eliminated and other stages were negatively impacted.

----- VORTIOXETINE (Trintellex)

DRUG FACTS

SYNOPSIS: An SRI that targets many receptors, it is known to increase vigilance and will increase theta, alpha, and gamma power. The latter may be affected in EPs. Frontal cortical delta, alpha and gamma EEG is increased.

Leiser, S. C., Pehrson, A. L., Robichaud, P. J., & Sanchez, C. (2014). Multimodal antidepressant vortioxetine increases frontal cortical oscillations unlike escitalopram and duloxetine--a quantitative EEG study in rats. British journal of pharmacology, 171(18), 4255–4272. https://doi.org/10.1111/bph.12782

Background and purpose: EEG studies show that 5-HT is involved in regulation of sleep-wake state and modulates cortical oscillations. Vortioxetine is a 5-HT3 , 5-HT7 , and 5-HT1D receptor antagonist, 5-HT1B partial agonist, 5-HT1A agonist, and 5-HT transporter inhibitor. Preclinical (animal) and clinical studies with vortioxetine show positive impact on cognitive metrics involving cortical function. Here we assess vortioxetine's effect on cortical neuronal oscillations in actively awake rats. Experimental approach: Telemetric EEG recordings were obtained with the following treatments (mg·kg(-1) , s.c.): vehicle, vortioxetine (0.1, 1.0, 3.0, 10), 5-HT1A agonist flesinoxan (2.5), 5-HT3 antagonist ondansetron (0.30), 5-HT7 antagonist SB-269970-A (10), escitalopram (2.0), duloxetine (10) and vortioxetine plus flesinoxan. Target occupancies were determined by ex vivo autoradiography. Key results: Vortioxetine dose-dependently increased wakefulness. Flesinoxan, duloxetine, ondansetron, but not escitalopram or SB-269970-A increased wakefulness. Quantitative spectral analyses showed vortioxetine alone and with flesinoxan increased θ (4-8 Hz), α (8-12 Hz) and γ (30-50 Hz) power. Duloxetine had no effect on θ and γ, but decreased α power, while escitalopram produced no changes. Ondansetron and SB-269970 (≈31-35% occupancy) increased θ power. Flesinoxan (≈41% occupancy) increased θ and γ power. Conclusions and implications: ***Vortioxetine increased wakefulness and increased frontal cortical activity, most likely because of its 5-HT7 and 5-HT3 antagonism and 5-HT1A agonism. Vortioxetine differs from escitalopram and duloxetine by increasing cortical ϑ, α and γ oscillations.*** These preclinical findings suggest a role of vortioxetine in modulating cortical circuits known to be recruited during cognitive behaviours and warrant further investigation as to their clinical impact.

Decreased evoked gamma

T Nissen, T. D., Laursen, B., Viardot, G., l'Hostis, P., Danjou, P., Sluth, L. B., Gram, M., Bastlund, J. F., Christensen, S. R., & Drewes, A. M. (2020). Effects of Vortioxetine and Escitalopram on Electroencephalographic Recordings - A Randomized, Crossover Trial in Healthy Males. Neuroscience, 424, 172–181. https://doi.org/10.1016/j.neuroscience.2019.09.039

The antidepressant drug vortioxetine has a multimodal action modulating neurotransmission through inhibition of the serotonin transporter and modulation of serotonin receptors. Vortioxetine has also been shown to alleviate cognitive symptoms in preclinical studies and in patients with depression. However, it is largely unclear how vortioxetine affects the brain processing in humans. The present study was conducted in 32 healthy males in a randomized, double-blinded, placebo-controlled, active comparator, four-way crossover design. Treatments were 10 and 20 mg/day vortioxetine, 15 mg/day escitalopram, and placebo, administered orally once daily for three days. Results were compared to placebo. Treatment effect was assessed by recording spontaneous electroencephalography (EEG) and 40 Hz auditory steady state responses. For the spontaneous EEG, both vortioxetine and escitalopram decreased the frequency content in the theta band (4-8 Hz) and increased power in the beta (12-32 Hz) and gamma (32-45 Hz) bands. Vortioxetine and escitalopram decreased connectivity during rest in the theta band and increased connectivity in the gamma bands. ***Finally, both treatments caused decreased power in the evoked gamma band in response to 40 Hz auditory stimulation. Although the global EEG changes were comparable between vortioxetine and escitalopram, subtle differences between treatment effects on the EEG in terms of effect size and regional distribution of the EEG changes were apparent.*** To our knowledge, the current results are the first data on how vortioxetine affects EEG in humans. The present study calls for further investigations addressing the possible electrophysiological and cognitive effects of vortioxetine.

----- NRIs (Norepinephrine Reuptake Inhibitors) -----

DRUG FACTS

SYNOPSIS: Prescribed for depression, narcolepsy, obesity, and ADHD, this class of drug has differing power effects to amphetamines in the frontal regions. It may elevate gamma during EPs, cause temporal slowing or normalize theta cordance. Alpha power may be a good predictor for drug success.

----- ATOMOXETINE (Strattera) -----

DRUG FACTS

SYNOPSIS: While considered an antidepressant, this drug is usually prescribed to ADHD when traditional amphetamines are not indicated. This drug will increase global beta power but may cause temporal focal slowing. Decreased theta cordance may normalize upon drug ingestion. The frontal site differences with amphetamines may confirm medication choice.

Frontal site differences with amphetamines may confirm medication choice.

Aldemir, R., Demirci, E., Bayram, A., Canpolat, M., Ozmen, S., Per, H. & Tokmakci, M. (2018). Evaluation of two types of drug treatment with QEEG in children with ADHD. Translational Neuroscience, 9(1), 106-116. https://doi.org/10.1515/tnsci-2018-0017

Aims: The aim of this study is to evalute the effects of methylphenidate and atomoxetine treatments on electroencephalography (EEG) signals in volunteer children diagnosed with Attention Deficit and Hyperactivity Disorder (ADHD). Methods: The study contained 40 children all of whom were between the ages of 7 and 17. The participants were classified into two groups as ADHD (n=20), which was in itself divided into two groups as ADHD-MPH (ADHD-Metylphenidate treatment) (n=10) and as ADHD-ATX (ADHD-Atomoxetin treatment) (n=10), and one control group (n=20). Following the first EEG recordings of the ADHD group, long-acting methylphenidate dose was applied to one ADHD group and atomoxetine dose was applied to the other ADHD group. The effect of optimal dosage is about for 4-6 weeks in general. Therefore, the response or lack of response to the treatment was evaluated three months after the beginning of the treatment. After methylphenidate and atomoxetine drug treatment, in order to obtain mean and maximum power values for delta, theta, alpha and beta band, the EEG data were analyzed. Results: ***The EEG power spectrum densities in all the bands yielded similar findings in both methylphenidate and atomoxetine. Although statistically significant frequency values of the electrodes were amplitude and maximally varied, in general, they appeared mostly at both frontal and temporal regions for methylphenidate and atomoxetine. Conclusion: Especially, after atomoxetine treatment, Quantitative Electroencephalography (QEEG) rates at frontal area electrodes were found statistically more significant than methylphenidate QEEG rates.*** What has been researched in this study is not only whether QEEG is likely to support the diagnosis, but whether changes on QEEG by treatment may be related to the severity of ADHD as well.

Increases global beta power

Barry, R. J., Clarke, A. R., Hajos, M., McCarthy, R., Selikowitz, M., & Bruggemann, J. M. (2009). Acute atomoxetine effects on the EEG of children with attention-deficit/hyperactivity disorder. Neuropharmacology, 57(7-8), 702–707. https://doi.org/10.1016/j.neuropharm.2009.08.003

Although stimulant medications are the most commonly-used treatments for Attention-Deficit/Hyperactivity Disorder (AD/HD), as many as 20% of treated children do not respond clinically to stimulants. This study investigated the effects of an acute dose of atomoxetine, a selective noradrenaline reuptake inhibitor (SNRI), on the electroencephalogram (EEG) and performance of children with AD/HD. An initial pre-medication EEG was recorded during an eyes-closed resting condition. Within two weeks, a second EEG was recorded 1 h after ingestion of 20 mg of atomoxetine. Data were Fourier transformed to provide absolute and relative power estimates for the delta, theta, alpha, beta and gamma bands. Compared to controls, the unmedicated AD/HD children had significantly elevated global absolute and relative delta, with reduced global relative alpha, and absolute and relative gamma, and many topographic differences. ***Atomoxetine produced significant global increases in absolute and relative beta, with several topographic changes in other bands, and a significant reduction in omission***

errors on a Continuous Performance Task. These results indicate that SNRIs can produce substantial normalisation of the AD/HD EEG profile, together with behavioural performance improvements. Although EEG changes induced by acute administration of psychostimulants (methylphenidate/dexamphetamine) and atomoxetine are not identical, both classes of AD/HD drugs produce similar EEG band changes. Further analysis of EEG responses to SNRIs and psychostimulants could reveal common neurophysiological processes closely linked to clinical improvement of AD/HD symptoms in response to pharmacotherapy, providing translational markers for clinical efficacy studies and potential translational biomarkers for AD/HD drug discovery.

Elevated alpha band may be a predictor of drug success

Chiarenza, G. A., Chabot, R., Isenhart, R., Montaldi, L., Chiarenza, M. P., Torto, M. G., & Prichep, L. S. (2016). The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders. International journal of psychophysiology : official journal of the International Organization of Psychophysiology, 104, 44–52. https://doi.org/10.1016/j.ijpsycho.2016.04.004

Objective: The aim of our study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are responders and non-responders to long-term treatment with Atomoxetine at baseline and after 6 and 12months of treatment. Patients with attention deficit hyperactivity disorder (ADHD) received atomoxetine titrated, over 7days, from 0.5 to 1.2mg/kg/day. QEEG and Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy. Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked earlobes. ***Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values. Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values. Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine.*** Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta.

May cause temporal focal slowing

Finsterer, J., & Scorza, F. A. (2020). Atomoxetine-induced focal seizures with contralateral hypoperfusion and hyper-CKemia. Radiology case reports, 16(2), 369–371. https://doi.org/10.1016/j.radcr.2020.11.049

One of the drugs used to treat attention deficit hyperactivity syndrome is atomoxetine. Usually, the drug is well tolerated but in rare cases adverse advents may occur. An 18-year-old female

under atomoxetine (60 mg/d) since 2 years for attention deficit hyperactivity syndrome since age 13 years, developed sudden onset headache, hemianopia to the right, hypoesthesia of the tongue and right arm, aphasia, and depersonalisation. Blood tests revealed hyper-CK-emia of 2860U/L, cerebral magnetic resonance imaging showed disturbed perfusion on the left temporo-parieto-occipital region, and electroencephalography (EEG) revealed focal slowing and spikes and sharp waves in the same projections. After discontinuation of atomoxetine, symptoms, EEG, and magnetic resonance imaging findings resolved spontaneously within 48 hours. In conclusion, atomoxetine may rarely cause severe side effects such as complex partial seizures with CK-elevation, transient hypoperfusion of the temporal, parietal and occipital lobes, and prolonged reorientation. Atomoxetine should be discontinued if such side effects occur.

Decreased theta cordance may normalize

Singh, G., Arun, P., Das, S., & Kaur, D. (2021). Can EEG Predict Response to Atomoxetine in attention deficit hyperactivity disorder at 1 Week? Journal of Attention Disorders, 25(5), 758–767. https://doi.org/10.1177/1087054719829574

Objective: The objective of the study is to predict the early changes in electroencephalography (EEG) at 1 week and its correlation to clinical response at 6 weeks after treatment with atomoxetine in children with ADHD. Method: In 50 children (6-14 years) with ADHD (Diagnostic and Statistical Manual of Mental Disorders [5th ed.; DSM-5]), Vanderbilt ADHD Parent Rating Scale (VADPRS) and Vanderbilt ADHD Teachers Rating Scale (VADTRS) were applied at baseline, 1, 4, and 6 weeks. EEG was recorded using International 10–20 System of electrode placement at baseline and at 1 week after atomoxetine treatment. EEG changes at 1 week after atomoxetine therapy was correlated to clinical response at 6 weeks. Results: Patients were classified as responders or nonresponders based on the VADPRS/VADTRS findings. ***After 1 week of treatment, responders' theta cordance values were decreased, whereas nonresponders' values didn't decrease significantly. Conclusion: Patients with decreased theta cordance values, especially in the left temporoparietal region, at 1 week were likely to respond to atomoxetine*** while those without any such change were likely to be nonresponders.

Event-related potentials reflect the efficacy of pharmaceutical treatments in children and adolescents with attention deficit/hyperactivity disorder

Yamamuro, K., Ota, T., Iida, J., Nakanishi, Y., Matsuura, H., Uratani, M., Okazaki, K., Kishimoto, N., Tanaka, S., & Kishimoto, T. (2016). Event-related potentials reflect the efficacy of pharmaceutical treatments in children and adolescents with attention deficit/hyperactivity disorder. Psychiatry research, 242, 288–294. https://doi.org/10.1016/j.psychres.2016.05.061

Few objective biological measures of pharmacological treatment efficacy exist for attention deficit/hyperactivity disorder (ADHD). Although we have previously demonstrated that event-related potentials (ERPs) reflect the effects of osmotic-release methylphenidate in treatment of naïve pediatric patients with ADHD, whether this is true for the therapeutic effects of atomoxetine (ATX) is unknown. Here, we used the Japanese version of the ADHD rating-scale IV to evaluate 14 patients with ADHD, and compared their ERP data with 14 age- and sex-matched controls. We measured P300 and mismatch negativity (MMN) components during an auditory

oddball task before treatment (treatment naïve) and after 2 months of ATX treatment. Compared with controls, P300 components at baseline were attenuated and prolonged in the ADHD group at Fz (fronto-central), Cz (centro-parietal), Pz (parietal regions), C3 and C4 electrodes. ATX treatment reduced ADHD symptomology, and after 2 months of treatment, P300 latencies at Fz, Cz, Pz, C3, and C4 electrodes were significantly shorter than those at baseline. Moreover, MMN amplitudes at Cz and C3 electrodes were significantly greater than those at baseline. Thus, ERPs may be useful for evaluating the pharmacological effects of ATX in pediatric and adolescent patients with ADHD.

----- REBOXETINE (Edronax)-----

DRUG FACTS

SYNOPSIS: May be prescribed off-label for ADHD or panic disorders. Slow wave sleep alpha power is affected when taken. Total EEG power increases. The antidepressant treatment response (ATR) of the EEG may be a good biomarker for prescribing this drug.

ATR (antidepressant treatment response) as biomarker

Caudill, M. M., Hunter, A. M., Cook, I. A., & Leuchter, A. F. (2015). The Antidepressant Treatment Response Index as a Predictor of Reboxetine Treatment Outcome in Major Depressive Disorder. Clinical EEG and Neuroscience, 46(4), 277–284. https://doi.org/10.1177/1550059414532443

Biomarkers to predict clinical outcomes early during the treatment of major depressive disorder (MDD) could reduce suffering and improve outcomes. A quantitative electroencephalogram (qEEG) biomarker, the Antidepressant Treatment Response (ATR) index, has been associated with outcomes of treatment with selective serotonin reuptake inhibitor antidepressants in patients with MDD. Here, we report the results of a post hoc analysis initiated to evaluate whether the ATR index may also be associated with reboxetine treatment outcome, given that its putative mechanism of action is via norepinephrine reuptake inhibition (NRI). Twenty-five adults with MDD underwent qEEG studies during open-label treatment with reboxetine at doses of 8 to 10 mg daily for 8 weeks. The ATR index calculated after 1 week of reboxetine treatment was significantly associated with overall Hamilton Depression Rating Scale (HAM-D) improvement at week 8 ($r = 0.605$, $P = .001$), even after controlling for baseline depression severity ($P = .002$). ***The ATR index predicted response (≥50% reduction in HAM-D) with 70.6% sensitivity and 87.5% specificity, and remission (final HAM-D ≤7) with 87.5% sensitivity and 64.7% specificity. These results suggest that the ATR index may be a useful biomarker of clinical response during NRI treatment of adults with MDD***. Future studies are warranted to investigate further the potential utility of the ATR index as a predictor of noradrenergic antidepressant treatment response.

Slow wave sleep alpha and total power changes

Herrmann, W. M., & Fuder, H. (1998). Reboxetine, a selective noradrenaline reuptake inhibitor, is non-sedative and does not impair psychomotor performance in healthy subjects. Human Psychopharmacology, 13(6), 425–433. https://doi.org/10.1002/(SICI)1099-1077(199808)13:63.0.CO;2-R

A double-blind, randomized, four-way crossover study was performed to assess the CNS effects of reboxetine, a unique selective noradrenaline reuptake inhibitor (NRI). Eighteen volunteers received reboxetine (1 or 3 mg), imipramine (75 mg) or placebo at weekly intervals. Pharmaco-electroencephalography was recorded under high- and low-vigilance conditions and spectral difference index, ***total power and alpha slow-wave index (ASI) were calculated***. In addition, skilled performance on psychometric tests and well-being were assessed. ***Absolute and relative power were relatively unaffected by reboxetine but increased by imipramine. Total power and ASI were unaffected or slightly increased by reboxetine, but reduced by imipramine***. Reboxetine and imipramine decreased fronto-central θ and fast β power. In pharmaco-electroencephalography, imipramine showed a left shift in the occipito-temporal lead, with an increase in δ and θ and a decrease in α power. Reboxetine increased α power. Following reboxetine administration, the results in performance tests either did not differ from placebo or were better (Pegboard test). After imipramine, a deterioration in the Steadiness and Pauli test occurred. Critical flicker fusion and Vienna test results were unaltered by either drug. In summary, reboxetine, unlike the tricyclic antidepressant imipramine, has no sedative effects of electroencephalography or on any behavioural variable indicative of a decline in vigilance. Furthermore, reboxetine showed a vigilance-enhancing effect.

Comparison of multiple antidepressants on the effects on slow wave sleep

Sterr, A., Padberg, F., Mergl, R., Amann, B., Mulert, C., Juckel, G., Grunze, H., Hegerl, U., & Pogarell, O. (2004). *EEG abnormalities associated with antidepressant treatment: A comparison of mirtazapine, citalopram, venlafaxine, reboxetine and amitriptyline*. Pharmacopsychiatry. https://doi.org/10.1055/s-2003-825522

Objectives: Abnormalities in electroencephalography (EEG) recordings may occasionally occur during treatment with antipsychotics. In contrast, limited data are available regarding antidepressants. We investigated EEG changes in patients receiving a stable monotherapy with mirtazapine, citalopram, reboxetine, venlafaxine, amitriptyline. Methods: Digital EEG recordings of 255 patients (80-mirtazapine, 58-citalopram, 22-reboxetine, 50-venlafaxine, 45-amitriptyline) were retrieved from a database and visually interpreted by two independent raters. Results: There was no statistically significant difference between groups regarding the frequency of ***EEG-abnormalities, which were found in 6(7.5%) patients with mirtazapine***, 4(6.9%) with citalopram, none with reboxetine, 9(18%) with venlafaxine, and 5(11.1%) with amitriptyline. Epileptiform activity was not observed in any group. Conclusion: ***Mildly abnormal EEG patterns may occur but are generally rare during antidepressive monotherapy. However, a higher frequency of abnormalities may be observed with venlafaxine or amitriptyline. No epileptiform EEG activity was observed as previously reported for mirtazapine***.

----- **VILOXAZINE (Qelbree) -----**

DRUG FACTS

SYNOPSIS: Originally prescribed for depression (brand name: Viloxazine), it is now given for ADHD. It may reduce epileptiform activity, reduce vigilance and has a negative effect on sleep EEG.

Reduction of EEG vigilance during driving

TBente, D., Chenchanna, P., Scheuler, W., & Sponagel, P. (1978). Zur Wirkung des Antidepressivums Viloxazin auf das hirnelektrische Verhalten und die Optimierung des Systems Fahrer-Fahrzeug-Strasse [On the effect of the antidepressant viloxazin on EEG and optimization of the system driver-vehicle-road (author's transl)]. Arzneimittel-Forschung, 28(8), 1308–1310.

The effects of a single dose of 100 mg 2-[(o-ethoxyphenoxy)-methyl]-morpholine hydrochloride (viloxazin) on EEG and optimizing control behaviour of drivers were investigated under double-blind conditions in 5 male subjects with many years' driving experience. The study was carried out on a special test course using a car equipped with measuring devices. The following signals were recorded: EEG and EOG, driving speed, steering torque, steering angle and angle rate, longitudinal and lateral acceleration, and yaw rate. ***As evaluated by means of spectral analysis with a subsequent principal component analysis the EEG showed an increase of the power in alpha- and beta-frequencies indicating a drug induced decrease of EEG vigilance.*** In correspondence the optimization of the system driver-vehicle-road was reduced indicating an impairment of the driver's control behaviour.

Possible reduction of epileptiform activity

Tartara, A., Bo, P., Maurelli, M., Savoldi, F., & Manzo, L. (1983). EEG profile of the anticonvulsant action of viloxazine in the rabbit. Il Farmaco; edizione scientifica, 28(3), 161–166.

The intravenous administration of the bicyclic antidepressant viloxazine, 0.5-2 mg/kg in rabbits, caused changes in the EEG profile with increased synchronous activity and shorter duration of the hippocampal after discharge following electrical stimulation. In animals exhibiting spontaneous epileptiform discharges, the injection of 1-2 mg/kg viloxazine was associated with disappearance of the paroxysmal EEG pattern that was substituted by a synchronous low frequency activity. This study also provided evidence of non-interactive effects of viloxazine (1-2 mg/kg i.v.) and alcohol (0.6 g/kg i.v.) on the EEG of normal rabbits.

Loss of sleep quality

Wilson, W.H., Freemon, F.R., Ban, T.A. et al. Acute effects of viloxazine HCl and flurazepam when given alone and in combination on sleep EEG: A double-blind interaction study with normals. Pav. J. Biol. Sci. 15, 68–73 (1980). https://doi.org/10.1007/BF03003685

Viloxazine, an aryl-oxypropanolamine type β-adreno-receptor antagonist, has been used in the treatment of depression. In a double-blind drug interaction study with flurazepam, a commonly used benzodiazepine hypnotic, ***viloxazine administered alone decreased the amount of time spent in REM sleep, increased the amount of time in the "light" stages of sleep, and increased the number of transitions to awake.*** However, no interactive effects of the combined administration of viloxazine and flurazepam could be detected.

----- TYPICAL ANTIDEPRESSANTS -----

DRUG FACTS

SYNOPSIS: This class includes MAOIs, SSRIs, SNRIs, and tricyclic antidepressants, which are commonly prescribed for clinical depression and other mood disorders. They generally take weeks to take effect.

----- MAOIs (Monoamine Oxidase Inhibitors) -----

DRUG FACTS

SYNOPSIS: Also used as anxiolytics, MAOIs are the least favored antidepressant due to their many side effects. They inhibit the breakdown of norepinephrine, serotonin, dopamine, and tyramine, retaining the molecules' availabilities.

----- ISOCARBOXAZID (Marplan) -----

DRUG FACTS

SYNOPSIS: Little is known about this drug and the EEG since it is not commonly prescribed.

Cortical slow wave high amplitude, subcortical fast activity in rabbits

Bueno, J.R., Pscheidt, G.R. & Himwich, H.E. Interactions of monoamine oxidase inhibitors and reserpine: an EEG, gross behavioral and biochemical analysis. Psychopharmacologia 12, 400–413 (1968). https://doi.org/10.1007/BF00401345

We have studied the interactions of reserpine and the monoamine oxidase inhibitors, nialamide and isocarboxazid, in rabbits. EEG recordings were made from animals with acute and chronically implanted electrodes. Gross behavioral observations were made in freely moving rabbits and brain amine concentrations of norepinephrine and serotonin were also determined. Emphasis was placed on observing drug effects over periods of time ranging up to 13 days. ***Rabbits given isocarboxazid or nialamide alone exhibit a phenomenon rarely seen in the control animals, namely partial activation, an EEG pattern in which slow waves of high amplitude are maintained in the cortex while fast activity appears in subcortical structures***. This effect was also observed in rabbits treated with nialamide and reserpine in combination. By appropriate dosage schedules in which reserpine was administered to animals pretreated with monoamine oxidase inhibitors it was possible to maintain extended periods of frank arousal or EEG activation over a period of several days. The absolute concentrations of brain amines bore little or no relationship to the EEG effects observed, however, increased ratios of serotonin to norepinephrine were observed in conjunction with EEG activation and signs of behavioral excitement.

----- PHENELZINE (Nardil) -----

DRUG FACTS

SYNOPSIS: Another MOAI that is rarely prescribed today. The wake EEG produced twofold theta power and the NREM EEG performed mildly differently from nondrug behaviors.

The wake EEG is greatly affected with this drug, but not in NREM sleep

Landolt, H. P., & Gillin, J. C. (2002). Different effects of phenelzine treatment on EEG topography in waking and sleep in depressed patients. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 27(3), 462–469. https://doi.org/10.1016/S0893-133X(02)00322-6

A novel approach to investigate the relationship between depression and changes in sleep-wake regulatory mechanisms used the monoamine oxidase inhibitor (MAOI) phenelzine that is known to suppress rapid-eye-movement (REM) sleep. Sleep architecture and EEG topography during wakefulness and sleep were studied in eight depressed patients before and after five weeks of treatment with phenelzine (30-90 mg/day), which induced a significant alleviation of depressive symptoms. ***Theta power (4.75-7.5 Hz) during a 5-min wake EEG prior to sleep increased two-fold during administration of phenelzine. REM sleep was almost completely eliminated. This latter effect was compensated by increased duration of stage 2, whereas total sleep time was not shortened. In non-REM sleep (stages 2, 3, and 4), treatment slightly reduced EEG power between 2.0-6.25 Hz and 8.5-13.75 Hz; power in the 16.75-25.0 Hz band increased. Activity in the delta band (2.0-3.25 Hz) tended to be reduced in the fronto-central derivation, but not in centro-parietal and parieto-occipital derivations. However, the Treatment X Derivation interaction was not significant. These data indicate that in contrast to wakefulness the effects of phenelzine treatment on the EEG in non-REM sleep were small***. Rank correlation analyses revealed no association between the antidepressant treatment response and the changes in sleep and EEG power spectra during administration of phenelzine.

----- TRANYLCYPROMINE (Parnate) -----

DRUG FACTS

SYNOPSIS: An MAO inhibitor, this drug is not recommended under many conditions – including polydrug intake. One study showed nonoptimal changes in REM, but not NREM sleep.

No changes in NRWM sleep profile in bipolar disorder, however 40% decrease in REM

Jindal, Ripu & Fasiczka, Amy & Himmelhoch, Jonathan & Mallinger, Alan & Thase, Michael. (2003). Effects of tranylcypromine on the sleep of patients with anergic bipolar depression. Psychopharmacology bulletin. 37. 118-26.

A significant proportion of patients with bipolar disorder are hypersomnolent. It is not clear if this affects response to treatment because few studies have systematically examined treatment effects on sleep in patients with bipolar depression. Reported herein are the results of what we believe to be the first study of the effects of the monoamine oxidase inhibitor tranylcypromine (average dose=37 mg/day) on the sleep of patients with bipolar depression. Twenty-three

patients with anergic bipolar depression completed sleep studies before and after pharmacotherapy. Changes in polysomnographic variables were examined using paired t tests. The patients experienced a 40% reduction in rapid eye movement (REM) sleep time, as well as significant decreases in REM percentage, REM activity, number of REM periods, and REM intensity. REM latency was prolonged by nearly 3-fold. The decrease in REM sleep was accompanied by a modest (8%) reduction in total sleep time and increased "light" sleep. There was no change in sleep continuity indices or slow wave sleep. Correlational analyses suggested that antidepressant response was only weakly associated with changes in REM sleep. These findings indicate that tranylcypromine's effects on REM sleep greatly surpass effects on sleep architecture or sleep maintenance. Moreover, effective treatment of bipolar depression did not "normalize" the hypersomnolence associated with bipolar depression.

----- SNRIs (Selective Norepinephrine Reuptake Inhibitors) -----

DRUG FACTS

----- DULOXETINE (Cymbalta) -----

DRUG FACTS

SYNOPSIS: This drug selectively inhibits serotonin and norepinephrine reuptake, which has been shown to reduce depression presentation. Sleep EEG is affected and EEG cordance may play a role in this medication's success rate.

Left frontal cordance

Aimee M. Hunter, PhD, Andrew F. Leuchter, MD, Ian A. Cook, MD, Michelle Abrams, RN, Barbara E. Siegman, MA, R.EEG.T., Daniel E. Furst, MD, Amy S. Chappell, MD, Brain *Functional Changes and Duloxetine Treatment Response in Fibromyalgia: A Pilot Study*, Pain Medicine, Volume 10, Issue 4, May 2009, Pages 730–738, https://doi.org/10.1111/j.1526-4637.2009.00614.x

Objectives. Serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant medications may have efficacy in relieving pain associated with fibromyalgia syndrome (FMS), even in the absence of major depressive disorder (MDD). Current practice is to use a trial-and-error treatment strategy, often requiring 8–12 weeks to determine the effectiveness of a given pharmacological intervention. The ability to predict response to antidepressant medications would facilitate clinical management of FMS. Prior work in MDD has shown that the quantitative electroencephalographic (QEEG) cordance biomarker of brain functional changes early in the course of antidepressant treatment is related to later clinical response. We hypothesized that cordance might also predict response to antidepressant medications for symptoms of FMS. Design. Twelve adults (9 females) meeting American College of Rheumatology criteria for FMS participated in a double-blind placebo-controlled treatment trial utilizing duloxetine 60 mg. QEEG cordance changes were examined over the first week of treatment. Primary clinical outcomes included change in average pain severity on the Brief Pain Inventory (BPI) and global improvement in pain on the Patient's Global Impressions of Improvement (PGI-I) scale at 12 weeks. Results***. Changes in left frontal QEEG cordance after***

the first week of duloxetine treatment significantly predicted BPI pain improvement (regression coefficient = 2.9, R2 = 0.93, P = 0.008) and PGI-I global improvement (regression coefficient = 0.94, R2 = 0.81, P = 0.04). Conclusions. This pilot study suggests that QEEG biomarkers may prove useful for predicting improvement in painful symptoms during SNRI treatment in FMS. Larger studies are needed to confirm this finding.

Decreased REM and SWS; increased wake time

Katoh, A., Eigyo, M., Ishibashi, C., Naitoh, Y., Takeuchi, M., Ibii, N., Ikeda, M., & Matsushita, A. (1995). *Behavioral and electroencephalographic properties of duloxetine (LY248686), a reuptake inhibitor of norepinephrine and serotonin, in mice and rats*. The Journal of pharmacology and experimental therapeutics, 272(3), 1067–1075.

Duloxetine is a dual inhibitor of norepinephrine and serotonin reuptake. Duloxetine (3.13-50 mg/kg p.o.) significantly prevented tetrabenazine (1 and 50 mg/kg s.c.)-induced ptosis in mice and rats. Moreover, duloxetine (1.56-12.5 mg/kg p.o.) also inhibited reserpine (1 mg/kg s.c.)-induced hypothermia in mice. When duloxetine (12.5-100 mg/kg p.o.) and 5-hydroxytryptophan (80 and 100 mg/kg i.p.), a precursor of serotonin, were administered simultaneously to mice and rats, head movement behavior and tremor were observed. In addition, duloxetine (25-100 mg/kg p.o.) significantly attenuated immobility in forced swimming in mice, as equally effective as commonly used antidepressant drugs. ***Duloxetine (12.5-25 mg/kg p.o.) significantly decreased rapid eye movement sleep and slow-wave deep sleep and increased the awake period, as shown in the rat EEG***. However, duloxetine (25-200 mg/kg p.o.) did not affect salivation and lacrimation induced by oxotremorine (1 mg/kg s.c.), a cholinergic agonist, whereas it (25-50 mg/kg) reduced the oxotremorine-induced tremor in part. These results indicated that duloxetine produced behavioral and electroencephalographic responses resulting from the inhibition of norepinephrine and serotonin reuptake in vivo, and that it had a weak anticholinergic action. Therefore, duloxetine may be clinically useful as an antidepressant.

----- MILNACIPRAN (Savella) -----

DRUG FACTS

SYNOPSIS: This medication, usually prescribed for fibromyalgia, will negatively affect REM sleep as noted below.

REM sleep compromised

Gervasoni, D., Panconi, E., Henninot, V., Boissard, R., Barbagli, B., Fort, P., & Luppi, P. H. (2002). Effect of chronic treatment with milnacipran on sleep architecture in rats compared with paroxetine and imipramine. Pharmacology, biochemistry, and behavior, 73(3), 557–563. https://doi.org/10.1016/s0091-3057(02)00812-2

A number of studies in humans and various other species have shown that chronic treatment with antidepressants, such as tricyclics or selective serotonin reuptake inhibitors (SSRIs), induces a decrease or suppression of rapid eye movement (REM) sleep. The effect of a new selective serotonin and noradrenaline reuptake inhibiting (SNRI) antidepressant, milnacipran, on REM sleep has been investigated and compared with that of the SSRI, paroxetine, and the

tricyclic, imipramine. Rats injected with vehicle or milnacipran twice a day showed, over 24 h, a similar amount of REM sleep, number and duration of REM sleep episodes to control rats. In contrast, ***rats treated acutely with imipramine or paroxetine showed a statistically significant decrease in the total quantity of REM sleep. The number of REM sleep episodes was decreased while their duration was increased***. A more detailed analysis showed further that the quantity of REM sleep was decreased for the first 4 h following the 9 a.m. injection but not the 7 p.m. injection for milnacipran, during the first 6 h for paroxetine and for the entire light-dark period for imipramine. For all drugs, ***the quantities of slow-wave sleep and waking over 24 h were not significantly different from control conditions and no rebound of REM sleep occurred during the day following withdrawal. Power spectrum analysis revealed no global changes in the different electroencephalogram (EEG) waves (delta, theta, gamma) between the control condition and the different treatments during waking, slow-wave sleep or REM sleep.*** Taken together our results indicate that the SNRI, milnacipran, at therapeutic doses, induces only minor disturbances of REM sleep compared with a SSRI and tricyclic antidepressant used. Possible mechanisms responsible for the difference of action on REM sleep of milnacipran are discussed**.**

Reduction in REM sleep

Rahmadi, M., Narita, M., Yamashita, A., Imai, S., Kuzumaki, N., & Suzuki, T. (2011). Sleep disturbance associated with an enhanced orexinergic system induced by chronic treatment with paroxetine and milnacipran. Synapse (New York, N.Y.), 65(7), 652–657. https://doi.org/10.1002/syn.20893

Recent reports have shown that acute or chronic treatment with selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI) causes unpleasant side effects in patients. ***In the present study, through the use of electroencephalography (EEG) and electromyography (EMG), we found that chronic treatment with the SSRI paroxetine or the SNRI milnacipran significantly induced sleep disturbance, which was characterized by an increase in the total wake time and decreased total nonrapid eye movement (NREM) sleep***. Furthermore, RT-PCR analysis demonstrated that chronic treatment with paroxetine or milnacipran significantly increased the mRNA levels of orexin 1 receptor and orexin 2 receptor in the hypothalamus and of histamine 1 receptor and histidine decarboxylase in the frontal cortex of mice. The present findings suggest that chronic treatment with either paroxetine or milnacipran causes sleep disturbance associated with an increase in orexinergic transmission in the hypothalamus and histaminergic transmission in the frontal cortex. Although further studies are needed, these imbalances in the orexinergic and histaminergic systems may be, at least in part, responsible for the pathogenesis of sleep disturbance induced by chronic treatment with SSRI or SNRI in rodents.

----- VENLAFAXINE (Effexor) -----

DRUG FACTS

SYNOPSIS: Venlafaxine is often prescribed for moderate pain modulation. The EEG showed the most change in the alpha band in the insula and inferior frontal gyrus compared to oxycodone.

Compared to Oxycodone in pain management

Lelic, D., Hansen, T. M., Mark, E. B., Olesen, A. E., & Drewes, A. M. (2017). The effects of analgesics on central processing of tonic pain: A cross-over placebo controlled study. Neuropharmacology, 123, 455–464. https://doi.org/10.1016/j.neuropharm.2017.06.022

Opioids and antidepressants that inhibit serotonin and norepinephrine reuptake (SNRI) are recognized as analgesics to treat moderate to severe pain, but the central mechanisms underlying their analgesia remain unclear. This study investigated how brain activity at rest and exposed to tonic pain is modified by oxycodone (opioid) and venlafaxine (SNRI). Twenty healthy males were included in this randomized, cross-over, double-blinded study. 61-channel electroencephalogram (EEG) was recorded before and after five days of treatment with placebo, oxycodone (10 mg extended-release b.i.d) or venlafaxine (37.5 mg extended release b.i.d) at rest and during tonic pain (hand immersed in 2 °C water for 80 s). Subjective pain and unpleasantness scores of tonic pain were recorded. ***Spectral analysis and sLORETA source localization were done in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–18 Hz) and beta2 (18–32 Hz) frequency bands. Oxycodone decreased pain and unpleasantness scores (P < 0.05), whereas venlafaxine decreased the pain scores (P < 0.05). None of the treatments changed the spectral indices or brain sources underlying resting EEG. Venlafaxine decreased spectral indices in alpha band of the EEG to tonic pain, whereas oxycodone decreased the spectral indices and brain source activity in delta and theta frequency bands (all P < 0.05). The brain source activity predominantly decreased in the insula and inferior frontal gyrus. The decrease of activity within insula and inferior frontal gyrus is likely involved in pain inhibition due to oxycodone treatment, whereas the decrease in alpha activity is likely involved in pain inhibition due to venlafaxine treatment.*** Oxycodone decreased delta and theta spectral indices of EEG to tonic pain. Oxycodone decreased the brain activity underlying delta and theta EEG bands. ***Venlafaxine decreased alpha spectral indices of EEG to tonic pain. Brain activity underlying lower EEG frequencies is likely important in opioid analgesia. Alpha EEG activity is likely important in SNRI analgesia***.

Comparison of multiple antidepressants on the effects on slow wave sleep

Sterr, A., Padberg, F., Mergl, R., Amann, B., Mulert, C., Juckel, G., Grunze, H., Hegerl, U., & Pogarell, O. (2004). EEG abnormalities associated with antidepressant treatment: A comparison of mirtazapine, citalopram, venlafaxine, reboxetine and amitriptyline. Pharmacopsychiatry. https://doi.org/10.1055/s-2003-825522

Objectives: Abnormalities in electroencephalography (EEG) recordings may occasionally occur during treatment with antipsychotics. In contrast, limited data are available regarding antidepressants. We investigated EEG changes in patients receiving a stable monotherapy with mirtazapine, citalopram, reboxetine, venlafaxine, amitriptyline. Methods: Digital EEG recordings of 255 patients (80-mirtazapine, 58-citalopram, 22-reboxetine, 50-venlafaxine, 45-amitriptyline) were retrieved from a database and visually interpreted by two independent raters. Results: There was no statistically significant difference between groups regarding the frequency of ***EEG-abnormalities, which were found in 6(7.5%) patients with mirtazapine***, 4(6.9%) with citalopram, none with reboxetine, 9(18%) with venlafaxine, and 5(11.1%) with amitriptyline. Epileptiform activity was not observed in any group. Conclusion: ***Mildly abnormal EEG patterns may occur but are generally rare during antidepressive monotherapy. However, a higher***

frequency of abnormalities may be observed with venlafaxine or amitriptyline. No epileptiform EEG activity was observed as previously reported for mirtazapine.

----- SSRIs (Selective Serotonin Reuptake Inhibitors) -----

DRUG FACTS

SYNOPSIS: A first choice medication for treating depression, and possibly anxiety disorders, including eating disorders. A selective serotonin receptor inhibitor – which means it blocks serotonin molecules from re-entering the presynaptic cell, making them available to the post synaptic cell until they become less effective.

EEG microstates

Lei, L., Liu, Z., Zhang, Y., Guo, M., Liu, P., Hu, X., Yang, C., Zhang, A., Sun, N., Wang, Y., & Zhang, K. (2022). *EEG microstates as markers of major depressive disorder and predictors of response to SSRIs therapy*. Progress in neuro-psychopharmacology & biological psychiatry, 116, 110514. https://doi.org/10.1016/j.pnpbp.2022.110514

Background: Major depressive disorder (MDD) is associated with abnormal neural activities and brain connectivity. EEG microstate is a voltage topology map that reflects transient activations of the brain network. A limited number of studies on EEG microstate in MDD have focused on differences between patients and healthy controls. However, EEG microstate changes in MDD patients before and after drug treatment have not been evaluated. We assessed EEG microstate characteristics and evaluated changes in brain network dynamics in MDD patients before and after drug treatment. Moreover, we evaluated the neuro-electrophysiological mechanisms of antidepressant therapies. Methods: 64-channel resting EEG was obtained from 101 patients with first-episode untreated depression (0 week) and 45 healthy controls (HC) from January to December 2020. MDD patients were treated with selective serotonin reuptake inhibitors (SSRI). EEG data for 51 MDD patients who had completed an 8-week follow-up was collected. ***After pre-processing, EEG data from different groups were subjected to microstate analysis, and the atomize and agglomerate hierarchical clustering (AAHC) was into 4 microstates. Next, EEG signals from each patient were fitted using templates of 4 microstates. Finally, microstate indices were collected and analyzed. Results: Global clustering generated 4 microstates (A, B, C, D) in all subjects, which explained 65-84% of the global variance. Compared to HC, the duration of microstate D reduced while those of microstates A and B increased in MDD patients.*** After the 8-week treatment period, the duration and coverage of microstate D increased, the frequency of microstate A and transition probability of microstate D to A reduced, while transition probability of microstate B to D and D to B increased in MDD patients. There were no differences in microstate features between HC and MDD at 8 weeks. In patients with first-episode untreated depression, lower average durations of microstate D, relatively higher frequencies of microstate C and lower transition probabilities of microstate D to B correlated with better effects after 8 weeks. The higher occurrence and proportion of microstate C at 8 weeks was positively correlated with the HAMD score and reduction rate. The same observation was reached for the transition probability of microstate A to C. However, the

transition probability of microstate D to B showed a negative correlation with the HAMD score at 8 weeks. Conclusion: Microstate D is a potential electrophysiological trait of MDD and can predict treatment outcomes of SSRIs. Therefore, EEG microstate analysis may not only be an objective method for evaluating treatment outcomes of depression, but is also a potential new approach for exploring the neuro-electrophysiological mechanisms of antidepressant therapy. Public title: Multidimensional diagnosis, individualized treatment and management techniques based on clinic-pathological characteristics of depressive disorder; Registration number: ChiCTR1900026600; Date of registration: 2019-10-15; URL: http://www.chictr.org.cn/index.aspx.

Frontal theta reduction in responders, but do not predict behavioral treatment response in many SSRIs

Singh, A., Arun, P., Singh, G. P., Kaur, D., & Kaur, S. (2022). *QEEG Predictors of Treatment Response in Major Depressive Disorder- A Replication Study from Northwest India. Clinical EEG and neuroscience*, 15500594221142396. Advance online publication. https://doi.org/10.1177/15500594221142396

Background: Predicting treatment response with antidepressant is a challenging task for clinicians and researchers. An important limitation of an antidepressant trial is the increased time spent before an adequacy of trial can be decided. Quantitative Electroencephalography has shown some evidence in identifying early changes seen with antidepressants. No data has been reported from Indian population on its predictive capabilities. Aim: To examine whether early changes in frontal and prefrontal theta value in QEEG could predict antidepressant treatment response. Methods: Structured clinical assessments were conducted at baseline and after one week in a sample of treatment-seeking adults with major depressive disorder (n = 50). Patients were started on SSRI (Escitalopram, fluoxetine, paroxetine or sertraline) and followed for 8 weeks. QEEG recordings were carried out at baseline and week 1 and its parameters (relative theta power and cordance) were assessed to identify its predictive value for treatment response. Treatment response was assessed using Hamilton depression rating scale with 50% reduction after 8 weeks being considered as response. Results: Mean age of the sample was 39 ± 10 years and majority of them were females (64%). ***A significant reduction was found in relative frontal theta value (p = 0.021) from baseline to one week in responders. However, linear regression revealed that this change could not predict the treatment response (p = 0.37). Conclusions: QEEG changes are observed in initial phase of antidepressant treatment but these changes can't predict the treatment response.***

----- CITALOPRAM (Celexa) -----

DRUG FACTS

SYNOPSIS: can be prescribed for depression as well as eating and other anxiety disorders. This drug showed the best effect on slow wave sleep EEG compared to other medications.

Comparison of multiple antidepressants on the effects on slow wave sleep

Sterr, A., Padberg, F., Mergl, R., Amann, B., Mulert, C., Juckel, G., Grunze, H., Hegerl, U., & Pogarell, O. (2004). EEG abnormalities associated with antidepressant treatment: A

comparison of mirtazapine, citalopram, venlafaxine, reboxetine and amitriptyline. Pharmacopsychiatry. https://doi.org/10.1055/s-2003-825522

Objectives: Abnormalities in electroencephalography (EEG) recordings may occasionally occur during treatment with antipsychotics. In contrast, limited data are available regarding antidepressants. We investigated EEG changes in patients receiving a stable monotherapy with mirtazapine, citalopram, reboxetine, venlafaxine, amitriptyline. Methods: Digital EEG recordings of 255 patients (80-mirtazapine, 58-citalopram, 22-reboxetine, 50-venlafaxine, 45-amitriptyline) were retrieved from a database and visually interpreted by two independent raters. Results: There was no statistically significant difference between groups regarding the frequency of ***EEG-abnormalities, which were found in 6(7.5%) patients with mirtazapine***, 4(6.9%) with citalopram, none with reboxetine, 9(18%) with venlafaxine, and 5(11.1%) with amitriptyline. Epileptiform activity was not observed in any group. Conclusion: ***Mildly abnormal EEG patterns may occur but are generally rare during antidepressive monotherapy. However, a higher frequency of abnormalities may be observed with venlafaxine or amitriptyline. No epileptiform EEG activity was observed as previously reported for mirtazapine***.

----- ESCITALOPRAM (Lexapro) -----

DRUG FACTS

SYNOPSIS: The ATR may have a predicative value in assessing drug response. Baseline symmetry and activity in the rACC may also be predictive. Chronic exposure to this drug effects sleep architecture differently to acute exposure. It may affect gamma power during EPs.

Antidepressant Treatment Response (ATR) algorithm to predict best antidepressant outcome

Cook, I. A., Hunter, A. M., Caudill, M. M., Abrams, M. J., & Leuchter, A. F. (2020). *Prospective testing of a neurophysiologic biomarker for treatment decisions in major depressive disorde*r: The PRISE-MD trial. *Journal of psychiatric research*, *124*, 159–165. https://doi.org/10.1016/j.jpsychires.2020.02.028

Management of Major Depressive Disorder (MDD) might be improved by a biomarker to predict whether a selected medication is likely to lead to remission. We previously reported on a quantitative electroencephalogram-based biomarker, the Antidepressant Treatment Response (ATR) index, that integrated recordings at baseline and after one week of treatment. The present study prospectively tested whether treatment directed by the biomarker increased the likelihood of remission; we hypothesized that continued treatment with a drug predicted to lead to remission (i.e., high ATR values) would be associated with better outcomes than if the drug was predicted not to lead to remission (i.e., low ATR values). We enrolled 180 adult outpatients with unipolar MDD from the community. ***After one week of escitalopram treatment to determine the biomarker, stratified randomization (high vs. low ATR [antidepressant treatment response]) was used to assign subjects to either continued escitalopram or a switch to bupropion as a blinded control condition, for seven additional weeks.*** For the 73 evaluable subjects assigned to continued escitalopram treatment, the remission rate was significantly higher for those in whom ATR had predicted remission versus non-remission (60.4% vs. 30.0%, respectively, p = 0.01). Accuracy was enhanced by combining 1-week depressive symptom change with ATR (68.6% vs 28.9%). This prospective validation study supports further development of the ATR biomarker, alone or together with early

symptom change, to improve care by identifying individuals unlikely to remit with their current treatment and support the decision to change treatment after one week rather than after failing a full, prolonged course of medication.
[from manuscript]: ***The three qEEG features incorporated into ATR were relative combined theta and alpha power (3–12 Hz), alpha1 absolute power (8.5–12 Hz), and alpha2 absolute power (9–11.5 Hz). Relative combined theta and alpha power (3–12 Hz) was calculated as the ratio of absolute combined theta and alpha power, divided by total power (2–20 Hz). ATR (version 4.1) employed a weighted combination of relative theta and alpha power at week 1, and the difference between alpha1 power at baseline and alpha2 power at week 1, scaled to range from 0 (low probability of remission) to 100 (high probability)***. This is the same computation of the ATR values as was used in the earlier studies (the same software was used in both projects); the electrode locations have been shifted to reduce exclusion of subjects for ECG-contamination of the ear electrodes.

Effects on sleep cycles differs between acute and chronic exposure

Papp, N., Vas, S., Bogáthy, E., Kátai, Z., Kostyalik, D., & Bagdy, G. (2018). Acute and chronic escitalopram alter EEG gamma oscillations differently: relevance to therapeutic effects. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 121, 347–355. https://doi.org/10.1016/j.ejps.2018.06.012

Brain oscillations in the gamma frequency band of the electroencephalogram (EEG) have been implicated in several sensory and cognitive processes, and have also been associated with numerous neuropsychiatric disorders, including depression. The widely prescribed selective serotonin reuptake inhibitors (SSRIs), similarly to other antidepressants, are known to produce markedly different effects on sleep and behavioral measures with acute and chronic administration. Although there are studies examining the acute effect of escitalopram on slower (<30 Hz) oscillations, we hardly could find any data about the effect of the drug on higher-frequency EEG oscillations (>30 Hz) in different sleep-wake stages, particularly comparing the acute and chronic effects of the drug concerning gamma oscillations. Our aim was to investigate, how escitalopram affects gamma power in different sleep-wake stages, and to discover possible differential effects between acute and chronic treatment. EEG-equipped Wistar rats were treated with escitalopram or vehicle acutely (10 mg/kg, i.p.) or chronically (10 mg/kg/day for 21 days, osmotic minipumps) and frontoparietal EEG, electromyogram and motor activity were recorded during the first 3 h of passive phase. We found that acute and chronic escitalopram treatment affected gamma oscillations differently. ***While acute escitalopram caused a reduction in gamma power during rapid eye movement sleep (REMS) and intermediate stage of sleep (IS), chronic treatment caused an elevation in gamma power during non-REMS stages, namely in light and deep slow-wave sleep (SWS-1 and SWS-2, respectively) and in IS.*** However, gamma activity during active and passive wakefulness (AW and PW, respectively) was not influenced by either acute or chronic dosing of escitalopram. Furthermore, we found that in drug-free (vehicle-treated) rats, a relatively high gamma power was present during wakefulness and REMS, while a much lower power was measured during non-REMS stages. These findings indicate that acute and chronic administration of escitalopram

alter gamma activity differently, moreover, in a sleep-wake stage dependent manner that may be related to differential therapeutic and/or side effects.

Treatment success based upon baseline theta2 and alpha2 symmetry in rACC

Jaworska, N., Blondeau, C., Tessier, P., Norris, S., Fusee, W., Blier, P., & Knott, V. (2014). *Examining relations between alpha power as well as anterior cingulate cortex-localized theta activity and response to single or dual antidepressant pharmacotherapies*. Journal of psychopharmacology (Oxford, England), 28(6), 587–595. https://doi.org/10.1177/0269881114523862

Electrocortical indices may be useful in predicting antidepressant response. Greater pretreatment alpha power and high rostral anterior cingulate cortex (rACC) theta activity tend to index a favorable outcome. The predictive utility of alpha power asymmetry has been under-explored. ***Baseline alpha2 (10.5-13.0 Hz) power/asymmetry, rACC theta2 (6.0-8.0 Hz) activity and early (one week) changes in these measures were assessed in relation to antidepressant response by week 12 to three treatment regimens (escitalopram (ESC) + bupropion (BUP), ESC or BUP) in patients with major depressive disorder (N=51). No treatment differences in response existed at week 12. Overall, treatment responders exhibited high, and non-responders low, frontal baseline alpha2 power. Frontal alpha2 power weakly discriminated responders/non-responders overall while posterior alpha2 power and BA25-localized theta2 activity strongly discriminated ESC responders/non-responders. No associations with alpha2 asymmetry and response emerged. BUP responders exhibited high, and BUP non-responders low, baseline rACC theta2 activity. Greater early decreases in rACC theta2 activity existed in ESC+BUP non-responders versus ESC+BUP responders. BUP responders exhibited greater rACC theta2 activity decreases than ESC responders. These preliminary results indicate that baseline and early changes in alpha2 and rACC theta2 activity associate with response and have implications for tailoring antidepressant treatments.***

Decreased evoked gamma

T Nissen, T. D., Laursen, B., Viardot, G., l'Hostis, P., Danjou, P., Sluth, L. B., Gram, M., Bastlund, J. F., Christensen, S. R., & Drewes, A. M. (2020). Effects of Vortioxetine and Escitalopram on Electroencephalographic Recordings - A Randomized, Crossover Trial in Healthy Males. Neuroscience, 424, 172–181. https://doi.org/10.1016/j.neuroscience.2019.09.039

The antidepressant drug vortioxetine has a multimodal action modulating neurotransmission through inhibition of the serotonin transporter and modulation of serotonin receptors. Vortioxetine has also been shown to alleviate cognitive symptoms in preclinical studies and in patients with depression. However, it is largely unclear how vortioxetine affects the brain processing in humans. The present study was conducted in 32 healthy males in a randomized, double-blinded, placebo-controlled, active comparator, four-way crossover design. Treatments were 10 and 20 mg/day vortioxetine, 15 mg/day escitalopram, and placebo, administered orally once daily for three days. Results were compared to placebo. Treatment effect was assessed by recording spontaneous electroencephalography (EEG) and 40 Hz auditory steady state responses. For the spontaneous EEG, both vortioxetine and escitalopram decreased the frequency content in the theta band (4-8 Hz) and increased power in the beta (12-32 Hz) and

gamma (32-45 Hz) bands. Vortioxetine and escitalopram decreased connectivity during rest in the theta band and increased connectivity in the gamma bands. ***Finally, both treatments caused decreased power in the evoked gamma band in response to 40 Hz auditory stimulation. Although the global EEG changes were comparable between vortioxetine and escitalopram, subtle differences between treatment effects on the EEG in terms of effect size and regional distribution of the EEG changes were apparent.*** To our knowledge, the current results are the first data on how vortioxetine affects EEG in humans. The present study calls for further investigations addressing the possible electrophysiological and cognitive effects of vortioxetine.

----- FLUOXETINE (Prozac) -----

DRUG FACTS

SYNOPSIS: This drug is prescribed to alleviate depression. As is with many medications, alpha behavior is an important indicator. Other findings indicate general normalization across all frequency bands in relative power. Its effects on sleep differ from fluoxetine.

Increase in stage 1 sleep, REM intensity in children

Armitage, R., Emslie, G., & Rintelmann, J. (1997). The effect of fluoxetine on sleep EEG in childhood depression: a preliminary report. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 17(4), 241–245. https://doi.org/10.1016/S0893-133X(97)00048-1

Fluoxetine is associated with substantial objective and subjective sleep disturbance in adults with major depressive disorders. In this preliminary report, the effects of fluoxetine on sleep electroencephologram (EEG) are described in 6 children and adolescents with nonpsychotic major depression. ***Fluoxetine increased light Stage 1 sleep, the number of arousals and rapid eye movement (REM) density. REM latency was largely unaffected***. Oculomotor abnormalities were also evident on treatment, accompanied by an increase in myoclonic activity. Subjective sleep was also disturbed on treatment. These results are in keeping with those observed in depressed adults treated with fluoxetine.

REM theta power normalized

Matsuda, Y., Ozawa, N., Shinozaki, T., Aoki, K., Nihonmatsu-Kikuchi, N., Shinba, T., & Tatebayashi, Y. (2021). *Chronic antidepressant treatment rescues abnormally reduced REM sleep theta power in socially defeated rats*. Scientific Reports, 11(1), 16713–16713. https://doi.org/10.1038/s41598-021-96094-0

Abstract: The effects of chronic antidepressant (AD) treatment on sleep disturbances in rodent chronic stress models have not been thoroughly investigated. Here, we show that chronic social defeat stress (SDS) in rats induces prolonged social avoidance, alterations in sleep architecture (increased total rapid eye movement [REM] sleep duration, bout, and shortened REM latency), and contextual but not cued fear memory deficits, even 1 month after the last SDS. These abnormalities were associated with changes in electroencephalography (EEG) spectral powers, including reduced REM sleep theta power during the light phase. Chronic treatment with two different classes of antidepressants (ADs), imipramine and fluoxetine, significantly ameliorated these behavioral, sleep, and EEG abnormalities. Interestingly, ***REM theta power was normalized by chronic (1 month) but not 1 week AD administration*** and solely correlated with

the ratio (an objective indicator) of social interaction 1 month after the last SDS. These data suggest that reductions in REM sleep theta power, an EEG parameter that has never been directly investigated in humans, is a core sleep symptom in socially defeated rats, and, potentially, also in patients with stress-related psychiatric disorders, including major depressive and posttraumatic stress disorders.

Normalization of EEG relative power after medication

Omel'chenko, V.P., Zaika, V.G. Changes in the EEG-Rhythms in Endogenous Depressive Disorders and the Effect of Pharmacotherapy. Human Physiology 28, 275–281 (2002). https://doi.org/10.1023/A:1015596416791

The study of a series of EEG indices in endogenous depressive disorders and their changes after pharmacotherapy was conducted. The EEG changes in depressed patients versus healthy individuals were found to be characterized by a significant increase in the relative power of the Δ- and θ-activity and a decrease in the α- and β-activity, as well as by a decrease in the regional differences between the anterior and posterior divisions of the brain and an increase in the activity of the right hemisphere in relation to the left hemisphere. The use of amitriptyline, fluoxetine, and moclobemide contributed to the improvement in the mental state, which was accompanied by an increase in the EEG amplitude, a decrease in the relative power of the Δ- and θ-activity, and an increase in the α-rhythm power; however, on discharge, the patients retained deviations from a number of values compared to healthy subjects.

Differing effects on sleep EEG than nefazodone

Rush, A. J., Armitage, R., Gillin, J. C., Yonkers, K. A., Winokur, A., Moldofsky, H., Vogel, G. W., Kaplita, S. B., Fleming, J. B., Montplaisir, J., Erman, M. K., Albala, B. J., & McQuade, R. D. (1998). Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biological psychiatry, 44(1), 3–14. https://doi.org/10.1016/s0006-3223(98)00092-4

Background: Sleep disturbances are common in major depressive disorder. In previous open-label trials, nefazodone improved sleep continuity and increased rapid eye movement (REM) sleep, while not affecting stage 3/4 sleep or REM latency: in contrast, fluoxetine suppressed REM sleep. This study compared the objective and subjective effects of nefazodone and fluoxetine on sleep. Methods: This paper reports combined results of three identical, multisite, randomized, double-blind, 8-week, acute-phase trials comparing nefazodone (n = 64) with fluoxetine (n = 61) in outpatients with nonpsychotic major depressive disorder and insomnia. Sleep electroencephalographic (EEG) recordings were gathered at baseline and weeks 2, 4, and 8. Clinical ratings were obtained at weeks 1-4, 6, and 8. Results: **Nefazodone and fluoxetine were equally effective in reducing depressive symptoms; however, nefazodone differentially and progressively increased (while fluoxetine reduced) sleep efficiency and reduced (while fluoxetine increased) the number of awakenings in a linear fashion over the 8-week trial. Fluoxetine, but not nefazodone, prolonged REM latency and suppressed REM sleep. Nefazodone significantly increased total REM sleep time.** Clinical evaluations of sleep quality were significantly improved with nefazodone compared with fluoxetine. Conclusions: Nefazodone and fluoxetine were equally effective antidepressants. Nefazodone was associated with normal objective, and clinician- and patient-rated assessments of sleep when compared

with fluoxetine. These differential sleep EEG effects are consistent with the notion that nefazodone and fluoxetine may have somewhat different modes and spectra of action.

Adding Mg may augment positive outcome of Fluoxetine therapy with optimal EEG changes

Skalski M, Mach A, Januszko P, Ryszewska-Pokraśniewicz B, Biernacka A, Nowak G, Pilc A, Poleszak E, Radziwoń-Zaleska M. **Pharmaco-Electroencephalography-Based Assessment of Antidepressant Drug Efficacy—The Use of Magnesium Ions in the Treatment of Depression**. Journal of Clinical Medicine. 2021; 10(14):3135. https://doi.org/10.3390/jcm10143135

Pharmaco-electroencephalography (pharmaco-EEG) is a technique used to assess the effects of psychotropic medications on the bioelectrical activity of the brain. The purpose of this study was to assess the treatment response with the use of the Hamilton Depression Rating Scale (HDRS) and via EEG. Over an 8-week period, we analyzed electroencephalographic tracings of 91 patients hospitalized for major depression at the Medical University of Warsaw. Thirty-nine of those patients received tricyclic antidepressants (TCAs), 35 received fluoxetine, and 17 received fluoxetine augmented with magnesium (Mg) ions. ***All patients had their serum drug levels monitored. The highest proportion of patients (88.2%) who showed adequate responses to treatment was observed in the fluoxetine+Mg group, whereas the lowest rates of treatment response were observed in the TCA group (58.3%).*** This difference was statistically significant ($p = 0.029$, Phi = 0.30). Our study demonstrated a relationship between achieving remission (HDRS ≤ 6 at week 8 of treatment) and obtaining a positive pharmaco-EEG profile 6 h after administration of the first dose in the group receiving fluoxetine augmented with Mg ions ($p = 0.035$, Phi = 0.63).

[from manuscript]: ***The EEG patterns considered to constitute a positive pharmaco-EEG profile of antidepressants exhibited the following characteristics: increased power of beta, delta, and theta oscillations; decreased power of alpha oscillations; and slower alpha rhythms***.

Posterior alpha indicators – left parietal balance

Sedoruk, Tenke, Stewart, McGrath, & Bruder. 2005. Poster link: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://psychophysiology.cpmc.columbia.edu/mmedia/spr2005/SPR2005b.pdf

One of the most commonly prescribed medications for treating depression is fluoxetine (Prozac), yet few studies have examined changes in brain activity following treatment. The present study examined the effect of fluoxetine on the alpha power measures of regional hemisphere activity. A resting EEG (eyes open and closed; nose reference) was recorded at 28 electrode sites (plus two eye channels) in 18 depressed patients (13 male; 20-56 years old; 12 treatment responders) when they were off medication and again at the end of 12 weeks of treatment with fluoxetine. Treatment-related differences in log alpha power were evaluated using a repeated measures ANOVA, using session (pre/post-treatment), hemisphere, and recording sites as within subjects factors and treatment response as a between subject factor. ***Overall responders had significantly greater alpha power than non-responders. Alpha was significantly greater over the left than right frontal sites across treatment response groups, but only responders showed greater alpha (less activity) over right posterior sites. However, there was no evidence of change in either amplitude or topography of alpha with treatment.***

At all electrodes, test-retest reliability of alpha amplitude was high for both responders (.88 <r<.99) and non-responders (.79<r<.96). Alpha asymmetry (right minus left) was also reproducible for all electrodes sites (.66<r<.92). Results suggest that EEG alpha indicators of fluoxetine response may be treatment-independent traits.

Beta reduction after 4 weeks

Tarn, M., Edwards, J. G., & Sedgwick, E. M. (1993). Fluoxetine, amitriptyline and the electroencephalogram. Journal of affective disorders, 29(1), 7–10. https://doi.org/10.1016/0165-0327(93)90112-w

Electroencephalograms recorded before and after 4 weeks treatment of depressed patients with fluoxetine or amitriptyline were assessed visually and by power spectrum analysis blind to patient, treatment and whether the recordings were carried out before or after treatment. No significant between-group differences in alpha, beta or theta activity were found on visual assessment. ***Power spectrum analysis revealed a significant decrease in the amount of beta activity at week 4***. There was no EEG evidence of drowsiness or epileptiform activity in either of the treatment groups.

----- PAROXETINE (Paxil, Pexeva) -----

DRUG FACTS

SYNOPSIS: While paroxetine is commonly prescribed for depression and anxiety, it has been indicated in suicidal behaviors. It's influence on the EEG is non-sedative and reductive of delta and theta activity. Frontal alpha pathologies are shown to normalize after one week. Gamma activity may be prognostic to treatment success.

Normalization of frontal alpha power and symmetry in OCD treatment

Arıkan, M. K., Oba, M. Ç., İlhan, R., & Mat, M. C. (2023). When to Choose Paroxetine Treatment in Skin-Picking Disorder: A Case Report. Clinical EEG and neuroscience, 54(2), 168–172. https://doi.org/10.1177/15500594211073390

Skin picking disorder (SPD) characterized by repetitive compulsive scratching in the absence of a primary skin disease is strongly associated with psychiatric comorbidities, including obsessive-compulsive disorder (OCD) and depression (MDD). Selective serotonin reuptake inhibitors (SSRIs) have been used in the treatment of SPD with variable success. Nevertheless, the optimum treatment choice for SPD is an issue for clinicians. This case report presents a 32-year-old female SPD patient treated with four-week paroxetine monotherapy. Based upon the clinical interview and standardized questionnaires, the patient was diagnosed with OCD with depressive features and Skin Picking Disorder. ***In addition to symptom severity scales, quantitative electroencephalography (qEEG) was also applied. Paroxetine treatment was started (titrated from 5 to 40 mg/day) and doubled each week. After four-week paroxetine monotherapy, OCD symptoms were diminished, and skin lesions were completely regressed leaving solely post inflammatory hyperpigmentation. Post-treatment qEEG assessment also showed a normalization of frontal alpha power and amplitude asymmetry. It can be concluded that if OCD includes SPD with abnormal EEG patterns; then the treatment success using paroxetine will be very high***.

Baseline gamma power may be an indicator of treatment success

Arikan, M. K., Metin, B., & Tarhan, N. (2018). EEG gamma synchronization is associated with response to paroxetine treatment. Journal of affective disorders, 235, 114–116. https://doi.org/10.1016/j.jad.2018.04.041

Background: Resistance to medication is a significant problem in psychiatric practice, and effective methods for predicting response are needed to optimize treatment efficacy and limit morbidity. Gamma oscillations are considered as an index of the brain's general cognitive activity; however, the role of gamma oscillations in disease has not been studied sufficiently. Aim: This study aimed to determine if gamma power during rest can be used to predict response to anti-depressant medication treatment. Method: Hamilton Depression Rating Scale (HDRS) score and resting state gamma power was measured in 18 medication-free patients during an episode of major depression. After 6 weeks of paroxetine monotherapy HDRS was administered again. Results: ***Baseline gamma power at frontal, central and temporal electrodes before treatment was significantly related to post-treatment change in HDRS scores***. Conclusion: The results indicate that gamma oscillations could be considered a marker of response to paroxetine treatment in patients with major depression.

Decrease in delta and theta power in healthy volunteers

McClelland, G. R., & Raptopoulos, P. (1984). EEG and blood level of the potential antidepressant paroxetine after a single oral dose to normal volunteers. Psychopharmacology, 83(4), 327–329. https://doi.org/10.1007/BF00428539

The quantitative electroencephalogram (EEG) and plasma concentration of the antidepressant paroxetine were monitored in five normal volunteers after a single oral dose of 70 mg paroxetine and placebo. Peak plasma concentration occurred 4-6 h post-dose. ***Placebo had little effect on the EEG, but the effects of paroxetine were statistically significant at 6 h post-dose. The EEG changes after treatment consisted of a decrease in delta and theta activity (less than 8 Hz) and increase in beta activity (greater than 12 Hz). These changes were still evident 72 h after treatment. The EEG profile obtained with 70 mg paroxetine is similar to that reported for other antidepressant 5-HT uptake inhibitors, but dissimilar to the classical, sedative antidepressants***.

Reduction in REM sleep

Rahmadi, M., Narita, M., Yamashita, A., Imai, S., Kuzumaki, N., & Suzuki, T. (2011). Sleep disturbance associated with an enhanced orexinergic system induced by chronic treatment with paroxetine and milnacipran. Synapse (New York, N.Y.), 65(7), 652–657. https://doi.org/10.1002/syn.20893

Recent reports have shown that acute or chronic treatment with selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI) causes unpleasant side effects in patients. ***In the present study, through the use of electroencephalography (EEG) and electromyography (EMG), we found that chronic treatment with the SSRI paroxetine or the SNRI milnacipran significantly induced sleep disturbance, which was characterized by an increase in the total wake time and decreased total nonrapid eye movement (NREM) sleep***. Furthermore, RT-PCR analysis demonstrated that chronic treatment with paroxetine or milnacipran significantly increased the mRNA levels of orexin 1 receptor and orexin 2 receptor

in the hypothalamus and of histamine 1 receptor and histidine decarboxylase in the frontal cortex of mice. The present findings suggest that chronic treatment with either paroxetine or milnacipran causes sleep disturbance associated with an increase in orexinergic transmission in the hypothalamus and histaminergic transmission in the frontal cortex. Although further studies are needed, these imbalances in the orexinergic and histaminergic systems may be, at least in part, responsible for the pathogenesis of sleep disturbance induced by chronic treatment with SSRI or SNRI in rodents.

----- SERTRALINE (Zoloft, Lustral) -----

DRUG FACTS

SYNOPSIS: An antidepressant that may regulate the EEG and depressive symptoms better than other antidepressants based upon normalization in power in normal subjects and and CSD in penile dysfunction.

CSD changes in patients with penile dysfunction

Kwon, O. Y., Kam, S. C., Choi, J. H., Do, J. M., & Hyun, J. S. (2011). *Effects of sertraline on brain current source of the high beta frequency band: analysis of electroencephalography during audiovisual erotic stimulation in males with premature ejaculation. International journal of impotence research,* 23(5), 213–219. https://doi.org/10.1038/ijir.2011.30

To identify the effects of sertraline, a selective serotonin reuptake inhibitor, for the treatment of premature ejaculation (PE), changes in brain current-source density (CSD) of the high beta frequency band (22-30 Hz) induced by sertraline administration were investigated during audiovisual erotic stimulation. Eleven patients with PE (36.9±7.8 yrs) and 11 male volunteers (24.2±1.9 years) were enrolled. Scalp electroencephalography (EEG) was conducted twice: once before sertraline administration and then again 4 h after the administration of 50 mg sertraline. Statistical non-parametric maps were obtained using the EEG segments to detect the current-density differences in the high beta frequency bands (beta-3, 22-30 Hz) between the EEGs before and after sertraline administration in the patient group and between the patient group and controls after the administration of sertraline during the erotic video sessions. Comparing between before and after sertraline administration in the patients with PE, the CSD of the high beta frequency band at 4 h after sertraline administration increased significantly in both superior frontal gyri and the right medial frontal gyrus ($P<0.01$). ***The CSD of the beta-3 band of the patients with PE were less activated significantly in the middle and superior temporal gyrus, lingual and fusiform gyrus, inferior occipital gyrus and cuneus of the right cerebral hemisphere compared with the normal volunteers 4 h after sertraline administration (P<0.01). In conclusion, sertraline administration increased the CSD in both the superior frontal and right middle temporal gyrus in patients with PE. The results suggest that the increased neural activity in these particular cerebral regions after sertraline administration may be associated with inhibitory effects on ejaculation in patients with PE***.

Sertraline normalizes EEG better than other antidepressants.

van der Vinne, N., Vollebregt, M. A., Boutros, N. N., Fallahpour, K., van Putten, M. J. A. M., & Arns, M. (2019). Normalization of EEG in depression after antidepressant treatment with

sertraline? A preliminary report. Journal of affective disorders, 259, 67–72. https://doi.org/10.1016/j.jad.2019.08.016

Background: MDD patients with abnormal EEG patterns seem more likely to be non-responsive to the antidepressants escitalopram and venlafaxine, but not sertraline, than patients without EEG abnormalities. This finding suggests that patients with both MDD and abnormal EEGs may differentially respond to antidepressant treatment. In the current study, we investigated whether depressed patients with an abnormal EEG show a normalization of the EEG related to antidepressant treatment and response and whether such effect is drug specific, and whether having had early life stress (ELS) increases the chance of abnormal activity. Methods: Baseline and week 8 EEGs and depression symptoms were extracted from a large multicenter study (iSPOT-D, n = 1008) where depressed patients were randomized to escitalopram, sertraline, or venlafaxine-XR treatment. We calculated Odds Ratios of EEG normalization and depression response in patients with an abnormal EEG at baseline, comparing sertraline versus other antidepressants. Results: ***Fifty seven patients with abnormal EEGs were included. EEGs did not normalize significantly more with sertraline compared to other antidepressants (OR = 1.9, p = .280). However, patients with a normalized EEG taking sertraline were 5.2 times more likely to respond than subjects taking other antidepressants (p = .019).*** ELS was not significantly related to abnormal activity. Limitations: Neurophysiological recordings were limited in time (two times 2-minute EEGs) and statistical power (n = 57 abnormal EEGs). Conclusions: ***Response rates in patients with normalized EEG taking sertraline were significantly larger than in subjects treated with escitalopram/venlafaxine.*** This adds to personalized medicine and suggests a possible drug repurposing for sertraline.

----- TCAs (Tricyclic antidepressants) -----

DRUG FACTS

SYNOPSIS: less prescribed due to its side effects than SSRIs, they are used most often in MDD. They reverse EEG hypersynchrony after intake of clonidine, which has sedative qualities.

Frequency interaction similar to increase in vigilance

Herrmann, W. M., & Kubicki, S. (1981). Beispiele für die Projektion von Substanzwirkungen typischer Psychopharmaka auf eine elektrophysiologische Messebene [*The use of electrophysiological techniques to project typical psychotropic drug effects: some examples* (author's transl)]. EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete, 12(1), 21–32.

A long existing hypothesis, i.e. that the EEG effects, in lead O2A2, of typical psychotropic drugs are substance class specific, when given as single oral dosages to healthy volunteers, is discussed. Using the technique of pharmacoelectroencephalograhpy, five typical representatives of neuroleptics, anxiolytics, antidepressives, psychostimulants (Fig. 2) as well as placebo were investigated in 75 volunteers, each receiving one representative of each substance class in a double blind 5-fach change over latin square design (Fig. 3). A five minute EEG record for lead O2A2 was obtained pre, 1 h and 3 hrs post drug intake under RR (Relaxed Recording) conditions. Typical samples of th EEG records are shown in Figs. 4--7. Parametrisation was done using power spectrum analysis. Then 3 x 7 target variables were

formed--six relative power values in predetermined frequency bands and the total power between 1.5 and 30.0 Hz for 3 occasions of measurement (Fig. 4--7). Using a (five-group) linear discriminant analysis the substance effects on the EEG were transformed into 5 probability measures for the five substance classes (Fig. 4--7). The present paper should provide a demonstration of some typical examples, using single subjects, of the projection of substance effects onto an electrophysiological level using a vector of 21 components (7 target variables for 3 occasions of measurement) as can be seen from Table 1. Furthermore, the transformation into probability measures of the five substance classes are shown in Table 2. Table 3 shows five examples of projections of substance effects, which do not fit into the classifications to which they belong. An attempt is made to explain, whether single target variables from the power spectrum can contribute differently to the discrimination between single substances of different substance classes. Within the accepted system of 4 psychotropic drug classes, the following variables seem to be of importance: a) The benzodiazepine anxiolytics show a marked increase in beta F1 (12.0--18.0 Hz) power and activity and, related to sedation, an increase in delta F-power and a decrease in alpha-power; b) The psychostimulants of the amphetamine type show an increase in total power and alpha-power, an increase in the power of the frequency ranges near to the alpha-band (slow beta, fast theta) and a decrease in delta F (1.5--5.5 Hz)-power, when delta F-power is high in the pre-values, indicating a stabilization in vigilance; c) The neuroleptics show a marked increase in theta F (5.5--8.5 Hz)-power, some increase in the delta F--and a decrease in the beta F1-and beta F3-power; d) ***Tricyclic antidepressants show an interaction between delta F-theta F-, alpha- and beta-power, in the sense of a dissociative shift in vigilance.***

Changes after tricyclic intake after clonidine

Parale, M. P., Nayar, U., & Kulkarni, S. K. (1986). Modification by tricyclic antidepressants of cortical EEG changes induced by clonidine in conscious rats. Indian Journal of Physiology and Pharmacology, 30(1), 70–78.

The effects of various tricyclic antidepressants on clonidine-induced electroencephalographic changes were investigated in rats. The EEG pattern of conscious rats was recorded by means of bipolar electrodes, implanted chronically. Clonidine (50, 150 and 300 micrograms/kg) not only synchronized cortical EEG pattern but also evoked signs of behavioural depression within 15 min of its administration. Pretreatment with imipramine, desipramine, trimipramine, amitriptyline, nortriptyline and doxepin reduced clonidine-induced EEG synchrony without showing any effects per se. ***Acute treatment with tricyclic antidepressants failed to modify but, chronic treatment abolished the clonidine-induced behavioural depressive signs. Chronic administration of tricyclic antidepressants (10 mg/kg/day) evoked more pronounced antagonism of the EEG effects of clonidine.*** Yohimbine (200 micrograms/kg) pretreatment inhibited both, clonidine-induced EEG synchrony and behavioural effects. Guanfacine as well as B-HT 920, elicited clonidine-like effects on cortical EEG pattern and behaviour. The present data suggests that antagonism of clonidine-induced EEG synchronization in conscious animals could serve as a useful test for screening of antidepressant drugs.

----- AMITRIPTYLINE -----

DRUG FACTS

SYNOPSIS: Another depression drug, which may cause REM suppression and altered percent of duration of each of the NREM stages.

REM suppression and NREM percent changes

Kupfer, D. J., Spiker, D. G., Coble, P., & McPartland, R. J. (1978). *Amitriptyline and EEG sleep in depressed patients*: I. Drug effect. Sleep (New York, N.Y.), 1(2), 149–159. https://doi.org/10.1093/sleep/1.2.149

The paucity of studies on the tricyclic antidepressants led us to conduct an investigation on 30 drug-free patients treated with amitryptyline in a double-blind protocol over a 4-week period. ***Consistent with previous reports, there was an immediate REM suppression on 50 mg, which was more pronounced at the 100-mg level.*** However, no significant incremental changes were noticed on 150 or 200 mg with regard to REM sleep suppression. Drug administration was associated with changes in other sleep variables such as stage 1 percent, stage 2 percent, and various measures of sleep continuity. The incomplete tolerance of the drug on certain REM sleep variables enhances our understanding of amitryptyline effects on the EEG sleep of depressed patients.

Comparison of multiple antidepressants on the effects on slow wave sleep

Sterr, A., Padberg, F., Mergl, R., Amann, B., Mulert, C., Juckel, G., Grunze, H., Hegerl, U., & Pogarell, O. (2004). *EEG abnormalities associated with antidepressant treatment: A comparison of mirtazapine, citalopram, venlafaxine, reboxetine and amitriptyline*. Pharmacopsychiatry. https://doi.org/10.1055/s-2003-825522

Objectives: Abnormalities in electroencephalography (EEG) recordings may occasionally occur during treatment with antipsychotics. In contrast, limited data are available regarding antidepressants. We investigated EEG changes in patients receiving a stable monotherapy with mirtazapine, citalopram, reboxetine, venlafaxine, amitriptyline. Methods: Digital EEG recordings of 255 patients (80-mirtazapine, 58-citalopram, 22-reboxetine, 50-venlafaxine, 45-amitriptyline) were retrieved from a database and visually interpreted by two independent raters. Results: There was no statistically significant difference between groups regarding the frequency of ***EEG-abnormalities, which were found in 6(7.5%) patients with mirtazapine***, 4(6.9%) with citalopram, none with reboxetine, 9(18%) with venlafaxine, and 5(11.1%) with amitriptyline. Epileptiform activity was not observed in any group. Conclusion: ***Mildly abnormal EEG patterns may occur but are generally rare during antidepressive monotherapy. However, a higher frequency of abnormalities may be observed with venlafaxine or amitriptyline. No epileptiform EEG activity was observed as previously reported for mirtazapine***.

----- IMIPRAMINE HYDROCHLORIDE (Tofranil) -----

DRUG FACTS

SYNOPSIS: In addition to depression, this drug can be prescribed for bedwetting, anxiety, eating and panic disorders. It can be prescribed for ADHD and show some effects, but there is not a baseline EEG pattern that may predict the outcome of this drug. It will shorten the duration of

REM sleep, alter its theta power, and extend its onset, as well as affect other cycles. While relative and absolute power were slightly increased, overall total power was unaffected.

ADHD changes in EEG after drug intake, but no prognostic EEG patterns prior

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2008). Effects of imipramine hydrochloride on the EEG of children with Attention-Deficit/Hyperactivity Disorder who are non-responsive to stimulants. International Journal of Psychophysiology, 68(3), 186–192. https://doi.org/10.1016/j.ijpsycho.2008.01.007

Although stimulant medications are the most commonly-used treatments for Attention-Deficit/Hyperactivity Disorder (AD/HD), as many as 20% of treated children do not respond clinically to stimulants. One non-stimulant medication that has been widely used when the stimulants fail is a tricyclic antidepressant, imipramine hydrochloride. This study investigated the effects of imipramine on the EEG of children with AD/HD who were poor responders to dexamphetamine and ritalin, but who showed clinical improvement on a six month trial of imipramine. An initial pre-medication EEG was recorded during an eyes-closed resting condition, with data Fourier transformed to provide absolute and relative power estimates for the delta, theta, alpha and beta bands. A second EEG was recorded at the end of the imipramine trial. ***Compared to controls, the unmedicated AD/HD children had significant global increases in absolute and relative theta, with decreased global absolute and relative alpha, increased posterior relative delta, and decreased posterior absolute beta. No change in the EEG was found as a result of administering the medication. These results suggest that good responders to imipramine have an underlying EEG abnormality different from that in children who respond to the stimulants, and that an initial pre-treatment EEG may be useful in selecting a trial medication. However, as no change in the EEG was found with imipramine, it is unlikely that the EEG will be useful in evaluating responsivity to this medication.***

REM sleep compromised

Gervasoni, D., Panconi, E., Henninot, V., Boissard, R., Barbagli, B., Fort, P., & Luppi, P. H. (2002). Effect of chronic treatment with milnacipran on sleep architecture in rats compared with paroxetine and imipramine. Pharmacology, biochemistry, and behavior, 73(3), 557–563. https://doi.org/10.1016/s0091-3057(02)00812-2

A number of studies in humans and various other species have shown that chronic treatment with antidepressants, such as tricyclics or selective serotonin reuptake inhibitors (SSRIs), induces a decrease or suppression of rapid eye movement (REM) sleep. The effect of a new selective serotonin and noradrenaline reuptake inhibiting (SNRI) antidepressant, milnacipran, on REM sleep has been investigated and compared with that of the SSRI, paroxetine, and the tricyclic, imipramine. Rats injected with vehicle or milnacipran twice a day showed, over 24 h, a similar amount of REM sleep, number and duration of REM sleep episodes to control rats. In contrast, ***rats treated acutely with imipramine or paroxetine showed a statistically significant decrease in the total quantity of REM sleep. The number of REM sleep episodes was decreased while their duration was increased***. A more detailed analysis showed further that the quantity of REM sleep was decreased for the first 4 h following the 9 a.m. injection but not the 7 p.m. injection for milnacipran, during the first 6 h for paroxetine and for the entire light-dark period for imipramine. For all drugs, ***the quantities of slow-wave sleep and waking over***

24 h were not significantly different from control conditions and no rebound of REM sleep occurred during the day following withdrawal. Power spectrum analysis revealed no global changes in the different electroencephalogram (EEG) waves (delta, theta, gamma) between the control condition and the different treatments during waking, slow-wave sleep or REM sleep. Taken together our results indicate that the SNRI, milnacipran, at therapeutic doses, induces only minor disturbances of REM sleep compared with a SSRI and tricyclic antidepressant used. Possible mechanisms responsible for the difference of action on REM sleep of milnacipran are discussed**.**

Slow wave sleep alpha and total power changes

Herrmann, W. M., & Fuder, H. (1998). Reboxetine, a selective noradrenaline reuptake inhibitor, is non-sedative and does not impair psychomotor performance in healthy subjects. Human Psychopharmacology, 13(6), 425–433. https://doi.org/10.1002/(SICI)1099-1077(199808)13:63.0.CO;2-R

A double-blind, randomized, four-way crossover study was performed to assess the CNS effects of reboxetine, a unique selective noradrenaline reuptake inhibitor (NRI). Eighteen volunteers received reboxetine (1 or 3 mg), imipramine (75 mg) or placebo at weekly intervals. Pharmaco-electroencephalography was recorded under high- and low-vigilance conditions and spectral difference index, ***total power and alpha slow-wave index (ASI) were calculated***. In addition, skilled performance on psychometric tests and well-being were assessed. ***Absolute and relative power were relatively unaffected by reboxetine but increased by imipramine. Total power and ASI were unaffected or slightly increased by reboxetine, but reduced by imipramine***. Reboxetine and imipramine decreased fronto-central θ and fast β power. In pharmaco-electroencephalography, imipramine showed a left shift in the occipito-temporal lead, with an increase in δ and θ and a decrease in α power. Reboxetine increased α power. Following reboxetine administration, the results in performance tests either did not differ from placebo or were better (Pegboard test). After imipramine, a deterioration in the Steadiness and Pauli test occurred. Critical flicker fusion and Vienna test results were unaltered by either drug. In summary, reboxetine, unlike the tricyclic antidepressant imipramine, has no sedative effects of electroencephalography or on any behavioural variable indicative of a decline in vigilance. Furthermore, reboxetine showed a vigilance-enhancing effect.

REM theta power normalized

Matsuda, Y., Ozawa, N., Shinozaki, T., Aoki, K., Nihonmatsu-Kikuchi, N., Shinba, T., & Tatebayashi, Y. (2021). *Chronic antidepressant treatment rescues abnormally reduced REM sleep theta power in socially defeated rats*. Scientific Reports, 11(1), 16713–16713. https://doi.org/10.1038/s41598-021-96094-0

Abstract: The effects of chronic antidepressant (AD) treatment on sleep disturbances in rodent chronic stress models have not been thoroughly investigated. Here, we show that chronic social defeat stress (SDS) in rats induces prolonged social avoidance, alterations in sleep architecture (increased total rapid eye movement [REM] sleep duration, bout, and shortened REM latency), and contextual but not cued fear memory deficits, even 1 month after the last SDS. These abnormalities were associated with changes in electroencephalography (EEG) spectral powers, including reduced REM sleep theta power during the light phase. Chronic treatment with two

different classes of antidepressants (ADs), imipramine and fluoxetine, significantly ameliorated these behavioral, sleep, and EEG abnormalities. Interestingly, ***REM theta power was normalized by chronic (1 month) but not 1 week AD administration*** and solely correlated with the ratio (an objective indicator) of social interaction 1 month after the last SDS. These data suggest that reductions in REM sleep theta power, an EEG parameter that has never been directly investigated in humans, is a core sleep symptom in socially defeated rats, and, potentially, also in patients with stress-related psychiatric disorders, including major depressive and posttraumatic stress disorders.

Changes in sleep

Suzuki, H., Yamadera, H., Nakamura, S., & Endo, S. (2002). Effects of Trazodone and Imipramine on the Biological Rhythm: An Analysis of Sleep EEG and Body Core Temperature. Journal of Nippon Medical School = Nippon Ika Daigaku Zasshi, 69(4), 333–341. https://doi.org/10.1272/jnms.69.333

Depression commonly involves abnormalities of the sleep-wake rhythm, the temperature rhythm, and other biological rhythms. The changes of these biological rhythms are caused in remission by medications. However, it has yet to be clarified whether the biological rhythms are changed as a result of recovery from depression or from the direct pharmacological effects of the antidepressants. Therefore, we have undertaken a study on the direct effects of the antidepressants trazodone and imipramine on the biological rhythms of healthy volunteers. The study involved 12 healthy male volunteers (ages 21～28 years, mean age 23.9±1.7 years) who had given written informed consent. Placebo, trazodone, and imipramine were each administered in a single blind manner four times a day, during the three-day study period. The total daily dosage of trazodone was 100 mg (50 mg in one subject), and of imipramine 40 mg (20 mg in one subject). Subjects were submitted to polysomnography (PSG) and body core temperature (rectal temperature) measurements during the study period. We compared the data concerning the antidepressants to those of the placebo. The results show that, with regard to the sleep rhythm, trazodone significantly increased slow wave sleep (SWS), but no changes were observed in REM (rapid eye movement) sleep. ***Imipramine significantly decreased REM sleep and prolonged the REM cycle.*** With regard to the temperature rhythm, trazodone showed a tendency to advance the appearance time of the minimal temperature. Imipramine significantly lowered the maximal temperature and decreased the difference between the maximal and the minimal temperature, but no changes in the phases were observed. Neither antidepressant had any effect on the temperature cycle. Trazodone and imipramine showed different effects on PSG. Furthermore, they had different effects on the temperature rhythm. The changes of the sleep-wake rhythm were greater than those of the temperature rhythm. Although the two antidepressants had different mechanisms of action, it is worthy of note that both directly influenced the biological rhythms of healthy volunteers.

----- NORTRIPTYLINE (Pamelor) -----

DRUG FACTS

SYNOPSIS: Often prescribed for nerve and other forms of pain and neuralgia, it is primarily given for depression and commonly in elder patients. It increases REM sleep phases, which

reverts to normal after cessation of drug intake. LORETA imaging reveals higher theta power in rACC during drug protocol.

Increases REM phases

Buysse, D. J., Reynolds, C. F., Hoch, C. C., Houck, P. R., Kupfer, D. J., Mazumdar, S., & Frank, E. (1996). Longitudinal effects of nortriptyline on EEG sleep and the likelihood of recurrence in elderly depressed patients. Neuropsychopharmacology (New York, N.Y.), 14(4), 243–252. https://doi.org/10.1016/0893-133X(95)00114-S

Our objectives were to determine the effects of nortriptyline and placebo on subjective and EEG sleep measures over 1 year of maintenance therapy in elderly depressed patients and to determine the relationship of such effects to recurrence in nortriptyline or placebo-treated patients during maintenance therapy. EEG and subjective sleep assessments were conducted before and during a maintenance therapy study of patients suffering from major depression. During acute treatment all patients received nortriptyline plus interpersonal psychotherapy (IPT). During maintenance treatment patients were randomly assigned to double-blind treatment in one of four cells: nortriptyline with IPT; nortriptyline with medication clinic (no IPT); placebo with IPT; or placebo with medication clinic. Sleep evaluations were conducted at one point before treatment, one point following remission during continuation nortriptyline/IPT treatment, and at three time points after random assignment to maintenance treatment. The setting was the sleep laboratory of the outpatient depression treatment clinic, and subjects were a convenience sample of media-recruited and clinically referred elderly outpatient depressed patients (n = 72). Complete sleep analyses were conducted for 21 nortriptyline-and W placebo-treated patients throughout 1 year of maintenance treatment. The main outcome measures were subjective and EEG sleep measures and the recurrence of major depression. ***Our results show that nortriptyline acutely and persistently decreased REM sleep, increased phasic REM activity, decreased sleep apnea, and had no effect on periodic limb movements during sleep. Recurrence on maintenance nortriptyline was associated with lower phasic REM activity during early continuation therapy, but EEG sleep measures did not predict recurrence during placebo maintenance therapy. Patients treated with nortriptyline had a lower recurrence rate than those treated with placebo. Better subjective sleep quality and maintenance IPT were associated with a lower rate of recurrence regardless of nortriptyline treatment. It seems that nortriptyline has persistent effects on REM sleep and sleep apnea in elderly depressed patients. Maintenance nortriptyline, maintenance IPT, good subjective sleep quality, and high-phasic REM activity are associated with a reduced likelihood of the recurrence of depression during maintenance therapy***.

LORETA imaging reveals higher theta power in rACC.

Pizzagalli, D., Pascual-Marqui, R. D., Nitschke, J. B., Oakes, T. R., Larson, C. L., Abercrombie, H. C., Schaefer, S. M., Koger, J. V., Benca, R. M., & Davidson, R. J. (2001). Anterior Cingulate Activity as a Predictor of Degree of Treatment Response in Major Depression: Evidence From Brain Electrical Tomography Analysis. The American Journal of Psychiatry, 158(3), 405–415. https://doi.org/10.1176/appi.ajp.158.3.405

OBJECTIVE: The anterior cingulate cortex has been implicated in depression. Results are best interpreted by considering anatomic and cytoarchitectonic subdivisions. Evidence suggests

depression is characterized by hypoactivity in the dorsal anterior cingulate, whereas hyperactivity in the rostral anterior cingulate is associated with good response to treatment. The authors tested the hypothesis that activity in the rostral anterior cingulate during the depressed state has prognostic value for the degree of eventual response to treatment. Whereas prior studies used hemodynamic imaging, this investigation used EEG. METHOD: The authors recorded 28-channel EEG data for 18 unmedicated patients with major depression and 18 matched comparison subjects. Clinical outcome was assessed after nortriptyline treatment. Of the 18 depressed patients, 16 were considered responders 4-6 months after initial assessment. A median split was used to classify response, and the pretreatment EEG data of patients showing better (N=9) and worse (N=9) responses were analyzed with low-resolution electromagnetic tomography, a new method to compute three-dimensional cortical current density for given EEG frequency bands according to a Talairach brain atlas. RESULTS: ***The patients with better responses showed hyperactivity (higher theta activity) in the rostral anterior cingulate (Brodmann's area 24 32).*** Follow-up analyses demonstrated the specificity of this finding, which was not confounded by age or pretreatment depression severity. CONCLUSIONS: These results, based on electrophysiological imaging, not only support hemodynamic findings implicating activation of the anterior cingulate as a predictor of response in depression, but they also suggest that differential activity in the rostral anterior cingulate is associated with gradations of response

Effects on REM sleep during intake

Taylor, M. P., Reynolds, C. F., Frank, E., Dew, M. A., Mazumdar, S., Houck, P. R., & Kupfer, D. J. (1999). EEG Sleep Measures in Later-Life Bereavement Depression: A Randomized, Double-Blind, Placebo-Controlled Evaluation of Nortriptyline. The American Journal of Geriatric Psychiatry, 7(1), 41–47. https://doi.org/10.1097/00019442-199902000-00006

The authors examined 1) effects of nortriptyline (NT) on electroencephalographic (EEG) sleep measures in elderly patients with bereavement-related depression in remission under randomized, double-blind, placebo-controlled conditions, and 2) the effects of clinical remission on sleep after discontinuation of medication. Subjects were classified as responders to placebo (n=9) or NT (n=18) and had EEG sleep studies at three time-points: before treatment (T1), remitted on medication or placebo (T2), and remitted off medication or placebo (T3). As compared with placebo, ***NT was differentially associated with decreases in REM sleep time and percent and increases in REM sleep density (T2). No changes in EEG sleep measures occurred in placebo responders. REM sleep measures in NT responders reverted to T1 levels after T3, with persistence of robust clinical remission and normal subjective sleep quality. These data suggest that NT alters REM sleep, but that EEG sleep characteristics in bereavement-related depression persist into remission.***

ANTIHISTAMINES (H1, 2, 3, 4-Receptor Antagonists)

DRUG FACTS

SYNOPSIS: Prescribed to relieve topical itching, and for anxiety, nausea, heartburn, and other gut disorders, allergies, or as a sedative. H1 receptor antagonists and most sedating and least used.

Concerns for epileptic convulsions, polymedication implications,
Yokoyama, H., & Iinuma, K. (1996). *Histamine and Seizures*. CNS Drugs, 5, 321-330.
Summary: Experimental studies have indicated that the central histaminergic neuron system plays an important role in the inhibition of seizures through stimulation of histamine H1 receptors, especially in the developmental period. This has therapeutic implications for currently available drugs that act at histamine receptors. ***H1 receptor antagonists, including classical antihistamines and anti-allergy drugs, occasionally induce convulsions in healthy children and patients with epilepsy.*** In particular, promethazine, carbinoxamine, mepyramine (pyrilamine) and ketotifen should be used with caution in these patients. These drugs are widely used as components of over-the-counter medications. The use of the d-chlorphenamine (d-chlorpheniramine) ***activation study with EEG monitoring is useful for assessing the seizure susceptibility of patients who have had convulsions secondary to administration of H1 receptor antagonists. H2 receptor antagonists have also occasionally been reported to induce convulsions in critically ill and polymedicated patients, and patients with chronic renal or hepatic failure.*** However, experimental findings have not been consistent with these clinical reports, such that the role of these receptors and their ligands in inducing seizures cannot be confirmed. Recently, ***H3 receptor antagonists, which enhance endogenous histamine release in the brain, have been demonstrated to have a potent anticonvulsant action***. Therefore, these compounds may represent a new avenue for the development of antiepileptic drugs. Considering that H3 receptor antagonists also induce arousal patterns on the EEG, it is possible that they will not be associated with the sedative effects of many conventional antiepileptic drugs.

----- H1 RECEPTOR ANTAGONISTS -----

SYNOPSIS: Prescribed to relieve topical itching, and occasionally for anxiety since it is a serotonin agonist and sedating. Some reports note increase in slow wave power, reduction in peak alpha, no effect at all, and negative changes in sleep. There may also be negative effects on spike and wave paroxysms.

----- DIPHENHYDRAMINE (Benadryl) -----

DRUG FACTS

SYNOPSIS: Benadryl is a common over the counter medication for allergies.

Negative effects on sleep; convulsive spikes

Marzanatti, M., Monopoli, A., Trampus, M., & Ongini, E. (1989). *Effects of nonsedating histamine H1-antagonists on EEG activity and behavior in the cat*. Pharmacology, biochemistry, and behavior, 32(4), 861–866. https://doi.org/10.1016/0091-3057(89)90049-x

The central effects of the newly-developed antihistamines (H1-receptor antagonists) loratadine, astemizole, mequitazine and terfenadine were evaluated by studying brain electrical activity (EEG), sleep-waking patterns and behavior in the cat. The different stages of the sleep-waking cycle, i.e., wakefulness (W), spindle sleep (SS), slow wave sleep (SWS) and REM sleep (REM) were evaluated. The power spectrum analysis of the EEG was obtained by a computerized technique. For comparison, the sedating agent diphenhydramine was examined. Given at 3 mg/kg orally, a dose slightly above that effective therapeutically, diphenhydramine markedly affected behavior and all sleep stages. ***In particular, it depressed REM and increased SS (drowsiness). The EEG showed occasional spikes typical of subconvulsive states.*** Loratadine did not modify either sleep patterns or behavior over the 3-30 mg/kg dose range orally, which is far above that used clinically. The EEG, evaluated either visually or by spectral power analysis, was unaffected. Astemizole at 10 and 30 mg/kg PO reduced REM, markedly altered behavior at 30 mg/kg, but did not modify EEG activity. Mequitazine, at low doses (1-10 mg/kg PO), enhanced SS and decreased SWS and REM. Like diphenhydramine, mequitazine induced EEG changes typical of subconvulsive states and affected EEG power over the frequency range of 0.1-15.0 Hz. Terfenadine did not change sleep patterns and slightly affected behavior only at the high dose of 30 mg/kg orally; EEG activity was not influenced. These data show that: a) diphenhydramine and mequitazine appear to produce CNS effects by altering basic processes within the brain; b) astemizole and terfenadine seem to cross the blood-brain barrier at high doses only; c) loratadine has the lowest liability to produce central side effects. Of the sleep features examined, REM appeared to be the most sensitive stage to blockade of central H1-receptor pathways.

Reduction in slow wave activity; increase in spike and wave paroxisms

Rogelio Diaz-Guerrero, Rhoda Feinstein, Jacques S. Gottlieb, EEG findings following intravenous injection of diphenhydramine hydrochloride (benadrylR), Electroencephalography and Clinical Neurophysiology, Volume 8, Issue 2, 1956, Pages 299-306, ISSN 0013-4694, https://doi.org/10.1016/0013-4694(56)90121-3.

Abstract: A study was made of the effects of intravenously injected diphenhydramine hydrochloride (BenadrylR) on the electroencephalogram. The subjects consisted of: (1) a control series made up of persons without known disease of the central nervous system; (2) patients with known or suspected seizures; (3) patients undergoing electric convulsive therapy. All recordings were taken with the subject in fasting state. Hyperventilation and photic stimulation were used as provocative procedures. ***There were no changes in the EEGs of the control subjects following intravenous injection of BenadrylR. Patients who had bilaterally synchronous bursts of diffuse slow activity in the pre-BenadrylR record showed a significant reduction of the slow activity after BenadrylR. Patients with focal spiking, or focal spike wave activity, in the pre-BenadrylR record showed a marked increase in the per cent time of the same type of abnormal activity. In addition, BenadrylR was able to provoke focal spike and spike wave activity in patients who had normal records before administration of BenadrylR***.

----- FEXOFENADINE (Allegra) -----

DRUG FACTS

SYNOPSIS: May aid in inflammation reduction, so prescribed for arthritis, asthma, pruitus (itchy skin), and inflammatory pain.

No change in cognitive and psychometric assessments

Hindmarch I, Shamsi Z, Stanley N, Fairweather DB. A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function. Br J Clin Pharmacol. 1999 Aug;48(2):200-6. doi: 10.1046/j.1365-2125.1999.00993.x. PMID: 10417497; PMCID: PMC2014291.

Aims: To assess whether fexofenadine in a range of doses from 80 to 180 mg has any disruptive effects on aspects of psychomotor and cognitive function in comparison with placebo, loratadine and promethazine, an antihistamine known to produce psychomotor and cognitive impairment.

Methods: Twenty-four healthy volunteers received fexofenadine 80 mg, 120 mg and 180 mg, loratadine 10 mg, promethazine 30 mg (as a positive internal control) and placebo in a six-way crossover, double-blind study. Following each dose, subjects were required to perform a series of tests of cognitive function and psychomotor performance at 1.5, 3, 6, 9, 12 and 24 h post dose. The test battery included critical flicker fusion (CFF), choice reaction time (CRT) and assessment of subjective sedation (LARS). Overall levels of activity were monitored by means of wrist mounted actigraphs throughout each of the 24 h experimental periods.

Results: Fexofenadine at all doses tested was not statistically different from placebo in any of the tests used and loratadine did not cause any significant impairment of cognitive function. Significant impairments were found following promethazine. Promethazine caused a significant reduction in CFF threshold and this effect was evident up to 12 h post dose ($P < 0.05$). There was a significant increase in recognition reaction time at 3 and 6 h post promethazine administration, and the drug caused a significant ($P < 0.002$) increase in the percentage of 'sleep-like' activity from actigraph records during the daytime.

Conclusions: ***Fexofenadine at doses up to 180 mg appears free from disruptive effects on aspects of psychomotor and cognitive function in a study where the psychometric assessments have been shown to be sensitive to impairment***, as evidenced by the effects of the verum control promethazine 30 mg.

----- HYDROXYZINE (Atarax, Vistaril) -----

DRUG FACTS

Slow wave and beta1 power increase; slowing of alpha

Pechadre, J. C., Beudin, P., Trolese, J. F., Gabet, J. Y., & Eschalier, A. (1993). *A comparison of the electroencephalographic spectral modifications induced by diazepam and by hydroxyzine*. The Journal of international medical research, 21(5), 234–242. https://doi.org/10.1177/030006059302100502

A double-blind, randomized controlled trial using an electroencephalograph computerized analysis and cartography was carried out to investigate the spectral modifications induced by diazepam and hydroxyzine***. Without monitoring response to stimulation, the spectra found for diazepam and for hydroxyzine were qualitatively very similar, showing increase of the slow waves, reduction of the alpha rhythm and accentuation of the beta 1 rhythms.*** These traces suggested strongly that both drugs had produced a sedative, anti-anxiety effect. The intensity of the effect produced by 50 mg of hydroxyzine appeared to be less than that produced by 10 mg diazepam. After monitoring response to stimulation, the spectra were modified and the reactivity of the two drugs differed with regard to the slow delta, theta and alpha 1 frequency bands. It was possible to distinguish between the sedative and anti-anxiety effects of both diazepam and hydroxyzine. Even if the two drugs had some similar effects, the mode of action in the central nervous system was certainly different, as can be seen from the characteristics of distribution of the slow waves, their reactivity and, with regard to frequency, the fluctuation of the dominant frequency of rapid rhythms.

No effect on EEG

Anderson, E. M., & Gibbs, F. A. (1967). *Negative effect on the electroencephalogram of hydroxyzine pamoate at therapeutic dosage*. Diseases of the Nervous System, 28(5), 297.

High and low dosages of hydroxyzine pamoate (vistaril) were given both orally and intramuscularly to children of various ages on whom previous EEG recordings had been taken. ***No changes were found in the background activity when EEG examination was repeated and compared with previous tracings***.

Reduction in sleep onset latency and waking

Alford, C., Rombaut, N., Jones, J., Foley, S., Idzikowski, C. and Hindmarch, I. (1992), Acute effects of hydroxyzine on nocturnal sleep and sleep tendency the following day: A C-EEG study. Hum. Psychopharmacol. Clin. Exp., 7: 25-35. https://doi.org/10.1002/hup.470070104

The acute hypnotic effects of hydroxyzine 25 mg and 50 mg nocte were examined in six male and six female volunteers. Continuous electrophysiological measures (C-EEG) were taken to assess both nocturnal sleep and sleep tendency the following day. ***Both doses produced significant reductions in sleep onset latency and decreases in waking during sleep; reciprocal increases in sleep duration were also seen***. Female subjects demonstrated a greater hypnotic response, including a dose-dependent decrease in sleep onset latency. Increases in sleep duration following both doses were significant for the female group alone. C-EEG measures of increased drowsiness the following day failed to achieve significance; although the largest effects on daytime sleepiness, including dose-dependent increases, were again seen with the female subject group, and corresponded with subjective ratings. These results demonstrate the hypnotic efficacy of hydroxyzine whilst failing to detect significant C-EEG hangover effects. However, variability in response to antihistamines, registered here as differences between the sexes, requires further consideration.

----- TERFENADINE (Seldane) -----
DRUG FACTS

SYNOPSIS: Slow wave power increase. This drug was removed from the market due to negative cardiovascular effects.

Comparative study of terfenadine and cetirizine in hay fever: assessment of efficacy and central nervous system effects.

Bonifazi, F., Provinciali, L., Antonicelli, L., Bilò, M. B., Pucci, S., Signorino, M., Franciolini, B., Censori, B., Pagelli, P., & Iudice, A. (1995). Comparative study of terfenadine and cetirizine in hay fever: assessment of efficacy and central nervous system effects. Journal of investigational allergology & clinical immunology, 5(1), 40–46.

A daily dose of either terfenadine 120 mg or cetirizine 10 mg was compared in two parallel groups of patients suffering from hay fever. According to a double-blind, double-dummy, randomized design, 28 patients were treated with one of the two drugs once daily in the morning for 2 weeks during the 1990 grass pollen season. The severity of nasal congestion, rhinorrhea, sneezing, nasopharyngeal itching and itchy, watery, red eyes was evaluated by the investigator after a 1-week run-in period and at the end of the treatment. The patients made a daily record of the severity of symptoms on a diary card. In addition, drug-related central nervous system (CNS) effects were assessed at baseline and at the end of the treatment by neuropsychological tests aimed at investigating selective and sustained attention, visuomotor abilities and anxiety, and by quantitative, bit-mapped EEG. Both terfenadine and cetirizine produced a significant improvement in symptoms at endpoint without any significant difference between the two drugs. Drowsiness was referred by one patient in each treatment group. No significant impairment of psychomotor performance occurred with either drug. ***Quantitative EEG showed a significant power increase in the relative (%) delta band in both groups of treated patients.*** Although the difference was not statistically significant, a tendency towards greater involvement of the CNS was observed with the use of cetirizine. In conclusion, the results of this study confirm that terfenadine and cetirizine are equally effective in the management of hay fever. Some differentiated untoward EEG changes were also observed in relation to the drugs used, without any variation in neuropsychological performance.

Comparison of the central and peripheral effects of cetirizine and terfenadine.

Pechadre, J. C., Vernay, D., Trolese, J. F., Bloom, M., Dupont, P., & Rihoux, J. P. (1988). Comparison of the central and peripheral effects of cetirizine and terfenadine. European journal of clinical pharmacology, 35(3), 255–259. https://doi.org/10.1007/BF00558262

The peripheral and central effects of 10 mg cetirizine 2 HCl and 60 mg terfenadine have been compared with placebo in 9 healthy male volunteers. The peripheral effect, in terms of cutaneous reactivity to 1 microgram histamine i.d., was measured by planimetry of the wheal and erythemas. Central effects were assessed with a self-evaluation visual scale and from the results of electroencephalographic spectrum analysis. Peripheral inhibition of histamine reactivity was more intense and quicker for cetirizine than for terfenadine. On the self-evaluation scale, no significant difference between terfenadine, cetirizine and placebo was

noted. ***The quantified EEG did not show any variation in spectral parameters at any time after cetirizine. By contrast, at 6 h terfenadine had increased slow waves and had inhibited the alpha band.*** Thus, 10 mg cetirizine 2 HCl had less effect on the central nervous system than terfenadine 60 mg, whilst its peripheral action appeared more quickly and was more intense.

----- H2 RECEPTOR ANTAGONISTS -----

----- CIMETIDIDE (Tagamet) -----
DRUG FACTS

SYNOPSIS: Prescribed for stomach acid, heartburn, GERD, and peptic ulcers, This drug replaced Ranitidine (Zantac) in the US. Still, this drug is carefully doled out due to negative side effects in the esophagus and possible seizure activity.

----- FAMOTIDINE (Zantac) -----
DRUG FACTS

SYNOPSIS: An over-the-counter drug used to treat ulcers and GERD. Unlike H1-receptor antagonists, these drugs may speed the mean frequencies of the slower waves.

Slow frequencies sped up

T Prast, H., Grass, K., & Philippu, A. (1996). Influence of histamine receptor agonists and antagonists on ultradian rhythm of EEG in the posterior hypothalamus of the rat. Neuroscience letters, 216(1), 21–24. https://doi.org/10.1016/0304-3940(96)12992-x

he delta and theta frequency bands of the electroencephalogram (EEG) in the posterior hypothalamic area (PH) of rats vary according to an ultradian rhythm with a frequency of approximately 1 cycle/100 min. The influence of histamine-related drugs on the ultradian hypothalamic EEG rhythm was now studied in urethane anaesthetized rats. Injected into the lateral ventricle, metoprine (inhibitor of histamine catabolism) and alpha-fluoromethylhistidine (inhibitor of histamine synthesis) did not alter the duration of the rhythmic changes. The H1 receptor agonist 2-(2-aminoethyl)-thiazole was ineffective, while mepyramine (H1 receptor antagonist) prolonged the cycle duration of delta and theta frequency bands. ***Stimulation of H2 and H3 receptors by amthamine and immepip, respectively, also prolonged the cycle duration of these frequency bands, while the H2 antagonist famotidine and the H3 antagonist thioperamide exerted the opposite effects. Our results indicate that the ultradian EEG rhythm in the PH is susceptible to regulatory influences mediated by the histaminergic system of the brain***.

----- H3 RECEPTOR ANTAGONISTS -----

DRUG FACTS

SYNOPSIS: These drugs are designed to block H3 receptors. There is no information about effects on EEG.

----- H4 RECEPTOR ANTAGONISTS -----

DRUG FACTS

SYNOPSIS: These drugs are designed to block H4 receptors. There is no information about effects on EEG.

ANTIHYPERTENSIVES

DRUG FACTS

SYNOPSIS: Prescribed to lower blood pressure. It produces elevation of growth hormone. Has been used to reduce pain or as a sedative in children.

----- CLONIDINE (Catapres, Kapvay, Jenloga, Nexiclon) -----

DRUG FACTS

SYNOPSIS: Prescribed to treat high blood pressure or in combination with other medications used to control symptoms of ADHD. Acts as an alpha-agonist hypotensive agent; decreased theta and increased alpha.

Decrease theta, increased alpha, and increased power.

Emilien G. (1989). *Effect of drugs acting on monoaminergic and cholinergic systems on the quantified EEG of rats*. Neuropsychobiology, 21(4), 205–215. https://doi.org/10.1159/000118578.

Five different classes of drugs (clonidine: 0, 0.10, 0.30, 0.50 mg/kg; yohimbine: 0, 2, 4, 8 mg/kg; haloperidol: 0, 0.02, 0.04, 0.08 mg/kg; piracetam: 0, 150, 300, 600 mg/kg, and eserine: 0, 0.10, 0.30, 0.50 mg/kg) were studied on two cortical EEG derivations as well as a deep structure, the locus ceruleus in the rats. Each drug affected the EEG in its own particular manner. ***Clonidine significantly decreased frequency in the theta band (3.7-7.5 Hz) and increased it in the alpha band (7.6-13.5 Hz). A general significant increase in power was observed***. Yohimbine's effects on the EEG varied according to the regions studied. There were significant modifications of power and frequency in the theta, alpha and beta bands in the three derivations studied. Notable effects of haloperidol were observed as an increase in power in all frequency bands at all doses administered particularly in the anteroparietal and posteroparietal derivations. In the locus ceruleus derivation, power was significantly increased at all doses only in the alpha and beta frequency bands. Concerning piracetam, while no significant effects were noted on the EEG frequency, this drug significantly increased EEG power in the posteroparietal and anteroparietal derivations. The most important effects are obtained at the lowest dose (150 mg/kg) administered. Finally, it was shown that eserine significantly decreased power in the delta bandwidth shortly after its administration. Afterwards, the power gradually regained its original level.

Decreased P3a ampllitude

Kruiper, C., Glenthøj, B. Y., & Oranje, B. (2019). *Effects of clonidine on MMN and P3a amplitude in schizophrenia patients on stable medication*. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 44(6), 1062–1067. https://doi.org/10.1038/s41386-019-0351-6.

Schizophrenia is a complex brain disease involving several neurotransmitter systems, including aberrant noradrenergic activity, which might underlie cognitive deficits. Clonidine is an α2A-

agonist and previous research has demonstrated that single dosages of clonidine normalize sensori(motor) gating in schizophrenia. Currently, we investigated whether clonidine is able to normalize mismatch negativity (MMN) and P3a amplitude deficits in this same group of patients. This is important, since reports have shown that MMN amplitude is associated with cognitive functioning and daily life functions in schizophrenia. Twenty chronically ill, male schizophrenia patients were tested with the MMN paradigm from the Copenhagen Psychophysiological Test Battery (CPTB) on 5 occasions, separated by a week. Patients received randomized, yet balanced, either a placebo or a single dose (25, 50, 75 or 150 µg) of clonidine (each dose only once) on top of their usual medication on each occasion. Patients were matched on age and gender with 20 healthy controls (HC) who did not receive any treatment. We found ***decreased MMN and P3a amplitudes*** in our patients compared to HC. Although clonidine did neither significantly increase MMN nor P3a amplitude in our patients, it did increase certain levels of MMN and P3a amplitude such that these were not significantly different anymore from the healthy controls. Together with our previous reports indicating normalized sensori(motor) gating in the same patients following administration of clonidine, our results could be of potential high clinical relevance in treating schizophrenia. Future studies should focus on longer trial periods to investigate if clonidine also improves cognitive functioning in schizophrenia.

Reduced levels of P50 suppression

Oranje, B., & Glenthøj, B. Y. (2014). *Clonidine normalizes levels of P50 gating in patients with schizophrenia on stable medication*. Schizophrenia bulletin, 40(5), 1022–1029. https://doi.org/10.1093/schbul/sbt144

Sensory gating deficits are among the core features of schizophrenia. Recently, we reported significantly increased sensorimotor gating following additional administration of single dosages of clonidine to the treatment of stably medicated patients with schizophrenia who, in spite of their medication, showed gating deficits. In the current study, we investigated whether this result is generalizable to filtering of sensory information as a whole, by examining clonidine's effect on P50 suppression in the same group of patients. Methods: In a double-blind, placebo-controlled, randomized yet balanced cross-over design, 20 male schizophrenia patients on stable medication were assessed in a psychophysiological test battery, including a sensory gating paradigm on 5 occasions: once after oral administration of placebo and after single doses of 25, 50, 75, and 150 µg of clonidine. Their results were compared with 20 age-matched healthy male volunteers, who received no treatment. Results: ***Patients showed significantly reduced levels of P50 suppression in the placebo session compared with controls***. All dosages of clonidine significantly diminished these deficits to such levels that they no longer differed significantly from the healthy controls (except the highest dose). Conclusions: This is the first study to show that even a single low dose of clonidine administered to stably medicated patients with schizophrenia not only significantly increases their levels of P50 suppression but also normalizes them. The results indicate that α2-noradrenergic agonists are capable of normalizing levels of P50 gating, which has a potentially high clinical relevance for the medical treatment of schizophrenia.

EEG synchronization.

Passarelli, F., & de Carolis, A. S. (1982). *Effects of chronic treatment with imipramine on the behavioural and electroencephalographic modifications induced by clonidine in the rat.* Neuropharmacology, 21(6), 591–593. https://doi.org/10.1016/0028-3908(82)90053-3.

The influence of repeated administration of imipramine on the EEG and behavioural effects of clonidine has been studied in the rat bearing chronic electrodes. ***Clonidine induced behavioural depression and EEG synchronization in control rats.*** Mydriasis, hyperirritability, stereotyped behaviour and EEG desynchronization were elicited by clonidine on the first and second days after discontinuation of the treatment with imipramine (15 mg/kg, i.p., daily for 21 days). On the 9th. day the animals responded to clonidine with sedation and EEG synchronization. These results support the hypothesis that chronic treatment with tricyclic antidepressant drugs changes the sensitivity of central noradrenergic neurones.

Increase EEG power

Sebban, C., Zhang, X. Q., Tesolin-Decros, B., Millan, M. J., & Spedding, M. (1999). *Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission*. British journal of pharmacology, 128(5), 1045–1054. https://doi.org/10.1038/sj.bjp.0702894.

1. The electroencephalographic (EEG) effects of drugs interacting with dopaminergic and noradrenergic systems were studied in conscious rats. Power spectra (0 - 30 Hz) were recorded from electrodes implanted bilaterally in the prefrontal cortex. Drug effects on EEG power were calculated as the spectral power following drug administration divided by the spectral power after vehicle administration. 2. Dopaminergic agonists at low doses, (apomorphine 0. 01 mg kg-1 s.c., quinpirole 0.01 mg kg-1 i.p.) and dopaminergic antagonists (haloperidol 1 mg kg-1 i.p., raclopride 2.5 mg kg-1 s.c.), which decrease dopaminergic transmission, induced an increase of EEG power. Conversely, dopaminergic agonists at higher doses (apomorphine 0.5 mg kg-1 s.c., quinpirole 0.5 mg kg-1 i.p.) which increase activation of postsynaptic D2 and D3 receptors, induced a decrease of EEG power. 3. The alpha1-adrenoceptor antagonists (phenoxybenzamine 0.64 mg kg-1 s.c., prazosin 0.32 mg kg-1 s.c.) ***and the alpha2-adrenoceptor agonists (UK 14304 0.05 mg kg-1 s.c., clonidine 0.025 mg kg-1 i.p.), which decrease noradrenergic transmission, induced an increase of EEG power.*** Conversely, the alpha1-adrenoceptor agonist, cirazoline (0.05 mg kg-1 s.c.), the adrenergic agent modafinil (250, 350 mg kg-1 i.p.) and alpha2-adrenoceptor antagonists (RX 821002 0.01 mg kg-1 s.c., yohimbine 0.5 mg kg-1 i.p.), which increase noradrenergic transmission, induced a decrease of EEG power. The effects of prazosin (0.64 mg kg-1 s.c.) were dose-dependently antagonized by co-administration with modafinil and cirazoline, but not by apomorphine. 4. In conclusion, pharmacological modulation of dopaminergic and noradrenergic transmission may result in consistent EEG changes: decreased dopaminergic or noradrenergic activity induces an increase of EEG spectral power; while increased dopaminergic or noradrenergic activity decreases EEG spectral power.

----- PROPANOLOL -----

DRUG FACTS

SYNOPSIS: Prescribed to treat high blood pressure, certain types of tremors and to prevent chest pain and migraine headaches. It is a beta blocker that works by relaxing blood vessels, slowing heart rate, decrease blood pressure and improve blood flow.

Increased P3s to auditory stimuli and modulates P3 visual stimuli.

de Rover, M., Brown, S. B., Band, G. P., Giltay, E. J., van Noorden, M. S., van der Wee, N. J., & Nieuwenhuis, S. (2015). *Beta receptor-mediated modulation of the oddball P3 but not error-related ERP components in humans*. Psychopharmacology, 232(17), 3161–3172. https://doi.org/10.1007/s00213-015-3966-2

The P3 is a ubiquitous component of stimulus-driven neural activity that can be observed in scalp electrophysiological recordings. Multiple lines of evidence suggest an important role for the noradrenergic system in the generation of the P3. However, pharmacological studies of the P3 using noradrenergic manipulations have so far been limited to agents that affect α2-receptor signaling. Objectives: The present study investigated whether β-adrenergic receptors are involved in the generation of the P3 and the error positivity (Pe), a component of the event-related potential that is elicited by errors and that bears many similarities to the P3. Methods: We used a double-blind, placebo-controlled, crossover design in which we examined in human participants (N = 16) the effect of a single dose of propranolol (80 mg) on the amplitudes of the P3 observed in visual and auditory oddball tasks and the Pe observed in a flanker task. Results: We found that ***P3s to auditory stimuli were increased in amplitude following treatment with propranolol. Propranolol also modulated the P3 to visual stimuli***, but in a direction dependent on participants' level of trait anxiety: In participants with lower trait anxiety, propranolol resulted in a (non-significant) decrease in P3 amplitudes; in participants with higher trait anxiety, propranolol significantly enhanced P3 amplitude. Propranolol did not modulate the amplitude of the Pe or behavioral measures of conflict/error-related performance adjustments. Conclusions: These results provide the first evidence for involvement of β-adrenergic receptors in P3 generation. We speculate that propranolol affected the P3 through actions at β2-receptors in the locus coeruleus.

ATYPICAL ANTIPSYCHOTICS (ATAPs) (Neuroleptics)

CLASS FACTS

SYNOPSIS: Used in treatments for anxiety, muscle relaxants, panic, seizures, depression, schizophrenia, mania and bipolar disorder.

----- AMISULPRIDE -----

DRUG FACTS

Amisulpride--an open clinical study of a new benzamide in schizophrenic patients.

Mann, K., Bartels, M., Bauer, H., & Gaertner, H. J. (1984). *Amisulpride--an open clinical study of a new benzamide in schizophrenic patients*. Pharmacopsychiatry, 17(4), 111–115. https://doi.org/10.1055/s-2007-1017419.

In pharmacological screening amisulpride produces no catalepsy, no inhibition of stereotypic movements, yet a blockade of drug-induced vomiting. During an open clinical trial lasting 4 weeks, 14 patients (13 schizophrenics) were treated with the compound. The (BPRS-) syndromes anxiety/depression, thought disorder, activity, hostility and the global score showed significant improvement. With the AMDP system significant changes were seen in the paranoid-hallucinatory, manic, depressive and hostility syndromes as well as in the global score. No changes were revealed in anergia (BPRS) and apathia (AMDP). ***In the EEG a significant decrease in the frequency of alpha-rhythms was found.*** The scores of the Simpson-scale for extrapyramidal side effects were low, but there was an acute dystonic reaction in one patient. In three cases akathisia occurred; biperiden administration was necessary three times. In conclusion, amisulpride showed good antipsychotic efficacy without sedation. Contrary to expectations based on the pharmacological screening, we did find extrapyramidal side effects.

Effects of 50mg amisulpride on EEG, psychomotor and cognitive functions in healthy sleep-deprived subjects.

Patat, A., Rosenzweig, P., Miget, N., Allain, H., & Gandon, J. M. (1999). *Effects of 50mg amisulpride on EEG, psychomotor and cognitive functions in healthy sleep-deprived subjects*. Fundamental & clinical pharmacology, 13(5), 582–594. https://doi.org/10.1111/j.1472-8206.1999.tb00365.x.

Amisulpride, a substituted benzamide, binds selectively to the dopamine D2- and D3-receptors. It has higher affinity for limbic compared to striatal dopamine receptors in vivo. At low doses, amisulpride facilitates dopamine transmission via a selective blockade of presynaptic D2- and D3-receptors. Amisulpride is an active antipsychotic compound effective at low doses for negative symptoms and at high doses for positive symptoms of schizophrenia. The CNS profile of multiple doses of a low dosage regimen of amisulpride (50 mg once daily for 4 days) was assessed in a randomised, double-blind, 3-way crossover, placebo-controlled study carried out in 12 young sleep-deprived (for 36 h) subjects, using EEG and various measures of psychomotor and cognitive functions. Caffeine slow release (600 mg) was used as a positive reference. Multiple doses of 50 mg amisulpride once daily were devoid of any detrimental effects on EEG and psychomotor performance and cognitive function after total sleep deprivation. In addition,

***50mg amisulpride partially antagonized the deleterious effects of sleep deprivation on EEG and subjective sedation as shown by trends, and a significant increase in EEG relative beta power and a decrease in subjective sedation*.** These effects were more pronounced at the end of sleep deprivation, suggesting possible alerting effects of amisulpride at this dose level. Caffeine significantly antagonized the detrimental effects of sleep deprivation on vigilance (increase in EEG beta waves, speed of reaction, sustained attention and reduction in subjective sedation). In conclusion, ***the present results demonstrate that 50 mg amisulpride is devoid of detrimental effects on EEG, psychomotor and cognitive performance after sleep deprivation, a situation well-known to amplify such effects if they exist*.** Moreover, some data suggest possible alerting effects of this low dosage regimen of amisulpride.

EEG mapping showed a decrease of delta/theta and increase of beta activity

Saletu, B., Küfferle, B., Grünberger, J., Földes, P., Topitz, A., & Anderer, P. (1994*). Clinical, EEG mapping and psychometric studies in negative schizophrenia: comparative trials with amisulpride and fluphenazine*. Neuropsychobiology, 29(3), 125–135. https://doi.org/10.1159/000119075

Based on recent quantitative EEG findings of increased slow activity in negative schizophrenia indicating organicity, it was hypothesized that neuroleptics decreasing delta/theta activity should be beneficial for schizophrenics with predominantly negative symptoms. Thus, a double-blind, clinical, psychometric and neurophysiological study was carried out in 40 hospitalized patients with unproductive schizophrenia (mean age: 31 years; ICD diagnoses: 295.0, 295.1 and 295.6) who were treated randomly either with the benzamide amisulpride (AMI; n = 19) or low doses of fluphenazine (FLU; n = 21). In the first 2 weeks the daily doses were 50 mg AMI or 2 mg FLU, respectively, from the third week on up to the sixth week 100 mg AMI and 4 mg FLU. Clinical evaluations, psychometry and EEG mapping were performed on day 1 (hours 0 and 4--acute effect), on day 14 (hour 0--subacute effect) and on day 42 (hours 0 and 4--chronic and superimposed effects). Three AMI patients discontinued therapy prematurely because of productive symptoms (days 14, 28 and 35), while in the FLU group 2 patients dropped out due to depressive symptoms (days 21, 28), 1 due to productive symptoms (day 35), 1 due to ineffectiveness (day 28), and 1 because of an akinetic crisis (day 6). Statistical evaluation demonstrated a significant improvement in the AMDP apathy and Andreasen SANS score in both groups with the patients remaining severely ill as rated by the CGI. FLU-treated patients needed significantly more anticholinergic medication than the AMI-treated group. Psychometric evaluation showed in regard to the noopsyche significant improvement after subacute, chronic and superimposed AMI, while FLU-treated patients showed significant improvement only after subacute treatment. AMI was significantly superior to FLU at the hours 0 and 4 of day 42. The thymopsyche improved after subacute, chronic and superimposed administration of both compounds with a significant superiority of AMI on days 14 and 42 (4 h postdrug). ***EEG mapping showed a decrease of delta/theta and increase of beta activity*** as well as an acceleration of the centroid after acute and superimposed AMI on day 42 as compared with baseline; FLU patients exhibited a decrease of delta/theta activity and an acceleration of the total centroid too, while alpha activity was augmented and beta activity tended to be reduced. Our study demonstrated that, in addition to the new benzamide AMI,

FLU in low doses may also be regarded as a neuroleptic with activating properties and may be utilized in the treatment of schizophrenics with predominantly negative symptoms.

----- ARIPIPRAZOLE (Abilify)-----

DRUG FACTS

Increase in slow power and decrease in fast power

Herrmann, W. M., & Kubicki, S. (1981). *Beispiele für die Projektion von Substanzwirkungen typischer Psychopharmaka auf eine elektrophysiologische Messebene [The use of electrophysiological techniques to project typical psychotropic drug effects: some examples (author's transl)].* EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete, 12(1), 21–32.

A long existing hypothesis, i.e. that the EEG effects, in lead O2A2, of typical psychotropic drugs are substance class specific, when given as single oral dosages to healthy volunteers, is discussed. Using the technique of pharmacoelectroencephalograhpy, five typical representatives of neuroleptics, anxiolytics, antidepressives, psychostimulants (Fig. 2) as well as placebo were investigated in 75 volunteers, each receiving one representative of each substance class in a double blind 5-fach change over latin square design (Fig. 3). A five minute EEG record for lead O2A2 was obtained pre, 1 h and 3 hrs post drug intake under RR (Relaxed Recording) conditions. Typical samples of th EEG records are shown in Figs. 4--7. Parametrisation was done using power spectrum analysis. Then 3 x 7 target variables were formed--six relative power values in predetermined frequency bands and the total power between 1.5 and 30.0 Hz for 3 occasions of measurement (Fig. 4--7). Using a (five-group) linear discriminant analysis the substance effects on the EEG were transformed into 5 probability measures for the five substance classes (Fig. 4--7). The present paper should provide a demonstration of some typical examples, using single subjects, of the projection of substance effects onto an electrophysiological level using a vector of 21 components (7 target variables for 3 occasions of measurement) as can be seen from Table 1. Furthermore, the transformation into probability measures of the five substance classes are shown in Table 2. Table 3 shows five examples of projections of substance effects, which do not fit into the classifications to which they belong. An attempt is made to explain, whether single target variables from the power spectrum can contribute differently to the discrimination between single substances of different substance classes. Within the accepted system of 4 psychotropic drug classes, the following variables seem to be of importance: a) The benzodiazepine anxiolytics show a marked increase in beta F1 (12.0--18.0 Hz) power and activity and, related to sedation, an increase in delta F-power and a decrease in alpha-power; b) The psychostimulants of the amphetamine type show an increase in total power and alpha-power, an increase in the power of the frequency ranges near to the alpha-band (slow beta, fast theta) and a decrease in delta F (1.5--5.5 Hz)-power, when delta F-power is high in the pre-values, indicating a stabilization in vigilance; c) ***The neuroleptics show a marked increase in theta F (5.5--8.5 Hz)-power, some increase in the delta F--and a decrease in the beta F1-and beta F3-power;*** d) Tricyclic antidepressants show an interaction between delta F-theta F-, alpha- and beta-power, in the sense of a dissociative shift in vigilance.

Normalized delta and theta

Cañive, J. M., Lewine, J. D., Edgar, J. C., Davis, J. T., Miller, G. A., Torres, F., & Tuason, V. B. (1998). *Spontaneous brain magnetic activity in schizophrenia patients treated with aripiprazole*. Psychopharmacology bulletin, 34(1), 101–105..

This magnetoencaphalographic (MEG) study was conducted as part of a multicenter clinical trial to study the efficacy of aripiprazole. Participants included 5 DSM-IV schizophrenia subjects and 10 age-matched normal controls. The schizophrenia subjects underwent a second MEG recording after 8 weeks of open-label treatment with aripiprazole. Overall, control subjects showed no abnormal spontaneous magnetic brain activity. ***At washout, 3 patients showed increased delta and theta activity along with paraxosymal bitemporal slow waves*.** In 2 of these patients, the slow waves were generated in the superior temporal plane, as determined by dipole modeling. In the third patient, the slow waves appeared to have been generated at multiple regions throughout the temporal and inferior parietal lobes. As a group, schizophrenia patients, when compared with normal controls, demonstrated significant decreases in alpha peak frequency and power. Following treatment**, *aripiprazole had a significant normalizing effect on delta and theta activity***. Patients on ***aripiprazole continued to demonstrate significant abnormalities in alpha frequency and power***.

Normalized EEG?

Okruszek, L., Jernajczyk, W., Wierzbicka, A., Waliniowska, E., Jakubczyk, T., Jarema, M., & Wichniak, A. (2014). *Daytime sleepiness and EEG abnormalities in patients treated with second generation antipsychotic agents*. Pharmacological reports : PR, 66(6), 1077–1082. https://doi.org/10.1016/j.pharep.2014.07.007.

Background: The aim of this study was to verify whether or not an increased prevalence of excessive daytime sleepiness (EDS) or EEG abnormalities is observed in patients with schizophrenia spectrum disorders (SSD), and to compare the effects of second generation antipsychotics (SGA) on patients' daytime sleepiness level and EEG recordings. **Methods:** EEG recordings and self-reports of EDS, assessed with Epworth (ESS) and Stanford (SSS) Sleepiness Scales, were compared between 244 patients with SSD and 82 patients with anxiety, personality or behavioral disorders (non-psychotic disorders, NPD). To examine the effects of various SGA, patients treated in monotherapy with ***aripiprazole, olanzapine, clozapine, risperidone and sertindole were compared. Results: A higher prevalence of abnormal EEG recordings was observed in SSD patients.*** No significant differences in average daytime sleepiness were found between patients with SSD and NPD; however, patients with SSD had longer sleep duration. Aripiprazole treatment was ***associated with significantly smaller and less frequent EEG abnormalities than treatment with any other SGA, while treatment with clozapine and olanzapine was related to an increased prevalence of severe EEG abnormalities.*** Patients with SSD treated with SGA in monotherapy were less sleepy than unmedicated patients with NPD. **Conclusions:** Although ***antipsychotics may have profound effects on EEG patients with schizophrenia who do not have higher daytime sleepiness than patients with anxiety/personality disorders.*** Patients with schizophrenia may compensate sedative effects of antipsychotic treatment with sleep duration prolongation and report even less sleepiness than non-psychotic patients.

----- CLOZAPINE -----

(Clozaril, Azaleptin, Leponex, Fazaclo, Froidir; Denzapine, Klozapol, Clopine, and Zaponex)

DRUG FACTS

Increase in slow wave power

Ozaki, T., Toyomaki, A., Hashimoto, N., & Kusumi, I. (2021). *Quantitative Resting State Electroencephalography in Patients with Schizophrenia Spectrum Disorders Treated with Strict Monotherapy Using Atypical Antipsychotics*. Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology, 19(2), 313–322. https://doi.org/10.9758/cpn.2021.19.2.313.

Objective: The effect of antipsychotic drugs on quantitative electroencephalography (EEG) has been mainly examined by the administration of a single test dose or among patients using combinations of other psychotropic drugs. We therefore investigated the effects of strict monotherapy with antipsychotic drugs on quantitative EEG among schizophrenia patients. **Methods:** Data from 2,364 medical reports with EEG results from psychiatric patients admitted to the Hokkaido University Hospital were used. We extracted EEG records of patients who were diagnosed with schizophrenia spectrum disorders and who were either undergoing strict antipsychotic monotherapy or were completely free of psychotropic drugs. The spectral power was compared between drug-free patients and patients using antipsychotic drugs. We also performed multiple regression analysis to evaluate the relationship between spectral power and the chlorpromazine equivalent daily dose of antipsychotics in all the patients. **Results:** We included 31 monotherapy and 20 drug-free patients. Compared with drug-free patients, ***patients receiving antipsychotic drugs demonstrated significant increases in theta, alpha and beta power. When patients taking different types of antipsychotics were compared with drug-free patients,*** we found no significant change in any spectrum power for the aripiprazole or blonanserin groups. Patients taking risperidone demonstrated significant increases in alpha and beta power. Patients ***taking clozapine and olanzapine demonstrated significant slow wave increases***. Multiple regression analysis revealed that the chlorpromazine equivalent dose was positively associated with theta power. Conclusion: Use of ***any antipsychotic drug by patients was associated with a dose-dependent increase in theta power.*** However, each type of antipsychotic demonstrated different spectral power changes.

----- OLANZAPINE (Zyprexa)-----

DRUG FACTS

Importance in monitoring EEG

Degner, D., Nitsche, M. A., Bias, F., Rüther, E., & Reulbach, U. (2011). *EEG alterations during treatment with olanzapine.* European Archives of Psychiatry and Clinical Neuroscience, 261(7), 483–488. https://doi.org/10.1007/s00406-011-0208-4.

The aim of this naturalistic observational study was to investigate EEG alterations in patients under olanzapine treatment with a special regard to olanzapine dose and plasma

concentration. Twenty-two in-patients of a psychiatric university ward with the monodiagnosis of paranoid schizophrenia (ICD-10: F20.0), who received a monotherapy of olanzapine were included in this study. All patients had a normal alpha-EEG before drug therapy, and did not suffer from brain-organic dysfunctions, as verified by clinical examination and cMRI scans. EEG and olanzapine plasma levels were determined under steady-state conditions (between 18 and 22 days after begin of treatment). In 9 patients (40.9%), pathological EEG changes (one with spike-waves) consecutive to olanzapine treatment were observed. The dose of olanzapine was significantly higher in patients with changes of the EEG than in patients without changes (24.4 mg/day (SD: 8.1) vs. 12.7 mg/day (SD: 4.8); T = -4.3, df = 21, P < 0.001). In patients with EEG changes, the blood plasma concentration of olanzapine (45.6 µg/l (SD: 30.9) vs. 26.3 µg/l (SD: 21.6) tended to be also higher. The sensitivity of olanzapine dosage to predict EEG changes was 66.7%, the specificity 100% (Youden-index: 0.67). ***EEG abnormalities during olanzapine treatment are common. These are significantly dose dependent. Thus, EEG control recordings should be mandatory during olanzapine treatment with special emphasis on dosages exceeding 20 mg per day, although keeping in mind that EEGs have only a limited predictive power regarding future epileptic seizures.***

Increase in awake theta and loss of slow wave sleep

Giménez, S., Romero, S., Mañanas, M. A., & Barbanoj, M. J. (2011). *Waking and sleep electroencephalogram variables as human sleep homeostatic process biomarkers after drug administration.* Neuropsychobiology, 63(4), 252–260. https://doi.org/10.1159/000321806.

Background/aims: The correlation between theta activity during wakefulness and slow-wave activity (SWA) during sleep observed after sleep deprivation suggests such patterns can be used as electroencephalogram (EEG) biomarkers of the sleep homeostasis process. Since these EEG components would be very useful objective measures to assess CNS drug effects, we investigated whether the relationship between sleep homeostatic EEG biomarkers could be reproduced after an experimental pharmacological intervention. **Methods:** Seventeen healthy volunteers took part in a phase I randomized, double-blind, crossover design study. To increase sleep propensity, all participants received a single morning oral dose of olanzapine (5 mg) and placebo. Quantitative EEG analysis was done by power spectra calculations: theta activity (3.5-7.5 Hz) during wakefulness and SWA (0.5-4.0 Hz) during sleep. The relationship between the 2 EEG parameters was assessed by correlating the rise rate (percent/hour) of theta activity in wakefulness and the increase (percent) of SWA in the first non-REM sleep episode. **Results:** Following olanzapine administration we observed ***increases in theta activity during wakefulness, and increases in total sleep time, sleep efficiency and slow-wave sleep time during sleep. However, a weak and unreliable correlation was observed between the increases in theta activity and changes in sleep SWA***. **Conclusions:** From these results, we cannot affirm that these waking and sleep EEG variables behave as biomarkers of human sleep homeostasis after drug administration. It is possible that these EEG biomarkers reflect different physiological mechanisms if they are assessed during drug CNS effects.

----- QUETIAPINE (Seroquel) -----

DRUG FACTS

Reduced P50 suppression

Oranje, B., Aggernaes, B., Rasmussen, H., Ebdrup, B. H., & Glenthøj, B. Y. (2013). *P50 suppression and its neural generators in antipsychotic-naive first-episode schizophrenia before and after 6 months of quetiapine treatment*. Schizophrenia bulletin, 39(2), 472–480. https://doi.org/10.1093/schbul/sbr183

Background: Numerous studies have demonstrated sensory gating deficits in schizophrenia. However, only a few longitudinal studies report on the effects of antipsychotic treatment on sensory gating deficits and their results are inconsistent. In the present study, P50 suppression and its neural generators were investigated in antipsychotic-naïve first-episode patients with schizophrenia before and after 6 months of treatment with quetiapine. **Methods:** Thirty-four antipsychotic-naïve first-episode schizophrenia patients and age and gender matched healthy controls were tested in an auditory sensory gating paradigm at baseline and after 6 months. During this period, the patients were treated with quetiapine, while controls received no treatment. Sixteen patients completed the study. **Results:** Patients ***showed significant reduced P50 suppression compared with controls at baseline but not at follow-up. Furthermore, a significant positive correlation between baseline P50 suppression and dose of quetiapine at follow-up was found.*** P50 suppression in patients receiving above median dosages of quetiapine increased significantly from baseline to follow-up. At baseline, a frontocentral source was significantly more active in patients than in controls at the time of the testing stimulus. **Conclusions:** The present findings suggest that P50 suppression deficits are already present at an early stage of schizophrenia. Furthermore, particularly those patients with more severe gating deficits appeared to need higher dosages of quetiapine, although their clinical symptoms did not seem to indicate this. Quetiapine treatment significantly improved these gating deficits. Furthermore, a frontocentral source in the brain appeared to be involved in the deficient P50 gating of the patients.

Decreased latency and increased amplitude of P300

Park, E. J., Han, S. I., & Jeon, Y. W. (2010). *Auditory and visual P300 reflecting cognitive improvement in patients with schizophrenia with quetiapine: a pilot study*. Progress in neuro-psychopharmacology & biological psychiatry, 34(4), 674–680. https://doi.org/10.1016/j.pnpbp.2010.03.011.

We recorded event-related potentials (ERPs) in patients with schizophrenia before and after treatment with quetiapine, to investigate this drug's effects on cognitive function. Auditory and visual oddball stimulus discrimination paradigms were presented to patients with schizophrenia (N=20) before and after 3months' treatment with quetiapine. The 2-stimulus auditory oddball paradigm used a standard tone (1000Hz, 75dB, 80%) and a target tone (2000Hz, 75dB, 20%). The 2-stimulus visual oddball paradigm used a standard stimulus (small circle, 80%) and a target stimulus (large circle, 20%). Patients' severity of psychopathology was initially evaluated with the Positive and Negative Syndrome Scale (PANSS) and was likewise re-evaluated after treatment. ***After treatment with quetiapine, patients' P300 amplitudes increased over baseline for both tasks (auditory stimuli, P<0.01; visual stimuli, P<0.01) and their P300***

latencies for both target stimuli decreased significantly (auditory stimuli, P<0.001; visual stimuli, P<0.01). Visual P300 amplitude was negatively correlated with the severity of positive symptoms at the Fz electrode before the treatment (r=-0.45, P<0.05). After treatment with quetiapine, there were no significant correlations between severity of positive or negative symptoms and visual P300 amplitudes for midline electrodes. *These* ***findings suggest that the reduced and delayed P300 may be a state marker for schizophrenia, which may in turn be modulated by positive symptoms, and also suggest that the amplitude and latency for both auditory and visual tasks may be decreased by quetiapine treatment*****.*** Based on these results, we suggest that the atypical antipsychotic quetiapine may improve some aspects of cognitive domains in patients with schizophrenia.

Improvements in P400 in minority of subjects

Zhang Y, Lehmann M, Shobeiry A, Höfer D, Johannes S, Emrich HM, Dietrich DE. *Effects of quetiapine on cognitive functions in schizophrenic patients: a preliminary single-trial ERP analysis*. Pharmacopsychiatry. 2009 Jul;42(4):129-34. doi: 10.1055/s-0028-1112133. Epub 2009 Jul 7. PMID: 19585390.

Aim: The study aimed to explore by means of single-trial event-related potentials (ERPs), whether and how the medication change from older neuroleptics to quetiapine in schizophrenic patients led to a significant cognitive enhancement. This single-trial ERP analysis helps to investigate attention and memory processes in the single patient before and after treatment. **Patients and methods:** Thirteen schizophrenic patients (mean age: 40.1+/-13.5 years) were followed up for 16 weeks and assessed for changes of clinical symptoms and ERP components P300 representing target detection processes and N400 indexing context integration in word recognition processes. Three subjects had to be excluded from the ERP recording sessions because of excessive blink artefacts and movements. **Results:** Regarding ***the P300 components of the target detection, there were significant increases of amplitudes in 5 of 10 patients (50%) at week 16 comparing with week 0. Regarding the N400 components of the word recognition, there were significant increases of amplitudes in 4 of 10 patients (40%) at week 16 comparing with week 0.*** **Discussion:** The mean scores of PANSS, MADRS, Bf-S, SCL-90 and CGI-S at the end of study (week 16) showed significant improvements compared to the baselines (week 0) ($p<0.05$). During the study, no extrapyramidal symptoms as well as akathisia were reported after quetiapine treatment. These preliminary data suggest that quetiapine might partially improve the cognitive functions in the context integration and target detection processing in these patients. This technical procedure (single-trial ERP) may help to differentially assess cognitive enhancements in each single patient under treatment.

----- REMOXIPRIDE (Roxiam) -----

DRUG FACTS

Synopsis: Was withdrawn in 1993 after it was found to be associated with an increased incidence of aplastic anemia.

EEG-brain mapping in schizophrenics with predominantly positive and negative symptoms. Comparative studies with remoxipride/haloperidol.

Saletu, B., Küfferle, B., Anderer, P., Grünberger, J., & Steinberger, K. (1990). *EEG-brain mapping in schizophrenics with predominantly positive and negative symptoms.* Comparative studies with remoxipride/haloperidol. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 1(1), 27–36. https://doi.org/10.1016/0924-977x(90)90007-w.

EEG brain maps obtained in 48 drug-free hospitalized schizophrenics diagnosed according to DSMIII demonstrated significant differences as compared with normal controls characterized by a ***decrease of alpha-1 activity, increase of beta activity and acceleration of the centroid*.** These findings suggest a state of sustained hyperarousal in schizophrenia. While the patients with negative schizophrenia showed ***a bi-temporal and frontal augmentation of delta/theta activity***, patients with florid symptomatology exhibited just the opposite findings***. Alpha-1 activity was attenuated, beta activity augmented in both groups with the findings more pronounced in the positive schizophrenia group.*** The increase of slow activity suggests an organic factor in the pathogenesis of the negative syndrome, which was supported by correlation maps between EEG measures and the apathy syndrome as measured by the AMDP system. ***Treatment of schizophrenics with predominantly positive symptoms with 2 different neuroleptics such as remoxipride and haloperidol resulted also in differential effects on brain activity: while haloperidol augmented delta/theta and alpha activity and decreased beta activity, remoxipride produced a decrease of slow and increase of beta activity as well as an acceleration of the centroid suggesting vigilance-promoting properties of the drug*.** These differential effects on the neurophysiological level were also reflected at the behavioural one evaluated by psychometry, while global clinical evaluation showed, as expected, similar improvement with both drugs (apart from extrapyramidal side effects being significantly more pronounced after haloperidol than remoxipride). Our findings suggest that brain electrical signal topography is a promising method in regard to a better understanding of pathogenesis and treatment in schizophrenia.

----- RISPERIDONE -----

DRUG FACTS

Increase of P50 ERP

Csomor, P. A., Preller, K. H., Geyer, M. A., Studerus, E., Huber, T., & Vollenweider, F. X. (2014). *Influence of aripiprazole, risperidone, and amisulpride on sensory and sensorimotor gating in healthy 'low and high gating' humans and relation to psychometry*. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 39(10), 2485–2496. https://doi.org/10.1038/npp.2014.102

Despite advances in the treatment of schizophrenia spectrum disorders with atypical antipsychotics (AAPs), there is still need for compounds with improved efficacy/side-effect ratios. Evidence from challenge studies suggests that the assessment of gating functions in humans and rodents with naturally low-gating levels might be a useful model to screen for novel compounds with antipsychotic properties. To further evaluate and extend this translational approach, three AAPs were examined. Compounds without antipsychotic properties served as negative control treatments. In a placebo-controlled, within-subject design, healthy males received either single doses of aripiprazole and **risperidone** (n=28),

amisulpride and lorazepam (n=30), or modafinil and valproate (n=30), and placebo. Prepulse inhibiton (PPI) and P50 suppression were assessed. Clinically associated symptoms were evaluated using the SCL-90-R. ***Aripiprazole, risperidone, and amisulpride increased P50 suppression in low P50 gaters. Lorazepam, modafinil, and valproate did not influence P50 suppression in low gaters***. Furthermore, low P50 gaters scored significantly higher on the SCL-90-R than high P50 gaters. Aripiprazole increased PPI in low PPI gaters, whereas modafinil and lorazepam attenuated PPI in both groups. Risperidone, amisulpride, and valproate did not influence PPI**.** P50 suppression in low gaters appears to be an antipsychotic-sensitive neurophysiologic marker. This conclusion is supported by the association of low P50 suppression and higher clinically associated scores. Furthermore, PPI might be sensitive for atypical mechanisms of antipsychotic medication. The translational model investigating differential effects of AAPs on gating in healthy subjects with naturally low gating can be beneficial for phase II/III development plans by providing additional information for critical decision making.

Effects from lower doses

Dias Alves, M., Micoulaud-Franchi, J. A., Simon, N., & Vion-Dury, J. (2018). *Electroencephalogram Modifications Associated With Atypical Strict Antipsychotic Monotherapies.* Journal of clinical psychopharmacology, 38(6), 555–562. https://doi.org/10.1097/JCP.0000000000000953

Background: Antipsychotics produce electroencephalogram (EEG) modifications and increase the risk of epileptic seizure. These modifications remain sparsely studied specifically for atypical antipsychotics. In this context, our study focuses on EEG modifications associated with atypical strict antipsychotic monotherapies. **Methods:** Electroencephalogram recordings of 84 psychiatric patients treated with atypical antipsychotics in strict monotherapy (clozapine, n = 22; aripiprazole, n = 22; olanzapine, n = 17; risperidone, n = 9; quetiapine, n = 8; risperidone long-acting injection, n = 4; and paliperidone long-acting injection, n = 2) were analyzed. The modifications were ranked according to both slowing and excitability scores. **Results:** Electroencephalogram modifications (in 51 subjects, 60.71%) were graded according to 4 stages combining general slowing and sharp slow waves and/or epileptiform activities. ***The presence of sharp or epileptiform activities was significantly greater for clozapine (90.9%) compared with other second-generation antipsychotics (aripiprazole, 50%; olanzapine, 58.8%; quetiapine, 37.5%; risperidone, 44.4%)*****.** Age, duration of disease progression, and diagnosis were not associated as risk factors. Electroencephalogram modifications were associated with lower doses for treatment with quetiapine but not for specific antipsychotics. Electroencephalogram modifications and severe excitability were associated with higher chlorpromazine equivalent doses. ***Conclusions: Atypical antipsychotics (clozapine, aripiprazole, quetiapine, olanzapine, and risperidone) induce EEG modifications, and these are significantly greater for clozapine and appear dependent on chlorpromazine equivalent dose.*** No encephalopathy was observed in these antipsychotic monotherapies, whatever dose.

Shorter latency in P300

Iwanami, A. (2001). *Effects of Risperidone on Event-related Potentials in Schizophrenic Patients.* Pharmacopsychiatry, 34(2), 73–79. https://doi.org/10.1055/s-2001-15181

In order to examine the effects of risperidone on cognitive impairment in schizophrenia, event-related potentials (ERPs) were recorded before and after switching from conventional neuroleptics to risperidone in schizophrenic patients. ERPs were recorded during two auditory discrimination tasks (an oddball task and a distraction task) in 10 medicated schizophrenic patients during conventional neuroleptic and risperidone treatments. The amplitudes and latencies of N 100 and P300 component were measured in ERPs for target stimuli in the oddball task and in ERPs for target and novel stimuli in the distraction task. Although N 100 amplitude and latency and P 300 amplitude did not change significantly after switching the drug compared to that during conventional neuroleptic treatment, ***P300 latency for target stimuli shortened significantly during risperidone treatment in both tasks, accompanied by the shortening of the reaction time in the distraction task*****.** The P 300 latency change did not correlate with the change of the severity of psychopathology. These ***findings suggest that risperidone may speed the information processing in schizophrenic patients, contributing to the improvement of cognitive functions*****.**

Risperidone increased N400 latency

Wu, R.-Q., Lin, C.-G., Zhang, W., Lin, X.-D., Chen, X.-S., Chen, C., Zhang, L.-J., Huang, Z.-Y., Chen, G.-D., Xu, D.-L., Lin, Z.-G., & Zhang, M.-D. (2018*). Effects of Risperidone and Paliperidone on Brain-Derived Neurotrophic Factor and N400 in First-Episode Schizophrenia*. Chinese Medical Journal, 131(19), 2297–2301. https://doi.org/10.4103/0366-6999.241802**.**

Background: Risperidone and paliperidone have been the mainstay treatment for schizophrenia and their potential role in neuroprotection could be associated with brain-derived neurotrophic factor (BDNF) and N400 (an event-related brain potential component). So far, different effects on both BDNF and N400 were reported in relation to various antipsychotic treatments. However, few studies have been conducted on the mechanism of risperidone and paliperidone on BDNF and N400. This study aimed to compare the effects of risperidone and paliperidone on BDNF and the N400 component of the event-related brain potential in patients with first-episode schizophrenia. **Methods:** Ninety-eight patients with first-episode schizophrenia were randomly divided into the risperidone and paliperidone groups and treated with risperidone and paliperidone, respectively, for 12 weeks. Serum BDNF level, the latency, and amplitude of the N400 event-related potential before and after the treatment and Positive and Negative Syndrome Scale (PANSS) scores were compared between the two groups. **Results:** A total of 94 patients were included in the final analysis (47 patients in each group). After the treatment, the serum BDNF levels in both groups increased (all $P < 0.01$), while no significant difference in serum BDNF level was found between the groups before and after the treatment (all $P > 0.05$). After the treatment, N400 amplitudes were increased (from 4.73 ± 2.86 μv and 4.51 ± 4.63 μv to 5.35 ± 4.18 μv and 5.52 ± 3.08 μv, respectively) under congruent condition in both risperidone and paliperidone groups (all $P < 0.01$). Under incongruent conditions, ***the N400 latencies were shortened in the paliperidone group (from 424.13 ± 110.42 ms to 4.7.41 ± 154.59 ms, P < 0.05), and the N400 amplitudes were increased in the risperidone group (from 5.80 ± 3.50 μv to 7.17 ± 5.51 μv, P < 0.01*****).** After treatment, the total PANSS score in both groups decreased significantly (all $P < 0.01$), but the difference between the groups was not significant ($P > 0.05$). A negative correlation between the reduction rate of the PANSS score and the increase in serum BDNF level after the treatment was found in the paliperidone group but

not in the risperidone group. **Conclusions:** Both ***risperidone and paliperidone could increase the serum BDNF levels in patients with first-episode schizophrenia and improve their cognitive function (N400 latency and amplitude),*** but their antipsychotic mechanisms might differ.

----- SULPIRIDE (Dogmatil) -----

DRUG FACTS

Anterior and posterior differences

Chavanon, M. L., Wacker, J., & Stemmler, G. (2013). *Paradoxical dopaminergic drug effects in extraversion: dose- and time-dependent effects of sulpiride on EEG theta activity*. Frontiers in human neuroscience, 7, 117. https://doi.org/10.3389/fnhum.2013.00117

Dopaminergic drugs frequently produce paradoxical effects depending on baseline performance levels, genotype, or personality traits. The present study for the first time aimed to specify the mechanisms underlying such opposite effects using the following recently reported scenario as an example: depending on the personality trait agentic extraversion (agentic facet, aE; i.e., assertiveness, dominance, ambition, positive emotionality) the ***selective dopamine D2 receptor antagonist sulpiride (200 mg) had opposite effects on resting posterior vs. anterior theta activity in the electroencephalogram (EEG)***. In order to better describe these opposite pharmaco-EEG effects and to generate hypotheses regarding the underlying mechanisms, we measured the EEG intermittently over 5 h in 80 healthy male volunteers extremely high or low in aE who had received either placebo or one of three doses of sulpiride (50, 200, or 400 mg). The findings suggest a model postulating stronger pre- vs. postsynaptic subreceptor effects in high aE individuals compared to low aE individuals. Future studies may now systematically apply the model to other examples of paradoxical dopaminergic drug effects and examine the molecular basis of individual differences in pre- vs. postsynaptic dopamine D2 subreceptor sensitivities and densities.

Decreased alpha power

Liem-Moolenaar, M., Gray, F., de Visser, S., Franson, K., Schoemaker, R., Schmitt, J., Cohen, A., & van Gerven, J. (2010). Psychomotor and cognitive effects of a single oral dose of talnetant (SB223412) in healthy volunteers compared with placebo or haloperidol. Journal of Psychopharmacology (Oxford), 24(1), 73–82. https://doi.org/10.1177/0269881108094524

Central Nervous System (CNS) effects of talnetant, an NK-3 antagonist in development for schizophrenia, were compared to those of haloperidol and placebo. The study was randomised, double-blind, three-way crossover of talnetant 200 mg, haloperidol 3 mg or placebo. Twelve healthy males participated and EEG, saccadic and smooth pursuit eye movements, adaptive tracking, body sway, finger tapping, hormones, visual analogue scales (VAS) for alertness, mood and calmness and psychedelic effects, left/right distraction task, Tower of London and Visual and Verbal Learning Task were assessed. Haloperidol showed (difference to placebo; 95% CI; p-value) decreases in EEG alpha power (-0.87microV; -1.51/-0.22; p = 0.0110), saccadic inaccuracy (2.0%; 0.5/3.6; p = 0.0133), smooth pursuit eye movements (-7.5%; -12.0/-3.0; p = 0.0026), adaptive tracking (-3.5%; -5.4/-1.7; p = 0.0009), alertness (-6.8 mm; -11.1/-2.4; p = 0.0039),

negative mood (-4.6 mm; -8.6/-0.6; p = 0.0266), the ability to control thoughts (1.2 mm; 0.2/2.3; p = 0.0214), and an increase of serum prolactin (ratio 4.1; 3.0/5.6; p < 0.0001). Talnetant ***showed decreased alpha power (-0.69 muV; -1.34/-0.04; p = 0.0390***), improved adaptive tracking (1.9%; 0.1/3.7; p = 0.0370) and reduced calmness on VAS Bond and Lader (-4.5 mm; -8.0/-1.0; p = 0.0151). Haloperidol effects were predominantly CNS-depressant, while those of talnetant were slightly stimulatory. The results suggest that talnetant penetrates the brain, but it remains to be established whether this dose is sufficient and whether the observed effect profile is class-specific for NK3-antagonists.

N300 a marker for drug

Lueckel, M., Panitz, C., Nater, U. M., & Mueller, E. M. (2018). *Reliability and robustness of feedback-evoked brain-heart coupling after placebo, dopamine, and noradrenaline challenge.* International Journal of Psychophysiology, 132(Pt B), 298–310. https://doi.org/10.1016/j.ijpsycho.2018.01.010.

External and internal performance feedback triggers not only neural but also cardiac modulations, suggesting communication between brain and heart during feedback processing. Using Cardio-Electroencephalographic Covariance Tracing (CECT), it has accordingly been shown that feedback-evoked centromedial single-trial EEG at the P300 latency intraindividually predicts subsequent changes in heart period - the so called N300H phenomenon. While previous findings suggest that the N300H depends on serotonin, its relationship to central dopamine and noradrenaline is currently unknown. Here, we tested (1) the psychometric properties of this CECT-based component and (2) its putative catecholaminergic mechanisms. N = 54 healthy male participants received either a α2-adrenoceptor antagonist (yohimbine, 10 mg; n = 18), D_2-dopamine-receptor antagonist (sulpiride, 200 mg; n = 18), or a placebo (n = 18). Afterwards, they performed a gambling task with feedback after each trial, while EEG and ECG were recorded. Feedback ***successfully evoked a significant N300H both across all 54 participants and within each substance group. Importantly, we show that N300H can be reliably measured in a priori defined time windows*** with as few as 240 feedback trials and is relatively unaffected when removing extreme single-trial values. However, we could not find any significant substance effects on N300H magnitude as well as on univariate feedback-related measures (FRN, P300, heart period). Altogether, the ***N300H component proves as a robust and reliable marker of cortico-cardiac coupling evoked by feedback. Furthermore, these findings suggest a subordinate role of catecholamines (i.e., noradrenaline and dopamine) and sympathetic pathways in feedback-evoked brain-heart communication as measured with N300H.***

Midline changes

Mueller, E. M., Makeig, S., Stemmler, G., Hennig, J., & Wacker, J. (2011). *Dopamine effects on human error processing depend on catechol-O-methyltransferase VAL158MET genotype.* The Journal of neuroscience : the official journal of the Society for Neuroscience, 31(44), 15818–15825. https://doi.org/10.1523/JNEUROSCI.2103-11.2011.

Brain dopamine (DA) has been linked to error processing. Because high and low (vs medium) prefrontal cortex (PFC) DA levels may facilitate D2-receptor-related modulations of PFC neural activation patterns, we hypothesized that high and low DA predicts increased error-specific

transitions of PFC activity. Male human participants (n = 169) were genotyped for the catechol-O-methyltransferase (COMT) Val158Met polymorphism, associated with low (Val) and medium (Met) PFC DA levels. In addition, DRD2TaqIa and 5-HTTLPR, associated with striatal D(2) receptor density and serotonin uptake, respectively, were assessed. Participants received placebo or a selective DA-D(2) receptor blocker (sulpiride, 200 mg) and performed a Flanker task. ***EEG was recorded and decomposed into independent brain components (ICs) using independent component analysis. After errors, participants displayed (1) a negative deflection in ICs source-localized to the proximity of the anterior midcingulate cortex [IC-error-related negativity (IC-ERN)], (2) increased midcingulate cortex IC power in the delta/theta frequency range, and (3) slowing in the subsequent trial [posterror slowing (PES)]. Importantly, all, IC-ERN, delta/theta power, and PES were modulated by COMT × Substance interactions such that the Val allele predicted elevated IC-ERN, delta/theta power, and PES after placebo; this association was reversed under sulpiride.*** Because low doses of sulpiride presumably increase PFC DA levels, the COMT × Substance interaction supports the hypothesis that low (Val, placebo) and high (Met, sulpiride) versus medium (Val, sulpiride; Met, placebo) DA levels elevate reactivity to errors. Consistent with an influence of serotonin on PFC DA, the COMT × Substance interaction was modulated by 5-HTTLPR.

----- TRIAZOLAM (Halcion) -----

DRUG FACTS

Decrease in right frontal 9-10 Hz activity

McNaughton, N., Swart, C., Neo, P., Bates, V., & Glue, P. (2013). *Anti-anxiety drugs reduce conflict-specific "theta"--a possible human anxiety-specific biomarker*. Journal of affective disorders, 148(1), 104–111. https://doi.org/10.1016/j.jad.2012.11.057.

Background: Syndromes of fear/anxiety are currently ill-defined, with no accepted human biomarkers for anxiety-specific processes. A unique common neural action of different classes of anxiolytic drugs may provide such a biomarker. In rodents, a reduction in low frequency (4-12 Hz; "theta") brain rhythmicity is produced by all anxiolytics (even those lacking panicolytic or antidepressant action) and not by any non-anxiolytics. This rhythmicity is a key property of the Behavioural Inhibition System (BIS) postulated to be one neural substrate of anxiety. We sought homologous anxiolytic-sensitive changes in human surface EEG rhythmicity. **Method:** Thirty-four healthy volunteers in parallel groups were administered double blind single doses of triazolam 0.25mg, buspirone 10mg or placebo 1 hour prior to completing the stop-signal task. Right frontal conflict-specific EEG power (previously shown to correlate with trait anxiety and neuroticism in this task) was extracted as a contrast between trials with balanced approach-avoidance (stop-go) conflict and the average of trials with net approach and net avoidance. **Results:** Compared with placebo, ***both triazolam and buspirone decreased right-frontal, 9-10 Hz, conflict-specific-powe*****r. Limitations:** Only one dose of each of only two classes of anxiolytic and no non-anxiolytics were tested, so additional tests are needed to determine generality. **Conclusions:** There is a distinct rhythmic system in humans that is sensitive to both classical/GABAergic and novel/serotonergic anxiolytics. This conflict-specific rhythmicity should provide a biomarker, with a strong pre-clinical neuropsychology, for a novel approach to classifying anxiety disorders.

Goal specific EEG rhythmicity shifts in 4-12 Hz

Shadli, S. M., Glue, P., McIntosh, J., & McNaughton, N. (2015). *An improved human anxiety process biomarker: characterization of frequency band, personality and pharmacology*. Translational psychiatry, 5(12), e699. https://doi.org/10.1038/tp.2015.188

Anxiety disorders are among the most common mental illness in the western world with a major impact on disability. But their diagnosis has lacked objective biomarkers. We previously demonstrated a human anxiety process biomarker, goal-conflict-specific electroencephalography (EEG) rhythmicity (GCSR) in the stop-signal task (SST). Here we have developed and characterized an improved test appropriate for clinical group testing. We modified the SST to produce balanced numbers of trials in clearly separated stop-signal delay groups. As previously, ***right frontal (F8) GCSR was extracted as the difference in EEG log Fourier power*** between matching stop and go trials (that is, stop-signal-specific power) of a quadratic contrast of the three delay values (that is, power when stopping and going are in balanced conflict compared with the average of when stopping or going is greater). Separate experiments assessed drug sensitivity (n=34) and personality relations (n=59). GCSR in this new SST was reduced by three chemically distinct anxiolytic drugs (administered double-blind): buspirone (10 mg), triazolam (0.25 mg) and pregabalin (75 mg); had a frequency range (4-12 Hz) consistent with rodent model data; and positively correlated significantly with neuroticism and nonsignificantly with trait anxiety scores. GCSR, measured in our new form of the SST, should be suitable as a biomarker for one specific anxiety process in the testing of clinical groups and novel drugs and in the development of measures suitable for individual diagnosis.

----- ZOTEPINE (Zoleptil) -----

DRUG FACTS

Zotepine was never approved by the FDA. In 1993, it was classified as inactive drug substance (Status I, Type II) and in 1995 the FDA studied the manufacturing procedures of Zotepine tablets in Germany, but the status remained inactive. When the analysis of antipsychotics was retaken in 2016 by the FDA, zotepine did not reach the threshold effect to be further studied. In the EMA, by 2015 it was under pharmacovigilance studies for the potential treatment of acute renal failure.

Relation between blood levels and average quantitative EEG and psychometrically assessed pharmacodynamic changes following zotepine.

Saletu, B., Grünberger, J., Anderer, P., & Chwatal, K. (1991). *Zur Beziehung zwischen Blutspiegeln und mittels quantitativem EEG und Psychometrie gemessenen pharmakodynamischen Veränderungen nach Zotepin [Relation between blood levels and average quantitative EEG and psychometrically assessed pharmacodynamic changes following zotepine]*. Fortschritte der Neurologie-Psychiatrie, 59 Suppl 1, 45–55. https://doi.org/10.1055/s-2007-1000735.

In a double-blind, placebo-controlled study, the relationships between blood levels and pharmacodynamics of zotepine were investigated in 15 healthy subjects. They received randomized at weekly intervals single oral doses of 25, 50 and 100 mg zotepine and 50 mg

clozapin as reference substance. Blood sampling for zotepine and prolactin plasma levels, quantitative EEG analyses, psychometry and tolerability measures were carried out at the hours 0, 1, 2, 4, 6 and 8. There was a dose-dependent increase in zotepine plasma levels with a tmax between 2-4 hours post-drug and cmax: 6.9, 14.8 and 19.6 ng/ml for the 3 doses, respectively and a slow decline thereafter. Prolactin levels also rose dose dependently, peaking in the 4th hour. Regression and correlation analyses demonstrated: the ***higher the zotepine plasma levels, the more delta/theta, the less alpha activity and the slower the centroid in the spectral analysed EEG and the more decrease in reaction time performance, numerical memory and CFF in psychometry*.** Neurophysiological changes started at 8 ng/ml, psychometric ones at 9 ng/ml. Our pharmacodynamic findings suggested zotepine to be a sedative broad-band neuroleptic, which was also reflected in the side effects.

Comparative placebo-controlled pharmacodynamic studies with zotepine and clozapine utilizing pharmaco-EEG and psychometry.

Saletu, B., Grünberger, J., Linzmayer, L., & Anderer, P. (1987). *Comparative placebo-controlled pharmacodynamic studies with zotepine and clozapine utilizing pharmaco-EEG and psychometry*. Pharmacopsychiatry, 20(1 Spec No), 12–27. https://doi.org/10.1055/s-2007-1017125.

In a double-blind, placebo-controlled study the encephalotropic and psychotropic properties of zotepine - a new tricyclic dibenzothiepine with antidopaminergic, adrenolytic and antiserotoninergic properties - were investigated utilizing quantitative EEG, psychometric and psychophysiological tests as well as clinical observations. Fifteen normal volunteers received randomized (Latin square design) and at weekly intervals single oral doses of placebo, 25 mg, 50 mg and 100 mg zotepine as well as 50 mg clozapine as reference compound. Plasma samplings for blood levels, EEG recordings, and evaluation of blood pressure, pulse rate and side-effects were carried out at the hours 0, 1, 2, 4, 6 and 8, while psychometric data were recorded at the same time except the first hour. ***Computer-assisted spectral analysis of the EEG demonstrated after all three doses significant changes as compared with placebo characterized by an augmentation of delta and theta activity, decreased of alpha and beta activity, slowing of the centroid of the total activity and alpha activity, and decrease of the dominant frequency and its absolute and relative power*.** Such changes are typical for low-potency basic neuroleptics of the sedative type such as chlorpromazine. Clozapine also augmented slow activities, decreased alpha activity, the dominant frequency and the alpha centroid, but induced in contrast to zotepine a concomitant increase of fast beta activity, acceleration of the beta centroid and no slowing of the dominant frequency, while the total power was significantly attenuated. These findings confirm earlier reports about the pharmaco-EEG profile of clozapine, which has a resemblance to profiles of anticholinergic antidepressants of the amitriptyline type. Psychometric tests demonstrated after the higher doses of zotepine and clozapine a deterioration of noopsychic and thymopsychic functions which was more pronounced after the reference compound than after zotepine. The lowest dose of zotepine, 25 mg, even produced an improvement in numerical memory and complex reaction. CFF, skin conductance, pupillary diameter and pupillary response measurements decreased after both compounds. Dose-efficacy calculations showed 100 mg zotepine and clozapine to be the most CNS-effective compounds, followed by 50 mg and 25 mg zotepine, while placebo induced the

least changes. Time-efficacy calculations showed neurophysiological and behavioral peak effects after zotepine at the 4th and 6th hour, as compared with the 2nd and 4th hour after clozapine. Pulse rate increased with both compounds; blood pressure decreased after clozapine but remained unchanged after zotepine. Side-effects were the usual ones observed in normals after neuroleptics. They were characterized by tiredness, dizziness/giddiness, slurred speech, dry mouth, nausea and vomiting, with the latter slightly more pronounced after clozapine than after zotepine and lasting after the two higher doses of zotepine end the reference compound in some instances until the day after single dose administration.

TYPICAL ANTIPSYCHOTICS (NEUROLEPTICS)

CLASS FACTS

----- HALOPERIDOL -----

DRUG FACTS

SYNOPSIS: Haloperidol is a first-generation (typical) antipsychotic that is a commonly used drug worldwide. Haloperidol is used to manage positive symptoms of schizophrenia, such as hallucinations and delusions. It is FDA-approved for treating schizophrenia, Tourette syndrome, severe behavioral disorders in children (combative and explosive hyperexcitability), and hyperactivity in children (impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance).

A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry.

Aiyer, R., Novakovic, V., Barkin,R.L. *A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry*. Postgrad Med. 2016 Sep;128(7):656-64. doi: 10.1080/00325481.2016.1218261. Epub 2016 Aug 8. PMID: 27467441.

Objectives: It is known that psychotropic medications have an impact on the readings found in Electroencephalogram (EEG). In the field of psychiatry, there are several psychotropics utilized by clinicians. This review seeks to investigate all the available data for psychotropic drugs and their impact on EEG changes. **Methods:** A systematic review of all the published and ongoing literature was conducted via PubMed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used for each search. Key words for searches include 'EEG and Psychotropics', 'EEG and Mood Stabilizers', 'EEG and Clozapine', 'EEG and Bupropion', 'EEG and SSRI', 'EEG and Lamotrigine', 'EEG and Carbamazepine', 'EEG and Lithium' and 'EEG and Valproate', 'EEG and Haloperidol', 'EEG and Aripiprazole', 'EEG and Methylphenidate', 'EEG and Topiramate', 'EEG and Gabapentin' and 'EEG and Oxcarbamazepine'. After applying the inclusion criteria, 201 articles were eligible and reviewed. **Results:** Following an extensive review of selected studies from the 201 articles, ***the studies indicate that each of the psychotropic medications reviewed impact alpha, beta, delta and theta waves independently and differently from each other. Additionally, certain medications, particularly haloperidol and valproic acid, have dissimilar results exemplified in all waveforms.*** **Conclusions:** This PRISMA systematic review illustrates that while there is available data on psychotropic medications and their proposed effect on EEG activity, further research is needed to confirm these findings to help allow clinical correlations to be made between the patient's response and the psychotropic agent.

Event-related potentials reflect impaired temporal interval learning following haloperidol administration.

Forster SE, Zirnheld P, Shekhar A, Steinhauer SR, O'Donnell BF, Hetrick WP. *Event-related potentials reflect impaired temporal interval learning following haloperidol*

administration. Psychopharmacology (Berl). 2017 Sep;234(17):2545-2562. doi: 10.1007/s00213-017-4645-2. Epub 2017 Jun 10. PMID: 28601965.

Background: Signals carried by the mesencephalic dopamine system and conveyed to anterior cingulate cortex are critically implicated in probabilistic reward learning and performance monitoring. A common evaluative mechanism purportedly subserves both functions, giving rise to homologous medial frontal negativities in feedback- and response-locked event-related brain potentials (the feedback-related negativity (FRN) and the error-related negativity (ERN), respectively), reflecting dopamine-dependent prediction error signals to unexpectedly negative events. Consistent with this model, the dopamine receptor antagonist, haloperidol, attenuates the ERN, but effects on FRN have not yet been evaluated. **Methods:** ERN and FRN were recorded during a temporal interval learning task (TILT) following randomized, double-blind administration of haloperidol (3 mg; n = 18), diphenhydramine (an active control for haloperidol; 25 mg; n = 20), or placebo (n = 21) to healthy controls. ***Centroparietal positivities, the Pe and feedback-locked P300, were also measured and correlations between ERP measures and behavioral indices of learning, overall accuracy, and post-error compensatory behavior were evaluated*.** We hypothesized that haloperidol would reduce ERN and FRN, but that ERN would uniquely track automatic, error-related performance adjustments, while FRN would be associated with learning and overall accuracy. **Results:** As predicted, ERN was reduced by haloperidol and in those exhibiting less adaptive post-error performance; however, these effects were limited to ERNs following fast timing errors. In contrast, the FRN was not affected by drug condition, although increased FRN amplitude was associated with improved accuracy. ***Significant drug effects on centroparietal positivities were also absent.*** **Conclusions:** Our results support a functional and neurobiological dissociation between the ERN and FRN.

Phenotypical Screening on Neuronal Plasticity in Hippocampal-Prefrontal Cortex Connectivity Reveals an Antipsychotic with a Novel Profile.

Spedding, M., Sebban, C., Jay, T. M., Rocher, C., Tesolin-Decros, B., Chazot, P., Schenker, E., Szénási, G., Lévay, G. I., Megyeri, K., Barkóczy, J., Hársing, J., Thomson, I., Cunningham, M. O., Whittington, M. A., Etherington, L.-A., Lambert, J. J., Antoni, F. A., & Gacsályi, I. (2022). *Phenotypical Screening on Neuronal Plasticity in Hippocampal-Prefrontal Cortex Connectivity Reveals an Antipsychotic with a Novel Profile*. Cells (Basel, Switzerland), 11(7), 1181–. https://doi.org/10.3390/cells11071181

Dysfunction in the hippocampus-prefrontal cortex (H-PFC) circuit is a critical determinant of schizophrenia. Screening of pyridazinone-risperidone hybrids on this circuit revealed EGIS 11150 (S 36549). EGIS 11150 ***induced theta rhythm in hippocampal slice preparations in the stratum lacunosum molecular area of CA1,*** which was resistant to atropine and prazosin. EGIS 11150 ***enhanced H-PFC coherence, and increased the 8–9 Hz theta band of the EEG power spectrum (from 0.002 mg/kg i.p, at >30× lower doses than clozapine, and >100× for olanzapine, risperidone, or haloperidol*)**. EGIS 11150 fully blocked the effects of phencyclidine (PCP) or ketamine on EEG. Inhibition of long-term potentiation (LTP) in H-PFC was blocked by platform stress, but was fully restored by EGIS 11150 (0.01 mg/kg i.p.), whereas clozapine (0.3

mg/kg ip) only partially restored LTP. EGIS 11150 has a unique electrophysiological profile, so phenotypical screening on H-PFC connectivity can reveal novel antipsychotics.

-----FLUPHENAZINE-----

DRUG FACTS

SYNOPSIS: Fluphenazine is a typical antipsychotic used for the symptomatic management of psychosis in patients with schizophrenia. There is a long-acting fluphenazine decanoate formulation used primarily as maintenance therapy for chronic schizophrenia and related psychotic disorders in patients who do not tolerate oral formulations or in patients where medication compliance is a concern of the provider. There is no current research.

----- CHLORPROMAZINE -----

DRUG FACTS

SYNOPSIS: Chlorpromazine is used to treat the symptoms of schizophrenia (a mental illness that causes disturbed or unusual thinking, loss of interest in life, and strong or inappropriate emotions) and other psychotic disorders (conditions that cause difficulty telling the difference between things or ideas that are real and things or ideas that are not real) and to treat the symptoms of mania (frenzied, abnormally excited mood) in people who have bipolar disorder (manic depressive disorder; a condition that causes episodes of mania, episodes of depression, and other abnormal moods). Chlorpromazine is also used to treat severe behavior problems such as explosive, aggressive behavior and hyperactivity in children 1 to 12 years of age.

Electroencephalogram Modifications Associated With Atypical Strict Antipsychotic Monotherapies.

Dias Alves, M., Micoulaud-Franchi, J. A., Simon, N., & Vion-Dury, J. (2018). *Electroencephalogram Modifications Associated With Atypical Strict Antipsychotic Monotherapies*. Journal of Clinical Psychopharmacology, 38(6), 555–562. https://doi.org/10.1097/JCP.0000000000000953

Background: Antipsychotics produce electroencephalogram (EEG) modifications and increase the risk of epileptic seizure. These modifications remain sparsely studied specifically for atypical antipsychotics. In this context, our study focuses on EEG modifications associated with atypical strict antipsychotic monotherapies. **Methods:** Electroencephalogram recordings of 84 psychiatric patients treated with atypical antipsychotics in strict monotherapy (clozapine, n = 22; aripiprazole, n = 22; olanzapine, n = 17; risperidone, n = 9; quetiapine, n = 8; risperidone long-acting injection, n = 4; and paliperidone long-acting injection, n = 2) were analyzed. The modifications were ranked according to both slowing and excitability scores. **Results:** ***Electroencephalogram modifications (in 51 subjects, 60.71%) were graded according to 4 stages combining general slowing and sharp slow waves and/or epileptiform activities.*** *The*

presence of sharp or epileptiform activities was significantly greater for clozapine *(90.9%)* ***compared with other second-generation antipsychotics*** (aripiprazole, 50%; olanzapine, 58.8%; quetiapine, 37.5%; risperidone, 44.4%). Age, duration of disease progression, and diagnosis were not associated as risk factors. Electroencephalogram modifications were associated with lower doses for treatment with quetiapine but not for specific antipsychotics. ***Electroencephalogram modifications and severe excitability were associated with higher chlorpromazine equivalent doses. Conclusions: Atypical antipsychotics (clozapine, aripiprazole, quetiapine, olanzapine, and risperidone) induce EEG modifications, and these are significantly greater for clozapine and appear dependent on chlorpromazine equivalent dose.*** No encephalopathy was observed in these antipsychotic monotherapies, whatever dose.

Electroencephalographic study of chlorpromazine alone or combined with alpha-lipoic acid in a model of schizophrenia induced by ketamine in rats.

Sampaio, L. R. L., Nunes Borges, L. T., Barbosa, T. M., Branco Matos, N. C., Lima, R. de F., Oliveira, M. N. de, Gularte, V. N., Patrocínio, M. C. A., Macêdo, D., Vale, O. C. do, & Vasconcelos, S. M. M. de. (2017). *Electroencephalographic study of chlorpromazine alone or combined with alpha-lipoic acid in a model of schizophrenia induced by ketamine in rats.* Journal of Psychiatric Research, 86, 73–82. https://doi.org/10.1016/j.jpsychires.2016.12.003.

Schizophrenia is characterized by behavioral symptoms, brain function impairments and electroencephalographic (EEG) changes. Dysregulation of immune responses and oxidative imbalance underpins this mental disorder. The present study aimed to investigate the effects of the typical antipsychotic chlorpromazine (CP) alone or combined with the natural antioxidant alpha-lipoic acid (ALA) on changes in the hippocampal average spectral power induced by ketamine (KET). Three days after stereotactic implantation of electrodes, male Wistar rats were divided into groups treated for 10 days with saline (control) or KET (10 mg/kg, IP). CP (1 or 5 mg/kg, IP) alone or combined with ALA (100 mg/kg, P.O.) was administered 30 min before KET or saline. Hippocampal EEG recordings were taken on the 1st, 5th and 10th days of treatment immediately after the last drug administration. KET significantly increased average spectral power of delta and gamma-high bands on the 5th and 10th days of treatment when compared to control. ***Gamma low-band significantly increased on the 1st, 5th and 10th days when compared to control group.*** This effect of KET was prevented by CP alone or combined with ALA. Indeed, the combination of ALA 100 + CP1 potentiated the **inhibitory effects of CP1 on gamma low-band oscillations**. In conclusion, our results showed that ***KET presents excitatory and time-dependent effects on hippocampal EEG bands activity****. KET* ***excitatory effects on EEG were prevented by CP alone and in some situations potentiated by its combination with ALA***.

Quantitative Resting State Electroencephalography in Patients with Schizophrenia Spectrum Disorders Treated with Strict Monotherapy Using Atypical Antipsychotics.

Ozaki, T., Toyomaki, A., Hashimoto, N., & Kusumi, I. (2021). *Quantitative Resting State*

Electroencephalography in Patients with Schizophrenia Spectrum Disorders Treated with Strict Monotherapy Using Atypical Antipsychotics. Clinical Psychopharmacology and Neuroscience : the Official Scientific Journal of the Korean College of Neuropsychopharmacology, 19(2), 313–322. https://doi.org/10.9758/cpn.2021.19.2.313.

Objective: The effect of antipsychotic drugs on quantitative electroencephalography (EEG) has been mainly examined by the administration of a single test dose or among patients using combinations of other psychotropic drugs. We therefore investigated the effects of strict monotherapy with antipsychotic drugs on quantitative EEG among schizophrenia patients. **Methods:** Data from 2,364 medical reports with EEG results from psychiatric patients admitted to the Hokkaido University Hospital were used. We extracted EEG records of patients who were diagnosed with schizophrenia spectrum disorders and who were either undergoing strict antipsychotic monotherapy or were completely free of psychotropic drugs. The spectral power was compared between drug-free patients and patients using antipsychotic drugs. We also performed multiple regression analysis to evaluate the relationship between spectral power and the chlorpromazine equivalent daily dose of antipsychotics in all the patients. **Results:** We included 31 monotherapy and 20 drug-free patients. Compared with drug-free patients, ***patients receiving antipsychotic drugs demonstrated significant increases in theta, alpha and beta power.*** When patients taking different types of antipsychotics were compared with drug-free patients, we found no significant change in any spectrum power for the aripiprazole or blonanserin groups. Patients taking risperidone demonstrated significant increases in alpha and beta power. Patients taking clozapine and olanzapine demonstrated significant slow wave increases. Multiple regression analysis revealed that the chlorpromazine equivalent dose was positively associated with theta power. **Conclusion:** ***Use of any antipsychotic drug by patients was associated with a dose-dependent increase in theta power. However, each type of antipsychotic demonstrated different spectral power changes.***

BARBITURATES

DRUG FACTS

SYNOPSIS: Prescribed to help sleep, relieve anxiety, muscle spasms, and prevent seizures.

----- AMOBARBITAL (Amytal sodium) -----

DRUG FACTS

SYNOPSIS: Prescribed to control seizures, anesthetic effects, relieve anxiety and prevent withdrawal symptoms who are dependent on another barbiturate medication.

Focal slowing of ipsilateral and contralateral frontal regions

Akman, C. I., Micic, V., Quach, M., Wilfong, A. A., Schultz, R., Riviello, J. J., Jr, & Chapieski, M. L. (2015). *Application of envelope trend to analyze early EEG changes in the frontal regions during intracarotid amobarbital procedure in children*. Epilepsy & behavior: E&B, 43, 66–73. https://doi.org/10.1016/j.yebeh.2014.08.011

Intracarotid amobarbital procedure (IAP) is acknowledged as the gold standard test for language lateralization. EEG is performed routinely during IAP to monitor the anesthetization of a brain hemisphere. Here, we studied the correlation between the early EEG changes using envelope trend and the clinical outcome of IAP. Method: Fifty consecutive patients underwent IAP at Texas Children's Hospital (2004-2009). Intracarotid amobarbital procedure was considered "complete" or "incomplete" based on the outcome if the procedure was completed or aborted due to behavior changes. Envelope trend was used to calculate the median EEG amplitude changes within the first 60s of IAP. Statistical analysis was performed to determine the role of EEG changes and clinical features on the procedure outcome. Results: Only 30 IAP-EEG files were available for review. Amobarbital was administered at the dose of 60-150mg (mean: 110±20). The intracarotid amobarbital procedure was recorded as complete in 23 patients and incomplete in 7 patients. ***EEG changes occurred within the first few seconds following amobarbital injection. Following amobarbital injection, focal slowing was present in the ipsilateral frontal region or both ipsilateral and contralateral frontal regions***. Elapsed time to the first EEG change or duration and change in median EEG amplitude in the ipsilateral frontal regions were indifferent between the complete and incomplete groups ($p>0.05$). However, the median amplitude changes between the ipsilateral and contralateral frontal regions within each group were found significant only in the complete group ($p<0.05$), suggesting ipsilateral without contralateral frontal slowing. Other than age at the time of IAP ($p=0.03$), none of the other clinical features correlated with the clinical outcome of IAP ($p>0.05$). Conclusion: Early EEG changes during IAP using envelope trend may predict successful completion of the IAP test. Younger children are at risk of behavioral changes during IAP.

Persistent increase in alpha power as residual anesthetic effects

Tu, Bin*; Assassi, Nadege J.†; Bazil, Carl W.*; Hamberger, Marla J.*; Hirsch, Lawrence J.‡. *Quantitative EEG Is an Objective, Sensitive, and Reliable Indicator of Transient Anesthetic Effects During Wada Tests*. Journal of Clinical Neurophysiology 32(2):p 152-158, April 2015. | DOI: 10.1097/WNP.0000000000000154

The intracarotid amobarbital or Wada procedure is a component of the presurgical evaluation for refractory epilepsy, during which monitoring the onset and offset of transient anesthetic effects is critical. In this study, the authors characterized changes of 8 quantitative measures during 26 Wada tests, which included alpha, beta, theta, and delta powers, alpha/delta power ratio, beta/delta power ratio, median amplitude-integrated EEG, and 90% spectral edge frequency (SEF90), and correlated them with contralateral hemiplegia. The authors found that on the side of injection, delta and theta powers, alpha/delta power ratio, beta/delta power ratio, and SEF90 peaked within 1 minute after injection of 70 to 150 mg amobarbital or 4 to 7 mg methohexital. When contralateral arm strength returned to 3/5, delta power and amplitude-integrated EEG decayed on average 24% and 19%, respectively, for amobarbital, similar to that of methohexital (27% and 18%). Because delta power resolution most closely mirrored that of the hemiplegia and amplitude-integrated EEG had the highest signal/noise ratio, these quantitative values appear to be the best measures for decay of anesthetic effects. ***Increase in alpha power persisted longest, and therefore may be the best measure of late residual anesthetic effects***.

----- METHOHEXITAL (Brevital) -----

DRUG FACTS

SYNOPSIS: Prescribed used in anesthesia for sedation.

Shorter durations of motor-, speech-, and EEG recovery

Conradi, N., Rosenberg, F., Biermann, L., Haag, A., Hermsen, A., Gorny, I., von Podewils, V., Gurschi, M., Keil, F., Hattingen, E., Menzler, K., Bauer, S., Schubert-Bast, S., Knake, S., Rosenow, F., & Strzelczyk, A. (2020*). Advantages of methohexital over amobarbital in determining hemispheric language and memory lateralization in the Wada test - A retrospective study*. Epilepsy & behavior : E&B, 113, 107551. https://doi.org/10.1016/j.yebeh.2020.107551

Due to supply shortage, amobarbital, the traditional anesthetic agent in Wada testing, was replaced by methohexital in many epilepsy centers. This study aimed to compare the two barbiturates to identify possible advantages or disadvantages of methohexital as compared to amobarbital with regard to the adequacy of language and memory testing during the Wada test. Methods: Data from 75 patients with temporal lobe epilepsy who underwent bilateral Wada tests using either amobarbital (n = 53) or methohexital (n = 22) as part of presurgical work-up were analyzed retrospectively. The two subgroups were compared regarding hemispheric language and memory lateralization results and Wada testing characteristics, and the adequacy of language and memory testing was assessed. Results: We observed ***shorter durations of motor-, speech-, and EEG recovery after each injection in patients receiving methohexital compared to amobarbital***. In addition, significantly more items could be presented during effective hemispheric inactivation in the methohexital group. Moreover,

significant correlations of Wada memory scores with standard neuropsychological memory test scores could be found in the methohexital group. Significance: Our findings confirm that methohexital is not only equally suitable for Wada testing but has several advantages over amobarbital. Wada testing can be performed more efficiently and under more constant hemispheric inactivation using methohexital. Furthermore, the adequacy of language and memory testing during the Wada test might be affected by the anesthetic agent used.

Activation of lateralized periodic discharge in ipsilateral hemisphere

Danoun, O. A., Beimer, N., Buchtel, H., Glynn, S., & Harris, D. (2021). *Methohexital - Induced lateralized periodic discharges during Wada test*. Clinical neurophysiology practice, 6, 225–228. https://doi.org/10.1016/j.cnp.2021.07.002

The Wada test is used to evaluate language lateralization and memory performance after inactivation of an isolated cerebral hemisphere. Methohexital a short-acting barbiturate has a history of use to induce interictal discharges during intraoperative corticography. We report a new finding of ***activation of lateralized periodic discharges (LPDs) after Methohexital injection***. Methods: We retrospectively reviewed 174 consecutive adult patients who underwent Wada testing in preparation for epilepsy surgery (N = 129, 74%) or brain tumor resection (N = 45, 26%) at the University of Michigan to determine the frequency of induced periodic discharges by methohexital. Results: Four epilepsy patients (2.29%) had methohexital-induced LPDs within a median of 2 s (1-99 s) of the injection and lasting a median of 4 min (3-10 min) after a total of 7 injections. All LPDs occurred ipsilateral to the injection hemisphere in the known region of interictal epileptiform discharges. LPDs were not induced in brain tumor patients. In one patient, LPDs occurred during memory testing, and this patient's memory performance was below expectation based on pre-test neuropsychological testing. Conclusions: ***Methohexital can induce LPDs in ipsilateral hemisphere and that can potentially affect memory performance***. Significance: This observation indicates that concurrent EEG monitoring during the Wada test is important and that induced discharges should be considered when interpreting Wada test results.

----- PENTOBARBITAL (Nembutal sodium) -----

DRUG FACTS

SYNOPSIS: Prescribed to manage seizures, intracranial pressure, insomnia and as a pre-anesthetic in the operating room.

High-amplitude burst suppression activity separated by brief episodes of isoelectric activity

Hristovska, I., Verdonk, F., Comte, J. C., Tsai, E. S., Desestret, V., Honnorat, J., Chrétien, F., & Pascual, O. (2020). *Ketamine/xylazine and barbiturates modulate microglial morphology and motility differently in a mouse model*. PloS one, 15(8), e0236594. https://doi.org/10.1371/journal.pone.0236594

Our current findings demonstrate that administration of two commonly used iv anesthetics in clinic and in research protocols, ketamine/xylazine and barbiturates, resulted in microglial surveillance reduction in vivo and morphological alterations that depended on the type of anesthetics administered and the brain region examined (S1 Table). Ketamine/xylazine

administration resulted in extensive and widespread reduction of microglial process complexity, whereas barbiturates affected the cytoplasm area in a limited manner. Ketamine/xylazine and barbiturates are commonly used as general anesthetics for surgery, imaging, or euthanasia preceding immunohistochemistry studies. For anesthesia, ketamine, a NMDAR antagonist is often used with an α2 adrenergic agonist, in our case xylazine, which provides sedation and analgesia [25,26]. Importantly, ketamine activates less GABAAR in comparison with other anesthetics, which allowed us to distinguish the effects of ketamine/xylazine and barbiturates that are GABAA agonists [27]. For the ex vivo and in vivo experiments, we used two types of barbiturates, an oxybarbiturate, i.e. pentobarbital, and thiobarbiturate, i.e. thiopental, characterized by different duration of action but presenting similar chemical structure and functions. Both of them act mainly by activating the gamma-aminobutyric acid A (GABAA) receptors, keeping the chlorine channel open, resulting in hyperpolarization of the post-synaptic membrane [28]. In the same manner, previous studies have shown that ***thiopental administration leads to changes similar to pentobarbital-induced EEG alterations, including burst suppression activity [29]. Thiopental is an ultra-short acting anesthetic that was used for ex vivo experiments whereas pentobarbital was preferred for the in vivo study because its action lasts 4 to 8 times longer than thiopental [30].*** Interestingly, different anesthetics generate distinct and specific patterns of neuronal activity. Our EEG recordings indicate that ketamine/xylazine anesthesia is characterized by slow, large amplitude waves with high delta power. More precise LFP and intracellular recordings showed that ketamine/xylazine administration results in long duration of silent states and increased gamma activity power [2]. On the other hand, ***pentobarbital anesthesia was associated with a different EEG pattern consisting in states of isoelectric activity with bursts of high-amplitude activity. It has already been shown that propofol, isoflurane and the barbiturate thiopental led to high-amplitude burst suppression activity separated by brief episodes of isoelectric activity*** [31]. Interestingly, in our study, the anesthetic inducing the greatest change in activity in comparison to wake also induced major microglial morphology and dynamics change. ***This possibility is supported by a recent study showing that inducing neural spiking activity at 40Hz leads to morphological changes of microglia*** [32]. These findings need further investigation, to determine whether and how different EEG patterns, in terms of frequency and amplitude, may impact microglial morphology and motility.

Induction of frontal oscillations 15 – 55 Hz.

Lambert, P. M., Ni, R., Benz, A., Rensing, N. R., Wong, M., Zorumski, C. F., & Mennerick, S. (2023). *Non-sedative cortical EEG signatures of allopregnanolone and functional comparators*. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 48(2), 371–379. https://doi.org/10.1038/s41386-022-01450-x

To investigate how the effects of AlloP compared with behaviorally similar doses of other GABAAR PAMs, we compared AlloP to pentobarbital and diazepam, two GABAAR PAMs with different degrees of subunit selectivity. ***We found that both pentobarbital and diazepam altered EEG with a timescale similar to that of AlloP*** (Fig. 2A, D). Although we selected a dose of diazepam that preserved enough active wake behavior necessary for our intended analysis during acute drug exposure, the animals receiving diazepam did exhibit more sleep behavior

during the hours immediately following drug injection (Fig. S4). ***Similar to the oscillatory changes induced by AlloP, the acute effects of pentobarbital and diazepam were strongest in mid frequency range oscillations (Fig. 2B, E). Interestingly, pentobarbital induced oscillations lower in the beta range (peak at ~35 Hz) than the oscillations induced by diazepam (peak at ~50 Hz), and pentobarbital increased the mid frequency oscillations more than diazepam***. Additionally, both GABAAR PAMs decreased the strength of the theta rhythm (Fig. 2C, F), similar to AlloP. Overall, pentobarbital recapitulated all the changes evident with AlloP, while diazepam only partially recapitulated the effects of the other GABA PAMs. In efforts to find common patterns of altered network activity induced by rapid-acting antidepressants, we compared the effects of AlloP to those induced by a sub-sedative dose of ketamine, an NMDA receptor antagonist that exhibits rapid antidepressant effects [25]. Following injection of ketamine, all mice remained active and showed drug-induced changes to the spectral content of both frontal and parietal EEG with rapid onset (Fig. 3A). Ketamine increased gamma frequency oscillations present during active wake, particularly in a higher end of the gamma range than the GABAAR targeting compounds (Fig. 3B). Moreover, unlike the compounds targeting GABAARs, ketamine decreased oscillations in the beta frequency range at both parietal and frontal sites (Fig. 3B, ~30 Hz). Interestingly, ketamine did not alter the strength of the theta frequency oscillations, based on one-way ANOVA (Fig. 3C), different from the other drugs in this study. However mean difference analysis suggested that vehicle lowered the theta peak probability (Fig. 3C, right). The basis of the apparent vehicle effect in Fig. 3C is unclear but could involve a small effect of acute stress, since pentobarbital and diazepam also showed small vehicle effects at limited frequencies within the theta band (Fig. 2B, E). Here we compared in mice the effects of AlloP and several comparators on EEG signals during active exploration. All compounds were compared at a just sub-sedative dose during active wake. We also report the first assessment of theta-gamma cross-frequency coupling measured in EEG during AlloP and pentobarbital treatment. ***Both AlloP and pentobarbital promoted frontal oscillations at 15–55 Hz, including the beta and low gamma bands***. AlloP and other GABAAR PAMs also disrupted higher order network organization measured by frontal-parietal coherence and theta-gamma PAC. Although we hypothesized that AlloP would distinguish from other non-antidepressant GABAAR PAMs, subsedative pentobarbital recapitulated with remarkable precision all AlloP-induced EEG signatures. Interestingly, diazepam, a more subunit-selective GABAAR PAM, showed a weaker increase of beta and low gamma frequency power. Finally, ketamine induced mostly distinct EEG features from the GABA PAMs. Several features (e.g., reduced parietal alpha bandpower) were shared by all drugs. Taken together, non-selective GABAAR PAMs, including AlloP, affect network activity very similarly, and ketamine's actions are distinct, complicating efforts to identify a rapid antidepressant signature.

Alterations in EEG microstructures

Lazic, K., Petrovic, J., Ciric, J., Kalauzi, A., & Saponjic, J. (2015). *Impact of anesthetic regimen on the respiratory pattern, EEG microstructure and sleep in the rat model of cholinergic Parkinson's disease neuropathology*. Neuroscience, 304, 1–13. https://doi.org/10.1016/j.neuroscience.2015.07.020

We hypothesized that the impact of distinct anesthetic regimens could be differently expressed during anesthesia and on post-anesthesia sleep in the neurodegenerative diseases. Therefore,

we followed the impact of ketamine/diazepam and pentobarbital anesthesia in a rat model of the severe Parkinson's disease cholinergic neuropathology on the electroencephalographic (EEG) microstructure and respiratory pattern during anesthesia, and on the post-anesthesia sleep. We performed the experiments on adult, male, spontaneously breathing Wistar rats chronically instrumented for sleep recording. The bilateral pedunculopontine tegmental nucleus (PPT) lesion was done by ibotenic acid microinfusion. Following postoperative recovery, we recorded sleep for 6h, induced anesthesia 24h later using ketamine/diazepam or pentobarbital, and repeated sleep recordings sessions 48h and 6days later. During 20min of each anesthesia we recorded both the EEG and respiratory movements. For sleep and EEG analysis, Fourier analysis was applied on 6-h recordings, and each 10-s epoch was differentiated as a state of wakefulness (Wake), non-rapid eye movement (NREM) or rapid eye movement (REM). Additionally, the group probability density distributions of all EEG frequency band relative amplitudes were calculated for each state, with particular attention during anesthesia. For respiratory pattern analysis we used Monotone Signal Segments Analysis. The PPT lesion was identified through nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase histochemistry. ***Our data show that the ketamine/diazepam anesthetic regimen in the PPT-lesioned rats induces more alterations in the EEG microstructure and respiratory pattern than does the pentobarbital anesthesia***. In addition, the equal time required to establish an anesthetized state, and the long-term effect on post-anesthesia sleep in the PPT-lesioned vs. control rats suggest this anesthetic regimen as potentially more beneficial both for anesthesia induction and for post-anesthesia sleep in the surgical procedures of the elderly, and Parkinson's, and Alzheimer's patients.

EEG burst suppression.

Reznik, M. E., Berger, K., & Claassen, J. (2016*). Comparison of Intravenous Anesthetic Agents for the Treatment of Refractory Status Epilepticus*. Journal of clinical medicine, 5(5), 54. https://doi.org/10.3390/jcm5050054

Until the advent of propofol and midazolam infusions, barbiturates were the agents of choice for treating RSE. Traditionally, pentobarbital has been the barbiturate used in the U.S., while thiopental is more commonly used in Europe. In current practice, though, barbiturates are typically reserved for the management of RSE that fails to respond to midazolam and/or propofol, also known as super-refractory SE (SRSE). Though the class of medications has a long history of successful use, a host of major side effects limit its appeal given the other available options. These side effects include severe hypotension (often necessitating the use of vasopressors) and overall cardiovascular depression, respiratory depression, paralytic ileus, lowering of core body temperature, immune suppression, and a potential risk for pancreatic and hepatic dysfunction. The IV formulation of pentobarbital (but not thiopental) also contains propylene glycol, leading to a risk of propylene glycol toxicity with prolonged infusions. In their favor, however, are several studies that suggest a possible benefit over other cIV-AEDs. A meta-analysis of 28 studies comparing midazolam, propofol, and pentobarbital infusions for RSE suggested that treatment with ***pentobarbital was associated with a significantly lower frequency of short-term treatment failure, breakthrough seizures, and changes to a different continuous infusion***. ***In a more recent single-center retrospective study, episodes of RSE in which barbiturates were used were associated with EEG burst suppression or complete***

suppression significantly more frequently than episodes in which they were not given. However, they were also associated with significantly longer hospital stays for surviving patients, while mortality and likelihood of returning to clinical baseline at discharge did not differ significantly compared to propofol or midazolam. Another recent single-center retrospective study confirmed these findings, and also found that weaning from pentobarbital appeared to be more successful (with lower incidence of withdrawal seizures) when phenobarbital was added before weaning. Finally, a previously-mentioned, small randomized trial comparing pentobarbital with propofol showed comparable mortality and return to clinical baseline between the two, along with similar rates of infection and hypotension, though pentobarbital was associated with a significantly longer duration of mechanical ventilation. ***Both pentobarbital and thiopental exert their effects via binding to the GABA receptor and prolonging the duration of opening of the associated chloride channel (as opposed to the increased frequency of opening caused by benzodiazepines), enhancing its inhibitory effects***. Since both barbiturates are highly lipophilic, they quickly distribute into the central nervous system, allowing for a fast time to onset for pentobarbital (15–20 min), and an ultra-fast time to onset for thiopental (30–60 s). However, this may also result in deposition into peripheral tissues and saturation of metabolic pathways even after relatively short infusions, leading to nonlinear metabolism and a long half-life (ranging from 15 to 60 h for pentobarbital, and 11 to 36 h for thiopental). They both also have a tendency toward autoinduction which typically takes days to occur, as well as numerous drug interactions. Both pentobarbital and thiopental are hepatically metabolized; the main metabolite of thiopental is pentobarbital. Therapeutic monitoring of pentobarbital levels may be useful for patients where brain death is considered, but should not be used to guide therapy for RSE. As mentioned in the retrospective study above, it may also be preferable to start phenobarbital in anticipation of weaning pentobarbital, to potentially reduce the risk of withdrawal seizures.

----- PHENOBARBITAL -----

DRUG FACTS

SYNOPSIS: Prescribed to control seizures, relieve anxiety and prevent withdrawal symptoms who are dependent on another barbiturate medication.

Suppressed hippocampal paroxysmal discharges

Duveau, V., Pouyatos, B., Bressand, K., Bouyssières, C., Chabrol, T., Roche, Y., Depaulis, A., & Roucard, C. (2016). *Differential Effects of Antiepileptic Drugs on Focal Seizures in the Intrahippocampal Kainate Mouse Model of Mesial Temporal Lobe Epilepsy*. CNS neuroscience & therapeutics, 22(6), 497–506. https://doi.org/10.1111/cns.12523

Mesial temporal lobe epilepsy (MTLE) is the most common form of drug-refractory epilepsy. Most of the morphological and electrophysiological features of human MTLE can be reproduced in a mouse by a unilateral intrahippocampal injection of kainate (MTLE mouse model). The effects of antiepileptic drugs (AEDs) on the occurrence of recurrent focal hippocampal seizures in this model remain to be specified. Here, we addressed the pharmacological reactivity of this model to the most commonly used AEDs. Methods: Using depth electroencephalographical (EEG) recordings, we tested the dose-response effects of acute injection of nine AEDs on the occurrence of hippocampal paroxysmal discharges (HPDs) as well as on ictal and interictal

power spectra in the MTLE mouse model. Results: Valproate, carbamazepine, and lamotrigine dose dependently suppressed HPDs and modified the general behavior and/or EEG activity. Levetiracetam and pregabalin suppressed HPDs at high doses but without any behavioral nor interictal EEG changes. Finally, ***phenobarbital, tiagabine, vigabatrin, and diazepam suppressed HPDs in a dose-dependent manner at doses devoid of obvious behavioral effects***.

Delayed effect terminating status epilepticus

Jackson, C., Ardinger, C., Winter, K. M., McDonough, J. H., & McCarren, H. S. (2019). *Validating a model of benzodiazepine refractory nerve agent-induced status epilepticus by evaluating the anticonvulsant and neuroprotective effects of scopolamine, memantine, and phenobarbital*. Journal of pharmacological and toxicological methods, 97, 1–12. https://doi.org/10.1016/j.vascn.2019.02.006

Organophosphorus nerve agents (OPNAs) irreversibly block acetylcholinesterase activity, resulting in accumulation of excess acetylcholine at neural synapses, which can lead to a state of prolonged seizures known as status epilepticus (SE). Benzodiazepines, the current standard of care for SE, become less effective as latency to treatment increases. In a mass civilian OPNA exposure, concurrent trauma and limited resources would likely cause a delay in first response time. To address this issue, we have developed a rat model to test novel anticonvulsant/ neuroprotectant adjuncts at delayed time points. Methods: For model development, adult male rats with cortical electroencephalographic (EEG) electrodes were exposed to soman and administered saline along with atropine, 2-PAM, and midazolam 5, 20, or 40 min after SE onset. We validated our model using three drugs: scopolamine, memantine, and phenobarbital. Using the same procedure outlined above, rats were given atropine, 2-PAM, midazolam and test treatment 20 min after SE onset. Results: Using gamma power, delta power, and spike rate to quantify EEG activity, we found that scopolamine was effective, memantine was minimally effective, and ***phenobarbital had a delayed effect on terminating SE***. Fluoro-Jade B staining was used to assess neuroprotection in five brain regions. Each treatment provided significant protection compared to saline + midazolam in at least two brain regions. Discussion: Because our data agree with previously published studies on the efficacy of these compounds, we conclude that this model is a valid way to test novel anticonvulsants/ neuroprotectants for controlling benzodiazepine-resistant OPNA-induced SE and subsequent neuropathology.

Increase signal intensities higher frequency activities, decreased lower frequency activity, and shorter and sharper spontaneous activity transient wave forms.

Malk, K., Metsäranta, M., & Vanhatalo, S. (2014). *Drug effects on endogenous brain activity in preterm babies*. Brain & development, 36(2), 116–123. https://doi.org/10.1016/j.braindev.2013.01.009

Our group has recently coined the term spontaneous activity transient (SAT), which refers to the family of intermittent EEG events in the preterm and early fullterm EEG that have previously have previously been called by a number of inherently ambiguous terms, such as delta brush, burst or temporal. In this context, it is intriguing that: (i) several experimental studies have shown a high sensitivity of the SAT-type activity to several environmental modulators (e.g. drugs), (ii) this activity is necessary for a normal brain, and (iii) human preterm babies are exposed to a considerable load of such treatments during the early weeks of

NICU stay. There are as yet no studies that would assess whether common drug treatments affect the intrinsic characteristics of the early intermittent brain activity. This study was set out as a pilot study to see whether potential effects of drugs on SAT activity can be seen when analysed from a retrospectively collected dataset. We studied seventeen EEG recordings from fifteen preterm infants at 26–33 weeks of conceptional age, with no lesions detectable by ultrasoun. Recordings were made for clinical purposes at the neonatal intensive care unit of Helsinki University Central Hospital. The EEG recordings used in our study were identified retrospectively from the department archives, starting from a search of all preterm EEGs of this age group during years 2001–2003, and subsequently excluding those babies with a detected ultrasound lesion (n = 5 exclusions). A detailed TF analysis with wavelets showed that SATs in both control and drug-treated groups were associated with bursts of oscillations at multiple frequency bands. Closer comparison, however, revealed clear differences between the groups: most importantly, ***both F and PB increased the signal intensity at all higher (>1 Hz) frequencies in the beginning of SAT, followed by a faster decline within 1–2 s into SAT***. This is clearly seen in the subtraction images (drug-controls; see Fig. 3A). TP, however, seemed to decrease middle (1–8 Hz) frequencies during SATs, as evident in both the raw TF graph and the subtraction image (theophylline vs. control; Fig. 3A). Finally, we quantified the oscillatory EEG activity in the lower and upper frequency range of neonatal EEG (<8 Hz and >8 Hz) during both 3 s prior to SAT (inter-SAT), and the first 2 s during SATs (Fig. 3B). During inter-SAT, the activity at both lower and higher frequencies was slightly increased by PB, but did not reach statistical significance ($p = 0.052$ and $p = 0.07$, respectively), whereas an increase in the activity at higher frequencies by TP was significant ($p = 0.006$). During the first 2 s of SAT, the ***activity at lower frequencies was decreased by PB*** and TP ($p < 0.05$), ***while only PB increased the activity at higher frequencies, ($p = 0.03$)***. The F group was not included into this analysis, due to a respirator artefact (10 Hz) in one of the EEG recordings. These results are fully compatible with the observations from the wavelet analyses where corresponding differences between drug treatments are readily seen in the subtraction figures (Fig. 3A). ***F and PB changed SATs to shorter and sharper, as seen in both the visual inspection of the raw waveforms analysis and in the TF analyses***. Based on the current ideas of how EEG activity is generated and transmitted from the cerebral cortex to scalp electrodes, the observed change in 'SAT carrier wave' (the large slow deflection) is most plausibly explained by a reduction in the spatial extent of the underlying cortical generator. Interestingly, recent in vivo animal studies on neonatal spindle bursts (SAT analogue in rodent models) have reported that the lateral spread of endogenous brain activity is modulated by GABAergic transmission, thus being compatible with the above interpretation of our findings. Our results show further that the ***intrinsic content of SATs is affected by PB, which is compatible with the earlier findings on rats that GABAergic drugs affect high frequencies of spindle bursts***. Indeed, recent animal studies have provided evidence that spindle burst in the rat cortex arise from pharmacologically distinct components, which can be modulated by at least GABAergic, glutamatergic and cholinergic drugs. The impact of GABAergic drugs on later brain development will obviously need prospective clinical studies, but it is easy to envisage that an enhanced compartmentalization of cortico-cortical communication may subsequently affect activity-dependent cortical wiring. To the best of our knowledge, the effects of opioids on the developmental brain activities have not been studied

in animal models. Our observations from TF analysis (see Fig. 3) suggest that at least the human SATs are sensitive to opioids as well.

Reduces amplitude and propagation of seizures

Mathieson, S. R., Livingstone, V., Low, E., Pressler, R., Rennie, J. M., & Boylan, G. B. (2016). *Phenobarbital reduces EEG amplitude and propagation of neonatal seizures but does not alter performance of automated seizure detection*. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 127(10), 3343–3350. https://doi.org/10.1016/j.clinph.2016.07.007

Phenobarbital increases electroclinical uncoupling and our preliminary observations suggest it may also affect electrographic seizure morphology. This may alter the performance of a novel seizure detection algorithm (SDA) developed by our group. The objectives of this study were to compare the morphology of seizures before and after phenobarbital administration in neonates and to determine the effect of any changes on automated seizure detection rates. Methods: The EEGs of 18 term neonates with seizures both pre- and post-phenobarbital (524 seizures) administration were studied. Ten features of seizures were manually quantified and summary measures for each neonate were statistically compared between pre- and post-phenobarbital seizures. SDA seizure detection rates were also compared. Results: Post-phenobarbital seizures showed significantly lower amplitude ($p<0.001$) and involved fewer EEG channels at the peak of seizure ($p<0.05$). No other features or SDA detection rates showed a statistical difference. Conclusion: These findings show that ***phenobarbital reduces both the amplitude and propagation of seizures*** which may help to explain electroclinical uncoupling of seizures. The seizure detection rate of the algorithm was unaffected by these changes.

Higher rate of generalized convulsive status epilepticus

Su, Y., Huang, H., Jiang, M., Pan, S., Ding, L., Zhang, L., Jiang, W., & Zhuang, X. (2021). *Phenobarbital versus valproate for generalized convulsive status epilepticus in adults (2): A multicenter prospective randomized controlled trial in China (China 2-P vs. V).* Epilepsy research, 177, 106755. https://doi.org/10.1016/j.eplepsyres.2021.106755

A multicenter study of phenobarbital versus valproate (i.e., the China 2-P vs. V study) was conducted to compare the efficacy and safety of phenobarbital and valproate for generalized convulsive status epilepticus (SE) in a multicenter trial design. Methods: Three improvements (uniform intravenous pumping, pump speed adjustment according to adverse events and blood drug level monitoring) over a previous study were made regarding an intravenous regimen of phenobarbital and valproate in a multicenter, prospective, randomized, controlled study. Long-term electroencephalography (EEG) monitoring was performed after initial drug treatment. Termination, relapse, adverse event and poor prognosis rates in patients with generalized convulsive status epilepticus (GCSE) were compared. Results: ***The rate of GCSE termination within one hour were significantly higher in the phenobarbital group (33 cases) than in the valproate group (36 cases) (84.8 % vs. 63.9 %, P = 0.048), but the rates of nontermination of EEG epileptic discharge within one hour were similar between the two groups (12.1 % vs. 8.3 %, P = 0.702)***. The relapse and adverse event rates were not significantly different between groups, but 3 hypoventilation events and 1 hypotension event occurred in the phenobarbital group compared to 0 in the valproate group. ***There were no cases of epileptiform EEG***

discharge relapse in the phenobarbital group, compared to 1 case in the valproate group. Conclusions: ***The phenobarbital regimen evaluated in this study has a higher GCSE termination rate than the valproate regimen***, indicating that the former is suitable for countries, regions and individuals with limited access to new antiepileptic drugs or limited economic means.

BENZODIAZEPINES

CLASS FACTS

SYNOPSIS: Taken orally as mild tranquilizers. They're generally prescribed for anxiety, sleep issues, and stress. They may cause reduced anxiety or stress or become a depressant as an extreme. They can be short-, intermediate-, or long-activating, with long activating types to have the harshest withdrawal effects. Benzodiazepines effect sleep profoundly by suppressing slow-wave sleep, and/or increasing sleep spindles. When taking a benzodiazepine, low delta/alpha ratio may be predictive for fibromyalgia. Beta power increases with dose.

Effect on sleep

Jang, D. J., Lim, D. K., & Kim, J. K. (2021). *Polysomnography Analysis of Electroencephalography in Patients Expending Benzodiazepine Drugs*. Korean Journal of Clinical Laboratory Science, 53(4), 333–341. https://doi.org/10.15324/kjcls.2021.53.4.333

Benzodiazepines (BDZs) drugs act on the GABAA receptor, function as nerve suppressors, and are used to treat anxiety, insomnia, and panic disorder. We analyzed the data of 30 individuals to determine any differences in the sleep-electroencephalogram findings among individuals varying in age, benzodiazepine use, and duration of benzodiazepine use. Comparisons between users and non-users of benzodiazepines, short-term and long-term users, older and younger users, and older short-term and older long-term users, were achieved using electroencephalographic findings obtained through polysomnography. The parameters evaluated included sleep latency, sleep efficiency, sleep-stage percentages, number of sleep spindles, and average frequency of sleep-spindle. The difference between benzodiazepine users and non-users was significant with respect to sleep-stage percentages and average frequency of sleep-spindle. Older and younger users differed significantly with respect to sleep efficiency and sleep-stage percentages, whereas significant difference for sleep efficiency was obtained between long-term and short-term users. ***Taken together, our results indicate that BDZ consumption suppresses slow-wave sleep and increases the frequency of sleep spindles.***

Effects in fibromyalgia may differentiate diagnosis

Rosenfeld VW, Rutledge DN, Stern JM. *Polysomnography with quantitative EEG in patients with and without fibromyalgia*. J Clin Neurophysiol. 2015 Apr;32(2):164-70. doi: 10.1097/WNP.0000000000000134. PMID: 25233248.

Purpose: Characterize the polysomnographic (PSG) and quantitative EEG (qEEG) features of fibromyalgia and determine whether fibromyalgia patients differ in these measures when compared with a control sleep disorder population. Methods: All undergoing all-night PSG for evaluation of a sleep disorder were evaluated for fibromyalgia. The PSGs were interpreted for routine sleep measures, and qEEG was performed to measure the delta and alpha frequency power during non-rapid eye movement sleep. Measures and qEEG were analyzed according to fibromyalgia diagnosis. Setting: Community-based sleep medicine center. Patients: All patients undergoing PSG over a 2-year period. Interventions: None. Results: Of the 385 patients in the study population, 133 had fibromyalgia according to American College of Rheumatology criteria. The population's average Epworth Sleepiness Score was 10.5, the average sleep

efficiency was 78%, and the Periodic Limb Movement disorder prevalence was 15%. None of these sleep measures differed significantly between the fibromyalgia and non-fibromyalgia groups. Obstructive sleep apnea was present in 45% of the fibromyalgia group. ***Significant differences were present in the qEEG ratio of delta to alpha frequency power, which was 95% specific for fibromyalgia when ≤1. A qEEG ratio ≤10.5 was 85% sensitive for fibromyalgia, and a qEEG ratio >10.5 had an 89% negative predictive value for fibromyalgia. Among patients with fibromyalgia who were not taking a benzodiazepine or benzodiazepine agonist, a qEEG ratio ≤10.5 was 84% specific and had a 78% positive predictive value.*** Conclusions: Sleep disorders identified by routine PSG, including obstructive sleep apnea, are common in fibromyalgia, but periodic leg movement disorder and poor sleep efficiency are not. A ***qEEG low delta/alpha ratio during non-rapid eye movement sleep can differentiate patients with fibromyalgia from others who are referred for PSG. Consideration of benzodiazepine and benzodiazepine agonist use is important when interpreting the delta/alpha ratio***.

Beta frequency increases with dose

Nickolls SA, Gurrell R, van Amerongen G, Kammonen J, Cao L, Brown AR, Stead C, Mead A, Watson C, Hsu C, Owen RM, Pike A, Fish RL, Chen L, Qiu R, Morris ED, Feng G, Whitlock M, Gorman D, van Gerven J, Reynolds DS, Dua P, Butt RP. *Pharmacology in translation: the preclinical and early clinical profile of the novel α2/3 functionally selective $GABA_A$ receptor positive allosteric modulator PF-06372865*. Br J Pharmacol. 2018 Feb;175(4):708-725. doi: 10.1111/bph.14119. Epub 2018 Jan 18. Erratum in: Br J Pharmacol. 2019 Jan;176(1):127. PMID: 29214652; PMCID: PMC5786456.

Background and purpose: Benzodiazepines, non-selective positive allosteric modulators (PAMs) of $GABA_A$ receptors, have significant side effects that limit their clinical utility. As many of these side effects are mediated by the α1 subunit, there has been a concerted effort to develop α2/3 subtype-selective PAMs. Experimental approach: In vitro screening assays were used to identify molecules with functional selectivity for receptors containing α2/3 subunits over those containing α1 subunits. In vivo receptor occupancy (RO) was conducted, prior to confirmation of in vivo α2/3 and α1 pharmacology through quantitative EEG (qEEG) beta frequency and zolpidem drug discrimination in rats respectively. PF-06372865 was then progressed to Phase 1 clinical trials. Key results: PF-06372865 exhibited functional selectivity for those receptors containing α2/3/5 subunits, with significant positive allosteric modulation (90-140%) but negligible activity (≤20%) at $GABA_A$ receptors containing α1 subunits. PF-06372865 exhibited concentration-dependent occupancy of $GABA_A$ receptors in preclinical species. ***There was an occupancy-dependent increase in qEEG beta frequency*** and no generalization to a $GABA_A$ α1 cue in the drug-discrimination assay, clearly demonstrating the lack of modulation at the $GABA_A$ receptors containing an α1 subtype. In a Phase 1 single ascending dose study in healthy volunteers, evaluation of the pharmacodynamics of PF-06372865 demonstrated a robust increase in saccadic peak velocity (a marker of α2/3 pharmacology), ***increases in beta frequency qEEG*** and a slight saturating increase in body sway. Conclusions and implications: PF-06372865 has a unique clinical pharmacology profile and a highly predictive translational data package from preclinical species to the clinical setting.

Increase in beta and delta; decrease in alpha

Herrmann, W. M., & Kubicki, S. (1981). *Beispiele für die Projektion von Substanzwirkungen typischer Psychopharmaka auf eine elektrophysiologische Messebene [The use of electrophysiological techniques to project typical psychotropic drug effects: some examples (author's transl)].* EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete, 12(1), 21–32.

A long existing hypothesis, i.e. that the EEG effects, in lead O2A2, of typical psychotropic drugs are substance class specific, when given as single oral dosages to healthy volunteers, is discussed. Using the technique of pharmacoelectroencephalograhpy, five typical representatives of neuroleptics, anxiolytics, antidepressives, psychostimulants (Fig. 2) as well as placebo were investigated in 75 volunteers, each receiving one representative of each substance class in a double blind 5-fach change over latin square design (Fig. 3). A five minute EEG record for lead O2A2 was obtained pre, 1 h and 3 hrs post drug intake under RR (Relaxed Recording) conditions. Typical samples of th EEG records are shown in Figs. 4--7. Parametrisation was done using power spectrum analysis. Then 3 x 7 target variables were formed--six relative power values in predetermined frequency bands and the total power between 1.5 and 30.0 Hz for 3 occasions of measurement (Fig. 4--7). Using a (five-group) linear discriminant analysis the substance effects on the EEG were transformed into 5 probability measures for the five substance classes (Fig. 4--7). The present paper should provide a demonstration of some typical examples, using single subjects, of the projection of substance effects onto an electrophysiological level using a vector of 21 components (7 target variables for 3 occasions of measurement) as can be seen from Table 1. Furthermore, the transformation into probability measures of the five substance classes are shown in Table 2. Table 3 shows five examples of projections of substance effects, which do not fit into the classifications to which they belong. An attempt is made to explain, whether single target variables from the power spectrum can contribute differently to the discrimination between single substances of different substance classes. Within the accepted system of 4 psychotropic drug classes, the following variables seem to be of importance: a) **The benzodiazepine anxiolytics show a marked increase in beta F1 (12.0--18.0 Hz) power and activity and, related to sedation, an increase in delta F-power and a decrease in alpha-power;** b) The psychostimulants of the amphetamine type show an increase in total power and alpha-power, an increase in the power of the frequency ranges near to the alpha-band (slow beta, fast theta) and a decrease in delta F (1.5--5.5 Hz)-power, when delta F-power is high in the pre-values, indicating a stabilization in vigilance; c) The neuroleptics show a marked increase in theta F (5.5--8.5 Hz)-power, some increase in the delta F--and a decrease in the beta F1-and beta F3-power; d) Tricyclic antidepressants show an interaction between delta F-theta F-, alpha- and beta-power, in the sense of a dissociative shift in vigilance.

----- ALPRAZOLAM (Xanax)-----

DRUG FACTS

SYNOPSIS: Xanax is a commonly prescribed anxiolytic and EEG effects are often dose-specific. Relative power is noted to increase localized beta and decrease delta. Connectivity is negatively affected depending on dose. Pathological slow background activity may normalize.

Linear and nonlinear EEG shifts

Alonso JF, Mañanas MA, Romero S, Rojas-Martínez M, Riba J. *Cross-conditional entropy and coherence analysis of pharmaco-EEG changes induced by alprazolam*. Psychopharmacology (Berl). 2012 Jun;221(3):397-406. doi: 10.1007/s00213-011-2587-7. Epub 2011 Nov 30. PMID: 22127555**.**

Rationale: Quantitative analysis of electroencephalographic signals (EEG) and their interpretation constitute a helpful tool in the assessment of the bioavailability of psychoactive drugs in the brain. Furthermore, psychotropic drug groups have typical signatures which relate biochemical mechanisms with specific EEG changes. **Objectives:** To analyze the pharmacological effect of a dose of alprazolam on the connectivity of the brain during wakefulness by means of linear and nonlinear approaches. **Methods:** EEG signals were recorded after alprazolam administration in a placebo-controlled crossover clinical trial. Nonlinear couplings assessed by means of corrected cross-conditional entropy were compared to linear couplings measured with the classical magnitude squared coherence. **Results:** Linear variables evidenced a statistically significant drug-induced decrease, whereas nonlinear variables showed significant increases. All changes were highly correlated to drug plasma concentrations. The spatial distribution of the observed connectivity changes clearly differed from a previous study: changes before and after the maximum drug effect were mainly observed over the anterior half of the scalp. Additionally, a new variable with very low computational cost was defined to evaluate nonlinear coupling. This is particularly interesting when all pairs of EEG channels are assessed as in this study. **Conclusions:** Results showed that alprazolam induced changes in terms of uncoupling between regions of the scalp, with opposite trends depending on the variables: decrease in linear ones and increase in nonlinear features. ***Maps provided consistent information about the way brain changed in terms of connectivity being definitely necessary to evaluate separately linear and nonlinear interactions***.

Increased power of different frequencies and locations

Berro LF, Overton JS, Reeves-Darby JA, Rowlett JK. *Alprazolam-induced EEG spectral power changes in rhesus monkeys: a translational model for the evaluation of the behavioral effects of benzodiazepines*. Psychopharmacology (Berl). 2021 May;238(5):1373-1386. doi: 10.1007/s00213-021-05793-z. Epub 2021 Feb 16. PMID: 33594504; PMCID: PMC8177744.

Rationale: Benzodiazepines induce electroencephalography (EEG) changes in rodents and humans that are associated with distinct behavioral effects and have been proposed as quantitative biomarkers for $GABA_A$ receptor modulation. Specifically, central EEG beta and occipital EEG delta activity have been associated with anxiolysis and sedation, respectively. The extent to which nonhuman primates show the same dose- and topography-dependent effects remained unknown. **Objectives:** We aimed at establishing a nonhuman primate model for the evaluation of benzodiazepine EEG pharmacology. **Methods:** Four adult male rhesus monkeys were prepared with fully implantable telemetry devices that monitored activity, peripheral body temperature, and contained two EEG (central and occipital), one electromyography (EMG), and one electrooculography channel. We investigated daytime alprazolam-induced changes in EEG spectral power, sleep-wake states, EMG activity, locomotor activity, and body

temperature. Alprazolam (0.01-1.8 mg/kg, i.m.) or vehicle was administered acutely, and telemetry recording was conducted for 1 h. **Results:** ***Daytime alprazolam dose-dependently increased central EEG power (including beta activity), increased occipital EEG delta power, and decreased occipital EEG alpha, theta, and sigma power.*** *There was an* ***~8-fold difference in the potency of alprazolam to increase central EEG beta vs. occipital EEG delta activity (based on relative EEG power). The highest dose, which increased both central EEG beta and occipital EEG delta relative power, induced sedative effects (increased time spent in N1 and N2 sleep stages) and decreased peripheral body temperature and locomotor activity*****.** **Conclusions:** Alprazolam induces dose- and topography-dependent EEG changes in rhesus monkeys and provides a valuable model for studying benzodiazepine pharmacology.

Positive dose and effect correlation

Berro, L. F., Overton, J. S., Reeves-Darby, J. A., & Rowlett, J. K. (2021). *Alprazolam-induced EEG spectral power changes in rhesus monkeys: a translational model for the evaluation of the behavioral effects of benzodiazepines*. Psychopharmacology, 238(5), 1373–1386. https://doi.org/10.1007/s00213-021-05793-z.

Rationale: Benzodiazepines induce electroencephalography (EEG) changes in rodents and humans that are associated with distinct behavioral effects and have been proposed as quantitative biomarkers for GABAA receptor modulation. Specifically, central EEG beta and occipital EEG delta activity have been associated with anxiolysis and sedation, respectively. The extent to which nonhuman primates show the same dose- and topography-dependent effects remained unknown. Objectives: We aimed at establishing a nonhuman primate model for the evaluation of benzodiazepine EEG pharmacology. Methods: Four adult male rhesus monkeys were prepared with fully implantable telemetry devices that monitored activity, peripheral body temperature, and contained two EEG (central and occipital), one electromyography (EMG) and one electrooculography channel. We investigated daytime alprazolam-induced changes in EEG spectral power, sleep-wake states, EMG activity, locomotor activity and body temperature. Alprazolam (0.01–1.8 mg/kg, i.m.) or vehicle were administered acutely, and telemetry recording was conducted for 1h. Results: Daytime alprazolam dose-dependently increased central EEG power (including beta activity), increased occipital EEG delta power, and decreased occipital EEG alpha, theta and sigma power. ***There was an ~8-fold difference in the potency of alprazolam to increase central EEG beta vs. occipital EEG delta activity (based on relative EEG power).*** The highest dose, which increased both central EEG beta and occipital EEG delta relative power, induced sedative effects (increased time spent in N1 and N2 sleep stages) and decreased peripheral body temperature and locomotor activity. Conclusions: Alprazolam induces dose- and topography-dependent EEG changes in rhesus monkeys, and provides a valuable model for studying benzodiazepine pharmacology.

Connectivity

Alonso, J. F., Mañanas, M. A., Romero, S., Hoyer, D., Riba, J., & Barbanoj, M. J. (2010). *Drug effect on EEG connectivity assessed by linear and nonlinear couplings*. Human brain mapping, 31(3), 487–497. https://doi.org/10.1002/hbm.20881.

Quantitative analysis of human electroencephalogram (EEG) is a valuable method for evaluating psychopharmacological agents. Although the effects of different drug classes on EEG spectra

are already known, interactions between brain locations remain unclear. In this work, cross mutual information function and appropriate surrogate data were applied to assess linear and nonlinear couplings between EEG signals. The main goal was to evaluate the pharmacological effects of alprazolam on brain connectivity during wakefulness in healthy volunteers using a cross-over, placebo-controlled design. Eighty-five pairs of EEG leads were selected for the analysis, and connectivity was evaluated inside anterior, central, and posterior zones of the scalp. Connectivity between these zones and interhemispheric connectivity were also measured. ***Results showed that alprazolam induced significant changes in EEG connectivity in terms of information transfer in comparison with placebo. Trends were opposite depending on the statistical characteristics: decreases in linear connectivity and increases in nonlinear couplings. These effects were generally spread over the entire scalp. Linear changes were negatively correlated, and nonlinear changes were positively correlated with drug plasma concentrations; the latter showed higher correlation coefficients.*** The use of both linear and nonlinear approaches revealed the importance of assessing changes in EEG connectivity as this can provide interesting information about psychopharmacological effects.

----- BROMAZEPAM (Lexotan) -----

DRUG FACTS

Temporal and parietal activity theta activity

Araújo, F., Machado, S., Paes, F., Cunha, M., Budde, H., Cagy, M., Basile, L. F., Arias-Carrión, O., Velasques, B., Piedade, R., & Ribeiro, P. (2011). *The effects of bromazepam over the temporo-parietal areas during the performance of a visuomotor task: A qEEG study.* Neuroscience Letters, 496(2), 116–120. https://doi.org/10.1016/j.neulet.2011.03.095

This study investigated the effects of bromazepam on qEEG when 14 healthy subjects were asked to perform a visuomotor task (i.e., motor vehicle driving task). The subjects were exposed to two experimental conditions: the placebo (PL) and 6 mg of bromazepam (Br 6 mg), following a randomized, double-blind design on different days. Specifically, we observe absolute power extracted from qEEG data for theta band. We expected to see a decrease in absolute theta power in the temporal and parietal areas due to the influence of bromazepam for the experimental group when compared with the placebo group. We found a ***main effect for the condition factor for electrodes T3, T4, P3 and P4. We also observed a main effect for the period factor for electrodes P3 and P4.*** We observed that the ingestion of 6 mg of bromazepam ***induces different patterns in theta power at the temporal and parietal sites*****.** We concluded that 6 mg of ***bromazepam was an important factor in the fluctuation of the activities in the temporal and parietal areas*****.** We then hypothesize about the specific role of this drug during the execution of a visuomotor task and within the sensorimotor integration process.

Frontal and central site changes in alpha

Fortunato, S., Tanaka, G. K., Araújo, F., Bittencourt, J., Aprigio, D., Gongora, M., Teixeira, S., Pompeu, F. A. M. S., Cagy, M., Basile, L. F., Ribeiro, P., & Velasques, B. (2015). *The effects of bromazepam over the central and frontal areas during a motor task: an EEG study.* Arquivos de Neuro-Psiquiatria, 73(4), 321–329. https://doi.org/10.1590/0004-282X20150011.

The present study investigates the influence of bromazepam while executing a motor task. Specifically, we intend to analyze the changes in alpha absolute power under two experimental conditions, bromazepam and placebo. We also included analyses of theta and beta frequencies. We collected electroencephalographic data before, during, and after motor task execution. We used a Two Way ANOVA to investigate the condition (PL × Br6 mg) and moment (pre and post) variables for the following electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, C3, CZ and C4. We found a ***main effect for condition on the electrodes FP1, F7, F3, Fz, F4, C3 and CZ, for alpha and beta bands. For beta band we also found a main effect for condition on the electrodes Fp2, F8 and C4; for theta band we identified a main effect for condition on C3, Cz and C4 electrodes. This finding suggests that the motor task did not have any influence on the electrocortical activity in alpha, and that the existing modifications were a consequence due merely to the drug use.*** Despite its anxiolytic and sedative action, bromazepam did not show any significant changes when the individuals executed a finger extension motor task.

Right lateral frontal changes in theta

Gongora, M., Peressuti, C., Velasques, B., Bittencourt, J., Teixeira, S., Arias-Carrión, O., Cagy, M., & Ribeiro, P. (2015). *Absolute Theta Power in the Frontal Cortex During a Visuomotor Task: The Effect of Bromazepam on Attention*. Clinical EEG and Neuroscience, 46(4), 292–298. https://doi.org/10.1177/1550059414535576.

Bromazepam is a benzodiazepine, which has been widely employed in the treatment of anxiety. We investigated the electrophysiological changes in absolute theta power within the frontal cortex when individuals performed a visuomotor task under bromazepam. The sample of 17 healthy individuals was randomized into 2 experimental conditions, under which bromazepam 6 mg and placebo were administered on different days. All subjects were right -handed, with no mental or physical illness and were not using any psychoactive or psychotropic substance during the entire period of the study. We found an increase in reaction time under bromazepam compared with placebo . With regard to the electrophysiological variable, we found a ***lower theta power value in the prefrontal cortex prior to task execution, compared with after***. We therefore suggested that this could be an increase of neural activity in this region, because of the subjects' readiness to perform the task, that is, because of their higher alertness. The ***right lateral frontal region showed lower theta power under bromazepam for pre- and post-finger movement.*** This could have occurred because of more effort to execute the task. In the left frontal region: premovement did not demonstrate any difference between conditions, possibly because the proposed task was simple to execute. In conclusion, ***theta power plays an important role in the analysis of visuomotor performance, assuming that bromazepam causes impairment on sustained attention and sensory perception.***

Alpha symmetry (higher on left)

Silva, P. R., Marinho, V., Magalhães, F., Farias, T., Gupta, D. S., Barbosa, A. L. R., Velasques, B., Ribeiro, P., Cagy, M., Bastos, V. H., & Teixeira, S. (2022). *Bromazepam increases the error of the time interval judgments and modulates the EEG alpha asymmetry during time estimation*. Consciousness and Cognition, 100, 103317–103317. https://doi.org/10.1016/j.concog.2022.103317.

Aim: This study investigated the bromazepam effects in male subjects during the time estimation performance and EEG alpha asymmetry in electrodes associated with the frontal and motor cortex. Material and methods: This is a double-blind, crossover study with a sample of 32 healthy adults under control (placebo) vs. experimental (bromazepam) during visual time-estimation task in combination with electroencephalographic analysis. Results: The results demonstrated that the bromazepam increased the relative error in the 4 s, 7 s, and 9 s intervals ($p = 0.001$). In addition, ***oral bromazepam modulated the EEG alpha asymmetry in cortical areas*** during the time judgment ($p \leq 0.025$). Conclusion: The ***bromazepam decreases the precision of time estimation judgments and modulates the EEG alpha asymmetry, with greater left hemispheric dominance during time perception.*** Our findings suggest that bromazepam influences internal clock synchronization via the modulation of GABAergic receptors, strongly relating to attention, conscious perception, and behavioral performance.

Left motor cortex changes in mid-range power

Silva, J. G., Arias-Carrion, O., Paes, F., Velasques, B., Teixeira, S., Basile, L. F., Cagy, M., Piedade, R., Nardi, A. E., Machado, S., & Ribeiro, P. (2011). *Bromazepam impairs motor response: an ERSP study.* CNS & neurological disorders drug targets, 10(8), 945–950. https://doi.org/10.2174/187152711799219361

This study aimed to investigate the acute modulatory effect of bromazepam, a benzodiazepine derivative drug, on alpha and beta bands (8-35Hz) in primary motor areas (M1) through event-related spectral perturbation (ERSP). Ten healthy subjects were submitted to a cross-over double-blind design. Subjects performed a visuomotor task where they had to identify rapidly the ball launched horizontally and catch it quickly, while electroencephalographic activity was acquired. We found a ***statistically significant difference on the time windows of 2920 ms for 13Hz in the electrodes C3 and Cz, and on the time window of 2000 ms for 18Hz in the electrodes C3, when compared the bromazepam and placebo conditions. We concluded that the acute effects of bromazepam provoked changes in information process in the left M1 represented by electrode C3 in both 13 Hz and 18 Hz. Our paradigm is relevant for a better understanding of the brain dynamics due to the information related to bromazepam effects on sensorimotor processes.*** We consider this report an invitation to conduct more studies in order to associate electro-cortical activity and psychometric tests.

Alpha symmetry

Silva, P. R., Marinho, V., Magalhães, F., Farias, T., Gupta, D. S., Barbosa, A. L. R., Velasques, B., Ribeiro, P., Cagy, M., Bastos, V. H., & Teixeira, S. (2022). *Bromazepam increases the error of the time interval judgments and modulates the EEG alpha asymmetry during time estimation*. Consciousness and Cognition, 100, 103317–103317. https://doi.org/10.1016/j.concog.2022.103317.

Aim: This study investigated the bromazepam effects in male subjects during the time estimation performance and EEG alpha asymmetry in electrodes associated with the frontal and motor cortex. **Material and methods:** This is a double-blind, crossover study with a sample of 32 healthy adults under control (placebo) vs. experimental (bromazepam) during visual time-estimation task in combination with electroencephalographic analysis. **Results:** The results demonstrated that the bromazepam increased the relative error in the 4 s, 7 s, and 9 s intervals

(p = 0.001). In addition, ***oral bromazepam modulated the EEG alpha asymmetry in cortical areas during the time judgment (p ≤ 0.025). Conclusion: The bromazepam decreases the precision of time estimation judgments and modulates the EEG alpha asymmetry, with greater left hemispheric dominance during time perception*.** Our findings suggest that bromazepam influences internal clock synchronization via the modulation of GABAergic receptors, strongly relating to attention, conscious perception, and behavioral performance.

----- CHLORDIAZEPOXIDE (Librium) -----

DRUG FACTS

SYNOPSIS: A long-acting schedule IV-controlled drug (due to dependency risk), acting like a sedative. May reduce background slowing and has multiple effects on the sleep EEG related to paradoxical sleep.

Reduction in abnormal background slow

Jeavons, P.M. (1962), *The Effect of Chlordiazepoxide on the Electroencephalogram*. Epilepsia, 3: 110-116. https://doi.org/10.1111/j.1528-1157.1962.tb05236.x

Chlordiazepoxide was given to 41 patients suffering from epilepsy of various types and electroencephalograms were taken before and after treatment. Paroxysmal discharges in the EEG were reduced in 17 cases, and in 18 there was an increase in normal alpha activity. ***The most unusual finding was a reduction in abnormal background slow activity***. Fast activity was induced in more than half the cases. The clinical effects were unpredictable, but there was reduction in infantile spasms and petit mal attacks. The effect on other forms of epilepsy was equivocal. Behavior improved in some cases and worsened in others.

Multiple effects on sleep EEG and perception of sleep quality

Kantor, S., Jakus, R., Molnar, E., Gyongyosi, N., Toth, A., Detari, L., & Bagdy, G. (2005). *Despite similar anxiolytic potential, the 5-hydroxytryptamine 2C receptor antagonist SB-242084 [6-chloro-5-methyl-1-[2-(2-methylpyrid-3-yloxy)-pyrid-5-yl carbamoyl] indoline] and chlordiazepoxide produced differential effects on electroencephalogram power spectra*. The Journal of pharmacology and experimental therapeutics, 315(2), 921–930. https://doi.org/10.1124/jpet.105.086413

Serious efforts have been made to develop anxiolytics with improved clinical utility and reduced side effects. 5-Hydroxytryptamine (5-HT)(2C) receptor antagonists are potential anxiolytics; however, their effects on vigilance are not well characterized. To compare the effects of benzodiazepines and subtype-selective 5-HT(2C) receptor antagonists on anxiety, vigilance, and electroencephalogram (EEG) power density, social interaction test and polygraphic recordings were performed in male Sprague-Dawley rats after chlordiazepoxide (CDP; 4.0 mg/kg i.p.) and SB-242084 (6-chloro-5-methyl-1-[2-(2-methylpyrid-3-yloxy)-pyrid-5-yl carbamoyl] indoline) (0.1, 0.3, and 1.0 mg/kg i.p.) treatment. ***CDP and SB-242084 (0.3 and 1.0 mg/kg) had similar anxiolytic effects. Spectral analysis of EEG in wakefulness (W) and paradoxical sleep (PS) showed an opposite effect on activity (5-9 Hz); it decreased after CDP, whereas it increased after SB-242084 (even at 0.1 mg/kg). In addition, CDP significantly decreased slow-wave activity (0.5-4 Hz) in deep slow-wave sleep (SWS-2) and increased power at frequencies above 12 Hz mainly in W and PS.*** A markedly increased intermediate stage of sleep was also found

after CDP treatment. At the highest dose, SB-242084 increased W and decreased SWS-2. In summary, low but potent anxiolytic doses of the subtype-selective 5-HT(2C) receptor antagonist SB-242084 did not affect vigilance states but caused an increased activity in W, raising the possibility of a cognitive-enhancing effect of the drug. In contrast, acute CDP administration, based on spectral analysis of the EEG, produced a more superficial sleep along with a decreased activity.

----- CLONAZEPAM (Klonopin) -----

DRUG FACTS

SYNOPSIS: Generally prescribed for panic disorders, and sleep/arousal issues some sleep studies show HSDA (hypersynchronous delta activity) may be alleviated before and after arousal with medication. This drug can be used to stabilize sleep EEG pathologies. It may normalize faster power during REM sleep and/or minimize slow wave sleep.

Post arousal hypersynchronous delta activity

Kang, M. K., Shin, D. S., Lee, H. C., Provini, F., & Jung, K. Y. (2023). *A case of disorder of arousal with prolonged postarousal hypersynchronous delta activity*. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine, 10.5664/jcsm.10548. Advance online publication. https://doi.org/10.5664/jcsm.10548

Disorder of arousal (DOA) is a form of nonrapid eye movement (NREM) sleep parasomnia caused by partial or incomplete arousal from deep sleep. Most previous studies of DOA patients analyzed prearousal hypersynchronous delta activity (HSDA), but few studies have described postarousal HSDA. Herein, we report a 23-year-old man with a history of abrupt arousal during sleep, confused behavior and speech since he was 14 years old. ***During video EEG monitoring (VEEG), he had nine arousal events of getting up, sitting on the bed, looking around or simple arousal, including eyes open, looking at the ceiling or head flexion. During all arousal events, the postarousal EEG pattern was prolonged HSDA for approximately 40 seconds***. The patient was treated unsuccessfully for more than 2 years with an antiseizure medication (lacosamide); eventually, he responded to clonazepam that was administered for the possibility of DOA. Prolonged rhythmic HSDA without spatiotemporal evolution can appear as a postarousal EEG pattern of DOA. When diagnosing DOA, it is important to recognize that postarousal HSDA can appear as a characteristic EEG pattern of DOA.

Clonazepam somewhat normalizes dysregulated REM power spectrum above 15Hz.

Ferri, R., Rundo, F., Silvani, A., Zucconi, M., Bruni, O., Ferini-Strambi, L., Plazzi, G., & Manconi, M. (2017). *REM Sleep EEG Instability in REM Sleep Behavior Disorder and Clonazepam Effects*. Sleep (New York, N.Y.), 40(8). https://doi.org/10.1093/sleep/zsx080

Study Objectives: We aimed to analyze quantitatively rapid eye movement (REM) sleep electroencephalogram (EEG) in controls, drug-naïve idiopathic REM sleep behavior disorder patients (iRBD), and iRBD patients treated with clonazepam. Methods: Twenty-nine drug-naïve iRBD patients (mean age 68.2 years), 14 iRBD patients under chronic clonazepam therapy (mean age 66.3 years), and 21 controls (mean age 66.8 years) were recruited. Power spectra were obtained from sleep EEG (central derivation), using a 2-second sliding window, with 1-

second steps. The power values of each REM sleep EEG spectral band (one every second) were normalized with respect to the average power value obtained during sleep stage 2 in the same individual. Results: ***In drug-naïve patients, the normalized power values showed a less pronounced REM-related decrease of power in all bands with frequency <15 Hz than controls and an increase in the beta band, negatively correlated with muscle atonia; in patients treated with clonazepam there was a partial return of all bands <15 Hz toward the control values.*** The standard deviation values of the normalized power were higher for untreated patients in all EEG bands and were almost completely normalized in patients treated with clonazepam. Conclusions: The REM sleep EEG structure changes found in this study disclose subtle but significant alterations in the cortical electrophysiology of RBD that might represent the early expression of the supposed neurodegenerative processes already taking place at this stage of the disease and might be the target of better and effective future therapeutic strategies for this condition.

Sleep EEG normalization

Ferri, R., Zucconi, M., Marelli, S., Plazzi, G., Schenck, C. H., & Ferini-Strambi, L. (2013). *Effects of long-term use of clonazepam on nonrapid eye movement sleep patterns in rapid eye movement sleep behavior disorder*. Sleep Medicine, 14(5), 399–406. https://doi.org/10.1016/j.sleep.2013.01.007

Objective: We aim to analyze in detail the characteristics of nonrapid eye movement (NREM) sleep in drug-free patients with idiopathic rapid eye movement sleep behavior disorder (iRBD). We compare drug-free iRBD patients to both normal controls and drug-free patients with narcolepsy/RBD and evaluate the changes following the long-term use of bedtime clonazepam. Participants and methods: Forty-six participants were recruited: 15 with iRBD (13 men, 2 women; mean age, 65.8 ± 4.39 years), 13 with narcolepsy/RBD (10 men, 3 women; mean age, 63.0 ± 6.73 years), and 18 normal controls (10 men, 8 women; mean age 69.4 ± 7.72 years). Sleep was video polysomnographically recorded and the RBD severity scale (RBDSS) was obtained. Chin electromyography (EMG) amplitude was quantitatively assessed and the atonia index was computed. Additionally, NREM sleep instability was evaluated using an automatic quantitative analysis. Participants with iRBD were re-evaluated after 2.75 ± 1.62 years of regular therapy with 0.5 to 1-mg clonazepam at bedtime. Results: Slow transient electroencephalography (EEG) events were increased in iRBD and decreased in narcolepsy/RBD, while fast transient events decreased in iRBD and increased in narcolepsy/RBD. During rapid eye movement (REM) sleep the atonia index was reduced in both iRBD and narcolepsy/RBD groups and during NREM sleep atonia index was increased in iRBD participants, remaining low in narcolepsy/RBD participants. ***After long-term therapy with clonazepam, wakefulness after sleep onset was decreased together with an increase in both slow-wave sleep (SWS) and sleep stage 2, in which the latter reached statistical significance; sleep stages 1 and 2 instability significantly decreased and the duration of EEG transients also slightly but significantly decreased.*** Finally, chin tone was not modified by clonazepam. Conclusions Our study confirms that clonazepam modifies some aspects of NREM sleep in iRBD participants with a decrease in its instability. Moreover, we also show that a complex modification of sleep chin atonia exists in these participants, which also involves NREM sleep; for iRBD more complex neuropathologic models encompassing REM sleep and NREM sleep mechanisms are needed.

Slows EEG

Arnulf, I. (2012). *REM sleep behavior disorder: motor manifestations and pathophysiology: REM sleep behavior disorder*. Movement Disorders, 27(6), 677–689. https://doi.org/10.1002/mds.24957.

Patients with REM sleep behavior disorder (RBD) enact violent dreams during REM sleep in the absence of normal muscle atonia. This disorder is highly frequent in patients with synucleinopathies (60%-100% of patients) and rare in patients with other neurodegenerative disorders. The disorder is detected by interview plus video and sleep monitoring. Abnormal movements expose the patients and bed partners to a high risk of injury and sleep disruption. The disorder is usually alleviated with melatonin and clonazepam. Limb movements are mainly minor, jerky, fast, pseudohallucinatory, and repeated, with a limp wrist during apparently grasping movements, although body jerks and complex violent (fights) and nonviolent culturally acquired behaviors are also observed. Notably, parkinsonism disappears during RBD-associated complex behaviors in patients with Parkinson's disease and with multiple system atrophy, suggesting that the upper motor stream bypasses the basal ganglia during REM sleep. Longitudinal studies show that idiopathic RBD predisposes patients to later develop Parkinson's disease, dementia with Lewy bodies, and, more rarely, multiple system atrophy, with a rate of conversion of 46% within 5 years. During this time window, patients concomitantly develop nonmotor signs (decreased olfaction and color vision, orthostatic hypotension, altered visuospatial abilities, increased harm avoidance) and have abnormal test results (decreased putamen dopamine uptake, ***slower EEG***). Patients with idiopathic RBD have higher and faster risk for conversion to Parkinson's disease and dementia with Lewy bodies if abnormalities in dopamine transporter imaging, transcranial sonography, olfaction, and color vision are found at baseline. They constitute a highly specific target for testing neuroprotective agents.

----- DIAZEPAM (Valium) -----

DRUG FACTS

SYNOPSIS: Another sleep medication, which effects the EEG in both REM and NREM sleep as well as the awake state by decreasing slow wave activity and increasing faster activity. There may be changes over time after medication intake in theta and alpha activity. There may be interference with healthy frontal alpha during wake in power and synchrony. Shifts in the EEG may revert to baseline after 6 or so months of intake.

Slow wave and beta1 power increase; slowing of alpha

Pechadre, J. C., Beudin, P., Trolese, J. F., Gabet, J. Y., & Eschalier, A. (1993). *A comparison of the electroencephalographic spectral modifications induced by diazepam and by hydroxyzine*. The Journal of international medical research, 21(5), 234–242. https://doi.org/10.1177/030006059302100502

A double-blind, randomized controlled trial using an electroencephalograph computerized analysis and cartography was carried out to investigate the spectral modifications induced by diazepam and hydroxyzine***. Without monitoring response to stimulation, the spectra found for***

diazepam and for hydroxyzine were qualitatively very similar, showing increase of the slow waves, reduction of the alpha rhythm and accentuation of the beta 1 rhythms. These traces suggested strongly that both drugs had produced a sedative, anti-anxiety effect. The intensity of the effect produced by 50 mg of hydroxyzine appeared to be less than that produced by 10 mg diazepam. After monitoring response to stimulation, the spectra were modified and the reactivity of the two drugs differed with regard to the slow delta, theta and alpha 1 frequency bands. It was possible to distinguish between the sedative and anti-anxiety effects of both diazepam and hydroxyzine. Even if the two drugs had some similar effects, the mode of action in the central nervous system was certainly different, as can be seen from the characteristics of distribution of the slow waves, their reactivity and, with regard to frequency, the fluctuation of the dominant frequency of rapid rhythms.

Effects on nREM and REM sleep

Authier, S., Bassett, L., Pouliot, M., Rachalski, A., Troncy, E., Paquette, D., & Mongrain, V. (2014). *Reprint of "Effects of amphetamine, diazepam and caffeine on polysomnography (EEG, EMG, EOG)-derived variables measured using telemetry in Cynomolgus monkeys."* Journal of Pharmacological and Toxicological Methods, 70(3), 287–294. https://doi.org/10.1016/j.vascn.2014.10.004

Introduction: Medication-induced sleep disturbances are a major concern in drug development as a multitude of prescription drugs alter sleep patterns, often negatively. Polysomnography is used in clinical diagnostics but is also applicable to animal models. Rodent sleep architecture (nocturnal) differs from larger diurnal mammals, including humans, increasing the translational potential of non-rodent species to the clinic. This study aimed to characterize the response to pharmacological agents known to affect sleep structure and EEG activity in a non-human primate (Macaca fascicularis) using telemetry-based polysomnography. **Methods:** Animals were instrumented with telemetry transmitters for continuous electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) monitoring combined with video. EEG, EMG and EOG were monitored for 12 to 24h to establish baseline values, followed by administration of pharmacological agents (saline, d-amphetamine, diazepam or caffeine). **Results:** Amphetamine (0.3 and 1mg/kg, by oral administration (PO)) significantly reduced total sleep time, including the duration of both non-rapid eye movement [NREM] sleep and REM sleep. It also decreased EEG activity in low frequencies (i.e., 4-6Hz) during wakefulness. ***Diazepam (2mg/kg, PO) did not significantly alter sleep duration, but importantly reduced EEG activity in low frequencies (approximately 2-12Hz) during wakefulness, NREM and REM sleep*****.** Finally, caffeine (10 and 30mg/kg, PO) decreased both NREM and REM sleep duration. In addition, ***spectral analysis revealed important decreases in low frequency activity (i.e., 1-8Hz) during wakefulness with a parallel increase in high frequency activity (i.e., 20-50Hz) during NREM sleep.*** **Discussion:** As these observations are similar to previously reported pharmacological effects in humans, results support that EEG, EOG and EMG monitoring by telemetry in Cynomolgus monkeys represents a useful non-clinical model to investigate and quantify drug-induced sleep disturbances.

EEG response to hypnotics based on rat behavior

van Lier, H., Drinkenburg, W. H., van Eeten, Y. J., & Coenen, A. M. (2004). *Effects of diazepam and zolpidem on EEG beta frequencies are behavior-specific in rats*. *Neuropharmacology*, *47*(2), 163–174. https://doi.org/10.1016/j.neuropharm.2004.03.017

A pharmacological dissociation of the relation between electroencephalographic (EEG) activity and behavior has been described for the benzodiazepines. ***While a decrease in high frequency EEG activity is associated with a decrease in arousal in drug-free conditions, sedative benzodiazepines increase beta activity.*** Non-benzodiazepine GABA(A) receptor modulators can increase beta activity as well. To further study the relationship between rat behavior and EEG under GABA(A) receptor modulation, EEG effects of diazepam (2.5 mg/kg) and zolpidem (2.5 mg/kg) were studied during different behaviors. Both drugs modulate the GABA(A) receptor, albeit that zolpidem shows alpha(1) subunit selectivity while diazepam is non-selective. A detailed analysis of rat open field behavior was made with a distinction of 25 behavioral elements. The EEG was segmented according to each behavioral element and a corresponding power spectrum calculated. ***Both diazepam and zolpidem increased EEG beta frequencies, characteristic for the benzodiazepines. However, the beta and gamma increase was specific for active behavior and not for inactivity.*** Interestingly, diazepam and zolpidem seemed to amplify, rather than dissociate, the relation between behavior and the EEG. It is hypothesized that the large increase in beta-3/gamma activity caused by diazepam and zolpidem is a compensatory mechanism that allows for behavioral activation, despite pharmacologically induced sedation.

Delta increase

Hambrecht-Wiedbusch, V. S., Gauthier, e. A., Baghdoyan, H. A., & Lydic, R. (2010). Benzodiazepine Receptor Agonists Cause Drug-Specific and State-Specific Alterations in EEG Power and Acetylcholine Release in Rat Pontine Reticular Formation. Sleep (New York, N.Y.), 33(7), 909–918. https://doi.org/10.1093/sleep/33.7.909.

Study objectives: Benzodiazepine (BDZ) and non-benzodiazepine (NBDZ) hypnotics enhance GABAergic transmission and are widely used for the treatment of insomnia. In the pontine reticular formation (PRF), GABA inhibits rapid eye movement (REM) sleep and acetylcholine (ACh) release. No previous studies have characterized the effects of BDZ and NBDZ hypnotics on ACh release in the PRF. This study tested 2 hypotheses: (1) that microdialysis delivery of zolpidem, eszopiclone, and diazepam to rat PRF alters ACh release in PRF and electroencephalographic (EEG) delta power and (2) that intravenous (i.v.) administration of eszopiclone to non-anesthetized rat alters ACh release in the PRF, sleep, and EEG delta power. **Design:** A within- and between-groups experimental design. **Setting:** University of Michigan. **Patients or participants:** Adult male Crl:CD*(SD) (Sprague-Dawley) rats (n = 57). **Interventions:** In vivo microdialysis of the PRF in rats anesthetized with isoflurane was used to derive the concentration-response effects of zolpidem, eszopiclone, and diazepam on ACh release. Chronically instrumented rats were used to quantify the effects of eszopiclone (3 mg/kg, i.v.) on ACh release in the PRF, sleep-wake states, and cortical EEG power. **Measurements and results:** ACh release was significantly increased by microdialysis delivery to the PRF of zolpidem and eszopiclone but not diazepam. ***EEG delta power was increased by***

***zolpidem and diazepam but not by eszopiclone administered to the PRF*.** Eszopiclone (i.v.) decreased ACh release in the PRF of both anesthetized and non-anesthetized rats. Eszopiclone (i.v.) prevented REM sleep and increased EEG delta power. **Conclusion:** The concentration-response data provide the first functional evidence that multiple GABA(A) receptor subtypes are present in rat PRF. Intravenously administered eszopiclone prevented REM sleep, decreased ACh release in the PRF, and increased EEG delta power. The effects of eszopiclone are consistent with evidence that ACh release in the PRF is lower during NREM sleep than during REM sleep, and with data showing that cholinergic stimulation of the PRF activates the cortical EEG.

2–5-minute shifts in EEG during recording

Jobert, M., & Wilson, F. J. (2015). *Advanced Analysis of Pharmaco-EEG Data in Humans*. Neuropsychobiology, 72(3-4), 165–177. https://doi.org/10.1159/000431096.

The results obtained when comparing post-pre (1.5 h vs. baseline) differences for placebo and 10 mg diazepam in 4 frequency bands under the RS_c recording condition (electrode Pz), whereby the evaluation is made for segments of 5 min (session as one block) and for the last 2 min of the recording, leading to the following observations: ***for the theta band, a significant difference between diazepam and placebo is only visible in the last 2 min of the session; for alpha, the difference is significant for the 5-min segment, but it is even more pronounced at the end of the recording, a configuration that is reversed in the case of beta where the difference between placebo and diazepam is more significant for the 5-min segment as compared to the last 2 min of the recording; no significant change is observed for alpha. The results obtained here for 1 lead (Pz) are consistent with the observations reported above demonstrating that both the natural diurnal variations and the RS-related changes are enhanced by diazepam administration*.**

Disruption of alpha synchrony

Muñoz-Torres, Z., del Río-Portilla, Y., & Corsi-Cabrera, M. (2011). *Diazepam-induced changes in EEG oscillations during performance of a sustained attention task*. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 28(4), 394–399. https://doi.org/10.1097/WNP.0b013e318227323a

The primary aim of the present study was to test diazepam (DZ) effect, a benzodiazepine (BDZ) usually prescribed to reduce anxiety and to induce sleep, on EEG activity while performing a visual sustained attention task. The EEG activity was recorded in a double-blind placebo experiment, and prestimulus spectral power and inter- and intrahemispheric temporal coupling were assessed during visual sustained attention task performance. A single DZ dose (5 mg) was enough to increase reaction times during visual sustained attention task responses. ***DZ decreased prestimulus EEG power in the 1- to 6-, 8- to 12-, and 19- to 35-Hz bands and disrupted right intrahemispheric temporal coupling in the α-frequency range (8-12 Hz). The combined reduction in power and temporal coupling suggests both local and interregional DZ-induced disruption of neuronal synchronicity especially in the right hemisphere in agreement with the prominent attention-related networks in this hemisphere. These data support the notion that the influence of DZ on behavior goes beyond sedative effects and can potentially compromise higher cognitive functions with negative consequences to daily life situations***.

Changes in sleep cycle and spike and wave EEG

Sánchez Fernández, I., Peters, J. M., An, S., Bergin, A. M., Takeoka, M., Rotenberg, A., Kothare, S. V., Riviello, J. J., Jr, & Loddenkemper, T. (2013). *Long-term response to high-dose diazepam treatment in continuous spikes and waves during sleep*. Pediatric neurology, 49(3), 163–170.e4. https://doi.org/10.1016/j.pediatrneurol.2013.04.027

Background: This study evaluated whether the reduction in epileptiform activity after treatment with high-dose diazepam in continuous spikes and waves during sleep persists over time. **Patients:** Patients aged 1 to 21 years with continuous spikes and waves during sleep who received high-dose nocturnal diazepam and who had electroencephalogram follow-up were included. Twenty-nine patients met the inclusion criteria and underwent a total of 48 high-dose diazepam treatment cycles. **Results:** An ***overnight reduction of the spike wave percentage of at least 25% (i.e., 75-50%) occurred in 29 cycles (20 patients), and persisted within 6 months in 16 of 29 cycles (12 patients), but returned to baseline in three of 29 cycles (three patients). An overnight reduction of at least 50% (i.e., 75-25%) occurred in 15 cycles (13 patients), and persisted within 6 months in eight of 15 cycles (eight patients), but returned to baseline in three cycles (three patients)***. Twenty of 29 cycles that responded in the short term had persistent response on follow-up. Thirteen cycles of treatment were associated with mild side effects that did not recur with repeated treatment cycles. **Conclusions:** Treatment with ***high-dose diazepam reduced epileptiform activity in continuous spikes and waves during sleep in the short term***, and improvement persisted for several months in most cycles. Short-term response predicted persistence of this effect on subsequent follow-up.

Increased synchrony in frontal and right temporoparietal areas

Wyczesany, M., Grzybowski, S. J., Barry, R. J., Kaiser, J., Coenen, A. M. L., & Potoczek, A. (2011). *Covariation of EEG Synchronization and Emotional State as Modified by Anxiolytics*. Journal of Clinical Neurophysiology, 28(3), 289–296. https://doi.org/10.1097/WNP.0b013e31821c34f7.

The relationships between subjective estimation of emotional state and synchronization patterns in cortical emotional systems were investigated. The emotional state varied between groups using **diazepam, buspirone, and placebo**. The University of Wales Institute of Science and Technology Mood Adjective Checklist was used for the assessment of emotional state in the drug condition, yielding three estimates of emotional state: Energetic Arousal, Tension Arousal, and Hedonic Tone. These measures were correlated with the Synchronization Likelihood index of the resting EEG. ***Increased affective valence and arousal were related to an increased level of synchronization between frontal and right temporoparietal emotional areas. Two identified centers of synchronization, localized in the temporal and centroparietal regions, appeared to be functionally distinct. Stable relationships between subjective emotional state measures and cortical EEG synchronization patterns were confirmed, especially for the valence and energetic arousal estimation. A higher synchronization is associated with increased emotional valence and arousal, and this can thus be seen as a neural correlate of emotional experiences*.**

Slow wave decrease during wake and sleep

Authier, S., Bassett, L., Pouliot, M., Rachalski, A., Troncy, E., Paquette, D., & Mongrain, V. (2014). *Reprint of "Effects of amphetamine, diazepam and caffeine on polysomnography (EEG, EMG, EOG)-derived variables measured using telemetry in Cynomolgus monkeys."* Journal of Pharmacological and Toxicological Methods, 70(3), 287–294. https://doi.org/10.1016/j.vascn.2014.10.004.

Introduction: Medication-induced sleep disturbances are a major concern in drug development as a multitude of prescription drugs alter sleep patterns, often negatively. Polysomnography is used in clinical diagnostics but is also applicable to animal models. Rodent sleep architecture (nocturnal) differs from larger diurnal mammals, including humans, increasing the translational potential of non-rodent species to the clinic. This study aimed to characterize the response to pharmacological agents known to affect sleep structure and EEG activity in a non-human primate (Macaca fascicularis) using telemetry-based polysomnography**.** Methods: Animals were instrumented with telemetry transmitters for continuous electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) monitoring combined with video. EEG, EMG and EOG were monitored for 12 to 24h to establish baseline values, followed by administration of pharmacological agents (saline, d-amphetamine, diazepam or caffeine). Results: Amphetamine (0.3 and 1mg/kg, by oral administration (PO)) significantly reduced total sleep time, including the duration of both non-rapid eye movement [NREM] sleep and REM sleep. It also decreased EEG activity in low frequencies (i.e., 4-6Hz) during wakefulness. ***Diazepam (2mg/kg, PO) did not significantly alter sleep duration, but importantly reduced EEG activity in low frequencies (approximately 2-12Hz) during wakefulness, NREM and REM sleep*****.** Finally, caffeine (10 and 30mg/kg, PO) decreased both NREM and REM sleep duration. In addition, ***spectral analysis revealed important decreases in low frequency activity (i.e., 1-8Hz) during wakefulness with a parallel increase in high frequency activity (i.e., 20-50Hz) during NREM sleep***. **Discussion:** As these observations are similar to previously reported pharmacological effects in humans, results support that EEG, EOG and EMG monitoring by telemetry in Cynomolgus monkeys represents a useful non-clinical model to investigate and quantify drug-induced sleep disturbances.

Delta power changes

Hambrecht-Wiedbusch, V. S., Gauthier, e. A., Baghdoyan, H. A., & Lydic, R. (2010). Benzodiazepine Receptor Agonists Cause Drug-Specific and State-Specific Alterations in EEG Power and Acetylcholine Release in Rat Pontine Reticular Formation. Sleep (New York, N.Y.), 33(7), 909–918. https://doi.org/10.1093/sleep/33.7.909.

Study objectives: Benzodiazepine (BDZ) and non-benzodiazepine (NBDZ) hypnotics enhance GABAergic transmission and are widely used for the treatment of insomnia. In the pontine reticular formation (PRF), GABA inhibits rapid eye movement (REM) sleep and acetylcholine (ACh) release. No previous studies have characterized the effects of BDZ and NBDZ hypnotics on ACh release in the PRF. This study tested 2 hypotheses: (1) that microdialysis delivery of zolpidem, eszopiclone, and diazepam to rat PRF alters ACh release in PRF and electroencephalographic (EEG) delta power and (2) that intravenous (i.v.) administration of eszopiclone to non-anesthetized rat alters ACh release in the PRF, sleep, and EEG delta power. Design: A within- and between-groups experimental design. Setting: University of Michigan.

Patients or participants: Adult male Crl:CD*(SD) (Sprague-Dawley) rats (n = 57). Interventions: In vivo microdialysis of the PRF in rats anesthetized with isoflurane was used to derive the concentration-response effects of zolpidem, eszopiclone, and diazepam on ACh release. Chronically instrumented rats were used to quantify the effects of eszopiclone (3 mg/kg, i.v.) on ACh release in the PRF, sleep-wake states, and cortical EEG power. Measurements and results: ACh release was significantly increased by microdialysis delivery to the PRF of zolpidem and eszopiclone but not diazepam. ***EEG delta power was increased by zolpidem and diazepam but not by eszopiclone administered to the PRF*.** Eszopiclone (i.v.) decreased ACh release in the PRF of both anesthetized and non-anesthetized rats. Eszopiclone (i.v.) prevented REM sleep and increased EEG delta power. Conclusion: The concentration-response data provide the first functional evidence that multiple GABA(A) receptor subtypes are present in rat PRF. Intravenously administered eszopiclone prevented REM sleep, decreased ACh release in the PRF, and increased EEG delta power. The effects of eszopiclone are consistent with evidence that ACh release in the PRF is lower during NREM sleep than during REM sleep, and with data showing that cholinergic stimulation of the PRF activates the cortical EEG.

Timing and alpha and theta changes after medication intake

Jobert, M., & Wilson, F. J. (2015). *Advanced Analysis of Pharmaco-EEG Data in Humans*. Neuropsychobiology, 72(3-4), 165–177. https://doi.org/10.1159/000431096.

The results obtained when comparing post-pre (1.5 h vs. baseline) differences for placebo and 10 mg diazepam in 4 frequency bands under the RS_c recording condition (electrode Pz), whereby the evaluation is made for segments of 5 min (session as one block) and for the last 2 min of the recording, leading to the following observations: ***for the theta band, a significant difference between diazepam and placebo is only visible in the last 2 min of the session; for alpha, the difference is significant for the 5-min segment, but it is even more pronounced at the end of the recording, a configuration that is reversed in the case of beta where the difference between placebo and diazepam is more significant for the 5-min segment as compared to the last 2 min of the recording; no significant change is observed for alpha. The results obtained here for 1 lead (Pz) are consistent with the observations reported above demonstrating that both the natural diurnal variations and the RS-related changes are enhanced by diazepam administration.***

Medication intake may affect wake cognitive processes

Muñoz-Torres, Z., del Río-Portilla, Y., & Corsi-Cabrera, M. (2011). *Diazepam-induced changes in EEG oscillations during performance of a sustained attention task.* Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 28(4), 394–399. https://doi.org/10.1097/WNP.0b013e318227323a.

The primary aim of the present study was to test diazepam (DZ) effect, a benzodiazepine (BDZ) usually prescribed to reduce anxiety and to induce sleep, on EEG activity while performing a visual sustained attention task. The EEG activity was recorded in a double-blind placebo experiment, and prestimulus spectral power and inter- and intrahemispheric temporal coupling were assessed during visual sustained attention task performance. A single DZ dose (5 mg) was enough to increase reaction times during visual sustained attention task responses. ***DZ***

decreased prestimulus EEG power in the 1- to 6-, 8- to 12-, and 19- to 35-Hz bands and disrupted right intrahemispheric temporal coupling in the α-frequency range (8-12 Hz). The combined reduction in power and temporal coupling suggests both local and interregional DZ-induced disruption of neuronal synchronicity especially in the right hemisphere in agreement with the prominent attention-related networks in this hemisphere. These data support the notion that the influence of DZ on behavior goes beyond sedative effects and can potentially compromise higher cognitive functions with negative consequences to daily life situations.

Shifts in EEG may revert after months of consumption

Sánchez Fernández, I., Peters, J. M., An, S., Bergin, A. M., Takeoka, M., Rotenberg, A., Kothare, S. V., Riviello, J. J., & Loddenkemper, T. (2013). *Long-Term Response to High-Dose Diazepam Treatment in Continuous Spikes and Waves During Sleep*. Pediatric Neurology, 49(3), 163–170.e4. https://doi.org/10.1016/j.pediatrneurol.2013.04.027.

Background: This study evaluated whether the reduction in epileptiform activity after treatment with high-dose diazepam in continuous spikes and waves during sleep persists over time. Patients: Patients aged 1 to 21 years with continuous spikes and waves during sleep who received high-dose nocturnal diazepam and who had electroencephalogram follow-up were included. Twenty-nine patients met the inclusion criteria and underwent a total of 48 high-dose diazepam treatment cycles. Results: An ***overnight reduction of the spike wave percentage of at least 25% (i.e., 75-50%) occurred in 29 cycles (20 patients), and persisted within 6 months in 16 of 29 cycles (12 patients), but returned to baseline in three of 29 cycles (three patients). An overnight reduction of at least 50% (i.e., 75-25%) occurred in 15 cycles (13 patients), and persisted within 6 months in eight of 15 cycles (eight patients), but returned to baseline in three cycles (three patients)***. Twenty of 29 cycles that responded in the short term had persistent response on follow-up. Thirteen cycles of treatment were associated with mild side effects that did not recur with repeated treatment cycles. Conclusions: Treatment with ***high-dose diazepam reduced epileptiform activity in continuous spikes and waves during sleep in the short term***, and improvement persisted for several months in most cycles. Short-term response predicted persistence of this effect on subsequent follow-up.

Synchrony effects

Wyczesany, M., Grzybowski, S. J., Barry, R. J., Kaiser, J., Coenen, A. M. L., & Potoczek, A. (2011). *Covariation of EEG Synchronization and Emotional State as Modified by Anxiolytics*. Journal of Clinical Neurophysiology, 28(3), 289–296. https://doi.org/10.1097/WNP.0b013e31821c34f7.

The relationships between subjective estimation of emotional state and synchronization patterns in cortical emotional systems were investigated. The emotional state varied between groups using ***diazepam, buspirone, and placebo***. The University of Wales Institute of Science and Technology Mood Adjective Checklist was used for the assessment of emotional state in the drug condition, yielding three estimates of emotional state: Energetic Arousal, Tension Arousal, and Hedonic Tone. These measures were correlated with the Synchronization Likelihood index of the resting EEG. ***Increased affective valence and arousal were related to an increased level of synchronization between frontal and right temporoparietal emotional areas. Two identified centers of synchronization, localized in the temporal and centroparietal***

***regions, appeared to be functionally distinct. Stable relationships between subjective emotional state measures and cortical EEG synchronization patterns were confirmed, especially for the valence and energetic arousal estimation. A higher synchronization is associated with increased emotional valence and arousal, and this can thus be seen as a neural correlate of emotional experiences*.**

----- LORAZEPAM (Ativan) -----

DRUG FACTS

SYNOPSIS: Lorazepam is prescribed for anxiety and sleep issues. Effects on the EEG may provide evidence that Lorazepam has effect on thalamic generators, might suppress the EEG power overall, while another study claims in will increase mid-range power. During sleep, it may increase NREM duration and increase beta and gamma power.

EEG global suppression

Stabley, J. P., Frear, E. J., Wine, M., & Kothari, M. J. (2000). *Benzodiazepine toxicity with profound suppression of the electroencephalogram*. The Journal of the American Osteopathic Association, 100(7), 435–.

The authors report the case of a 60-year-old man with respiratory distress secondary to exacerbation of chronic obstructive pulmonary disease, right lower lobe pneumonia, and severe bronchospasm. High doses of lorazepam were given intravenously after failure to control bronchospasm and agitation with bronchodilators and mucolytic agents; the patient was unresponsive to all stimuli while receiving lorazepam. ***Electroencephalography revealed a profoundly suppressed pattern without accompanying low-voltage fast activity--this was reversible following withdrawal of the lorazepam.***

Thalamic generator effected by lorazepam

Schreckenberger, M., Lange-Asschenfeld, C., Lochmann, M., Mann, K., Siessmeier, T., Buchholz, H.-G., Bartenstein, P., & Gründer, G. (2004). *The thalamus as the generator and modulator of EEG alpha rhythm: a combined PET/EEG study with lorazepam challenge in humans.* NeuroImage (Orlando, Fla.), 22(2), 637–644. https://doi.org/10.1016/j.neuroimage.2004.01.047https://doi.org/10.1016/j.neuroimage.2004.01.047.

Background: Purpose of this study was to investigate the functional relationship between electroencephalographic (EEG) alpha power and cerebral glucose metabolism before and after pharmacological alpha suppression by lorazepam. Methods: Ten healthy male volunteers were examined undergoing two F18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET) scans with simultaneous EEG recording: 1× placebo, 1× lorazepam. EEG power spectra were computed by means of Fourier analysis. The PET data were analyzed using SPM99, and the correlations between metabolism and alpha power were calculated for both conditions. Results: The comparison lorazepam versus placebo revealed reduced glucose metabolism of the bilateral thalamus and adjacent subthalamic areas, the occipital cortex and temporo-insular areas ($P < 0.001$). ***EEG alpha power was reduced in all derivations ($P < 0.001$). Under placebo, there was a positive correlation between alpha power and metabolism of the bilateral***

thalamus and the occipital and adjacent parietal cortex (P < 0.001). Under lorazepam, the thalamic and parietal correlations were maintained, whereas the occipital correlation was no longer detectable (P < 0.001). The correlation analysis of the difference lorazepam-placebo showed the alpha power exclusively correlated with the thalamic activity (P < 0.0001). Conclusions: ***These results support the hypothesis of a close functional relationship between thalamic activity and alpha rhythm in humans mediated by corticothalamic loops which are independent of sensory afferences***. The study paradigm could be a promising approach for the investigation of cortico-thalamo-cortical feedback loops in neuropsychiatric diseases.

May increase slow and fast power while suppressing mid-range power

Link, C., Leigh, T. and Fell, G. (1991), *Effects of granisetron and lorazepam, alone and in combination, on the EEG of human volunteers*. British Journal of Clinical Pharmacology, 31: 93-97. https://doi.org/10.1111/j.1365-2125.1991.tb03863.x

The EEG effects of granisetron, a potent and selective 5-HT3 receptor antagonist (160 micrograms kg-1), and lorazepam (2.5 mg) were examined in 12 healthy male volunteers. ***The results indicated that lorazepam had a marked effect on the CNS, significantly increasing power in the slow (1-7 Hz) and fast (13-20 Hz; 21-30 Hz) wavebands whilst reducing power in the mid range (8-12 Hz)***. 3. In contrast there was no demonstrable effect of granisetron on the EEG at the dose tested, and no evidence of a pharmacodynamic interaction between the two compounds.

Beta and gamma relative power increased during NREM sleep

Grözinger, M. K., P; Röschke, J. (2007). *Effects of Lorazepam on the Automatic Online Evaluation of Sleep EEG Data in Healthy Volunteers*. Pharmacopsychiatry, 31(02), 55–59. https://doi.org/10.1055/s-2007-979299

In earlier publications we described an automatic algorithm to detect rapid eye movement (REM) sleep from a single-channel EEG recording without using EMG or EOG information. This system consisted of an artificial neural network operating on the basis of preprocessed EEG data and was composed to provide a maximum of robustness for online applications. In the present study the influence of acute administration of lorazepam on the performance of the REM detection procedure was evaluated. Following an adaptation to laboratory conditions, sleep EEG data were obtained from healthy subjects in three nights each. On the evening of the second night the volunteers received a single dosage of 2.5 mg Lorazepam; the other two nights were drug-free. ***The sleep profile and the quantitative EEG data reflected the known changes following acute administration of benzodiazepines: during the treatment night the amount of non-REM sleep and the relative power of the EEG signal in the beta and gamma frequency bands was increased relative to the first night, while the amount of REM sleep was reduced***. The night of drug discontinuation still showed some characteristics of the treatment night. The discordance rate of the REM detection algorithm relative to the manual evaluation ranged from 9 % to 14.2 % for the different nights. Surprisingly, the percentage of correctly classified time periods was even higher for the lorazepam night as compared to the other nights.

----- OXAZEPAM (Serepax) -----

DRUG FACTS

SYNOPSIS: Used as an anxiolytic, treat irritability in elder populations, and seizure prevention during alcohol withdrawal. There tends to be a decline in healthy ERP patterns, negatively affecting performance. B2 power increased in conjunction with self-reported anxiety levels.

Effects on ERPs

van Leeuwen, T. H., Verbaten, M. N., Koelega, H. S., Slangen, J. L., van der Gugten, J., & Camfferman, G. (1995). *Effects of oxazepam on event-related brain potentials, EEG frequency bands, and vigilance performance. Psychopharmacology*, *122*(3), 244–262. https://doi.org/10.1007/BF02246546

Eighteen males performed two vigilance tasks with static and dynamic stimuli under the influence of oxazepam (20 and 40 mg) in a placebo-controlled, double blind, crossover design. Oxazepam dose-dependently impaired overall level of performance and aggravated the decrement with time in measures of accuracy and sensitivity relative to placebo. ***The drug reduced the amplitudes of the P1, N1, P2N2, and P3 (dose-dependently) waves of event-related potentials (ERPs).*** Oxazepam aggravated the linear decline with time of the P3 amplitude only. Oxazepam impaired accuracy was related to deterioration of central processing involved in stimulus discrimination (P2N2). ***Impairment of response-related performance measures (RT and RI) was associated with processing manifest in the P1, N1, and P3 waves. Oxazepam effects on the amplitudes of N1 and P3 correlated with drug effects on power in alpha 1 (8-10 Hz). Drug effects on overall performance and alpha were also related; the drug effect on response speed correlated only with the drug effect on beta 1 (12.5-21 Hz). Effects of time-on-task on performance and EEG were unrelated, but oxazepam induced performance declines with time may have been caused by declines in resource allocation, as manifest in the amplitude of P3.*** Time effects on EEG power bands and ERP amplitudes were not significantly related to the time course of oxazepam activity. A curious dissociation emerged: both oxazepam and time-on-task impaired performance, but the drug induced a decrease of theta and alpha 1 power, whereas time-on-task increased power. Various processes play a role in performance decrements with time, and various aspects of processing may be involved in signal-detection measures which makes terms such as sensitivity quite meaningless. So-called computational processing was indistinguishable from energetic processes, which questions the validity of the distinction between these two domains. Explanations of EEG activity in terms of a unidimensional theory of arousal are untenable.

Beta 2 increase and self-report of anxiety level

Ansseau, M., Doumont, A., Cerfontaine, J.-L., Mantanus, H., Rousseau, J.-C., & Timsit-Berthier, M. (1984). *Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam*. Neuropsychobiology, 12(4), 255–259. https://doi.org/10.1159/000118148

A new formulation of oxazepam especially designed to increase the speed of absorption and eliminate the need to use water (freeze-dried dosage formulation; FDDF) was compared in double-blind and crossover conditions with the standard tablets of the same compound. 5

inpatients with generalized anxiety disorder received at I-week intervals a single 30 mg dose of one of the compounds. Every 8 min for 96 min after drug intake, they completed a battery of visual analogue scales and had an EEG recording with computerized spectral analysis. Results showed a significantly more rapid onset of activity of FDDF oxazepam for both the self-reports of anxiety level ($p < 0.005$) and the specific B_2 EEG changes ($p < 0.0001$), which were significantly correlated ($r = -0.73$; $p < 0.01$). Moreover, all patients rated FDDF oxazepam as having faster onset of action in clinical change than regular tablets ($p < 0.05$). This study shows the value of visual analogue scales, pharmaco-EEG, and crossover design in well-selected anxious inpa-tients in substantiating clinical differences between anxiolytic pharmacotherapies.

----- PHENAZEPAM -----

DRUG FACTS

SYNOPSIS: This drug is available over the counter/internet and has been used inappropriately. It is mainly used to treat neurotic disorders. It's behavioral effects precede changes in the EEG.

Behavioral effects precede EEG changes

Uvarova, L. G., Zherdev, V. P., Neznamov, G. G., Khrulenko-Varnitskiĭ, I. O., & Sigunova, E. A. (1986). Sootnoshenie kliniko-farmakologicheskogo deĭstviia odnokratnoĭ dozy fenazepama, dinamiki EEG i farmakokinetiki *[Correlation of the clinical pharmacological action of a single dose of fenazepam with the EEG dynamics and pharmacokinetics].* Farmakologiia i toksikologiia, 49(1), 66–69.

Interaction between the clinical, EEG-effects and phenazepam concentration in the blood was studied in 111 patients with neurotic disorders after intake of the test drug dose (2 mg) administered singly and on the 14th day of the treatment. It was established that EEG changes commonly induced by benzodiazepines supervene primarily within the interval of 1 to 3 h after a single intake which correlates with the maximal degree of the tranquilizing, somnolent and myorelaxant drug action. It was demonstrated that the clinical and EEG-effects occur before attainment of the maximal phenazepam concentration and then become less potent, with preservation of the high blood drug level. Intake of the test dose during the treatment course is characterized, as compared with the effect of a single intake, by less marked clinical action of the drug and the lack of significant changes on the EEG and in the blood phenazepam concentration.

----- TEMAZEPAM (Restoril) -----

DRUG FACTS

SYNOPSIS: The effects of temazepam, which is prescribed for insomnia, on the EEG are decreased slow wave power and possibly a reduction in sleep spindle activity, while increasing the amplitude of the fewer spindles throughout the cortex.

Effects on SWA

Arbon, E. L., Knurowska, M., & Dijk, D.-J. (2015). *Randomised clinical trial of the effects of prolonged-release melatonin, temazepam and zolpidem on slow-wave activity during sleep in healthy people*. Journal of Psychopharmacology (Oxford), 29(7), 764–776. https://doi.org/10.1177/0269881115581963.

Current pharmacological treatments for insomnia include benzodiazepine and non-benzodiazepine hypnotics targeting γ-aminobutyric acid (GABA)A receptors, as well as agonists of the melatonin receptors MT1 and MT2. ***Melatonin, temazepam and zolpidem are thought to exert their effect through different mechanisms of action, but whether this leads to differential effects on electroencephalogram (EEG) power spectra during sleep in middle-aged people is currently not known***. To establish whether the effects of prolonged-release melatonin (2 mg) on the nocturnal sleep EEG are different to those of temazepam (20 mg) and zolpidem (10 mg). Sixteen healthy men and women aged 55-64 years participated in a double-blind, placebo-controlled, four-way cross-over trial. Nocturnal sleep was assessed with polysomnography and spectral analysis of the EEG. The effects of single oral doses of prolonged-release melatonin, temazepam and zolpidem on ***EEG slow-wave activity (SWA, 0.75-4.5 Hz)*** and other frequencies during nocturnal non-rapid eye movement (NREM) sleep were compared. In an entire night analysis prolonged-release melatonin did not affect SWA, whereas ***temazepam and zolpidem significantly reduced SWA compared with placebo. Temazepam significantly reduced SWA*** compared with prolonged-release melatonin. Prolonged-release melatonin only reduced SWA during the first third of the night compared with placebo. These data show that the effects of prolonged-release melatonin on the nocturnal sleep EEG are minor and are different from those of temazepam and zolpidem; this is likely due to the different mechanisms of action of the medications.

Decrease in slow wave activity

Plante, D. T., Goldstein, M. R., Cook, J. D., Smith, R., Riedner, B. A., Rumble, M. E., Jelenchick, L., Roth, A., Tononi, G., Benca, R. M., & Peterson, M. J. (2016). *Effects of oral temazepam on slow waves during non-rapid eye movement sleep in healthy young adults: A high-density EEG investigation*. International Journal of Psychophysiology, 101, 25–32. https://doi.org/10.1016/j.ijpsycho.2016.01.003.

Slow waves are characteristic waveforms that occur during non-rapid eye movement (NREM) sleep that play an integral role in sleep quality and brain plasticity. Benzodiazepines are commonly used medications that alter slow waves, however, their effects may depend on the time of night and measure used to characterize slow waves. Prior investigations have utilized minimal scalp derivations to evaluate the effects of benzodiazepines on slow waves, and thus the topography of changes to slow waves induced by benzodiazepines has yet to be fully elucidated. This study used high-density electroencephalography (hdEEG) to evaluate the effects of oral temazepam on slow wave activity, incidence, and morphology during NREM sleep in 18 healthy adults relative to placebo. ***Temazepam was associated with significant decreases in slow wave activity and incidence, which were most prominent in the latter portions of the sleep period. However, temazepam was also associated with a decrease in the magnitude of high-amplitude slow waves and their slopes in the first NREM sleep episode, which was most prominent in frontal derivations. These findings suggest that***

***benzodiazepines produce changes in slow waves throughout the night that vary depending on cortical topography and measures used to characterize slow waves. Further research that explores the relationships between benzodiazepine-induced changes to slow waves and the functional effects of these waveforms is indicated*.**

Altered spindle activity

Plante, D. T., Goldstein, M. R., Cook, J. D., Smith, R., Riedner, B. A., Rumble, M. E., Jelenchick, L., Roth, A., Tononi, G., Benca, R. M., & Peterson, M. J. (2016). *Effects of oral temazepam on slow waves during non-rapid eye movement sleep in healthy young adults: A high-density EEG investigation.* International Journal of Psychophysiology, 101, 25–32. https://doi.org/10.1016/j.ijpsycho.2016.01.003.

Slow waves are characteristic waveforms that occur during non-rapid eye movement (NREM) sleep that play an integral role in sleep quality and brain plasticity. Benzodiazepines are commonly used medications that alter slow waves, however, their effects may depend on the time of night and measure used to characterize slow waves. Prior investigations have utilized minimal scalp derivations to evaluate the effects of benzodiazepines on slow waves, and thus the topography of changes to slow waves induced by benzodiazepines has yet to be fully elucidated. This study used high-density electroencephalography (hdEEG) to evaluate the effects of oral temazepam on slow wave activity, incidence, and morphology during NREM sleep in 18 healthy adults relative to placebo. ***Temazepam was associated with significant decreases in slow wave activity and incidence, which were most prominent in the latter portions of the sleep period. However, temazepam was also associated with a decrease in the magnitude of high-amplitude slow waves and their slopes in the first NREM sleep episode, which was most prominent in frontal derivations. These findings suggest that benzodiazepines produce changes in slow waves throughout the night that vary depending on cortical topography and measures used to characterize slow waves. Further research that explores the relationships between benzodiazepine-induced changes to slow waves and the functional effects of these waveforms is indicated.***

Significant increases in spectral power from 10.33 to 13.83 Hz

Plante, D. ., Goldstein, M. ., Cook, J. ., Smith, R., Riedner, B. ., Rumble, M. ., Jelenchick, L., Roth, A., Tononi, G., Benca, R. ., & Peterson, M. . (2015). *Effects of oral temazepam on sleep spindles during non-rapid eye movement sleep: A high-density EEG investigation.* European Neuropsychopharmacology, 25(10), 1600–1610. https://doi.org/10.1016/j.euroneuro.2015.06.005.

Benzodiazepines are commonly used medications that alter sleep spindles during non-rapid eye movement (NREM) sleep, however the topographic changes to these functionally significant waveforms have yet to be fully elucidated. This study utilized high-density electroencephalography (hdEEG) to investigate topographic changes in sleep spindles and spindle-range activity caused by temazepam during NREM sleep in 18 healthy adults. After an accommodation night, sleep for all participants was recorded on two separate nights after taking either placebo or oral temazepam 15 mg. Sleep was monitored using 256-channel hdEEG. Spectral analysis and spindle waveform detection of sleep EEG data were performed for

each participant night. Global and topographic data were subsequently compared between temazepam and placebo conditions. ***Temazepam was associated with significant increases in spectral power from 10.33 to 13.83 Hz. Within this frequency band, temazepam broadly increased sleep spindle duration, and topographically increased spindle amplitude and density in frontal and central-posterior regions, respectively. Higher frequency sleep spindles demonstrated increased spindle amplitude and a paradoxical decrease in spindle density in frontal and centroparietal regions.*** Further analysis demonstrated ***temazepam both slowed the average frequency of spindle waveforms and increased the relative proportion of spindles at peak frequencies in frontal and centroparietal regions.*** These findings suggest that ***benzodiazepines have diverse effects on sleep spindles that vary by frequency and cortical topography.*** Further research that explores the relationships between topographic and frequency-dependent changes in pharmacologically-induced sleep spindles and the functional effects of these waveforms is indicated.

----- TRIAZOLAM (Halcion) -----

DRUG FACTS

SYNOPSIS: This drug is prescribed to treat insomnia and can be used to calm anxiety. It may increase beta relative power. Goal-conflict-specific EEG rhythmicity and theta changes may support the use of triazolam as a biomarker.

Theta power as possible biomarker

McNaughton, N., Swart, C., Neo, P., Bates, V., & Glue, P. (2013). *Anti-anxiety drugs reduce conflict-specific "theta"—A possible human anxiety-specific biomarker*. Journal of Affective Disorders, 148(1), 104–111. https://doi.org/10.1016/j.jad.2012.11.057.

Background: Syndromes of fear/anxiety are currently ill-defined, with no accepted human biomarkers for anxiety-specific processes. A unique common neural action of different classes of anxiolytic drugs may provide such a biomarker. In rodents, a reduction in low frequency (4-12 Hz; "theta") brain rhythmicity is produced by all anxiolytics (even those lacking panicolytic or antidepressant action) and not by any non-anxiolytics. This rhythmicity is a key property of the Behavioural Inhibition System (BIS) postulated to be one neural substrate of anxiety. We sought homologous anxiolytic-sensitive changes in human surface EEG rhythmicity. **Method:** Thirty-four healthy volunteers in parallel groups were administered double blind single doses of triazolam 0.25mg, buspirone 10mg or placebo 1 hour prior to completing the stop-signal task. Right frontal conflict-specific EEG power (previously shown to correlate with trait anxiety and neuroticism in this task) was extracted as a contrast between trials with balanced approach-avoidance (stop-go) conflict and the average of trials with net approach and net avoidance. **Results:** Compared with placebo, **both triazolam and buspirone decreased right-frontal, 9-10 Hz, conflict-specific-power. Limitations:** Only one dose of each of only two classes of anxiolytic and no non-anxiolytics were tested, so additional tests are needed to determine generality. **Conclusions:** There is a distinct rhythmic system in humans that is sensitive to both classical/GABAergic and novel/serotonergic anxiolytics. This conflict-specific rhythmicity should provide a biomarker, with a strong pre-clinical neuropsychology, for a novel approach to classifying anxiety disorders.

Goal-conflict-specific EEG rhythmicity as a possible anxiety biomarker

Shadli, S. M., Glue, P., McIntosh, J., & McNaughton, N. (2015). *An improved human anxiety process biomarker: characterization of frequency band, personality and pharmacology*. Translational Psychiatry, 5(12), e699–e699. https://doi.org/10.1038/tp.2015.188

Anxiety disorders are among the most common mental illness in the western world with a major impact on disability. But their diagnosis has lacked objective biomarkers. We previously demonstrated a human anxiety process biomarker, goal-conflict-specific electroencephalography (EEG) rhythmicity (GCSR) in the stop-signal task (SST). Here we have developed and characterized an improved test appropriate for clinical group testing. We modified the SST to produce balanced numbers of trials in clearly separated stop-signal delay groups. As previously, **right frontal (F8) GCSR was extracted as the difference in EEG log Fourier power** between matching stop and go trials (that is, stop-signal-specific power) of a quadratic contrast of the three delay values (that is, power when stopping and going are in balanced conflict compared with the average of when stopping or going is greater). Separate experiments assessed drug sensitivity (n=34) and personality relations (n=59). GCSR in this new SST was reduced by three chemically distinct anxiolytic drugs (administered double-blind**): buspirone (10 mg), triazolam (0.25 mg) and pregabalin (75 mg)**; had a **frequency range (4-12 Hz)** consistent with rodent model data; and positively correlated significantly with neuroticism and nonsignificantly with trait anxiety scores. GCSR, measured in our new form of the SST, should be suitable as a biomarker for one specific anxiety process in the testing of clinical groups and novel drugs and in the development of measures suitable for individual diagnosis.

BETA BLOCKERS

CLASS FACTS

SYNOPSIS: Beta-blocker treatment has been associated with a number of consequences for the central nervous system: fatigue, depression, sleep disorders and nightmares, visual hallucinations, delirium or psychosis, Parkinson's disease, and the risk of falling. Additionally, EEG analysis has confirmed that vigilance level is significantly decreased after administration of beta-blockers compared to placebo.

----- TYPICAL BETA BLOCKERS -----

----- PINDOLOL (Visken, Betapindol, Pinbetol, Prindolol, Pynastin+) -----

DRUG FACTS

Effects on sleep architecture of pindolol, paroxetine and their combination in healthy volunteers.

Bell, C., Wilson, S., Rich, A., Bailey, J., & Nutt, D. (2003). *Effects on sleep architecture of pindolol, paroxetine and their combination in healthy volunteers*. Psychopharmacology, 166(2), 102–110. https://doi.org/10.1007/s00213-002-1314-9

Rationale: The combination of pindolol with a serotonergic antidepressant has been used to speed up the antidepressant response and to augment in cases of resistant depression. Animal studies have suggested that this increased response occurs because of 5HT(1A) antagonist properties of pindolol, which in combination with a serotonergic antidepressant produces a synergistic increase in 5HT in the synapse. Objectives: To test whether the combination of pindolol with a serotonergic antidepressant produces a synergistic increase in synaptic 5HT by examining the effects on measures of sleep, psychomotor performance and ratings of anxiety. Methods: Twelve healthy male volunteers took part in randomised crossover study in which they received paroxetine 20 mg/day (or its placebo) for 9 days with a washout period of 5 days between. On day 7 and 9 of each treatment they also received pindolol 2.5 mg (or its placebo) three times a day. Sleep EEG recordings were made on each of the nights on pindolol (or its placebo) and ratings of saccadic eye movement parameters, subjective sleep, anxiety and other adverse events recorded on the following days. Four drug conditions were therefore tested: placebo, pindolol alone, paroxetine alone and paroxetine+pindolol. RESULTS: The combination of ***paroxetine+pindolol produced an increase in REM suppression and a reduction in SWS compared with other drug combinations. There were no significant effects on the other measures of 5HT function recorded in this study. Conclusions: REM suppression by the combination was approximately equal to the sum of REM suppression by each drug individually and thus does not show a synergistic effect. However, there was a significant reduction in SWS produced by only the combination treatment, which may suggest a specific effect of the combination on non-REM sleep mechanisms.***

Beta-blockers and sleep: a controlled trial.

Betts, T. A., & Alford, C. (1985). *Beta-blockers and sleep: a controlled trial*. European journal of clinical pharmacology, 28 Suppl, 65–68. https://doi.org/10.1007/BF00543712

The effects on sleep of four beta-blockers, atenolol, propranolol, metoprolol and pindolol, were studied in a placebo-controlled trial. Drugs were administered in random order to 10 female volunteers who acted as their own controls. Subjects were tested five times, each test period lasting 10 nights (2 baseline, 2 low dose, 4 high dose, and 2 withdrawal). A questionnaire concerning subjective appreciation of the quality of the previous night's sleep was completed each morning. Night recordings of muscle tension, eye movement, heart rate and electroencephalogram were recorded on paper and magnetic tape. Analysis of the subjective questionnaires showed that recollection of dreaming and awakening in the night was increased by the three lipophilic drugs, propranolol, metoprolol, and pindolol. These results confirm reports in the literature but are contrary to those expected from considering the effects of noradrenaline on sleep. Analysis of physiological records confirmed subjects' reports that waking was increased by the lipophilic drugs. ***Dreaming (rapid eye movement sleep, REM) was reduced***, as predicted from knowledge of the effect of noradrenaline on sleep. ***Increased awakening leads to an increase in remembered dreaming which explains the otherwise paradoxical results.*** Although atenolol had no effect on subjective measures of sleep this hydrophilic drug also reduced REM frequency, suggesting that either it has some central effect, or that REM reduction is due to a peripheral 'shielding' effect.

EEG effects of buspirone and pindolol: a method of examining 5-HT1A receptor function in humans.

McAllister-Williams, R. H., & Massey, A. E. (2003). *EEG effects of buspirone and pindolol: a method of examining 5-HT1A receptor function in humans*. Psychopharmacology, 166(3), 284–293. https://doi.org/10.1007/s00213-002-1339-0

Rationale: An involvement of 5-HT(1A) receptors is postulated in the pathophysiology of affective disorders and mechanism of action of antidepressants. Methods for studying their functional integrity in humans are, however, limited. Preliminary data suggests that activation of somatodendritic 5-HT(1A) receptors cause a negative shift in the EEG frequency spectrum. Animal research suggests that pindolol is an agonist at these receptors but an antagonist at postsynaptic 5-HT(1A) receptors. **Objective:** We postulated that while pindolol would antagonise known postsynaptic mediated neuroendocrine responses to the 5-HT(1A) agonist buspirone, both drugs would have a similar effect on the EEG frequency spectrum. **Methods:** Fourteen healthy men were administered placebo or pindolol (20 mg orally) 90 min before placebo or buspirone (30 mg orally) in a double blind cross-over study. Plasma prolactin and growth hormone were assayed and ***EEGs recorded before and after drug administration***. ***Results: A significant negative shift in the EEG frequency spectrum was found for both buspirone and pindolol***, with the combination producing a similar effect to each drug alone. In contrast, the neuroendocrine response to buspirone was significantly attenuated by pindolol. **Conclusions:** The data obtained are consistent with ***the EEG effects of buspirone and pindolol being mediated by somatodendritic 5-HT(1A) receptors***, in contrast to the neuroendocrine response, which is known to be mediated by postsynaptic receptors. The development of this novel method of assessing somatodendritic 5-HT(1A) receptors in humans is a potentially

important advance which may allow the testing of hypotheses of its involvement in depression and response to antidepressants.

------ PROPRANOLOL ------
(Inderal, Avlocardyl, Deralin, Dociton, Inderalici, Innopran, Sumial, Anaprilinum, Bedranol)

DRUG FACTS

Beta receptor-mediated modulation of the oddball P3 but not error-related ERP components in humans.

de Rover, M., Brown, S. B. R. E., Band, G. P., Giltay, E. J., van Noorden, M. S., van der Wee, N. J. A., & Nieuwenhuis, S. (2015). *Beta receptor-mediated modulation of the oddball P3 but not error-related ERP components in humans*. Psychopharmacology, 232(17), 3161–3172. https://doi.org/10.1007/s00213-015-3966-2.

Rationale: The P3 is a ubiquitous component of stimulus-driven neural activity that can be observed in scalp electrophysiological recordings. Multiple lines of evidence suggest an important role for the noradrenergic system in the generation of the P3. However, pharmacological studies of the P3 using noradrenergic manipulations have so far been limited to agents that affect α2-receptor signaling. **Objectives:** The present study investigated whether β-adrenergic receptors are involved in the generation of the P3 and the error positivity (Pe), a component of the event-related potential that is elicited by errors and that bears many similarities to the P3. M**ethods:** We used a double-blind, placebo-controlled, crossover design in which we examined in human participants (N = 16) the effect of a **single dose of propranolol (80 mg)** on the amplitudes of the P3 observed in visual and auditory oddball tasks and the Pe observed in a flanker task. **Results:** We found that ***P3s to auditory stimuli were increased in amplitude following treatment with propranolol. Propranolol also modulated the P3 to visual stimuli, but in a direction dependent on participants' level of trait anxiety: In participants with lower trait anxiety, propranolol resulted in a (non-significant) decrease in P3 amplitudes; in participants with higher trait anxiety, propranolol significantly enhanced P3 amplitude. Propranolol did not modulate the amplitude of the Pe or behavioral measures of conflict/error-related performance adjustments***. **Conclusions:** These results provide the first evidence for involvement of β-adrenergic receptors in P3 generation. We speculate that propranolol affected the P3 through actions at β2-receptors in the locus coeruleus.

Adrenoceptor blockade modifies regional cerebral blood flow responses to hyperbaric hyperoxia: Protection against CNS oxygen toxicity.

Gasier, H. G., Demchenko, I. T., Zhilyaev, S. Y., Moskvin, A. N., Krivchenko, A. I., & Piantadosi, C. A. (2018). *Adrenoceptor blockade modifies regional cerebral blood flow responses to hyperbaric hyperoxia: protection against CNS oxygen toxicity*. Journal of Applied Physiology (1985), 125(4), 1296–1304. https://doi.org/10.1152/japplphysiol.00540.2018

Exposure to extreme-hyperbaric oxygen (HBO2), > 5-6 atmospheres absolute (ATA), produces baroreflex impairment, sympathetic hyperactivation, hypertension, tachycardia, and cerebral hyperemia, known as Phase II, culminating in seizures. We hypothesized that attenuation of the

effects of high sympathetic outflow would preserve regional cerebral blood flow (rCBF) and protect against HBO2-induced seizures. To explore this possibility, we tested four adrenoceptor antagonists in conscious and anesthetized rats exposed to HBO2 at 5 and 6 ATA, respectively: phentolamine (nonselective α1 and 2), prazosin (selective α1), propranolol (nonselective β1 and 2) and atenolol (selective β1). In conscious rats, 4 drug-doses were administered to rats prior to HBO2 exposures, and seizure latencies were recorded. Drug-doses that provided similar protection against seizures were administered before HBO2 exposures in anesthetized rats to determine the effects of adrenoceptor blockade on mean arterial pressure, heart rate, rCBF and EEG spikes. All four drugs modified cardiovascular and rCBF responses in HBO2 that aligned with epileptiform discharges, but only phentolamine and ***propranolol effectively increased EEG spike latencies by ~20 and 36 min, respectively. When phentolamine and propranolol were delivered during HBO2 at the onset of phase II, only propranolol led to sustained reductions in heart rate and rCBF, preventing the appearance of epileptiform discharges*****.** The enhanced effectiveness of propranolol may extend beyond β-adrenoceptor blockade, i.e. membrane stability and reduced metabolic activity. These results indicate that adrenoceptor drug pre-treatment will minimize the effects of excessive sympathetic outflow on rCBF and extend HBO2 exposure time.

Propranolol selectively blocks the enhanced parietal old/new effect during long-term recollection of unpleasant pictures: a high density ERP study.

Weymar, M., Löw, A., Modess, C., Engel, G., Gründling, M., Petersmann, A., Siegmund, W., & Hamm, A. O. (2010). *Propranolol selectively blocks the enhanced parietal old/new effect during long-term recollection of unpleasant pictures: A high density ERP study*. NeuroImage (Orlando, Fla.), 49(3), 2800–2806. https://doi.org/10.1016/j.neuroimage.2009.10.025.

Evidence from both animal and human research suggests that the formation of emotional memories is triggered by the beta-adrenergic system. ***To confirm whether modulation of central beta-adrenergic transmission is specifically involved in the neural signature of memory performance, the pre-encoding effect of propranolol (80 mg) on event-related potentials (ERPs) was measured in a placebo-controlled, double-blind, parallel-group study in 46 male healthy subjects using high density EEG and source imaging analysis during encoding and retrieval*** (after 1 week) of IAPS pictures of unpleasant, neutral and pleasant contents; for recognition 90 old pictures were randomly mixed with 90 new pictures. During retrieval correctly remembered old pictures elicited a significantly larger positive voltage change over the centro-parietal cortex than new pictures. ***Propranolol significantly reduced this old/new difference of the mean ERP amplitudes (500-800 ms) for unpleasant but not for neutral and pleasant memories.*** This effect correlated with salivary alpha-amylase activity, a surrogate for central adrenergic stimulation. In conclusion, propranolol selectively blocked the neural signature of unpleasant memories by mechanisms in which the parietal cortex seems to be specifically involved.

CHOLINERGICS

CLASS FACTS

SYNOPSIS: Beta-blocker treatment has been associated with a number of consequences for the central nervous system: fatigue, depression, sleep disorders and nightmares, visual hallucinations, delirium or psychosis, Parkinson's disease, and the risk of falling. Additionally, EEG analysis has confirmed that vigilance level is significantly decreased after administration of beta-blockers compared to placebo.

----- TRIHEXYPHENIDYL (Artane, Apo-Trihex) -----

DRUG FACTS

The cholinergic system, EEG and sleep.

Platt, B., & Riedel, G. (2011). *The cholinergic system, EEG and sleep*. Behavioural brain research, 221(2), 499–504. https://doi.org/10.1016/j.bbr.2011.01.017.

Acetylcholine is a potent excitatory neurotransmitter, crucial for cognition and the control of alertness and arousal. Vigilance-specific recordings of ***the electroencephalogram (EEG) potently reflect thalamo-cortical and brainstem-cortical cholinergic activity that drives theta rhythms and task-specific cortical (de-synchronisation. Additionally, cholinergic projections from the basal forebrain act as a relay centre for the brainstem-cortical arousal system, but also directly modulate cortical activity, and thus promote wakefulness or rapid-eye movement (REM) sleep*.** Disease states such as sleep disorders, dementia and certain types of epilepsy are a further reflection of the potent cholinergic impact on CNS physiology and function, and highlight the relevance and inter-dependence of sleep and EEG. With novel technologies and computational tools now becoming available, advanced mechanistic insights may be gained and new avenues explored for diagnostics and therapeutics.

Safety, pharmacokinetics and quantitative EEG modulation of TAK-071, a novel muscarinic M1 receptor positive allosteric modulator, in healthy subjects.

Yin, W., Mamashli, F., Buhl, D. L., Khudyakov, P., Volfson, D., Martenyi, F., Gevorkyan, H., Rosen, L., & Simen, A. A. (2022). *Safety, pharmacokinetics and quantitative EEG modulation of TAK-071, a novel muscarinic M1 receptor positive allosteric modulator, in healthy subjects.* British journal of clinical pharmacology, 88(2), 600–612. https://doi.org/10.1111/bcp.14975.

Aims: TAK-071 is a muscarinic M_1 receptor positive allosteric modulator designed to have low cooperativity with acetylcholine. This was a first-in-human study to evaluate the safety, pharmacokinetics, and pharmacodynamics of TAK-071. **Methods:** TAK-071 was administered as single and multiple doses in a randomized, double-blind, placebo-controlled, parallel-group design in healthy volunteers alone and in combination with donepezil. Laboratory, electrocardiogram (ECG) and electroencephalogram (EEG) evaluations were performed. Cerebrospinal fluid and blood samples were taken to evaluate the pharmacokinetics (PK), relative bioavailability and food effect. **Results:** TAK-071 was safe and well tolerated, and no deaths or serious adverse events occurred. TAK-071 demonstrated a long mean (% coefficient

of variation) half-life of 46.3 (25.2%) to 60.5 (51.5%) hours and excellent brain penetration following oral dosing. Coadministration with donepezil had no impact on the PK of either drug. There was no food effect on systemic exposure. ***Quantitative EEG analysis revealed that TAK-071 40-80 mg increased power in the 7-9 Hz range in the posterior electrode group with eyes open and 120-160 mg doses increased power in the 16-18 Hz range and reduced power in the 2-4 Hz range in central-posterior areas with eyes open and eyes closed***. Functional connectivity was significantly reduced after TAK-071 at high doses and was enhanced with coadministration of donepezil under the eyes-closed condition. **Conclusions:** PK and safety profiles of TAK-071 were favorable, including those exceeding expected pharmacologically active doses based on preclinical data. When administered without donepezil TAK-071 was largely free of cholinergic adverse effects. Further clinical evaluation of TAK-071 is warranted.

Trihexyphenidyl increases delta activity in non-rapid eye movement sleep without impairing cognitive function in rodent models.

Zhou, J. C., Jiang, J. B., Guo, H., Yang, S. R., Liu, C. F., Qu, W. M., Huang, Z. L., & Ding, F. F. (2022). *Trihexyphenidyl increases delta activity in non-rapid eye movement sleep without impairing cognitive function in rodent models*. Neuropharmacology, 218, 109217–109217. https://doi.org/10.1016/j.neuropharm.2022.109217.

Both human and rodent studies suggest the link between non-rapid eye movement (NREM) sleep and cognition. ***Recent study indicated that selective activation of cholinergic neurons in basal forebrain inhibits electroencephalogram (EEG) delta power and shortens NREM sleep***. In the current study, we aimed to test the pharmacological effect of trihexyphenidyl (THP), a selective muscarinic M1 receptor antagonist, on EEG power spectra and sleep with or without the selective activation of basal forebrain cholinergic neurons. THP (1, 2, and 3 mg/kg) was administrated intraperitoneally in natural sleep phase. Basal forebrain cholinergic neurons expressing modified G protein-coupled muscarinic receptors (hM3Dq) were activated by intraperitoneal injection of clozapine-N-oxide in ChAT-IRES-Cre mice. EEG and electromyogram (EMG) signals were recorded in freely moving mice to analyze EEG power spectrum and sleep hypnogram. Y-maze and novel object recognition tests were used for testing cognition. THP 1 mg/kg significantly increased EEG delta power and facilitated NREM sleep in wildtype mice, while THP 3 mg/kg was required in ChAT-IRES-Cre mice treated with clozapine-N-oxide. THP with dosage up to 8 mg/kg did not induce cognitive impairments in wildtype mice. EEG delta power of NREM sleep is often used as an indicator of sleep depth or sleep quality, which tightly link with sleep-dependent cognition. Taken together, the data collected from rodents hinted that, THP could possibly be used as the NREM sleep facilitator in humans.

DOPAMINE AGONISTS

CLASS FACTS

SYNOPSIS: Dopamine agonists are used in patients with Parkinson disease. Dopamine agonists, such as ropinirole, are the first-line treatment for restless legs syndrome, while bromocriptine is given for neuroleptic malignant syndrome. Dopamine agonists are also prescribed to counteract dopamine antagonist-induced hyperprolactinemia. Additionally, Dopamine these types are classified as ergoline agonists.

Dopaminergic drugs alter beta coherence during motor imagery and motor execution in healthy adults.

Aprigio, D., Tanaka, G. K., Bittencourt, J., Gongora, M., Teixeira, S., Cagy, M., Budde, H., Orsini, M., Ribeiro, P., & Velasques, B. (2020). *Dopaminergic drugs alter beta coherence during motor imagery and motor execution in healthy adults*. Arquivos de Neuro-Psiquiatria, 78(4), 199–205. https://doi.org/10.1590/0004-282X20190186.

Background: Motor Imagery (MI) represents the cognitive component of the movement and recruits dopaminergic systems. **Objective:** To investigate the role of dopaminergic system through the action of methylphenidate and risperidone over beta coherence during execution, action observation and motor imagery. **Methods:** Electroencephalography (EEG) data were recorded before and after the substance intake. For statistical analysis, a three-way ANOVA was used to **identify changes in beta coherence** induced by the group, task and the moment variables. Statistical significance was set at p≤0.007. **Results:** We found a ***main effect for group for C3/CZ, and a main effect for task for CZ/C4 pairs of electrodes. Furthermore, significant differences were found in the post-drug administration between groups for C3/CZ pair of electrodes, and between task for C4/CZ pair of electrodes*****. Conclusion:** The administration of methylphenidate and risperidone was able to produce ***electrocortical changes of the cortical central regions, even when featuring antagonistic effects on the dopaminergic pathways. Moreover, the execution task allowed beta-band modulation increase.***

Conscious perception and the modulatory role of dopamine: no effect of the dopamine D2 agonist cabergoline on visual masking, the attentional blink, and probabilistic discrimination.

Boonstra, E. A., van Schouwenburg, M. R., Seth, A. K., Bauer, M., Zantvoord, J. B., Kemper, E. M., Lansink, C. S., & Slagter, H. A. (2020). *Conscious perception and the modulatory role of dopamine: no effect of the dopamine D2 agonist cabergoline on visual masking, the attentional blink, and probabilistic discrimination*. Psychopharmacology, 237(9), 2855–2872. https://doi.org/10.1007/s00213-020-05579-9.

Rationale: Conscious perception is thought to depend on global amplification of sensory input. In recent years, striatal dopamine has been proposed to be involved in gating information and conscious access, due to its modulatory influence on thalamocortical connectivity.
Objectives: Since much of the evidence that implicates striatal dopamine is correlational, we conducted a double-blind crossover pharmacological study in which we administered cabergoline-a dopamine D2 agonist-and placebo to 30 healthy participants. Under both conditions, we subjected participants to several well-established experimental conscious-

perception paradigms, such as backward masking and the attentional blink task**. Results:** We found no evidence in support of an effect of cabergoline on conscious perception**:** ***key behavioral and event-related potential (ERP) findings associated with each of these tasks were unaffected by cabergoline*****. Conclusions:** Our results cast doubt on a causal role for dopamine in visual perception. It remains an open possibility that dopamine has causal effects in other tasks, perhaps where perceptual uncertainty is more prominent.

A dopamine receptor d2-type agonist attenuates the ability of stress to alter sleep in mice.

Jefferson, F., Ehlen, J. C., Williams, N. S., Montemarano, J. J., & Paul, K. N. (2014). *A Dopamine Receptor D2-Type Agonist Attenuates the Ability of Stress to Alter Sleep in Mice*. Endocrinology (Philadelphia), 155(11), 4411–4421. https://doi.org/10.1210/en.2014-1134.

Although sleep disruptions that accompany stress reduce quality of life and deteriorate health, the mechanisms through which stress alters sleep remain obscure. Psychological stress can alter sleep in a variety of ways, but it has been shown to be particularly influential on rapid eye movement (REM) sleep. Prolactin (PRL), a sexually dimorphic, stress-sensitive hormone whose basal levels are higher in females, has somnogenic effects on REM sleep. In the current study, we examined the relationship between PRL secretion and REM sleep after restraint stress to determine whether: 1) the ability of stress to increase REM sleep is PRL-dependent, and 2) fluctuating PRL levels underlie sex differences in sleep responses to stress. Because dopamine D2 receptors in the pituitary gland are the primary regulator of PRL secretion, D2 receptor agonist, 1-[(6-allylergolin-8β-yl)-carbonyl]-1-[3-(dimethylamino) propyl]-3-ethylurea (cabergoline), was used to attenuate PRL levels in mice before 1 hour of restraint stress. Mice were implanted with electroencephalographic/electromyographic recording electrodes and received an ip injection of either 0.3-mg/kg cabergoline or vehicle before a control procedure of 1 hour of sleep deprivation by gentle handling during the light phase. Six days after the control procedure, mice received cabergoline or vehicle 15 minutes before 1 hour of restraint stress. ***Cabergoline blocked the ability of restraint stress to increase REM sleep amount in males but did not alter REM sleep amount after stress in females even though it reduced basal REM sleep amount in female controls. These data provide evidence that the ability for restraint stress to increase REM sleep is dependent on PRL and that sex differences in REM sleep amount may be driven by PRL*****.**

Reliability and robustness of feedback-evoked brain-heart coupling after placebo, dopamine, and noradrenaline challenge.

Lueckel, M., Panitz, C., Nater, U. M., & Mueller, E. M. (2018). Reliability and robustness of feedback-evoked brain-heart coupling after placebo, dopamine, and noradrenaline challenge. International Journal of Psychophysiology, 132(Pt B), 298–310. https://doi.org/10.1016/j.ijpsycho.2018.01.010.

External and internal performance feedback triggers not only neural but also cardiac modulations, suggesting communication between brain and heart during feedback processing. Using Cardio-Electroencephalographic Covariance Tracing (CECT), it has accordingly been shown that ***feedback-evoked centromedial single-trial EEG at the P300 latency intraindividually predicts subsequent changes in heart period - the so called N300H***

phenomenon. While previous findings suggest that the N300H depends on serotonin, its relationship to central dopamine and noradrenaline is currently unknown. Here, we tested (1) the psychometric properties of this CECT-based component and (2) its putative catecholaminergic mechanisms. N = 54 healthy male participants received either a α2-adrenoceptor antagonist (yohimbine, 10 mg; n = 18), D2-dopamine-receptor antagonist (sulpiride, 200 mg; n = 18), or a placebo (n = 18). Afterwards, they performed a gambling task with feedback after each trial, while EEG and ECG were recorded. ***Feedback successfully evoked a significant N300H both across all 54 participants and within each substance group*.** Importantly, we show that N300H can be reliably measured in a priori defined time windows with as few as 240 feedback trials and is relatively unaffected when removing extreme single-trial values. However, ***we could not find any significant substance effects on N300H magnitude as well as on univariate feedback-related measures (FRN, P300, heart period).*** Altogether, the N300H component proves as a robust and reliable marker of cortico-cardiac coupling evoked by feedback. Furthermore, ***these findings suggest a subordinate role of catecholamines (i.e., noradrenaline and dopamine) and sympathetic pathways in feedback-evoked brain-heart communication as measured with N300H***.

Effect of Rotigotine vs Placebo on Cognitive Functions Among Patients With Mild to Moderate Alzheimer Disease: A Randomized Clinical Trial.

Koch, G., Motta, C., Bonnì, S., Pellicciari, M. C., Picazio, S., Casula, E. P., Maiella, M., Di Lorenzo, F., Ponzo, V., Ferrari, C., Scaricamazza, E., Caltagirone, C., & Martorana, A. (2020). *Effect of Rotigotine vs Placebo on Cognitive Functions Among Patients With Mild to Moderate Alzheimer Disease: A Randomized Clinical Trial*. JAMA Network Open, 3(7), e2010372–e2010372. https://doi.org/10.1001/jamanetworkopen.2020.10372.

Importance: Impairment of dopaminergic transmission may contribute to cognitive dysfunction in Alzheimer disease (AD). **Objective:** To investigate whether therapy with dopaminergic agonists may affect cognitive functions in patients with AD. **Design, setting, and participants:** This phase 2, monocentric, randomized, double-blind, placebo-controlled trial was conducted in Italy. Patients with mild to moderate AD were enrolled between September 1, 2017, and December 31, 2018. Data were analyzed from July 1 to September 1, 2019. **Interventions:** A rotigotine 2 mg transdermal patch for 1 week followed by a 4 mg patch for 23 weeks (n = 47) or a placebo transdermal patch for 24 weeks (n = 47). **Main outcomes and measures:** The primary end point was change from baseline on the Alzheimer Disease Assessment Scale-Cognitive Subscale. Secondary end points were changes in Frontal Assessment Battery, Alzheimer Disease Cooperative Study-Activities of Daily Living, and Neuropsychiatric Inventory scores. Prefrontal cortex activity was evaluated by transcranial magnetic stimulation combined with electroencephalography. **Results:** Among 94 patients randomized (mean [SD] age, 73.9 [5.6] years; 58 [62%] women), 78 (83%) completed the study. Rotigotine, as compared with placebo, had no significant effect on the primary end point: estimated mean change in Alzheimer Disease Assessment Scale-Cognitive Subscale score was 2.92 (95% CI, 2.51-3.33) for the rotigotine group and 2.66 (95% CI, 2.31-3.01) for the placebo group. For the secondary outcomes, there were significant estimated mean changes between groups for Alzheimer Disease Cooperative Study-Activities of Daily Living score (-3.32 [95% CI, -4.02 to -2.62] for rotigotine and -7.24 [95% CI, -7.84 to -6.64] for placebo) and Frontal Assessment Battery score

(0.48 [95% CI, 0.31 to 0.65] for rotigotine and -0.66 [95% CI, -0.80 to -0.52] for placebo). There was no longitudinal change in Neuropsychiatric Inventory scores (1.64 [95% CI, 1.06-2.22] for rotigotine and 1.26 [95% CI, 0.77-1.75] for placebo group). ***Neurophysiological analysis of electroencephalography results indicated that prefrontal cortical activity increased in rotigotine but not in the placebo group.*** Adverse events were more common in the rotigotine group, with 11 patients dropping out compared with 5 in the placebo group. **Conclusions and relevance:** In this randomized clinical trial, rotigotine treatment did not significantly affect global cognition in patients with mild to moderate AD; however, improvement was observed in cognitive functions highly associated with the frontal lobe and in activities of daily living. ***These findings suggest that treatment with the dopaminergic agonist rotigotine may reduce symptoms associated with frontal lobe cognitive dysfunction*** and thus may delay the impairment of activities of daily living.

Altered Pain Processing Associated with Administration of Dopamine Agonist and Antagonist in Healthy Volunteers.

Martin, S. L., Jones, A. K. P., Brown, C. A., Kobylecki, C., Whitaker, G. A., El-Deredy, W., & Silverdale, M. A. (2022). *Altered Pain Processing Associated with Administration of Dopamine Agonist and Antagonist in Healthy Volunteers*. Brain Sciences, 12(3), 351–. https://doi.org/10.3390/brainsci12030351.

Striatal dopamine dysfunction is associated with the altered top-down modulation of pain processing. The dopamine D2-like receptor family is a potential substrate for such effects due to its primary expression in the striatum, but evidence for this is currently lacking. Here, we investigated the effect of pharmacologically manipulating striatal dopamine D2 receptor activity on the anticipation and perception of acute pain stimuli in humans. Participants received visual cues that induced either certain or uncertain anticipation of two pain intensity levels delivered via a CO_2 laser. Rating of the pain intensity and unpleasantness was recorded. ***Brain activity was recorded with EEG and analysed via source localisation to investigate neural activity during the anticipation and receipt of pain.*** Participants completed the experiment under three conditions, control (Sodium Chloride), D2 receptor agonist (Cabergoline), and D2 receptor antagonist (Amisulpride), in a repeated-measures, triple-crossover, double-blind study. The antagonist reduced an individuals' ability to distinguish between low and high pain following uncertain anticipation. ***The EEG source localisation showed that the agonist and antagonist reduced neural activations in specific brain regions associated with the sensory integration of salient stimuli during the anticipation and receipt of pain. During anticipation, the agonist reduced activity in the right mid-temporal region and the right angular gyrus, whilst the antagonist reduced activity within the right postcentral, right mid-temporal, and right inferior parietal regions.*** In comparison to control, the antagonist reduced activity within the insula during the receipt of pain, a key structure involved in the integration of the sensory and affective aspects of pain. Pain sensitivity and unpleasantness were not changed by D2R modulation. Our results support the notion that D2 receptor neurotransmission has a role in the top-down modulation of pain.

Sleep disturbance by pramipexole is modified by Meis1 in mice.

Salminen, A. V., Schormair, B., Flachskamm, C., Torres, M., Müller-Myhsok, B., Kimura, M., & Winkelmann, J. (2018). *Sleep disturbance by pramipexole is modified by Meis1 in mice*. Journal of Sleep Research, 27(4), e12557–n/a. https://doi.org/10.1111/jsr.12557.

Meis homeobox 1 (Meis1) is a transcription factor functioning in the development of the nervous system and the cardiovascular system. Both common and rare variants within the gene have been associated with restless legs syndrome (RLS), while its association with symptoms of insomnia has also been discovered recently. RLS is associated with sleep disturbances, and while Meis1 haploinsufficiency is one of the most promising strategies for an RLS animal model, sleep phenotyping of Meis1 knockout mice has never been conducted. We report a detailed sleep analysis of heterozygous Meis1 knockout mice and challenge it with pramipexole, a dopamine agonist used in the treatment of RLS. ***At baseline, the Meis1-haploinsufficient mice had a trend towards lower delta power in the electroencephalogram (EEG) during sleep compared to the wild-type littermates, possibly indicating reduced sleep quality, but not sleep fragmentation. Pramipexole had a sleep disrupting effect*** *in both genotype groups. In addition,* ***it exerted differential effects on the EEG power spectra*** of the two mouse lines, remarkably elevating the theta power of the mutant mice during recovery more than that of the wild-types. In conclusion, Meis1 haploinsufficiency seems to have only a modest effect on sleep, but the gene may interact with the sleep-disrupting effect of dopamine agonists.

Loss of Midbrain Dopamine Neurons and Altered Apomorphine EEG Effects in the 5xFAD Mouse Model of Alzheimer's Disease.

Vorobyov, V., Bakharev, B., Medvinskaya, N., Nesterova, I., Samokhin, A., Deev, A., Tatarnikova, O., Ustyugov, A. A., Sengpiel, F., & Bobkova, N. (2019*). Loss of Midbrain Dopamine Neurons and Altered Apomorphine EEG Effects in the 5xFAD Mouse Model of Alzheimer's Disease*. Journal of Alzheimer's disease : JAD, 70(1), 241–256. https://doi.org/10.3233/JAD-181246.

Cognitive malfunction, synaptic dysfunction, and disconnections in neural networks are core deficits in Alzheimer's disease (AD). 5xFAD mice, a transgenic model of AD, are characterized by an enhanced level of amyloid-β and abnormal neurotransmission. The dopaminergic (DA) system has been shown to be involved in amyloid-β transformations and neuronal plasticity; however, its role in functional network changes in familial AD still remains unclear. In 5xFAD and non-transgenic freely moving mice, electroencephalograms (EEGs) were simultaneously recorded from the secondary motor cortex (MC), superficial layers of the hippocampal CA1 area (HPC), substantia nigra (SN), and ventral tegmental area (VTA). EEGs and their frequency spectra were analyzed before and after systemic injection of a DA receptor agonist, apomorphine (APO). In ***the baseline EEG from MC and HPC of 5xFAD mice, delta and alpha oscillations were enhanced and beta activity was attenuated****,* compared to control mice. In VTA and SN of 5xFAD mice, ***delta-theta activity was decreased and beta oscillations dominated*****.** In control mice, APO suppressed delta activity in VTA to a higher extent than in MC, whereas in 5xFAD mice, this difference was eliminated due to attenuation of the delta suppression in VTA. APO increased beta activity in MC of mice from both groups while significant beta suppression was observed in VTA of 5xFAD mice. These mice were characterized by significant decrease of tyrosine hydroxylase immunopositive cells in both VTA and SN and of DA transporter in MC and hippocampal dentate gyrus. We suggest that ***the EEG***

modifications observed in 5xFAD mice are associated with alterations in dopaminergic transmission, resulting in adaptive changes in the cerebral networks in the course of familial AD development.

Cortical and Striatal Electroencephalograms and Apomorphine Effects in the FUS Mouse Model of Amyotrophic Lateral Sclerosis.

Vorobyov, V., Deev, A., Sengpiel, F., Nebogatikov, V., & Ustyugov, A. A. (2021). *Cortical and Striatal Electroencephalograms and Apomorphine Effects in the FUS Mouse Model of Amyotrophic Lateral Sclerosis.* Journal of Alzheimer's disease : JAD, 81(4), 1429–1443. https://doi.org/10.3233/JAD-201472

Background: Amyotrophic lateral sclerosis (ALS) is characterized by degeneration of motor neurons resulting in muscle atrophy. In contrast to the lower motor neurons, the role of upper (cortical) neurons in ALS is yet unclear. Maturation of locomotor networks is supported by dopaminergic (DA) projections from substantia nigra to the spinal cord and striatum. **Objective:** To examine the contribution of DA mediation in the striatum-cortex networks in ALS progression. **Methods:** We studied electroencephalogram (EEG) from striatal putamen (Pt) and primary motor cortex (M1) in ΔFUS(1-359)-transgenic (Tg) mice, a model of ALS. EEG from M1 and Pt were recorded in freely moving young (2-month-old) and older (5-month-old) Tg and non-transgenic (nTg) mice. EEG spectra were analyzed for 30 min before and for 60 min after systemic injection of a DA mimetic, apomorphine (APO), and saline. **Results:** In young Tg versus nTg mice, ***baseline EEG spectra in M1 were comparable, whereas in Pt, beta activity in Tg mice was enhanced. In older Tg versus nTg mice, beta dominated in EEG from both M1 and Pt, whereas theta and delta 2 activities were reduced.*** *In younger Tg versus nTg mice****, APO increased theta and decreased beta 2 predominantly in M1. In older mice, APO effects in these frequency bands were inversed and accompanied by enhanced delta 2 and attenuated alpha*** in Tg versus nTg mice.

Conclusion: We suggest that revealed **EEG modifications in ΔFUS(1-359)-transgenic mice are associated with early alterations in the striatum-cortex interrelations** and DA transmission followed by adaptive intracerebral transformations.

Loss of the Synuclein Family Members Differentially Affects Baseline- and Apomorphine-Associated EEG Determinants in Single-, Double- and Triple-Knockout Mice.

Vorobyov, V., Deev, A., Sukhanova, I., Morozova, O., Oganesyan, Z., Chaprov, K., & Buchman, V. L. (2022). *Loss of the Synuclein Family Members Differentially Affects Baseline- and Apomorphine-Associated EEG Determinants in Single-, Double- and Triple-Knockout Mice*. Biomedicines, 10(12), 3128. https://doi.org/10.3390/biomedicines10123128

Synucleins comprise a family of small proteins highly expressed in the nervous system of vertebrates and involved in various intraneuronal processes. The malfunction of alpha-synuclein is one of the key events in pathogenesis of Parkinson disease and certain other neurodegenerative diseases, and there is a growing body of evidence that malfunction of other two synucleins might be involved in pathological processes in the nervous system. The modulation of various presynaptic mechanisms of neurotransmission is an important function of synucleins, and therefore, it is feasible that their deficiency might affect global electrical activity detected of the brain. However, the effects of the loss of synucleins on the frequency

spectra of electroencephalograms (EEGs) have not been systematically studied so far. In the current study, we assessed changes in such spectra in single-, double- and triple-knockout mice lacking alpha-, beta- and gamma-synucleins in all possible combinations. EEGs were recorded from the motor cortex, the putamen, the ventral tegmental area and the substantia nigra of 78 3-month-old male mice from seven knockout groups maintained on the C57BL/6J genetic background, and 10 wild-type C57BL/6J mice for 30 min before and for 60 min after the systemic injection of a DA receptor agonist, apomorphine (APO). We found that almost ***any variant of synuclein deficiency causes multiple changes in both basal and APO-induced EEG oscillation profiles. Therefore, it is not the absence of any particular synuclein but rather a disbalance of synucleins that causes widespread changes in EEG spectral profiles.***

GABA ANALOGUES

CLASS FACTS

SYNOPSIS: GABA is an amino acid that is one of the most important neurotransmitters (chemical messengers) that we have in our nervous system. It is essential for maintaining the balance between nerve cell excitation and nerve cell inhibition. GABA acts like a brake in a car and slows down nerve cells that are over-excited. Because it calms the nervous system, it is called an inhibitory neurotransmitter. GABA analogs are medicines that have a very similar structure to GABA but act in a different way, although experts aren't exactly sure how they work. Most agree they bind to calcium-channels within the nerve cells, improving how well brain cells respond to GABA or making the release of GABA easier.

----- BACLOFEN (Ozobax) -----

DRUG FACTS

Toxicity

Triplett, J. D., Lawn, N. D., & Dunne, J. W. (2019). *Baclofen Neurotoxicity: A Metabolic Encephalopathy Susceptible to Exacerbation by Benzodiazepine Therapy*. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society, 36(3), 209–212. https://doi.org/10.1097/WNP.0000000000000565

Purpose: Baclofen has been reported to cause both a metabolic encephalopathy and nonconvulsive status epilepticus. Baclofen is typically used in the management of muscle spasticity but is being increasingly used to manage alcohol withdrawal and opiate dependency. Given the increasing use of baclofen we describe the clinical and electrographical features of baclofen neurotoxicity seen at our institution. **Methods:** The clinical and EEG features of patients with an encephalopathy in the setting of baclofen therapy were analyzed. Patients were identified via our hospital EEG database. **Results:** Fourteen patients were identified having presented with an acute confusional state without identifiable cause other than baclofen use. Five patients took a deliberate overdose, three of whom were baclofen naive, two patients presented after medication prescription error, and seven patients were on stable doses (30–140 mg daily). All patients presented with an encephalopathy, one patient was reported to have clinical seizures, and seven had multifocal myoclonus. ***EEGs were abnormal in all patients and showed moderate to severe generalized slowing. Generalized triphasic waves occurring at 1 to 2 Hz, sometimes with an anterior to posterior phase lag, were present in 10 patients (71%), and intermittent generalized suppression of the background was seen in three patients.*** Three patients received small doses of intravenous benzodiazepines, resulting in a marked depression of consciousness and respiration. All patients recovered within 48 hours of baclofen discontinuation. **Conclusions:** ***Baclofen toxicity can produce an acute encephalopathy even at modest doses, with the EEG showing generalized slowing and triphasic waves consistent with a toxic encephalopathy.*** Management consists of supportive care and cessation of baclofen. Patients with baclofen neurotoxicity exhibit a marked vulnerability to the depressant effects of benzodiazepines.

Baclofen and EEG slowing

Seyfert, S., & Straschill, M. (1982). *Elektroenzephalographische Veränderungen unter Baclofen [Electroencephalographic changes induced by baclofen].* EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete, 13(4), 161–166.

Electroencephalographic and clinical effects of baclofen were investigated in 46 neurological patients and 7 healthy volunteers. 27 cases showed an increase of slow EEG activity. Patients with spinal disease, brain-stem disease, disturbed vibratory sensation and also with renal insufficiency showed pronounced EEG-slowing***. Baclofen depresses the activity in primary afferents and reticulocortical afferents. These effects can lead to EEG slowing. One patient developed a reversible organic brain syndrome and myoclonias with marked EEG-slowing and bilateral synchronous sharp and slow waves.*** This was interpreted as an epileptic stupor induced by Baclofen. The patient had renal insufficiency and accumulated Baclofen. Both conditions may have contributed to the epileptic manifestation.

----- GABAPENTIN -----

DRUG FACTS

Effect of gabapentin on sleep and delta and theta EEG power in adult rats exposed to chronic intermittent ethanol vapor and protracted withdrawal during adolescence.

Ehlers CL, Sanchez-Alavez M, Wills D. *Effect of gabapentin on sleep and delta and theta EEG power in adult rats exposed to chronic intermittent ethanol vapor and protracted withdrawal during adolescence*. Psychopharmacology (Berl). 2018 Jun;235(6):1783-1791. doi: 10.1007/s00213-018-4888-6. Epub 2018 Mar 27. PMID: 29589069; PMCID: PMC5949268.

Rationale: Adolescents and young adults with alcohol problems may also have sleep difficulties. However, whether these sleep problems are a result of a history of drinking or arise due to other comorbid disorders is difficult to disentangle in human studies. Additionally, the mechanisms underlying adolescent alcohol-induced sleep disturbances and potential targets for therapy also remain under-investigated. Recent clinical trials have demonstrated that the anticonvulsant and analgesic drug gabapentin may have therapeutic value in normalizing sleep quality in adult recovering alcoholics, yet its potential for the treatment of adolescent sleep disturbances has not been investigated. **Objectives:** This study sought to evaluate the effects of a history of 5 weeks of chronic intermittent ethanol vapor exposure, administered during adolescence (AIE), on EEG sleep, in young adult rats (n = 29). The ability of two doses of gabapentin (30, 120 mg/kg) to modify sleep and slow wave activity were also investigated in these young adult rats exposed to alcohol vapor during adolescence. **Results:** Adolescent vapor exposure in the rat was ***found to result in deficits in delta (1-4 Hz) and theta (4-8 Hz) power during slow wave sleep.*** Administration of gabapentin caused a "normalization" of the delta power deficits but did not affect theta power. **Conclusions:** This report suggests that the potential mechanisms and therapeutic targets for sleep disturbance associated with adolescent alcohol exposure can be studied in preclinical models and that gabapentin may show partial efficacy in ameliorating these sleep deficits.

Effect of Gabapentin on Sleep and Event-Related Oscillations (EROs) in Rats Exposed to Chronic Intermittent Ethanol Vapor and Protracted Withdrawal.

Sanchez-Alavez M, Wills DN, Amodeo L, Ehlers CL. *Effect of Gabapentin on Sleep and Event-Related Oscillations (EROs) in Rats Exposed to Chronic Intermittent Ethanol Vapor and Protracted Withdrawal.* Alcohol Clin Exp Res. 2018 Mar;42(3):624-633. doi: 10.1111/acer.13588. Epub 2018 Jan 31. PMID: 29286538; PMCID: PMC5832602.

Background: Disturbances in sleep architecture, especially reductions in slow-wave sleep (SWS), are symptoms commonly observed in individuals with alcohol use disorders. Recent clinical trials have demonstrated that the anticonvulsant and analgesic drug gabapentin may have therapeutic value in normalizing sleep quality in recovering alcoholics. However, the brain mechanisms underlying this improvement in sleep following gabapentin treatment remain unknown. **Methods:** In this study, adult Wistar rats were exposed to 8 weeks of chronic intermittent ethanol [EtOH] vapor (blood EtOH concentrations averaged 128.2 ± 17.4 mg/dl) or control conditions and then withdrawn. Sleep electroencephalograms [EEGs] and event-related oscillations (EROs) were evaluated at baseline prior to EtOH exposure and 24 hours following EtOH withdrawal. Four weeks following EtOH withdrawal the effects of saline and 2 doses of gabapentin (30, 120 mg/kg), on EROs and sleep EEGs, were evaluated. **Results:** ***As compared to baseline, 24 hours following alcohol withdrawal SWS became fragmented as indexed by a significant increase in the number and a decrease in the duration of SWS episodes.*** Compared to controls, the EtOH-exposed group had more ERO energy in the beta frequency band in the parietal cortex. ***Gabapentin induced a dose-dependent decrease in the latency to the first SWS episode, and a reduction in sleep fragmentation. Gabapentin also produced a dose-dependent increase in ERO energy in the control group that was significantly attenuated in the EtOH-exposed group in the theta, and beta frequency bands.*** Conclusions: Taken together, these studies suggest that gabapentin can reverse some of the alcohol-induced sleep and EEG deficits but does not eliminate all of the enduring brain effects of EtOH exposure.

Effects of gabapentin on brain hyperactivity related to pain and sleep disturbance under a neuropathic pain-like state using fMRI and brain wave analysis.

Takemura Y, Yamashita A, Horiuchi H, Furuya M, Yanase M, Niikura K, Imai S, Hatakeyama N, Kinoshita H, Tsukiyama Y, Senba E, Matoba M, Kuzumaki N, Yamazaki M, Suzuki T, Narita M. *Effects of gabapentin on brain hyperactivity related to pain and sleep disturbance under a neuropathic pain-like state using fMRI and brain wave analysis*. Synapse. 2011 Jul;65(7):668-76. doi: 10.1002/syn.20898. Epub 2011 Feb 25. PMID: 21162109.

Neuropathic pain is the most difficult pain to manage in the pain clinic, and sleep problems are common among patients with chronic pain including neuropathic pain. In the present study, we tried to visualize the intensity of pain by assessing neuronal activity and investigated sleep disturbance under a neuropathic pain-like state in mice using functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG)/electromyogram (EMG), respectively. Furthermore, we investigated the effect of gabapentin (GBP) on these phenomena. In a model of neuropathic pain, sciatic nerve ligation caused a marked decrease in the latency of paw withdrawal in response to a thermal stimulus only on the ipsilateral side. Under this condition, fMRI showed that sciatic nerve ligation produced a significant increase in the blood oxygenation level-dependent (BOLD) signal intensity in the pain matrix, which was significantly decreased 2

h after the i.p. injection of GBP. ***Based on the results of an EEG/EMG analysis, sciatic nerve-ligated animals showed a statistically significant increase in wakefulness and a decrease in non-rapid eye movement (NREM) sleep during the light phase, and the sleep disturbance was almost completely alleviated by a higher dose of GBP in nerve-ligated mice. These findings suggest that neuropathic pain associated with sleep disturbance can be objectively assessed by fMRI and EEG/EMG analysis in animal models. Furthermore, GBP may improve the quality of sleep as well as control pain in patients with neuropathic pain*.**

HEADACHE MEDICATIONS (TRIPTANS)

CLASS FACTS

----- SUMATRIPTAN (IMITREX) -----

DRUG FACTS

Alpha power

van der Post, J., Schram, M. T., Schoemaker, R. C., Pieters, M. S., Fuseau, E., Pereira, A., Baggen, S., Cohen, A. F., & van Gerven, J. M. (2002). *CNS effects of sumatriptan and rizatriptan in healthy female volunteers*. Cephalalgia : an international journal of headache, 22(4), 271–281. https://doi.org/10.1046/j.1468-2982.2002.00344.x

This study investigates the CNS effects of sumatriptan and rizatriptan, with temazepam as an active comparator, in healthy female volunteers. Sixteen volunteers completed a randomized, double-blind, crossover study and on four separate occasions received either 100 mg sumatriptan, 20 mg rizatriptan or 20 mg temazepam. The main parameters were eye movements, EEG, body sway, visual analogue scales and a cognitive test battery. Rizatriptan and sumatriptan decreased saccadic peak velocity by 18.3 (95% CI: 5.7, 30.8) and 15.0 (2.2, 27.9) degrees/sec, respectively, about half the decrease induced by temazepam (35.0 (22.1, 47.8) degrees/sec). Body sway increased (30% for rizatriptan (16%, 45%) and 14% for sumatriptan (1%, 27%), respectively). ***Temazepam caused larger, similar effects. In contrast to temazepam, sumatriptan and rizatriptan decreased reaction times of recognition tasks and increased EEG alpha power (significant for sumatriptan, 0.477 (0.02, 0.935).*** Therapeutic doses of sumatriptan and rizatriptan caused CNS effects indicative of mild sedation. For EEG and recognition reaction times the effects were opposite to temazepam, indicating central stimulation.

----- RIZATRIPTAN (MAXALT) -----

DRUG FACTS

Increase of CNV amplitude

Zank, R., Strehl, U., Larbig, W., & Kotchoubey, B. (2008). *Effects of rizatriptan on the contingent negative variation in healthy women*. Cephalalgia, 28(9), 922–932. https://doi.org/10.1111/j.1468-2982.2008.01624.x

The effect of the antimigraine drug rizatriptan on the amplitude and habituation of the contingent negative variation (CNV) in healthy women was examined in a randomized, double-blind, placebo-controlled trial. The test persons were assigned either to a drug (n = 20) or a placebo group (n = 20). The CNV was recorded three times: before, directly after, and 24 h after drug or placebo intake***. The CNV paradigm was presented in a standard, a cued and a choice version. Rizatriptan led to an increase of CNV amplitude that depended on the level of difficulty of the task. Whereas there was no drug effect in the standard version, an amplitude increase was obtained mainly in the choice task*.** The results are in line with the ceiling theory of migraine, which assumes a rise of CNV amplitude if the serotonin level is lowered.

----- HORMONES -----

CLASS FACTS

Hormonal changes with comorbid epilepsy:

Herzog, A. G., Coleman, A. E., Jacobs, A. R., Klein, P., Friedman, M. N., Drislane, F. W., Ransil, B. J., & Schomer, D. L. (2003). *Interictal EEG discharges, reproductive hormones, and menstrual disorders in epilepsy.* Annals of neurology, *54*(5), 625–637. https://doi.org/10.1002/ana.10732

We evaluated reproductive endocrine function in women with unilateral temporolimbic epilepsy and normal control subjects to assess the effects of epilepsy, epilepsy laterality, and antiepileptic drug use on the cerebral regulation of hormonal secretion. ***The findings indicate that reproductive endocrine function differs between women with epilepsy and normal control subjects.*** Significant differences exist at all levels of the reproductive neuroendocrine axis, that is, hypothalamus, pituitary, and peripheral gland. Differences show significant relationships to the epilepsy itself as well as to medication use. Reproductive neuroendocrine changes occur in a stochastic manner such that the laterality of unilateral temporolimbic discharges is associated with predictable directional changes in hormonal secretion at all levels of the reproductive neuroendocrine axis. These directional changes are consistent with the finding that different reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy. Hormonal changes can show close temporal relationship to the occurrence of interictal epileptiform discharges and may vary in relation to the laterality of the discharges. Antiepileptic drugs differ in their effects on reproductive hormone levels. There are notable differences between enzyme-inducing and noninducing drugs. Menstrual disorders are more common among women with interictal discharges as well as women with abnormal hormonal findings.

Alpha power in parietal and occipital regions and menstrual cycle:

Gulsum Akdeniz, Emine Feyza Yurt, Gulsen Yilmaz, Gamze Dogan, P278 The EEG alpha response is affected by changes in sex hormone levels in two phases of menstrual cycle, Clinical Neurophysiology, Volume 128, Issue 9, 2017, Page e267, ISSN 1388-2457, https://doi.org/10.1016/j.clinph.2017.07.286. (https://www.sciencedirect.com/science/article/pii/S1388245717307733)

Abstract: Objectives: It is known that sex hormones affect the brain in women. However, there are not enough studies that explain the relationship between sex hormone fluctuations during menstrual cycle and brain waves. Our aim in this study is to show the effects of sex hormone fluctuations on the EEG alpha response in menstrual phase and follicular phase. Methods: EEG recordings on resting state was performed in 11 healthy volunteer women in two different phases (menstrual and follicular). The alpha power values were analyzed by artifact-free 45 epochs lasting 2s. Blood samples of volunteers were drawn simultaneously and estradiol, progesterone, FSH and LH were analyzed with electrochemiluminescence immunoassay method. The assessment of alpha power values and its relationship with hormone levels were performed in two phases of menstrual cycle. Results: The highest difference between the mean power value in the menstrual phase (46.06) and the follicular phase (36.08) was obtained from the parietal region of the brain. At the same time, the lowest difference between the mean power value (41.06) in the menstrual phase and the follicular phase (39.37) was obtained from the occipital region of the brain. Estrodiol, progesterone, FSH, LH mean levels were 30.2pg/ml; 0.17ng/ml; 6.7mIU/ml; 5.43mIU/ml in the menstrual cycle and 123.9pg/ml; 0.23ng/ml; 7.3mIU/ml; 17.12mIU/ml in the follicular phase, respectively. Conclusion: ***We found that increased estradiol levels in response to the elevation of LH levels in blood during follicular phase resulted in a***

decrease in the power of the alpha waves from the parietal region. Sex hormone fluctuations in menstrual cycle has minimal effect on the EEG alpha response in occipital region.

Hormones and Depression:

Solís-Ortiz, S. , Pérez-Luque, E. & Pacheco-Zavala, M. (2012). *Resting EEG Activity and Ovarian Hormones as Predictors of Depressive Symptoms in Postmenopausal Women without a Diagnosis of Major Depression*. *Psychology, 3,* 834-840. doi: 10.4236/psych.2012.329126.

The aim of this study was to examine the effects of depressive symptoms on resting EEG and their correlation with endogenous hormone levels in postmenopausal women without a diagnosis of major depression. Fifty postmenopausal women aged 48 to 60 years were assessed for depressive symptoms using the Beck Depression Inventory. EEG activity was recorded during rest with eyes closed in 23 participants with minimal and 27 with moderate depressive symptoms. Relative power for delta, theta, alpha1, alpha2, beta1 and beta2 were analyzed and compared between women with minimal and moderate depressive symptoms. Hormonal levels of estrone, estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone were obtained and correlated with the EEG parameters. ***The women with moderate depressive symptoms showed more relative alpha1 power (p = .01) and less relative beta 2 power (p = .03). Relative theta and alpha2 power, estradiol levels and menopausal years were predictors of depressive symptoms. Progesterone was negatively correlated with the theta band (p = .005) and positively correlated with the beta2 band (p = .02) in women with moderate depressive symptoms. Estrone was negatively correlated with the alpha2 band (p = .05), and estradiol was positively correlated with the theta band (p = .02) and negatively correlated with the beta2 band (p = .05) in women with minimal depressive symptoms.*** These findings suggest that slow and fast EEG relative power, menopausal status and estrogen levels predict depressive symptoms, and that progesterone is related with moderate depression.

Menstrual cycle and alpha:

Wuttke, W., Arnold, P., Becker, D., Creutzfeldt, O., Langenstein, S., & Tirsch, W. (1975). *Circulating hormones, EEG, and performance in psychological tests of women with and without oral contraceptives*. Psychoneuroendocrinology, 1(2), 141–151. https://doi.org/10.1016/0306-4530(75)90006-2

A comparative study was conducted to examine the interrelationships between changes in circulating hormones and the EEG and the performance in psychological tests both of women with normal menstrual cycles and of women using oral contraceptives. EEG and psychological data are analyzed in detail. Blood samples were taken at 2-day intervals for 16 women on normal menstrual cycles and for 16 women on pills. The hormonal results confirmed previous studies. ***Only the alpha-rhythm of the EEG was slightly but significantly accelerated during the luteal phase of the menstrual cycle, as a result of the influence of progesterone. Oral contraceptives tend to slow the alpha rhythm***. In performance tests for reaction time and mathematical ability, scores were better during the luteal phase when increased estradiol and progesterone levels occur but not as good during the immediate preovulatory phase when only estradiol levels are high. The groups using oral contraceptives reacted significantly slower during the luteal phase. This result indicates that 1 or more of the ingredients of combined oral contraceptives may interfere with mental abilities. It is concluded that there is a definite relationship between the alpha rhythm of the EEG, performance time and quality, and reaction time and between these factors and the levels of progesterone which change during the menstrual cycles.

Alpha and thyroid Levels

Hermann, H. T., & Quarton, G. C. (1964). *Changes in alpha frequency with change in thyroid*

hormone level. Electroencephalography and Clinical Neurophysiology, *16*(5), 515–518. https://doi.org/10.1016/0013-4694(64)90093-8

Several autocorrelograms of resting EEG were obtained on eleven hyper- and six hypothyroid patients as their level of hormone changed. Alpha frequency correlated positively with both PBI (0.60) and BMR (0.73). Change in alpha correlated with change in PBI (0.83) and change in BMR (0.85). ***Alpha frequency and thyroid indices remained positively correlated throughout the range of thyroid function***.

----- HYPNOTICS -----

CLASS FACTS

SYNOPSIS: A class of psychoactive drugs whose primary function is to induce sleep and to treat insomnia.

----- Zolpidem (Ambien) -----

DRUG FACTS

Alpha power and visual analogue scale (VAS) alertness score and increased body sway.

de Haas, S. L., Schoemaker, R. C., van Gerven, J. M., Hoever, P., Cohen, A. F., & Dingemanse, J. (2010). *Pharmacokinetics, pharmacodynamics and the pharmacokinetic/ pharmacodynamic relationship of zolpidem in healthy subjects*. Journal of psychopharmacology *(Oxford, England)*, *24*(11), 1619–1629. https://doi.org/10.1177/0269881109106898

Zolpidem is one of the most frequently prescribed hypnotics, as it is a very short-acting compound with relatively few side effects. Zolpidem's short duration of action is partly related to its short elimination half-life, but the associations between plasma levels and pharmacodynamic (PD) effects are not precisely known. In this study, the concentration-effect relationships for zolpidem were modelled. Zolpidem (10 mg) was administered in a double-blind, randomized, placebo-controlled trial to determine PD and pharmacokinetics (PK) in 14 healthy volunteers. Zolpidem was absorbed and eliminated quickly, with a median T(max) of 0.78 h (range: 0.33-2.50) and t(1/2) of 2.2 h. Zolpidem reduced saccadic peak velocity (SPV), adaptive tracking performance, ***electroencephalogram (EEG) alpha power and visual analogue scale (VAS) alertness score and increased body sway, EEG beta power and VAS 'feeling high'.*** Short- and long-term memory was not affected. Central nervous system effects normalized more rapidly than the decrease of plasma concentrations. For most effects, zolpidem's short duration of action could be adequately described by both a sigmoid E(max) model and a transit tolerance model. For SPV and EEG alpha power, the tolerance model seemed less suitable. These PK/PD models have different implications for the mechanism underlying zolpidem's short duration of action. A sigmoid E(max) model (which is based on ligand binding theory) would imply a threshold value for the drug's effective concentrations. A transit tolerance model (in which a hypothetical factor builds up with time that antagonizes the effects of the parent compound) is compatible with a rapid reversible desensitization of GABAergic subunits.

How benzodiazepine and non-benzodiazepine hypnotics differ in sleep effect

Feinberg, I., Maloney, T., & Campbell, I. G. (2000). *Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications*. Journal of psychiatric research, *34*(6), 423–438. https://doi.org/10.1016/s0022-3956(00)00038-8.

Benzodiazepine hypnotics increase NREM sleep and alter its EEG by reducing delta (0.3-3 Hz) and increasing sigma (12-15 Hz) and beta (15-23 Hz) activity. We tested whether the nonbenzodiazepine hypnotic, zolpidem (10 mg), produced the same pattern of sleep and EEG changes as two "classical" benzodiazepines, triazolam (0.25 mg) and temazepam (30 mg). Sleep EEG of 16 subjects was analyzed with period amplitude analysis for 3 nights during drug administration or placebo. The effects of zolpidem were in the same direction but generally of smaller magnitude than those of the classical benzodiazepines. These differences are more likely the result of non-equivalent dosages than different

pharmacologic actions. Period amplitude analysis showed that the decreased delta activity resulted mainly from a decrease in wave amplitude. In contrast, the increased sigma and beta activity were produced by increased wave incidence. Delta suppression increased with repeated drug administration, but sigma and beta stimulation did not. While these findings have little relevance for the clinical choice of hypnotics they may hold important implications for the brain mechanisms involved in hypnotic tolerance and withdrawal delirium.

Gaboxadol and Zolpidem and slow-wave sleep

Lundahl, J., Deacon, S., Maurice, D., & Staner, L. (2012). *EEG spectral power density profiles during NREM sleep for gaboxadol and zolpidem in patients with primary insomnia*. Journal of psychopharmacology *(Oxford, England)*, *26*(8), 1081–1087. https://doi.org/10.1177/0269881111424457

There is significant interest in the functional significance and the therapeutic value of slow-wave sleep (SWS)-enhancing drugs. A prerequisite for studies of the functional differences is characterization of the electroencephalography (EEG) spectra following treatment in relevant patients. We evaluate for the first time gaboxadol and zolpidem treatments in insomniac patients using power spectra analysis. We carried out two randomized, double-blind, crossover studies. Study 1, 38 patients received gaboxadol 10 mg and 20 mg and zolpidem 10 mg; study 2, 23 patients received gaboxadol 5 mg and 15 mg. Treatments were administered during two nights and compared with placebo. ***Gaboxadol 10, 15 and 20 mg enhanced slow-wave activity (SWA) and theta power. In 1 Hz bins gaboxadol 10 and 20 mg enhanced power up to 9 Hz. In study 2, 15 mg gaboxadol showed a similar effect pattern. Zolpidem suppressed theta and alpha power, and increased sigma power, with no effect on SWA. In the 1 Hz bins zolpidem suppressed power between 5-10 Hz. Gaboxadol dose-dependently increased SWA and theta power in insomniac patients. In contrast, zolpidem did not affect SWA, reduced theta and alpha activity and enhanced sigma power. EEG spectral power differences may be consequences of the different mechanisms of action for zolpidem and the SWS-enhancing agent, gaboxadol.***

EEG response to hypnotics based on rat behavior

van Lier, H., Drinkenburg, W. H., van Eeten, Y. J., & Coenen, A. M. (2004). *Effects of diazepam and zolpidem on EEG beta frequencies are behavior-specific in rats*. Neuropharmacology, *47*(2), 163–174. https://doi.org/10.1016/j.neuropharm.2004.03.017

A pharmacological dissociation of the relation between electroencephalographic (EEG) activity and behavior has been described for the benzodiazepines. ***While a decrease in high frequency EEG activity is associated with a decrease in arousal in drug-free conditions, sedative benzodiazepines increase beta activity.*** Non-benzodiazepine GABA(A) receptor modulators can increase beta activity as well. To further study the relationship between rat behavior and EEG under GABA(A) receptor modulation, EEG effects of diazepam (2.5 mg/kg) and zolpidem (2.5 mg/kg) were studied during different behaviors. Both drugs modulate the GABA(A) receptor, albeit that zolpidem shows alpha(1) subunit selectivity while diazepam is non-selective. A detailed analysis of rat open field behavior was made with a distinction of 25 behavioral elements. The EEG was segmented according to each behavioral element and a corresponding power spectrum calculated. ***Both diazepam and zolpidem increased EEG beta frequencies, characteristic for the benzodiazepines. However, the beta and gamma increase was specific for active behavior and not for inactivity.*** Interestingly, diazepam and zolpidem seemed to amplify, rather than dissociate, the relation between behavior and the EEG. It is hypothesized that the large increase in beta-3/gamma activity caused by diazepam and zolpidem is a compensatory mechanism that allows for behavioral activation, despite pharmacologically induced sedation.

Sex differences in EEG from hypnotics

Dijk, D. J., James, L. M., Peters, S., Walsh, J. K., & Deacon, S. (2010). *Sex differences and the effect of gaboxadol and zolpidem on EEG power spectra in NREM and REM sleep*. Journal of psychopharmacology *(Oxford, England)*, *24*(11), 1613–1618. https://doi.org/10.1177/0269881109105788

Hypnotics that interact with the GABA(A) receptor have marked effects on the electroencephalogram (EEG) during sleep. It is not known whether the effects of hypnotics on EEG power spectra differ between the sexes. The effects of 5, 10 and 15 mg of gaboxadol (GBX) and 10 mg of zolpidem (ZOL) on EEG power spectra were assessed in a randomized, double-blind, placebo-controlled, 5-way cross-over design study using a phase-advance model of transient insomnia. Sleep stage specific EEG power spectra were computed in 36 men and 45 women. GBX enhanced power density in delta and theta activity in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep and suppressed sleep spindle activity in NREM sleep. ***The increase of delta and theta activity in NREM and REM sleep was significantly larger for women than for men, but the suppression of spindle activity did not differ between the sexes. After ZOL administration, no sex differences were observed in the reduction of delta and theta activity in NREM sleep, but the increase in sleep spindle activity in NREM sleep was greater in women than in men.*** These sex dependent and differential effects of GBX and ZOL may be related to their differential affinity for GABA(A) receptor subtypes and their modulation by neurosteroids.

Eszopiclone and zolpidem effects on REM sleep and anxiety

Huang, M. P., Radadia, K., Macone, B. W., Auerbach, S. H., & Datta, S. (2010). *Effects of eszopiclone and zolpidem on sleep-wake behavior, anxiety-like behavior and contextual memory in rats*. Behavioural brain research, *210*(1), 54–66. https://doi.org/10.1016/j.bbr.2010.02.018

At present, eszopiclone and zolpidem are the most commonly prescribed drugs for treating insomnia. Despite the established relationship between sleep disturbance and anxiety, it remains unknown whether targeted treatment for insomnia may affect acute anxiety. Therefore, the objective of this study was to examine the effects of three different doses (1, 3, and 10mg/kg) of eszopiclone and zolpidem on the states of sleep and wakefulness, levels of anxiety-like behavior, and long-term contextual memory in foot shock-induced anxious rats. The results of this study demonstrated that the administration of eszopiclone and zolpidem both were equally effective in attenuating foot shock stressor-induced suppression of slow-wave sleep (SWS). ***The administration of eszopiclone at 1mg/kg or zolpidem at 1 and 3mg/kg doses showed a tendency for attenuating stressor-induced suppression of REM sleep. However, the REM sleep attenuating effects of these drugs disappeared when they were administered at higher doses. The administration of eszopiclone at 3 and 10mg/kg doses and zolpidem at all three doses reduced the power of electroencephalographic theta band frequencies during wakefulness.*** In addition, the administration of eszopiclone at 1 and 3mg/kg doses suppressed stressor-induced anxiety-like behavior. The administration of zolpidem at 1, 3, or 10mg/kg doses was not effective in attenuating stressor-induced anxiety-like behavior. Contextual memory after administration of eszopiclone at 1mg/kg dose had no effects but was reduced significantly with increased dosage. Contextual memory after administration of zolpidem, at all three doses, was severely disrupted. The results of this study suggest that eszopiclone at a low dose could be used effectively to control anxiety and anxiety-induced insomnia.

-----Nonselective Dopamine Agonists (NSDAs)-----

CLASS FACTS

SYNOPSIS: Newer dopamine agonists are known as non-ergoline agonists. These are pramipexole, ropinirole, rotigotine and apomorphine. They have not been associated with a risk of heart damage and can be prescribed.

The dopamine D2 agonist quinpirole impairs frontal mismatch responses to sound frequency deviations in freely moving rats.

Inaba H, Namba H, Kida S, Nawa H. The dopamine D2 agonist quinpirole impairs frontal mismatch responses to sound frequency deviations in freely moving rats. Neuropsychopharmacol Rep. 2021 Sep;41(3):405-415. doi: 10.1002/npr2.12199. Epub 2021 Jul 23. PMID: 34296531; PMCID: PMC8411315.

Aim: A reduced mismatch negativity (MMN) response is a promising electrophysiological endophenotype of schizophrenia that reflects neurocognitive impairment. Dopamine dysfunction is associated with symptoms of schizophrenia. However, whether the dopamine system is involved in MMN impairment remains controversial. In this study, we investigated the effects of the dopamine D2-like receptor agonist quinpirole on mismatch responses to sound frequency changes in an animal model. **Methods:** Event-related potentials were recorded from electrocorticogram electrodes placed on the auditory and frontal cortices of freely moving rats using a frequency oddball paradigm consisting of ascending and equiprobable (ie, many standards) control sequences before and after the subcutaneous administration of quinpirole. To detect mismatch responses, difference waveforms were obtained by subtracting nondeviant control waveforms from deviant waveforms. **Results:** Here, we show the significant effects of quinpirole on frontal mismatch responses to sound frequency deviations in rats. **Quinpirole delayed the frontal N18 and P30 mismatch responses and reduced the frontal N55 MMN-like response, which resulted from the reduction in the N55 amplitude to deviant stimuli.** Importantly, the magnitude of **the N55 amplitude was negatively correlated with the time of the P30 latency in the difference waveforms**. In contrast, quinpirole administration did not clearly affect the temporal mismatch responses recorded from the auditory cortex. **Conclusion:** These results suggest that the disruption of dopamine D2-like receptor signaling by quinpirole reduces frontal MMN to sound frequency deviations and that delays in early mismatch responses are involved in this MMN impairment.

Activation of D2 autoreceptors alters cocaine-induced locomotion and slows down local field oscillations in the rat ventral tegmental area.

Koulchitsky S, Delairesse C, Beeken T, Monteforte A, Dethier J, Quertemont E, Findeisen R, Bullinger E, Seutin V. Activation of D2 autoreceptors alters cocaine-induced locomotion and slows down local field oscillations in the rat ventral tegmental area. Neuropharmacology. 2016 Sep;108:120-7. doi: 10.1016/j.neuropharm.2016.04.034. Epub 2016 Apr 27. PMID: 27130904.

Psychoactive substances affecting the dopaminergic system induce locomotor activation and, in high doses, stereotypies. Network mechanisms underlying the shift from an active goal-directed behavior to a "seemingly purposeless" stereotypic locomotion remain unclear. In the present study we sought to determine the relationships between the behavioral effects of dopaminergic drugs and their effects on local field potentials (LFPs), which were telemetrically recorded within the ventral tegmental area (VTA) of freely moving rats. We used the D2/D3 agonist quinpirole in a low, autoreceptor-selective (0.1 mg/kg, i.p.) and in a high (0.5 mg/kg, i.p.) dose, and a moderate dose of cocaine (10 mg/kg, i.p.). In the control group, **power spectrum analysis revealed a prominent peak of LFP power in the theta frequency range**

during active exploration. Cocaine alone stimulated locomotion, but had no significant effect on the peak of the LFP power. In contrast, co-administration of low dose quinpirole with cocaine markedly altered the pattern of locomotion, from goal-directed exploratory behavior to recurrent motion resembling locomotor stereotypy. **This behavioral effect was accompanied by a shift of the dominant theta power toward a significantly lower (by ~15%) frequency. High dose quinpirole also provoked an increased locomotor activity with signs of behavioral stereotypies, and also induced a shift of the dominant oscillation frequency toward the lower range.** These results demonstrate a correlation between the LFP oscillation frequency within the VTA and a qualitative aspect of locomotor behavior, perhaps due to a variable level of coherence of this region with its input or output areas.

-----Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)-----

CLASS FACTS

SYNOPSIS: NSAIDs (aspirin, ibuprofen, naproxen, diclofenac, celecoxib) block the production of certain body chemicals that cause inflammation. NSAIDs are good at treating pain caused by slow tissue damage, such as arthritis pain. NSAIDs also work well fighting back pain, menstrual cramps and headaches. Additionally, NSAIDs work like corticosteroids (also called steroids), without many of the side effects of steroids. Steroids are man-made drugs that are similar to cortisone, a naturally occurring hormone. Like cortisone, NSAIDs reduce pain and inflammation that often come with joint and muscle diseases and injuries.

The effect of some immunomodulatory and anti-inflammatory drugs on Li-pilocarpine-induced epileptic disorders in Wistar rats.

Borham, L. E., Mahfoz, A. M., Ibrahim, I. A. ., Shahzad, N., Al-Refai, A. A., Labib, A. A., Bin Sef, B., Alshareef, A., Khan, M., Milibary, A., & Ghamdi, S. A. (2016). *The Effect of Some Immunomodulatory and Anti-Inflammatory Drugs on Li-Pilocarpine-Induced Epileptic Disorders in Wistar Rats*. Brain Research, 1648(Pt A), 418–424. https://doi.org/10.1016/j.brainres.2016.07.046

Evidence shows that inflammatory and immune processes within the brain might account for the pathophysiology of epilepsy. Therefore, developing new antiepileptic drugs that can modulate seizures through mechanisms other than traditional drugs is required for the treatment of refractory epilepsy. This study aims to determine the relationship between brain inflammation and epilepsy, to examine the contribution of some biochemical parameters involved in brain inflammation, and to address the effect of pharmacological interventions using some anti-inflammatory and immunomodulatory drugs in an experimental epilepsy model. Adult male rats were divided into seven groups of 20. G1 was the normal, non-treated control. G2 was the epileptic, non-treated group. G3-G7 were treated with celecoxib, methotrexate, azathioprine, dexamethasone, and valproate, respectively, for a period of three weeks. Induction of status epilepticus (SE) by Li-pilocarpine was performed on groups G2-G7. ***EEG tracing was conducted, and inflammatory mediators (brain and serum IL-1ß, IL 6, PGE2, HSP70, TGF-ß2, and IFNγ) were measured. The induction of SE increased the amplitude and frequency of EEG tracing and inflammatory mediators more than in the normal control group. Treatments of epileptic rats reduced the frequency and amplitude of EEG tracing and significantly decreased the levels of inflammatory mediators in some treated rats compared to G2. These findings demonstrate that some anti-inflammatory and immunomodulatory drugs can lower the frequency and amplitude of seizures and reduce some inflammatory mediators in epilepsy treatments***, strengthening the possibility that targeting these immunological and inflammatory pathways may represent another effective therapeutic approach to preventing epileptic seizures.

Effects of Diclofenac Sodium on Seizure Activity in Rats with Pentylenetetrazole-Induced Convulsions.

Erdogan A, Erdogan MA, Gurgul S, Erbas O. *Effects of Diclofenac Sodium on Seizure Activity in Rats with Pentylenetetrazole-Induced Convulsions*. Neurochem Res. 2023 May;48(5):1412-1423. doi: 10.1007/s11064-022-03838-z. Epub 2022 Dec 6. PMID: 36474102.

Epilepsy is a disease which affects between 1 and 2% of the population, and a large proportion of these people do not react to currently available anticonvulsant medications, indicating the need for further

research into novel pharmacological therapies. Numerous studies have demonstrated that oxidative stress and inflammation occur during epilepsy and may contribute to its development and progression, indicating higher levels of oxidative and inflammatory parameters in experimental models and clinical patients. This research aimed to assess the impact of diclofenac sodium, a nonsteroidal anti-inflammatory medicine, on seizure and levels of oxidative stress and inflammatory biomarkers in a rat model of epilepsy triggered by pentylenetetrazole (PTZ). 60 rats were randomly allocated to one of two groups: electroencephalography (EEG) recordings or behavioral evaluation. Rats received diclofenac sodium at three various doses (25, 50, and 75 mg/kg) intraperitoneally (IP) or a placebo, followed by intraperitoneal (IP) pentylenetetrazole, a powerful seizure-inducing medication. To investigate if diclofenac sodium had antiseizure properties, seizure activity in rats was evaluated using EEG recordings, the Racine convulsion scale (RCS) behaviour score, the duration of the first myoclonic jerk (FMJ), and the levels of MDA, TNF-α, and SOD. ***The average percentage of EEG spike waves decreased from 76.8% (placebo) to 64.1% (25 mg/kg diclofenac), 55.9% (50 mg/kg diclofenac), and 37.8% (75 mg/kg diclofenac*)**. FMJ had increased from a mean of 58.8 s (placebo), to 93.6 s (25 mg/kg diclofenac), 185.8 s (50 mg/kg diclofenac) and 231.7 s (75 mg/kg diclofenac). RCS scores decreased from a mean score of 5.6 (placebo), to 3.75 (25 mg/kg diclofenac), 2.8 (50 mg/kg diclofenac) and 1.75 (75 mg/kg diclofenac). MDA levels reduced from 14.2 ng/gr (placebo) to 9.6 ng/gr (25 mg/kg diclofenac), 8.4 ng/gr (50 mg/kg diclofenac) and 5.1 ng/gr (75 mg/kg diclofenac). Likely, TNF-α levels decreased from 67.9 ng/gr (placebo) to 48.1 ng/gr (25 mg/kg diclofenac), 33.5 ng/gr (50 mg/kg diclofenac) and 21.3 ng/gr (75 mg/kg diclofenac). SOD levels, however, enhanced from 0.048 U/mg (placebo) to 0.055 U/mg (25 mg/kg diclofenac), 0.14 U/mg (50 mg/kg diclofenac), and 0.18 U/mg (75 mg/kg diclofenac). ***Diclofenac sodium (25, 50, and 75 mg/kg i.p.) effectively lowered the spike percentages and RCS scores linked with PTZ-induced epilepsy in rats***, as well as significantly decreased MDA, TNF-α, IL-1β, PGE2 and increased SOD levels. Probably as a result of its anti-oxidative and anti-inflammatory effects, ***diclofenac sodium dramatically lowered seizure activity at both doses compared to placebo control*.** Each of these results were significant, with p-values of < 0.01, < 0.05. Therefore, the therapeutic application diclofenac sodium as a potential anticonvulsant should be investigated further.

Electroencephalographic signatures of pain and analgesia in rats.

LeBlanc, B. W., Bowary, P. M., Chao, Y.-C., Lii, T. R., & Saab, C. Y. (2016). *Electroencephalographic signatures of pain and analgesia in rats*. Pain (Amsterdam), 157(10), 2330–2340. https://doi.org/10.1097/j.pain.0000000000000652.

Pain modulates rhythmic neuronal activity recorded by Electroencephalography (EEG) in humans. Our laboratory previously showed that rat models of acute and neuropathic pain manifest increased power in primary somatosensory cortex (S1) recorded by electrocorticography (ECoG). In this study, we ***hypothesized that pain increases EEG power and corticocortical coherence*** in different rat models of pain, whereas treatments with clinically effective analgesics reverse these changes. Our results show increased cortical power over S1 and prefrontal cortex (PFC) in awake, freely behaving rat models of acute, inflammatory and neuropathic pain. Coherence between PFC and S1 is increased at a late, but not early, time point during the development of neuropathic pain. ***Electroencephalography power is not affected by ibuprofen in the acute pain model. However, pregabalin and mexiletine reverse the changes in power and S1-PFC coherence in the inflammatory and neuropathic pain models. These data suggest that quantitative EEG might be a valuable predictor of pain and analgesia in rodents.***

***Cortical theta is increased while thalamocortical coherence is decreased in rat models of acute and chronic pain*.**

S1 Effects

LeBlanc, B. W., Lii, T. R., Silverman, A. E., Alleyne, R. T., & Saab, C. Y. (2014). *Cortical theta is increased while thalamocortical coherence is decreased in rat models of acute and chronic pain*. Pain (Amsterdam), 155(4), 773–782. https://doi.org/10.1016/j.pain.2014.01.013.

Thalamocortical oscillations are critical for sensory perception. Although pain is known to disrupt synchrony in thalamocortical oscillations, evidence in the literature is controversial. Thalamocortical coherence has been reported to be increased in patients with neurogenic pain but decreased in a rat model of central pain. Moreover, ***theta (4 to 8 Hz) oscillations in primary somatosensory (S1) cortex are speculated to predict pain in humans*.** To date, the link between pain and network oscillations in animal models has been understudied. Thus, we tested the hypothesis that pain disrupts thalamocortical coherence and S1 theta power in two rat models of pain. We ***recorded electrocorticography (ECoG) waveforms over S1 and local field potentials (LFP) within ventral posterolateral thalamus in freely behaving rats under spontaneous (stimulus-independent) pain conditions*.** Rats received intradermal capsaicin injection (Cap) in the hindpaw, followed hours later by chronic constriction injury (CCI) of the sciatic nerve lasting several days. Our ***results show that pain decreases coherence between LFP and ECoG waveforms in the 2- to 30-Hz range, and increases ECoG power in the theta range***. These changes are short-lasting after Cap and longer-lasting after CCI. These data might be particularly relevant to preclinical correlates of spontaneous pain-like behavior, with potential implications to clinical biomarkers of ongoing pain.

Disturbances in slow-wave sleep are induced by models of bilateral inflammation, neuropathic, and postoperative pain, but not osteoarthritic pain in rats.

Leys, L. J., Chu, K. L., Xu, J., Pai, M., Yang, H. S., Robb, H. M., Jarvis, M. F., Radek, R. J., & McGaraughty, S. (2013). *Disturbances in slow-wave sleep are induced by models of bilateral inflammation, neuropathic, and postoperative pain, but not osteoarthritic pain in rats*. Pain (Amsterdam), 154(7), 1092–1102. https://doi.org/10.1016/j.pain.2013.03.019.

Preclinical assessment of pain has typically relied on measuring animal responses to evoked stimulation. Because of inherent limitations of these assays, there is a need to develop measures of animal pain/discomfort that are objective, not experimentally evoked, and mimic the human condition. Patients with chronic pain manifest a variety of co-morbidities, one of which is disturbances in sleep. We used electroencephalography to objectively assess 4 rat models of pain (inflammatory/complete Freund's adjuvant [CFA], neuropathic/chronic constriction injury [CCI], postoperative/skin incision, osteoarthritis/monosodium iodoacetate [MIA]) for the occurrence of sleep disturbances. ***Four different measures of slow-wave sleep (SWS) were examined: amplitude of 1- to 4-Hz waves, total time spent in SWS, time spent in SWS-1, and time spent in SWS-2.*** Bilateral injuries were more likely to induce a sleep disturbance than unilateral injuries in the CFA, CCI, and skin incision assays. ***Sleep disturbances occurred in the deeper stage of SWS, as the amplitude of 1- to 4-Hz waves and time spent in SWS-2 were significantly decreased in all models except the osteoarthritis model.*** Sleep disturbances lasted for approximately 3 to 14days, depending on the model, and were resolved despite continued hypersensitivity to evoked stimulation. Morphine, gabapentin, diclofenac, and ABT-102 (TRPV1 antagonist) all improved sleep in the bilateral CFA assay at doses that did not significantly alter SWS in

uninjured rats. Preclinical assessment of compounds should follow the path of clinical studies and take into account diverse aspects of the "pain condition." This would include evaluating nociceptive thresholds as well as other endpoints, such as cognition and sleep, that may be affected by the pathological state.

Impact of a selective cyclooxygenase-2 inhibitor, celecoxib, on cortical excitability and electrophysiological properties of the brain in healthy volunteers: A randomized, double-blind, placebo-controlled study.

Lim, J.-A., Jung, K.-Y., Park, B., Kim, T.-J., Jun, J.-S., Kim, K. T., Yang, T.-W., Lee, S.-T., Jung, K.-H., Chu, K., Lee, S. K., & Park, K.-I. (2019). *Impact of a selective cyclooxygenase-2 inhibitor, celecoxib, on cortical excitability and electrophysiological properties of the brain in healthy volunteers: A randomized, double-blind, placebo-controlled study*. PLoS ONE, 14(2), e0212689–e0212689. https://doi.org/10.1371/journal.pone.0212689.

The inflammatory response is considered a defence mechanism against physical or infectious insults and is prevalent within the central nervous system. Seizures also result in a robust inflammatory cascade, leading to enhanced activation of excitatory synaptic networks. Ample evidence based on animal models of epilepsy has demonstrated that celecoxib, a highly selective inhibitor of cyclooxygenase-2, has anticonvulsant effects. We aimed to evaluate the impact of celecoxib on the cortical excitability and electrophysiological properties of the brain in healthy humans. ***Electroencephalography (EEG) or transmagnetic stimulation (TMS) was used to measure neurophysiological activity*.** Forty healthy volunteers were randomized to 4 groups (n = 10 in each group): 1) celecoxib and EEG, 2) placebo and EEG, 3) celecoxib and TMS, and 4) placebo and TMS. For the EEG study, resting EEG was performed at baseline just before administering 400 mg of celecoxib or placebo and repeated 4 hours after administration. The subjects took 200 mg of celecoxib or placebo twice a day for 7 subsequent days, and a third EEG was conducted 4 hours after the final dose. Power spectra were compared at each time point. For the TMS study, the resting motor threshold (RMT), motor evoked potential (MEP) peak-to-peak amplitude, and cortical silent period (CSP) were measured at baseline and after taking 200 mg of celecoxib or placebo twice a day for 7 days. ***Celecoxib did not significantly change brain activity in the EEG study. However, the sum of power recorded from all electrodes tended to increase in the celecoxib group only at 4 hours after administration (p = 0.06). In detail, one dose of celecoxib (400 mg) transiently and significantly increased the alpha band power recorded in the frontal and parietal areas as well as in the whole brain (p = 0.049, 0.017, and 0.014, respectively) and the beta frequency in the central and parietal regions (p = 0.013 and 0.005, respectively), whereas the placebo did not.*** *This effect was abolished after 7 days of treatment.* ***In the TMS study, we found no statistically significant change in the RMT, MEP peak-to-peak amplitude or CSP. This evidence suggests that celecoxib transiently alters the electrophysiological properties of the brain but does not suppress neuronal excitability in healthy humans*.**

Poststroke Seizure and Epilepsy: A Review of Incidence, Risk Factors, Diagnosis, Pathophysiology, and Pharmacological Therapies.

Phan, J., Ramos, M., Soares, T., & Parmar, M. S. (2022). *Poststroke Seizure and Epilepsy: A Review of Incidence, Risk Factors, Diagnosis, Pathophysiology, and Pharmacological Therapies*. Oxidative Medicine and Cellular Longevity, 2022, 1–15. https://doi.org/10.1155/2022/7692215.

Stroke is the most common cause of epilepsy and ultimately leads to a decrease in the quality of life of those affected. Ischemic and hemorrhagic strokes can both lead to poststroke epilepsy (PSE). Significant risk factors for PSE include age < 65age less than 65 years, stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS), cortical involvement, and genetic factors such as TRPM6 polymorphism. The diagnosis of PSE is made by using imaging modalities, blood biomarkers, and prognostic criteria. Electroencephalography (EEG) is currently the gold standard to diagnose PSE, while new combinations of modalities are being tested to increase diagnostic specificity. This literature review uncovers a newly found mechanism for the pathology of poststroke epilepsy. The pathogenesis of early-onset and late-onset is characterized by sequelae of neuronal cellular hypoxia and disruption of the blood-brain barrier, respectively. Interleukin-6 is responsible for increasing the activity of glial cells, causing gliosis and hyperexcitability of neurons. Epinephrine, high-mobility group protein B1, downregulation of CD32, and upregulation of HLA-DR impact the pathology of poststroke epilepsy by inhibiting the normal neuronal immune response. Decreased levels of neuropeptide Y, a neurotransmitter, act through multiple unique mechanisms, such as inhibiting intracellular Ca^{2+} accumulation and acting as an anti-inflammatory, also implemented in the worsening progression of poststroke epilepsy. Additionally, CA1 hippocampal ***resonant neurons that increase theta oscillation are associated with poststroke epilepsy*.** Hypertensive small vessel disease may also have an implication in the temporal lobe epilepsy by causing occult microinfarctions. Furthermore, this review highlights the potential use of statins as primary prophylaxis against PSE, with multiple studies demonstrating a reduction in incidence using statins alone, statins in combination with antiepileptic drugs (AEDs), and statins with ***aspirin***. The evidence strongly suggests that the second generation AEDs are a superior treatment method for PSE. Data from numerous studies demonstrate their relative lack of significant drug interactions, increased tolerability, and potential superiority in maintaining seizure-free status.

Paroxysmal vascular events in Sturge-Weber syndrome: Role of aspirin.

Sanghvi, J., Mehta, S., & Mulye, S. (2014). *Paroxysmal vascular events in Sturge– Weber syndrome: Role of aspirin*. Journal of Pediatric Neurosciences, 9(1), 39–41. https://doi.org/10.4103/1817-1745.131483.

Sturge-Weber syndrome (SWS) is a rare, sporadically occurring neurocutaneous disorder with a frequency of approximately 1 per 50,000. The hallmark is an intracranial leptomeningeal vascular angioma in association with a port wine nevus, usually involving ophthalmic or maxillary distribution of trigeminal nerve. Other clinical findings associated with SWS are seizures, glaucoma, hemiparesis and mental retardation. ***The radiological hallmark is "Tram-line" or "Gyri-form" calcification. 25 to 56% of patients experience recurrent episodes of paroxysmal focal neurological deficits in form of transient hemiparesis, which may be due to vascular ischemia or postictal in origin. EEG helps to differentiate the exact etiology, as it is normal in former*.** Aspirin prophylaxis in those, due to ischemia decreases their recurrences and improves overall neurological prognosis. We report a 25-month-old child of SWS with recurrent episodes of transient hemiparesis and atypical midline location of facial vascular nevus.

Investigation of the predictive validity of laser-EPs in normal, UVB-inflamed and capsaicin-irritated skin with four analgesic compounds in healthy volunteers.

Schaffler, K., Nicolas, L. B., Borta, A., Brand, T., Reitmeir, P., Roebling, R., & Scholpp, J. (2017). *Investigation of the predictive validity of laser-EPs in normal, UVB-inflamed and capsaicin-irritated skin with four analgesic compounds in healthy volunteers: Predictivity of efficacy of four*

analgesics in normal, UVB-inflamed and capsaicin-irritated skin. British Journal of Clinical Pharmacology, 83(7), 1424–1435. https://doi.org/10.1111/bcp.13247.

Aims: The aim of the present study was to assess the predictivity of laser-(radiant-heat)-evoked potentials (LEPs) from the vertex electroencephalogram, using an algesimetric procedure, testing the anti-nociceptive/anti-hyperalgesic effects of single oral doses of four marketed analgesics (of different compound classes) vs. placebo, in healthy volunteers with three skin types. **Methods:** This was a randomized, placebo-controlled, single-blind, five-way-crossover trial. Twenty-five healthy male/female Caucasians were included (receiving celecoxib 200 mg, pregabalin 150 mg, duloxetine 60 mg, lacosamide 100 mg or placebo) in a Williams design, with CO2 laser-induced painful stimuli to normal, ultraviolet (UV) B-inflamed and capsaicin-irritated skin. LEPs and visual analogue scale ratings were taken at baseline and hourly for 6 h postdose from all three skin types. **Results:** In normal skin***, the averaged postdose LEP peak-to-peak-(PtP)-amplitudes were reduced by pregabalin*** (-2.68 μV; 95% confidence interval (CI) -4.16, 1.19) and duloxetine (-1.73 μV; 95% CI -3.21, -0.26) ***but not by lacosamide and celecoxib vs. placebo.*** On UVB-irradiated skin, reflecting inflammatory pain**, *celecoxib induced a pronounced reduction in LEP PtP amplitudes vs. placebo (-6.2 μV; 95% CI -7.88, -4.51),*** with a smaller reduction by duloxetine (-4.54 μV; 95% CI -6.21, -2.87) and pregabalin (-3.72 μV; 95% CI -5.40, -2.04), whereas lacosamide was inactive. ***LEP PtP amplitudes on capsaicin-irritated skin, reflecting peripheral/spinal sensitization, as in neuropathic pain, were reduced*** by pregabalin (-3.78 μV; 95% CI -5.31, -2.25) and duloxetine (-2.32 μV; 95% CI -3.82, -0.82) ***but not by celecoxib*** or lacosamide vs. placebo, which was in agreement with known clinical profiles. Overall, PtP amplitude reductions were in agreement with subjective ratings. **Conclusions:** LEP algesimetry is sensitive to analgesics with different modes of action and may enable the effects of novel analgesics to be assessed during early clinical development.

----- OPIATES -----

DRUG FACTS

SYNOPSIS: Drugs that come from the poppy plant.

----- MORPHINE (Arymo, Avinza, Kadian, Morphabond) -----

DRUG FACTS

SYNOPSIS: Prescribed to relieve moderate to severe pain.

Decrease in the relative theta (4-7.5 Hz) activity

Brokjær, A., Olesen, A. E., Kreilgaard, M., Graversen, C., Gram, M., Christrup, L. L., Dahan, A., & Drewes, A. M. (2015). *Objective markers of the analgesic response to morphine in experimental pain research*. Journal of pharmacological and toxicological methods, 73, 7–14. https://doi.org/10.1016/j.vascn.2015.01.005

Morphine increased tolerance to muscle pain, together with significant reductions in pupil diameter and increase in prolactin concentration (all $P < 0.001$). Miosis was induced simultaneously with the onset of analgesic effect 30 min after dosing, while a significant increase in prolactin concentration was seen after 45 min. The change in pupil diameter was negatively correlated to change in tolerated muscle pressure ($r = -0.40$, $P < 0.001$), whereas the increase in prolactin concentration was positively correlated ($r = 0.32$, $P = 0.001$). ***The effect of morphine on EEG was seen as a decrease in the relative theta (4-7.5 Hz) activity*** ($P = 0.03$), but was not significant until 120 min after dosing and did not correlate to the increase in tolerated muscle pressure ($r = -0.1$, $P=0.43$).

Reduced pain-induced activation in the right insula, anterior cingulate cortex and inferior parietal cortex.

Hansen, T. M., Olesen, A. E., Graversen, C., Drewes, A. M., & Frøkjaer, J. B. (2015). *The Effect of Oral Morphine on Pain-Related Brain Activation - An Experimental Functional Magnetic Resonance Imaging Study*. Basic & clinical pharmacology & toxicology, 117(5), 316–322. https://doi.org/10.1111/bcpt.12415

Knowledge about cerebral mechanisms underlying pain perception and effect of analgesic drugs is important for developing methods for diagnosis and treatment of pain. The aim was to explore altered brain activation before and after morphine treatment using functional magnetic resonance imaging recorded during experimental painful heat stimulation. Functional magnetic resonance imaging data were recorded and analysed in 20 healthy volunteers (13 men and 7 women, 24.9 ± 2.6 years) in a randomized, double-blind, placebo-controlled, cross-over study. Painful stimulations were applied to the right forearm using a contact heat evoked potential stimulator (CHEPS) before and after treatment with 30 mg oral morphine and placebo. CHEPS stimulations before treatment induced activation in the anterior cingulate cortex, secondary somatosensory cortex/insula, thalamus and cerebellum ($n = 16$, $p < 0.05$). In response to morphine treatment, the spatial extent of these pain-specific areas decreased ($n = 20$). ***Reduced***

pain-induced activation was seen in the right insula, anterior cingulate cortex and inferior parietal cortex after morphine treatment compared to before treatment (n = 16, p < 0.05), and sensory ratings of pain perception were significantly reduced after morphine treatment (p = 0.02). No effect on pain-induced brain activation was seen after placebo treatment compared to before treatment (n = 12, p > 0.05). In conclusion, heat stimulation activated areas in the 'pain matrix' and a clinically relevant dose of orally administered morphine revealed significant changes in brain areas where opioidergic pathways are predominant. The method may be useful to investigate the mechanisms of analgesics.

Reduced high-frequency β1 (13.5 to 20 Hz) and β2 (20 to 30Hz) electroencephalogram powers and decreased coherence between frontal and occipital β2 electroencephalogram activities

Montandon, G., Cushing, S. L., Campbell, F., Propst, E. J., Horner, R. L., & Narang, I. (2016). *Distinct Cortical Signatures Associated with Sedation and Respiratory Rate Depression by Morphine in a Pediatric Population*. Anesthesiology, 125(5), 889–903. https://doi.org/10.1097/ALN.0000000000001303

Opioid analgesia is an essential component of perioperative care, but effective analgesia can be limited by excessive sedation and respiratory depression. The cortical signatures associated with sedation by opioids and the relationship between changes in cortical activity and respiratory function are not well understood. The objectives of this study were to identify the electroencephalogram signatures of sedation and respiratory changes induced by morphine in a pediatric population after elective surgery. After otologic surgery, patients (14.8 ± 2.8 yr, n = 10) stayed overnight for pain relief with morphine (3 to 10 mg), hydration, and clinical observation. Electroencephalogram activity and polysomnography were performed before and after morphine, and electroencephalogram spectral properties and cardiorespiratory activities were analyzed. Compared to wakefulness and non-rapid eye movement sleep, ***morphine reduced high-frequency β1 (13.5 to 20 Hz) and β2 (20 to 30Hz) electroencephalogram powers (n = 10) and decreased coherence between frontal and occipital β2 electroencephalogram activities (n = 9), therefore indicating that morphine induced a deep sedative state***. Morphine also reduced respiratory rate by 8.3% (n = 10). Interestingly, there was a significant correlation between the reduction in β1 electroencephalogram activity and the depression in respiratory rate induced by morphine (R = 0.715, n = 10). ***With significant reduction in β1 power, respiratory rate was decreased by more than 25%***, suggesting that reduction in cortical arousal is associated with the severity of respiratory rate depression. Analgesic doses of morphine are associated with reduction in respiratory rate when accompanied by reduction in β1 electroencephalogram power, indicating a powerful effect of cortical arousal state per se in respiratory rate depression by morphine.

aEEG/EEG depression with more discontinuous background and less developed cyclicity and interburst intervals (IBI) were significantly increased.

Norman, E., Wikström, S., Rosén, I., Fellman, V., & Hellström-Westas, L. (2013). *Premedication for intubation with morphine causes prolonged depression of electrocortical background activity in preterm infants*. Pediatric research, 73(1), 87–94. https://doi.org/10.1038/pr.2012.153

Sedative and analgesic medications are used in critically ill newborns, but little is known about their effects on electrocortical activity in preterm infants. We hypothesized that morphine might induce prolonged neurodepression, independent of blood pressure, as compared with rapid sequence induction/intubation(RSI). Of 34 infants enrolled in a randomized controlled trial (RCT) comparing RSI (including thiopental 2-3 mg/kg and remifentantil 1 mcg/kg) with morphine (0.3 mg/kg) as premedication for intubation, 28 infants (n = 14 + 14; median gestational age 26.1 wk and postnatal age 138 h) had continuous two-channel amplitude-integrated electroencephalogram (aEEG/EEG) and blood pressure monitoring during 24 h after the intubation. Thirteen infants not receiving any additional medication constituted the primary study group. Visual and quantitative analyses of aEEG/EEG and blood pressure were performed in 3-h epochs. RSI was associated with aEEG/EEG depression lasting <3 h. ***Morphine premedication resulted in aEEG/EEG depression with more discontinuous background and less developed cyclicity for 24 h, and during the first 9 h, interburst intervals (IBI) were significantly increased as compared with those of RSI treatment.*** The difference was not related to blood pressure. Premedication with morphine is associated with prolonged aEEG/EEG depression independent of blood pressure changes and may not be optimal for short procedures.

Eliminated NREM sleep and REM sleep

O'Brien, C. B., Locklear, C. E., Glovak, Z. T., Zebadúa Unzaga, D., Baghdoyan, H. A., & Lydic, R. (2021). *Opioids cause dissociated states of consciousness in C57BL/6J mice*. Journal of neurophysiology, 126(4), 1265–1275. https://doi.org/10.1152/jn.00266.2021

The electroencephalogram (EEG) provides an objective, neural correlate of consciousness. Opioid receptors modulate mammalian neuronal excitability, and this fact was used to characterize how opioids administered to mice alter EEG power and states of consciousness. The present study tested the hypothesis that antinociceptive doses of fentanyl, morphine, or buprenorphine differentially alter the EEG and states of sleep and wakefulness in adult, male C57BL/6J mice. Mice were anesthetized and implanted with telemeters that enabled wireless recordings of cortical EEG and electromyogram (EMG). After surgical recovery, EEG and EMG were used to objectively score states of consciousness as wakefulness, rapid eye movement (REM) sleep, or non-REM (NREM) sleep. Measures of EEG power (dB) were quantified as δ (0.5-4 Hz), θ (4-8 Hz), α (8-13 Hz), σ (12-15 Hz), β (13-30 Hz), and γ (30-60 Hz). Compared with saline (control), fentanyl and morphine decreased NREM sleep, morphine eliminated REM sleep, and ***buprenorphine eliminated NREM sleep and REM sleep***. Opioids significantly and differentially disrupted the temporal organization of sleep/wake states, altered specific EEG frequency bands, and caused dissociated states of consciousness. The results are discussed relative to the fact that opioids, pain, and sleep modulate interacting states of consciousness. NEW & NOTEWORTHY ***This study discovered that antinociceptive doses of fentanyl, morphine, and buprenorphine significantly and differentially disrupt EEG-defined states of consciousness in C57BL/6J mice***. These data are noteworthy because: 1) buprenorphine is commonly used in medication-assisted therapy for opioid addiction, and 2) there is evidence that disordered sleep can promote addiction relapse. The results contribute to community phenotyping efforts by making publicly available all descriptive and inferential statistics from this study.

Lower delta/alpha ratio; significantly more active/unstable EEG .

Rowsell, L., Wu, J. G., Yee, B. J., Wong, K. K. H., Sivam, S., Somogyi, A. A., Grunstein, R. R., & Wang, D. (2021). *The effect of acute morphine on sleep in male patients suffering from sleep apnea: Is there a genetic effect? An RCT Study*. Journal of Sleep Research, 30(4), e13249–n/a. https://doi.org/10.1111/jsr.13249

Questionnaire-based studies have suggested genetic differences in sleep symptoms in chronic opioid users. The present study aims to investigate if there is a genetic effect on sleep architecture and quantitative electroencephalogram (EEG) in response to acute morphine. Under a randomized, double-blind, placebo-controlled, crossover design, 68 men with obstructive sleep apnea undertook two overnight polysomnographic studies conducted at least 1 week apart. Each night they received either 40 mg of controlled-release morphine or placebo. Sleep architecture and quantitative EEG were compared between conditions. Blood was sampled before sleep and on the next morning for genotyping and pharmacokinetic analyses. We analysed three candidate genes (OPRM1 [rs1799971, 118 A > G], ABCB1[rs1045642, 3435 C > T] and HTR3B [rs7103572 C > T]). We found that morphine decreased slow wave sleep and rapid eye movement sleep and increased stage 2 sleep. Those effects were less in subjects with HTR3B CT/TT than in those with CC genotype. Similarly, sleep onset latency was shortened in the ABCB1 CC subgroup compared with the CT/TT subgroup. Total sleep time was significantly increased in ABCB1 CC but not in CT/TT subjects. Sleep apnea and plasma morphine and metabolite concentration were not confounding factors for these genetic differences in sleep. ***With morphine, patients had significantly more active/unstable EEG (lower delta/alpha ratio) during sleep***.

No genetic effects on quantitative EEG were detected. In summary, we identified two genes (HTR3B and ABCB1) with significant variation in the sleep architecture response to morphine. Morphine caused a more active/unstable EEG during sleep. Our findings may have relevance for a personalized medicine approach to targeted morphine therapy.

----- OPIODS -----

DRUG FACTS

SYNOPSIS: Synthetic pain reliever.

Spectral EEGs showed greater amplitude density in β1, β2, and β3 frequencies across frontal, temporal-central and posterior areas and abnormal amplitude density increases in delta.

Corace, K., Baysarowich, R., Willows, M., Baddeley, A., Schubert, N., & Knott, V. (2022). *Resting State EEG Activity Related to Impulsivity in People with Prescription Opioid Use Disorder*. Psychiatry research. Neuroimaging, 321, 111447. https://doi.org/10.1016/j.pscychresns.2022.111447

Previous studies on EEG activity in prescription opioid use disorder (OUD) have reported neuronal dysfunction related to heroin use, most consistently reflected by increases in β-brain oscillations. As similar research has yet to examine EEG associated with non-medical use of prescription opioid and as inhibitory deficits are associated with OUD, this pilot study compared

quantitative EEGs of 18 patients with prescription OUD and 18 healthy volunteers and assessed relationships between oscillatory activity and impulsivity with the Barratt Impulsiveness Scale (BIS-11). ***Spectral EEGs showed greater amplitude density in β1, β2, and β3 frequencies across frontal, temporal-central and posterior recording areas in patients. Similar abnormal amplitude density increases were seen in δ but not in ϑ or α frequency bands***. Patients exhibited greater scores (impaired impulse control) on BIS-11 subscales (attention, motor, self-control) ***and impairment of these impulsive subtypes was associated with increases in β and δ oscillations***. In patients, β1, β2, and δ activity was positively associated with disorder severity. Taken together, the results suggest that altered brain oscillations in persons with prescription OUD show some similarities with reported oscillatory changes in heroin use and may indicate a chronic state of imbalance in neuronal networks regulating impulsive and inhibitory control systems.

Enhanced beta and alpha power activity, and high impulsivity

Ieong, H. F., & Yuan, Z. (2017). *Resting-State Neuroimaging and Neuropsychological Findings in Opioid Use Disorder during Abstinence: A Review*. Frontiers in human neuroscience, 11, 169. https://doi.org/10.3389/fnhum.2017.00169

Dependence to opiates, including illicit heroin and prescription pain killers, and treatment of the opioid use disorder (OUD) have been longstanding problems over the world. Despite intense efforts to scientific investigation and public health care, treatment outcomes have not significantly improved for the past 50 years. One reason behind the continuing use of heroin worldwide despite such efforts is its highly addictive nature. Brain imaging studies over the past two decades have made significant contribution to the understanding of the addictive properties as to be due in part to biological processes, specifically those in the brain structure and function. Moreover, traditional clinical neuropsychology studies also contribute to the account in part for the treatment-refractory nature of the drug abuse. However, there is a gap between those studies, and the rates of relapse are still high. Thus, a multidisciplinary approach is needed to understand the fundamental neural mechanism of OUD. How does the brain of an OUD patient functionally and cognitively differ from others? This brief review is to compare and contrast the current literature on non-invasive resting state neuroimaging and clinical neuropsychological studies with the focus on the abstinence stage in OUD. The results show as follow: Brain connectivity strength in the reward system, dysregulation of circuits associated with emotion and stress, ***enhanced beta and alpha power activity, and high impulsivity are induced by OUD***. Some recovery signs in cognition are demonstrated in OUD subjects after prolonged abstinence, but not in the subjects undergoing methadone treatment. Normalization in the composition of brain oscillations especially in the temporal region is induced and restored by methadone treatment in roughly 6 months in mean duration for OUDs having a mean opioid-use history of 10 years. We hope that the review provides valuable implications for clinical research and practice and paves a new insight into the future path to the identification of potential biomarkers and clinical outcome predictors in OUD in the domains of brain regions, functions, and behaviors.

Increased activity in delta bands (and higher bands) and decreased activity in evoked potentials.

Malver, L. P., Brokjær, A., Staahl, C., Graversen, C., Andresen, T., & Drewes, A. M. (2014). *Electroencephalography and analgesics.* British Journal of Clinical Pharmacology, 77(1), 72–95. https://doi.org/10.1111/bcp.12137

To assess centrally mediated analgesic mechanisms in clinical trials with pain patients, objective standardized methods such as electroencephalography (EEG) has many advantages. The aim of this review is to provide the reader with an overview of present findings in analgesics assessed with spontaneous EEG and evoked brain potentials (EPs) in humans. Furthermore, EEG methodologies will be discussed with respect to translation from animals to humans and future perspectives in predicting analgesic efficacy. We searched PubMed with MeSH terms 'analgesics', 'electroencephalography' and 'evoked potentials' for relevant articles. Combined with a search in their reference lists 15 articles on spontaneous EEG and 55 papers on EPs were identified. ***Overall, opioids produced increased activity in the delta band in the spontaneous EEG, but increases in higher frequency bands were also seen. The EP amplitudes decreased in the majority of studies***. Anticonvulsants used as analgesics showed inconsistent results. The N-methyl-D-aspartate receptor antagonist ketamine showed an increase in the theta band in spontaneous EEG and decreases in EP amplitudes. Tricyclic antidepressants increased the activity in the delta, theta and beta bands in the spontaneous EEG while EPs were inconsistently affected. Weak analgesics were mainly investigated with EPs and a decrease in amplitudes was generally observed. This review reveals that both spontaneous EEG and EPs are widely used as biomarkers for analgesic drug effects. Methodological differences are common and a more uniform approach will further enhance the value of such biomarkers for drug development and prediction of treatment response in individual patients.

----- BUPRENORPHINE (Belbuca) -----

DRUG FACTS

SYNOPSIS: Prescribed to relieve severe pain.

Increases in the theta, alpha and beta bands.

Gram, M., Graversen, C., Nielsen, A. K., Arendt-Nielsen, T., Mørch, C. D., Andresen, T., & Drewes, A. M. (2013). *A novel approach to pharmaco-EEG for investigating analgesics: assessment of spectral indices in single-sweep evoked brain potentials*. British journal of clinical pharmacology, 76(6), 951–963. https://doi.org/10.1111/bcp.12120

Aims: To compare results from analysis of averaged and single-sweep evoked brain potentials (EPs) by visual inspection and spectral analysis in order to identify an objective measure for the analgesic effect of buprenorphine and fentanyl. Methods: Twenty-two healthy males were included in a randomized study to assess the changes in EPs after 110 sweeps of painful electrical stimulation to the median nerve following treatment with buprenorphine, fentanyl or placebo patches. Bone pressure, cutaneous heat and electrical pain ratings were assessed. EPs and pain assessments were obtained before drug administration, 24, 48, 72 and 144 h after beginning of treatment. Features from EPs were extracted by three different approaches: (i) visual inspection of amplitude and latency of the main peaks in the average EPs, (ii) spectral distribution of the average EPs and (iii) spectral distribution of the EPs from single-sweeps. Results: Visual inspection revealed no difference between active treatments and placebo (all P

> 0.05). Spectral distribution of the averaged potentials showed a decrease in the beta (12-32 Hz) band for fentanyl (P = 0.036), which however did not correlate with pain ratings. ***Spectral distribution in the single-sweep EPs revealed significant increases in the theta, alpha and beta bands for buprenorphine (all P < 0.05) as well as theta band increase for fentanyl (P = 0.05)***. For buprenorphine, beta band activity correlated with bone pressure and cutaneous heat pain (both P = 0.04, r = 0.90). Conclusion: In conclusion single-sweep spectral band analysis increases the information on the response.

Longer latencies of the ERP components

Markovska-Simoska, S., Ignjatova, L., Trenchevska, G. K., & Pop-Jordanova, N. (2021). *The neurophysiological correlates of cognitive functions during methadone and buprenorphine maintenance treatment: The ERP study*. Heroin Addiction and Related Clinical Problems.

The treatment of opioid dependence with methadone and buprenorphine is equally effective with either of the two drugs, in terms of discontinuation and retention in treatment. Buprenorphine, unlike methadone, is, however, renowned for being a drug that gives a "clear head", which is encouraging for those who are students, or who are, in any case, engaged in intellectual work. Aim. The aim of this study has been to determine if there is a difference in the neurophysiological correlates of cognitive functions in individuals treated with methadone (MMT) versus those treated with buprenorphine (BMT). Methods. The study includes 10 participants belonging to the MMT group and 10 others involved in the BMT group; both these study groups were compared with the control group after matching had been carried out for age and gender. Brain activity was recorded with the QEEG Mitsar system while study participants were performing two neuropsychological tasks. The VCPT and ECPT as modifications of the Go/NoGo paradigm were applied in order to obtain cognitive event-related potentials (ERPs) as indexes of executive functions. Besides the behavioural parameters of test performance, amplitude and latency of CNV, Cue P3, P3 Go, P3NoGo, N2Go and N2 NoGo were explored at Fz, Cz and Pz, reflecting different stages of information processing. ***The MMT group showed longer latencies of the ERP components***, and the BMT participants showed slightly better results than those of the MMT group. Still, most of the parameters did not differ significantly from those of the control group. Behavioural parameters showed significantly higher values for variables in the results for reaction time and the number of errors of omission and commission found in the competing MMT vs BMT groups, as well as the control group. Conclusions. Neurophysiological evidence suggests that methadone and buprenorphine both have positive effects on neurophysiological functions, as fewer abnormalities were found in MMT or BMT patients than in healthy controls. It has been shown that the sensitivity and specificity of detecting drug effects increase significantly when adding neurophysiological measures to task performance.

Eliminated NREM sleep and REM sleep

O'Brien, C. B., Locklear, C. E., Glovak, Z. T., Zebadúa Unzaga, D., Baghdoyan, H. A., & Lydic, R. (2021). *Opioids cause dissociated states of consciousness in C57BL/6J mice*. Journal of neurophysiology, 126(4), 1265–1275. https://doi.org/10.1152/jn.00266.2021

The electroencephalogram (EEG) provides an objective, neural correlate of consciousness. Opioid receptors modulate mammalian neuronal excitability, and this fact was used to characterize how opioids administered to mice alter EEG power and states of consciousness. The present study tested the hypothesis that antinociceptive doses of fentanyl, morphine, or buprenorphine differentially alter the EEG and states of sleep and wakefulness in adult, male C57BL/6J mice. Mice were anesthetized and implanted with telemeters that enabled wireless recordings of cortical EEG and electromyogram (EMG). After surgical recovery, EEG and EMG were used to objectively score states of consciousness as wakefulness, rapid eye movement (REM) sleep, or non-REM (NREM) sleep. Measures of EEG power (dB) were quantified as δ (0.5-4 Hz), θ (4-8 Hz), α (8-13 Hz), σ (12-15 Hz), β (13-30 Hz), and γ (30-60 Hz). Compared with saline (control), fentanyl and morphine decreased NREM sleep, morphine eliminated REM sleep, and ***buprenorphine eliminated NREM sleep and REM sleep***. Opioids significantly and differentially disrupted the temporal organization of sleep/wake states, altered specific EEG frequency bands, and caused dissociated states of consciousness. The results are discussed relative to the fact that opioids, pain, and sleep modulate interacting states of consciousness. NEW & NOTEWORTHY ***This study discovered that antinociceptive doses of fentanyl, morphine, and buprenorphine significantly and differentially disrupt EEG-defined states of consciousness in C57BL/6J mice***. These data are noteworthy because: 1) buprenorphine is commonly used in medication-assisted therapy for opioid addiction, and 2) there is evidence that disordered sleep can promote addiction relapse. The results contribute to community phenotyping efforts by making publicly available all descriptive and inferential statistics from this study.

----- FENTANYL -----

DRUG FACTS

SYNOPSIS: Prescribed to treat breakthrough pain in cancer patients tolerant to narcotic pain medications.

Induces a frontal theta band (4 to 8 Hz) signature distinct from slow-delta oscillations related to sleep and sedation

Balanza, G. A., Bharadwaj, K. M., Mullen, A. C., Beck, A. M., Work, E. C., McGovern, F. J., Houle, T. T., Eric, T. P., & Purdon, P. L. (2022). *An electroencephalogram biomarker of fentanyl drug effects.* PNAS nexus, 1(4), pgac158. https://doi.org/10.1093/pnasnexus/pgac158

Opioid drugs influence multiple brain circuits in parallel to produce analgesia as well as side effects, including respiratory depression. At present, we do not have real-time clinical biomarkers of these brain effects. Here, we describe the results of an experiment to characterize the electroencephalographic signatures of fentanyl in humans. We find that increasing concentrations ***of fentanyl induce a frontal theta band (4 to 8 Hz) signature distinct from slow-delta oscillations related to sleep and sedation***. We also report that respiratory depression, quantified by decline in an index of instantaneous minute ventilation, occurs at ≈1700-fold lower concentrations than those that produce sedation as measured by reaction time. The electroencephalogram biomarker we describe could facilitate real-time monitoring of opioid drug effects and enable more precise and personalized opioid administration.

Decrease in EEG features in the alpha band

García, P. S., Kreuzer, M., Hight, D., & Sleigh, J. W. (2021). *Effects of noxious stimulation on the electroencephalogram during general anaesthesia: a narrative review and approach to analgesic titration.* British journal of anaesthesia, 126(2), 445–457. https://doi.org/10.1016/j.bja.2020.10.036.

The development of a steady-state alpha oscillation during general anaesthesia is primarily driven by hypnotic drugs interacting with underlying patient factors. For volatile anaesthetics, the alpha power is typically maximal in the moderate dose range, with diminished alpha power observed at both lower concentrations (<0.5 MAC) and at higher concentrations (where the EEG might be dominated by delta activity, discontinuities, or both). A sudden episodic loss of frontal alpha power is a relatively common response to noxious stimulation. Opioids can prevent or recover an alpha dropout.These observations have given rise to the concept that (frontal) maximal alpha power is a reasonable biomarker for the titration of intraoperative opioids. Hagihira and colleagues looked at the effect of abdominal surgery in patients anaesthetised with isoflurane or sevoflurane (0.7e0.8 MAC). They gave a bolus of fentanyl either 5 min before incision (looking at EEG at incision and 5 min after) or 5 min after incision (and looked at EEG 5 and 10 min after incision). They observed ***a decrease in EEG features in the alpha band*** after incision, which then recovered with subsequent fentanyl administration; in contrast, if fentanyl was given before incision to provide sufficient analgesia, the prominent alpha oscillatory activity did not decrease with incision. Mackay and colleagues looked at pre-vs post-stimulus changes in alpha power and burst suppression in response to two stimuli (intubation and incision) with three levels of fentanyl. Loss of alpha power was more pronounced in the low opioid (1 mg kg1) group. These studies highlight the capability of adequate analgesia management to prevent the stimulus induced decrease in EEG alpha power and hence possibly prevent pain triggered arousal events.

Decrease beta and increase in evoked potentials in theta band.

Gram, M., Graversen, C., Nielsen, A. K., Arendt-Nielsen, T., Mørch, C. D., Andresen, T., & Drewes, A. M. (2013). *A novel approach to pharmaco-EEG for investigating analgesics: assessment of spectral indices in single-sweep evoked brain potentials*. British journal of clinical pharmacology, 76(6), 951–963. https://doi.org/10.1111/bcp.12120

Aims: To compare results from analysis of averaged and single-sweep evoked brain potentials (EPs) by visual inspection and spectral analysis in order to identify an objective measure for the analgesic effect of buprenorphine and fentanyl. Methods: Twenty-two healthy males were included in a randomized study to assess the changes in EPs after 110 sweeps of painful electrical stimulation to the median nerve following treatment with buprenorphine, fentanyl or placebo patches. Bone pressure, cutaneous heat and electrical pain ratings were assessed. EPs and pain assessments were obtained before drug administration, 24, 48, 72 and 144 h after beginning of treatment. Features from EPs were extracted by three different approaches: (i) visual inspection of amplitude and latency of the main peaks in the average EPs, (ii) spectral distribution of the average EPs and (iii) spectral distribution of the EPs from single-sweeps. Results: Visual inspection revealed no difference between active treatments and placebo (all P > 0.05). ***Spectral distribution of the averaged potentials showed a decrease in the beta (12-32 Hz) band for fentanyl (P = 0.036), which however did not correlate with pain ratings. Spectral***

distribution in the single-sweep EPs revealed significant increases in the theta, alpha and beta bands for buprenorphine (all P < 0.05) as well as theta band increase for fentanyl (P = 0.05). For buprenorphine, beta band activity correlated with bone pressure and cutaneous heat pain (both P = 0.04, r = 0.90). Conclusion: In conclusion single-sweep spectral band analysis increases the information on the response of the brain to opioids and may be used to identify the response to analgesics.

Increased delta (1-3 Hz) frequency power but reduced alpha (7.5-13.5 Hz) and beta2 (20-30 Hz) powers

Montandon, G., & Horner, R. L. (2019). *Electrocortical changes associating sedation and respiratory depression by the opioid analgesic fentanyl.* Scientific reports, 9(1), 14122. https://doi.org/10.1038/s41598-019-50613-2

Opioid drugs are the mainstay of pain management but present the side-effect of respiratory depression that can be lethal with overdose. In addition to their respiratory effect, opioids also induce a profound sedative state and produce electrocortical features characteristic of a state of reduced brain arousal, similar to anaesthesia or sleep. In such states, respiratory activity depends more on the integrity of the brainstem respiratory network than it does during wakefulness. Accordingly, we propose that sedation by fentanyl induces specific electrocortical changes consistent with reduced brain arousal, and that the magnitude of respiratory depression is associated with distinct electrocortical changes. To these aims, we determined the effects of systemic injections of fentanyl (dosage 100 μg ·kg) versus control on electrocortical and respiratory activities of freely-behaving rats. We found that fentanyl induced electrocortical changes that differed from those observed in sleep or wakefulness. ***Fentanyl increased δ (1-3 Hz) frequency power (P < 0.001), but reduced α (7.5-13.5 Hz) and β2 (20-30 Hz) powers*** (P = 0.012 and P < 0.001, respectively), when compared to wakefulness. Interestingly, respiratory rate depression by fentanyl was significantly correlated with increased θ power (R = 0.61, P < 0.001), therefore showing a clear association between electrocortical activity and the magnitude of respiratory rate depression. Overall, we provide new evidence linking specific electrocortical changes to the severity of respiratory depression by opioids, which highlights the importance of considering the cortical and subcortical effects of opioids in addition to their impacts on breathing when evaluating opioid-induced respiratory depression.

Eliminated NREM sleep and REM sleep

O'Brien, C. B., Locklear, C. E., Glovak, Z. T., Zebadúa Unzaga, D., Baghdoyan, H. A., & Lydic, R. (2021). *Opioids cause dissociated states of consciousness in C57BL/6J mice*. Journal of neurophysiology, 126(4), 1265–1275. https://doi.org/10.1152/jn.00266.2021

The electroencephalogram (EEG) provides an objective, neural correlate of consciousness. Opioid receptors modulate mammalian neuronal excitability, and this fact was used to characterize how opioids administered to mice alter EEG power and states of consciousness. The present study tested the hypothesis that antinociceptive doses of fentanyl, morphine, or buprenorphine differentially alter the EEG and states of sleep and wakefulness in adult, male C57BL/6J mice. Mice were anesthetized and implanted with telemeters that enabled wireless recordings of cortical EEG and electromyogram (EMG). After surgical recovery, EEG and EMG were used to objectively score states of consciousness as wakefulness, rapid eye movement

(REM) sleep, or non-REM (NREM) sleep. Measures of EEG power (dB) were quantified as δ (0.5-4 Hz), θ (4-8 Hz), α (8-13 Hz), σ (12-15 Hz), β (13-30 Hz), and γ (30-60 Hz). Compared with saline (control), fentanyl and morphine decreased NREM sleep, morphine eliminated REM sleep, and ***buprenorphine eliminated NREM sleep and REM sleep***. Opioids significantly and differentially disrupted the temporal organization of sleep/wake states, altered specific EEG frequency bands, and caused dissociated states of consciousness. The results are discussed relative to the fact that opioids, pain, and sleep modulate interacting states of consciousness. NEW & NOTEWORTHY ***This study discovered that antinociceptive doses of fentanyl, morphine, and buprenorphine significantly and differentially disrupt EEG-defined states of consciousness in C57BL/6J mice***. These data are noteworthy because: 1) buprenorphine is commonly used in medication-assisted therapy for opioid addiction, and 2) there is evidence that disordered sleep can promote addiction relapse. The results contribute to community phenotyping efforts by making publicly available all descriptive and inferential statistics from this study.

----- HEROIN -----

DRUG FACTS

SYNOPSIS: Highly addictive illicit drug with affect in the high alpha, low beta frequency bands.

Weaker parietal regions and stronger functional connectivity were found left occipital regions.

Liu, Y., Chen, Y., Fraga-González, G., Szpak, V., Laverman, J., Wiers, R. ., & Ridderinkhof, K. . (2022). *Resting-state EEG, Substance use and Abstinence After Chronic use: A Systematic Review*. Clinical EEG and Neuroscience, 53(4), 344–366. https://doi.org/10.1177/15500594221076347

Resting-state EEG reflects intrinsic brain activity and its alteration represents changes in cognition that are related to neuropathology. Thereby, it provides a way of revealing the neurocognitive mechanisms underpinning chronic substance use. In addition, it is documented that some neurocognitive functions can recover following sustained abstinence. We present a systematic review to synthesize how chronic substance use is associated with resting-state EEG alterations and whether these spontaneously recover from abstinence. A literature search in Medline, PsycINFO, Embase, CINAHL, Web of Science, and Scopus resulted in 4088 articles, of which were included for evaluation. It covered the substance of alcohol, tobacco, cannabis, cocaine, opioids, methamphetamine, and ecstasy. EEG analysis methods included spectral power, functional connectivity, and network analyses. It was found that long-term substance use with or without substance use disorder diagnosis was associated with broad intrinsic neural activity alterations, which were usually expressed as neural hyperactivation and decreased neural communication between brain regions. Some studies found the use of alcohol, tobacco, cocaine, cannabis, and methamphetamine was positively correlated with these changes. ***Heroin and opiate users differed from controls in theta, alpha, beta (frontal and central regions), and gamma (widespread) bands power. These alternations signal potential cognitive function deficits.*** Specifically, heroin addicts' long-term memory, working/short-term memory, problem-solving abilities, and psychomotor speed performance were believed to be associated with

delta, theta, alpha, and beta band properties respectively. ***In addition, abnormally weaker and stronger functional connectivity were found in the parietal and the left occipital regions respectively***. More evidence was needed for both spectral power and functional connectivity analyses.

Higher beta power, decreased delta, theta, and alpha powers and decline of brain evoked potential amplitudes.

Motlagh, F., Ibrahim, F., Rashid, R., Seghatoleslam, T., & Habil, H. (2017). *Investigation of brain electrophysiological properties among heroin addicts: Quantitative EEG and event-related potentials.* Journal of Neuroscience Research, 95(8), 1633–1646. https://doi.org/10.1002/jnr.23988

This study aims to introduce a new approach of a comprehensive paradigm to evaluate brain electrophysiological properties among addicts. Electroencephalographic spectral power as well as amplitudes and latencies of mismatch negativity (MMN), P300, and P600 components were evaluated among 19 male heroin addicts and 19 healthy nonsmoker subjects using a paradigm consisting of three subparadigms, namely (1) digit span Wechsler test, (2) auditory oddball, and (3) visual cue-reactivity oddball paradigms. Task 1 provided auditory P300 and P600 in association with working memory. Task 2 provided auditory P300 as well as small and large deviant MMN event-related potential (ERPs). Finally, task 3 provided visual cue-reactivity P300. ***Results show that beta power was higher among heroin addicts while delta, theta, and alpha powers were decreased compared with healthy subjects. ERP analysis confirmed the decline of brainevoked potential amplitudes when compared with healthy subjects***, thus indicating a broad neurobiological vulnerability of preattentive and attentional processing including attentional deficits and compromise of discrimination abilities. The prolonged latency of ERPs reflects poor cognitive capacity in the engagement of attention and memory resources. On the other hand, an increase of attention towards the heroin-related stimuli could be concluded from the increase of P300 in the cue-reactivity condition among heroin addicts. Findings suggest that applying this paradigm in addiction studies benefits comprehensive evaluation of neuroelectrophysiological activity among addicts, which can promote a better understanding of drugs' effects on the brain as well as define new neuroelectrophysiological characteristics of addiction properties.

Chronic heroin addiction causes increased b and a2 power activity, latency of P300 and P600, and diminished P300 and P600 amplitude.

Motlagh, F., Ibrahim, F., Menke, J. M., Rashid, R., Seghatoleslam, T., & Habil, H. (2016). *Neuroelectrophysiological approaches in heroin addiction research: A review of literatures*. Journal of Neuroscience Research, 94(4), 297–309. https://doi.org/10.1002/jnr.23703.

Neuroelectrophysiological properties have been used in human heroin addiction studies. These studies vary in their approach, experimental conditions, paradigms, and outcomes. However, it is essential to integrate previous findings and experimental methods for a better demonstration of current issues and challenges in designing such studies. This Review examines methodologies and experimental conditions of neuroelectrophysiological research among heroin addicts during withdrawal, abstinence, and methadone maintenance treatment and presents the

findings. The results show decrements in attentional processing and dysfunctions in brain response inhibition as well as brain activity abnormalities induced by chronic heroin abuse. ***Chronic heroin addiction causes increased b and a2 power activity, latency of P300 and P600, and diminished P300 and P600 amplitude.*** Findings confirm that electroencephalography (EEG) band power and coherence are associated with craving indices and heroin abuse history. First symptoms of withdrawal can be seen in high frequency EEG bands, and the severity of these symptoms is associated with brain functional connectivity. EEG spectral changes and event-related potential (ERP) properties have been shown to be associated with abstinence length and tend to normalize within 3–6 months of abstinence. From the conflicting criteria and confounding effects in neuroelectrophysiological studies, the authors suggest a comprehensive longitudinal study with a multimethod approach for monitoring EEG and ERP attributes of heroin addicts from early stages of withdrawal until long-term abstinence to control the confounding effects, such as nicotine abuse and other comorbid and premorbid conditions.

Frequency shifts in alpha2 range in frontal and central derivations and slowing of alpha1 mean frequency, most prominent in central, temporal, and occipital derivations.

Polunina, A. G., & Davydov, D. M. (2004). *EEG spectral power and mean frequencies in early heroin abstinence*. Progress in neuro-psychopharmacology & biological psychiatry, 28(1), 73–82. https://doi.org/10.1016/j.pnpbp.2003.09.022

The purpose of the present study was to investigate cumulative heroin effects on brain functioning by studying relationships among electroencephalography (EEG) spectral power and mean frequencies and heroin abuse history. Eyes-closed resting EEG data were collected from the 19 monopolar electrode sites in 33 heroin abusers and 13 age-matched healthy volunteers. The mean age of the patients was 23.1+/-4.5 years, the duration of daily heroin abuse (DDHA) ranged from 4 to 44 months, the intravenous doses of heroin ranged from 0.04 to 1.00 g/day, the abstinence length ranged from 6 days to 4.5 months. General linear model (GLM) repeated measures procedure revealed a significant group effect on the distribution of the mean power spectrum between bands and mean frequencies in almost all analyzed derivations. Further analysis demonstrated that these intergroup differences were diversely related to at least three aspects of heroin-taking history. ***Frequency shifts in alpha2 range, most prominent in frontal and central derivations, were related to duration of daily heroin consumption. Slowing of alpha1 mean frequency, most prominent in central, temporal, and occipital derivations, was registered mainly in heroin addicts who abused high doses of the drug***. Spectral power characteristics of brain electrical activities in our patient population were strongly predicted by abstinence length. The present results give grounds to suppose that chronic heroin-taking induces neuronal oscillation frequency changes, which may contribute to the development of antisocial trends and some semantic processes disturbances in these patients. Supplementary neurophysiological deficit is characteristic for heroin addicts who takes high doses of the drug, however, its relation to heroin abuse remains unclear***. Pronounced desynchronization is observed in acute heroin withdrawal, and spectral power characteristics tend to normalize almost completely during several weeks of abstinence***.

Attenuated relative beta-2 power, increase of power spectrum density for theta at all locations, delta in the temporal, frontal and central, decreased its spectral power in all three

alpha bands (alpha-3 band in the FZ channel is more affected by heroin abuse than other frequency sub bands).

Seif, M., Yousefi, M. R., & Behzadfar, N. (2022*). EEG Spectral Power Analysis: A Comparison Between Heroin Dependent and Control Groups*. Clinical EEG and neuroscience, 15500594221089366. Advance online publication. https://doi.org/10.1177/15500594221089366

Previous studies indicated that heroin abuse would result in abnormal functional organization of the brain. However, studies of heroin abuse- related brain dysfunction are scarce. The purpose of the present study was to investigate heroin effects on brain function by studying relationships between Electroencephalograph (EEG) spectral power and heroin abuse. The resting EEG signals were acquired from 15 male heroin dependent group and 15 male control group. The differences in the EEG components of each group were evaluated using the statistical Mann-Whitney examination and Davis Bouldin Index. The results show that ***heroin dependent group has an attenuated relative beta-2 power compared with other EEG frequency sub bands. Nevertheless, the results indicate heroin dependent group have an increase of power spectrum density for theta at all locations, as well as delta in the temporal, frontal and central areas compared with control group. Compared to control group, the heroin dependent group decreased its spectral power more than the control group in all three alpha bands. The present findings using the Davis Bouldin Index provide evidence that alpha-3 band in the FZ channel is more affected by heroin abuse than other frequency sub bands.***

EEG signals in alpha band irregular and weaker in parietal lobe (BA3 and BA7), frontal lobe (BA4 and BA6), and limbic lobe (BA24).

Zhao, Q., Jiang, H., Hu, B., Li, Y., Zhong, N., Li, M., Lin, W., & Liu, Q. (2017). *Nonlinear Dynamic Complexity and Sources of Resting-state EEG in Abstinent Heroin Addicts*. IEEE transactions on nanobioscience, 16(5), 349–355. https://doi.org/10.1109/TNB.2017.2705689.

It has been reported that chronic heroin intake induces both structural and functional changes in human brain; however, few studies have investigated the carry-over adverse effects on brain after heroin withdrawal. In this paper, we examined the neurophysiological differences between the abstinent heroin addicts (AHAs) and healthy controls (HCs) using nonlinear dynamic analysis and source localization analysis in resting-state electroencephalogram (EEG) data; 5 min resting EEG data from 20 AHAs and twenty age-, education-, and gender-matched HCs were recorded using 64 electrodes. The results of nonlinear characteristics (e.g., the correlation dimension, Kolmogorov entropy, and Lempel-Ziv complexity) showed that the ***EEG signals in alpha band from AHAs were significantly more irregular. Moreover, the source localization results confirmed the neuronal activities in alpha band in AHAs were significantly weaker in parietal lobe (BA3 and BA7), frontal lobe (BA4 and BA6), and limbic lobe (BA24).*** Together, our analysis at both the sensor level and source level suggested the functional abnormalities in the brain during heroin abstinence, in particular for the neuronal oscillations in alpha band.

----- METHADONE -----

DRUG FACTS

SYNOPSIS: Prescribed to relieve severe pain that need pain medication around the clock for a long time and cannot be treated with other medications. It is also used to prevent withdrawal symptoms for those addicted to opiates.

Increase in alpha and theta wave activity in closed eyes, and an increase in alpha wave activity and a decrease in theta wave activity with an open eye condition.

Kusumandari, D. E., Suhendra, M. A., Ivonita S., A., Wendy, M. N. A. S., Turnip, A., Jahja, M., & Sobana, S. A. (2019). *Effects of Methadone Intake on Alpha and Theta Amplitude in Relaxing with Closed and Open Eyes Conditions.* 2019 2nd International Conference on Applied Engineering (ICAE), 1–5. https://doi.org/10.1109/ICAE47758.2019.9221679

Methadone therapy can help people who are addicted to achieving a drug-free state by detoxifying and achieving the ultimate goal of improving the health status and productivity of patients. Side effects that usually occur are constipation, lightheadedness, dizziness, drowsiness, unclear thoughts, sweating, nausea and vomiting. The main danger due to overdosing is breathing. If the dosage is too low, symptoms of dropping out of opiates can occur resulting in symptoms of abdominal cramps, irritability, and back and joint pain. Doses of methadone that are too high can be indicated by symptoms such as drowsiness, sleep, shortness of breath and shrinking eyebrows. In this research, an instrument to measure the change of brain wave according to the given methadone is developed and tested. The measured amplitudes are respectively open and close conditions before and after consuming methadone. The amplitude comparison the brain wave for each conditions of each subject are given. Based on the results obtained from the processing of experimental data, it can be seen that ***the effect of methadone therapy before and after it is given is an increase in alpha and theta wave activity in closed eyes, and an increase in alpha wave activity and a decrease in theta wave activity when done with an open eye condition.***

Longer latencies of the ERP components

Markovska-Simoska, S., Ignjatova, L., Trenchevska, G. K., & Pop-Jordanova, N. (2021). *The neurophysiological correlates of cognitive functions during methadone and buprenorphine maintenance treatment: The ERP study*. Heroin Addiction and Related Clinical Problems.

The treatment of opioid dependence with methadone and buprenorphine is equally effective with either of the two drugs, in terms of discontinuation and retention in treatment. Buprenorphine, unlike methadone, is, however, renowned for being a drug that gives a "clear head", which is encouraging for those who are students, or who are, in any case, engaged in intellectual work. Aim. The aim of this study has been to determine if there is a difference in the neurophysiological correlates of cognitive functions in individuals treated with methadone (MMT) versus those treated with buprenorphine (BMT). Methods. The study includes 10 participants belonging to the MMT group and 10 others involved in the BMT group; both these study groups were compared with the control group after matching had been carried out for age and gender. Brain activity was recorded with the QEEG Mitsar system while study participants were performing two neuropsychological tasks. The VCPT and ECPT as modifications of the Go/NoGo paradigm were applied in order to obtain cognitive event-related potentials (ERPs) as indexes of executive functions. Besides the behavioural parameters of test

performance, amplitude and latency of CNV, Cue P3, P3 Go, P3NoGo, N2Go and N2 NoGo were explored at Fz, Cz and Pz, reflecting different stages of information processing. ***The MMT group showed longer latencies of the ERP components***, and the BMT participants showed slightly better results than those of the MMT group. Still, most of the parameters did not differ significantly from those of the control group. Behavioural parameters showed significantly higher values for variables in the results for reaction time and the number of errors of omission and commission found in the competing MMT vs BMT groups, as well as the control group. Conclusions. Neurophysiological evidence suggests that methadone and buprenorphine both have positive effects on neurophysiological functions, as fewer abnormalities were found in MMT or BMT patients than in healthy controls. It has been shown that the sensitivity and specificity of detecting drug effects increase significantly when adding neurophysiological measures to task performance.

Evoked potentials enhancement after methadone administration associated with alpha and theta activity

Motlagh, F., Ibrahim, F., Rashid, R., Shafiabady, N., Seghatoleslam, T., & Habil, H. (2018). *Acute effects of methadone on EEG power spectrum and event-related potentials among heroin dependents.* Psychopharmacology, 235(11), 3273–3288. https://doi.org/10.1007/s00213-018-5035-0

Methadone as the most prevalent opioid substitution medication has been shown to influence the neurophysiological functions among heroin addicts. However, there is no firm conclusion on acute neuroelectrophysiological changes among methadone-treated subjects as well as the effectiveness of methadone in restoring brain electrical abnormalities among heroin addicts. This is the first study to explore the acute effects of methadone induction on both the resting EEG spatial-spectral and ERP properties. This study has further confirmed that opioid addiction significantly influences certain brain regions. Monitoring the immediate and short-term effects of methadone induction confirms the electrophysiological effects of methadone on subjects during MMT which may be influential in reorganizing their brain functions. It is noteworthy that the comparison of ERP trials for each participant indicates more variability among MMT subjects compared to controls which justify the necessity of using single-trial analysis of ERPs in such studies. It was also demonstrated that ***evoked potentials enhancement after methadone administration was associated with alpha and theta activity, which shows that methadone rapidly enhances pre-attentive and attentional processing***. This study describes the alteration of EEG frequency bands power at frontal and central regions associated with the severity of opioid withdrawal symptoms. The results indicate the significant spatial PSD alterations in association with methadone induction. Temporal-spatial-spectral changes proved that although there are ***significant enhancements in normalizing the EEG oscillation compositions during MMT, the abnormal activity of alpha rhythm might suggest that methadone treatment's side-effects on the brain activity dysfunction is a matter of concern in future progressive therapies***.

In low dose methadone patients, all power spectrum of frequency bands increase decrease for high dose methadone patients.

Simbolon, A. I., Nadiya, U., Suhendra, M. A., Kusumandari, D. E., Turnip, A., Sobana, S. A., & Istiqomah, A. N. (2019). *Alteration in Resting EEG for Different Dosage of Methadone Treatment*. 2019 International Conference of Computer Science and Information Technology (ICoSNIKOM), 1–4. https://doi.org/10.1109/ICoSNIKOM48755.2019.9111607

Methadone has a neurophysiological effect in humans that can be analyzed quantitatively using an electroencephalogram (EEG). This study considers the effects of neurophysiological for delta, theta, alpha, and beta frequency band in all brain regions for two dosage ranges categorized as low dose (<100 mg) and high dose (>100 mg). The EEG signals of methadone patients are compared to the healthy subject to analyze the brain alteration after one-hour methadone administration using resting condition (open-eyes and closed-eyes) test protocol. This study uses 17 channels with 10-20 international standard systems for the electrode caps. This study uses 4 th order Butterworth bandpass (0.3-70 Hz) filter and STFT Hanning-window to determine the power spectral density. The results indicate that ***for low dose methadone patient, all the power spectrum of frequency band increase relative to healthy subjects in all brain regions*** and still follow the trend of healthy subjects' EEG oscillation. Nevertheless, for ***high dose*** methadone patients, only the delta and theta that follow the trend of healthy subject's EEG oscillation, but the value of ***power spectrum decreases*** relative to healthy subjects in all brain regions. Further, the power spectrum of alpha and beta for high dose methadone patients has different values for different brain regions.

Increase power of beta and theta bands.

Wang, G. Y., Kydd, R., Wouldes, T. A., Jensen, M., & Russell, B. R. (2015). *Changes in resting EEG following methadone treatment in opiate addicts*. Clinical Neurophysiology, 126(5), 943–950. https://doi.org/10.1016/j.clinph.2014.08.021

This study investigated the electrophysiological activity associated with methadone maintenance treatment (MMT). The resting EEG spectrum of beta (14.5–30 Hz), alpha (8–13 Hz), theta (4–7.5 Hz) and delta (1.5–3.5 Hz) rhythm were measured in 32 patients undertaking chronic MMT, 17 opiate users and 25 healthy volunteers. Differences in the EEG components of each group were evaluated using a repeated measures Analyses of Variance (ANOVA). Post-hoc comparisons were Bonferroni corrected. Our results show that ***either patients undertaking MMT or active opiate users exhibited a significant increase in the power of beta and theta bands*** relative to healthy control subjects. However, the spectral power of patients undertaking MMT fell between that of current opiate users and healthy control subjects on many regional EEG measures. There was an ***inverse correlation between the power of beta or theta bands and cognitive performance***. The abnormal neural electrical activity present in those still using illicit opiates might be reduced following MMT.

Reduced disruption to resting state networks. Increased gamma power and dysfunctional neuronal activity in the occipital, parietal and frontal lobes.

Wang, G. Y., Kydd, R. R., & Russell, B. R. (2016). *Quantitative EEG and Low-Resolution*

Electromagnetic Tomography (LORETA) Imaging of Patients Undergoing Methadone Treatment for Opiate Addiction. Clinical EEG and Neuroscience, 47(3), 180–187. https://doi.org/10.1177/1550059415586705

Methadone maintenance treatment (MMT) has been used as a treatment for opiate dependence since the mid-1960s. Evidence suggests that methadone binds to mu opiate receptors as do other opiates and induces changes in neurophysiological function. However, little is known, about how neural activity within the higher frequency gamma band (>30 Hz) while at rest changes in those stabilized on MMT despite its association with the excitation-inhibition balance within pyramidal-interneuron networks. Our study investigated ***differences in resting gamma power (37-41 Hz) between patients undergoing MMT for opiate dependence, illicit opiate users, and healthy controls subjects***. Electroencephalographic data were recorded from 26 sites according to the international 10-20 system. Compared with the healthy controls subjects, people either undergoing MMT (mean difference [MD] = 0.32, 95% CI = 0.09-0.55, P < .01) or currently using illicit opiates (MD = 0.31, 95% CI = 0.06-0.56, P = .01) ***exhibited significant increased gamma power***. The sLORETA (standardized low-resolution electromagnetic tomography) between-group comparison revealed ***dysfunctional neuronal activity in the occipital, parietal, and frontal lobes in the patients undergoing MMT***. A more severe profile of dysfunction was observed in those using illicit opiates. Our findings suggest that long-term exposure to opioids is associated with disrupted resting state network, which may be reduced after MMT.

Benefit the recovery of impaired neural function in the dorsal striatum

Wang, Y., Wang, H., Li, W., Zhu, J., Gold, M. S., Zhang, D., Wang, L., Li, Y., Yan, X., Cheng, J., Li, Q., & Wang, W. (2014). *Reduced responses to heroin-cue-induced craving in the dorsal striatum: Effects of long-term methadone maintenance treatment*. Neuroscience Letters, 581, 120–124. https://doi.org/10.1016/j.neulet.2014.08.026

Caudate (dorsal striatum) acts as a major role in human substance dependence. It is the central component of cortical-basal ganglia network which consists of several parallel and segregated circuits, including reward circuit. By communicating with a wide range of cortex, such as limbic, associative and sensormotor cortex, caudate can interact with different parts of reward circuit and other associated circuits to play a part in reward processing, memory processing, decision making and drug seeking. Previous neuroimaging studies on brain reaction to DCIC demonstrate that exposure to drug-associated cue can increase caudate activity in a variety of substance dependents, such as cocaine, alcohol, nicotine and heroin addicts, which is consistent with the notion that dopamine in the dorsal striatum is involved with drug craving and a vital neuro-chemical responses for addiction. Although no significant heroin-related BOLD signal intensity change in the caudate was observed in MMT patients when compared with HC group, the results at MMT inter-group level confirmed the caudate was definitely involved in the neural reaction to DCIC. Furthermore, the positive correlation between heroin use history and the activation intensity in the right caudate confirm an impaired dorsal striatum function caused by chronic heroin use. Prior imaging evidences have shown the magnitude of caudate activation elicited by drug cue is correlated with addicts' subjective craving, addiction severity and measurements of withdrawal symptoms, which implicates the caudate reactivity to drug cue is a predictor for treatment outcomes. ***The reduced drug-related reaction in the caudate of***

former heroin patients with longer MMT and the negative correlation between the magnitude of BOLD signal in the caudate and MMT use history may imply that MMT could benefit the recovery of impaired neural function in the dorsal striatum and therefore diminish the behavioral effects of heroin. This is in line with clinical data, animal research and imaging researches. Because the acute effect of methadone and stimuli paradigm might be the contributors to the inconsistency between self- reported craving score on group level analysis and imaging data, future studies with
an improved experiment design and more proper scan time are needed to obtain behavioural data supporting to imaging findings.

Wang, G. Y., Kydd, R., & Russell, B. R. (2015). *Resting EEG and ERPs findings in methadone-substituted opiate users: a review*. Acta Neurologica Belgica, 115(4), 539–546. https://doi.org/10.1007/s13760-015-0476-2

Determining the effects of MMT on neuropsychological function using electroencephalography (EEG) combined with event-related potentials (ERP) has been used infrequently. However EEG and ERP provide a means of closely examining information processing to determine whether MMT induces any deficits. The purpose of this review was to investigate whether psychophysiological evidence supports cognitive impairment in association with MMT by focusing on research using EEG and ERPs. The findings of EEG studies to date appear not support the notion that cognitive impairments are attributable to the specific pharmacological effects of methadone suggested by some neuropsychological studies. It should be noted that this review has covered the methadone-related EEG studies over a period of 40 years; however, during this time, only a dozen of works has been published. Half of the papers were written in the seventies and then there was a gap until the past decade, when some new works appeared. The main problem is that those studies, even some of the most recent ones, used very small samples that seriously question the reliability of their results.

Larger N2 amplitudes than Go and longer P3 latencies.

Yang, L., Xu, Q., Li, S., Zhao, X., Ma, L., Zheng, Y., Zhang, J., & Li, Y. (2015). *The effects of methadone maintenance treatment on heroin addicts with response inhibition function impairments: Evidence from event-related potentials*. Journal of Food and Drug Analysis, 23(2), 260–266. https://doi.org/10.1016/j.jfda.2014.06.002

Response inhibition has been a core issue in addictive behavior. Many previous studies have found that response inhibition abilities are damaged in those with drug dependence. However, whether heroin addicts who are treated with methadone maintenance have an abnormal response inhibition ability is not clear. In order to investigate the response inhibition functions in heroin addicts who were treated with methadone maintenance, electroencephalography (EEG) was used to examine 14 heroin addicts treated with methadone maintenance (HDM), 17 heroin addicts (HD), and 18 healthy controls (HC) in an equiprobability Go\NoGo task. The reaction times (RTs) for the Go stimuli in the HD group were slower than those in the HDM and HC groups. ***Event-related potential (ERP) measurements showed that NoGo stimuli elicited larger N2 amplitudes than Go stimuli in the HDM and HC groups***. However, for the HD group, the N2 amplitudes were similar for the two conditions. In addition, the ***HDM and HD groups were associated with longer P3 latencies***. Our results demonstrated that methadone

maintenance treatment might ease the deficits in response inhibition that result from long-term drug abuse. However, compared to normal people, HDM patients have serious problems evaluating and inhibiting inappropriate behaviors.

----- OXYCODONE (Oxycotin, Oxecta, Roxicodone) -----

DRUG FACTS

SYNOPSIS: Prescribed to relieve moderate to severe pain.

Decreased functional connectivity between bilateral thalamus and the anterior cingulate cortex.

Croosu, S. S., Frøkjaer, J. B., Drewes, A. M., & Hansen, T. M. (2021). *Tapentadol and oxycodone affect resting-state functional brain connectivity: A randomized, placebo-controlled trial.* Journal of neuroimaging : official journal of the American Society of Neuroimaging, 31(5), 956–961. https://doi.org/10.1111/jon.12902

The changes in functional brain connectivity induced by treatment with analgesics are poorly investigated. Unfortunately, results from clinical studies investigating treatments in patients with pain are often confounded by co-medication and comorbidity. Thalamus is central in sensory processing, and we hypothesized that functional connectivity between thalamus and other brain areas in healthy volunteers was different in treatment with oxycodone, representing a pure opioid, compared to treatment with tapentadol, which has a dual effect on the opioidergic and adrenergic systems. Methods: Twenty-one healthy male volunteers were included in a randomized, double-blind, three-armed, placebo-controlled, cross-over study. All received tapentadol (50 mg extended release), oxycodone (10 mg extended release), or placebo twice daily for 14 days. Resting-state functional magnetic resonance imaging data were obtained before and after treatment. Seed-based functional connectivity analyses were performed between thalamus and other brain regions. Results: Compared to placebo, tapentadol increased functional connectivity between left thalamus and precentral cortex (P = .048), whereas ***oxycodone decreased functional connectivity between bilateral thalamus and the anterior cingulate cortex (P ≤ .005).*** Conclusions: This study has shown that the functional connectivity between thalamus and other brain areas central in pain processing was different for the tapentadol and oxycodone treatments compared to placebo. This supports that the two treatments exert different mechanism of action. Further studies with larger sample sizes need to be carried out in order to validate this.

Reduced functional coupling between the dorsal ACC and bilateral anterior insula/putamen and the rostral ACC and right insula.

Gorka, S. M., Fitzgerald, D. A., de Wit, H., Angstadt, M., & Phan, K. L. (2014). *Opioid modulation of resting-state anterior cingulate cortex functional connectivity.* Journal of psychopharmacology (Oxford, England), 28(12), 1115–1124. https://doi.org/10.1177/0269881114548436

Individuals misuse oxycodone, a widely prescribed opioid analgesic, in part to self-medicate physical and emotional pain. Physical and emotional pain is thought to be represented in the brain by a 'pain matrix,' consisting of the insula, thalamus, and somatosensory cortices, with

processing of the affective dimension of pain in the dorsal and rostral anterior cingulate cortex (ACC). The current study examined oxycodone's effects on resting-state functional connectivity between the dorsal ACC, rostral ACC, and other regions of the pain matrix using functional magnetic resonance imaging (fMRI). In a within-subjects, randomized, double-blind, placebo-controlled, dose-response design, 14 healthy subjects completed a resting-state scan following ingestion of placebo, 10 mg, or 20 mg of oxycodone. Functional correlations between the dorsal and rostral ACC seed regions and the pain matrix were examined and compared across sessions. Both doses of ***oxycodone reduced functional coupling between the dorsal ACC and bilateral anterior insula/putamen and the rostral ACC and right insula relative to placebo*** (no differences between doses). The findings do not withstand correction for multiple comparisons, and thus should be considered preliminary. However, they are consistent with the idea that oxycodone may produce its physical and emotional 'analgesic' effects through disruption of ACC-insula and ACC-putamen connectivity.

Decreased functional connectivity between limbic structures and to supralimbic areas

Hansen, T. M., Lelic, D., Olesen, A. E., Drewes, A. M., & Frøkjaer, J. B. (2018). *Differential effects of oxycodone and venlafaxine on resting state functional connectivity-A randomized placebo-controlled magnetic resonance imaging study*. CNS neuroscience & therapeutics, 24(9), 820–827. https://doi.org/10.1111/cns.12827

Different mechanisms may be involved in the antinociceptive effects of oxycodone (opioid) and venlafaxine (serotonin-norepinephrine reuptake inhibitor), and the aim of this study was to investigate the effect of these drugs on brain functional connectivity. Methods: Resting state functional magnetic resonance imaging was acquired in 20 healthy volunteers before and after a 5-day treatment with oxycodone, venlafaxine, or placebo in a randomized, double-blind, crossover study. Functional connectivity analyses were performed between four predefined seeds (dorsal anterior cingulate cortex, rostral anterior cingulate cortex, posterior insula, and prefrontal cortex), and the whole brain. Results: The overall interpretation was that there were differences between the effects of oxycodone and venlafaxine on functional connectivity. ***Oxycodone mainly showed decreased functional connectivity between limbic structures and to supralimbic areas*** (all $P < 0.05$). Venlafaxine also showed decreased functional connectivity between limbic structures and to supralimbic areas, but increased functional connectivity to structures in the midbrain and brain stem was also found (all $P < 0.05$). Conclusions: Oxycodone and venlafaxine showed differential effects on resting-state functional connectivity as compared to placebo. This supports that the two drugs exert different mechanisms, and that the drugs in combination may exert additive effects and could potentially improve pain therapy.

Decreased glutamate/creating levels at anterior cingulate

Hansen, T. M., Frøkjaer, J. B., Mark, E. B., & Drewes, A. M. (2022). *Tapentadol and oxycodone reduce cingulate glutamate in healthy volunteers*. British journal of clinical pharmacology, 88(3), 1358–1364. https://doi.org/10.1111/bcp.15050

Tapentadol and oxycodone are commonly used analgesics. Preclinical studies have shown that oxycodone modulates brain metabolites related to opioid pathways, whereas tapentadol also affects noradrenergic activity. However, knowledge about the function of the medications in the human brain is limited. The aim was to investigate effects of tapentadol and oxycodone on

brain glutamate, the most important neurotransmitter in pain processing. Magnetic resonance spectroscopy was obtained in 21 healthy subjects from the anterior cingulate cortex, prefrontal cortex, and insula at baseline and after 14 days of treatment with either 50 mg tapentadol, 10 mg oxycodone (equipotent dose, both extended release) or placebo twice daily in a randomized double-blind cross-over study. ***Compared to baseline, decreased glutamate/creatine levels were identified in anterior cingulate cortex after tapentadol (1.26 ± 0.14 vs. 1.35 ± 0.18, P = .04) and oxycodone (1.26 ± 0.10 vs. 1.35 ± 0.12, P = .05) treatments, both with 7% reduction***. This indicates that both analgesics modulate the glutamatergic system at the supraspinal level in humans.

Decreased spectral indices and brain source activity in delta and theta frequency bands.

Lelic, D., Hansen, T. M., Mark, E. B., Olesen, A. E., & Drewes, A. M. (2017). *The effects of analgesics on central processing of tonic pain: A cross-over placebo controlled study*. Neuropharmacology, 123, 455–464. https://doi.org/10.1016/j.neuropharm.2017.06.022

Opioids and antidepressants that inhibit serotonin and norepinephrine reuptake (SNRI) are recognized as analgesics to treat moderate to severe pain, but the central mechanisms underlying their analgesia remain unclear. This study investigated how brain activity at rest and exposed to tonic pain is modified by oxycodone (opioid) and venlafaxine (SNRI). Twenty healthy males were included in this randomized, cross-over, double-blinded study. 61-channel electroencephalogram (EEG) was recorded before and after five days of treatment with placebo, oxycodone (10 mg extended release b.i.d) or venlafaxine (37.5 mg extended release b.i.d) at rest and during tonic pain (hand immersed in 2 °C water for 80 s). Subjective pain and unpleasantness scores of tonic pain were recorded. Spectral analysis and sLORETA source localization were done in delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta1 (12-18 Hz) and beta2 (18-32 Hz) frequency bands. Oxycodone decreased pain and unpleasantness scores ($P < 0.05$), whereas venlafaxine decreased the pain scores ($P < 0.05$). None of the treatments changed the spectral indices or brain sources underlying resting EEG. Venlafaxine decreased spectral indices in alpha band of the EEG to tonic pain, whereas ***oxycodone decreased the spectral indices and brain source activity in delta and theta frequency bands*** (all $P < 0.05$). The brain source activity predominantly decreased in the insula and inferior frontal gyrus. The ***decrease of activity within insula and inferior frontal gyrus is likely involved in pain inhibition due to oxycodone treatment***, whereas the decrease in alpha activity is likely involved in pain inhibition due to venlafaxine treatment.

Increased subcortical P14, early cortical N30 amplitudes and the late cortical N60-80 latency. The brainstem and primary somatosensory cortex source strengths were increased.

Lelic, D., Valeriani, M., Fischer, I. W., Dahan, A., & Drewes, A. M. (2017). *Venlafaxine and oxycodone have different effects on spinal and supraspinal activity in man: a somatosensory evoked potential study*. British journal of clinical pharmacology, 83(4), 764–776. https://doi.org/10.1111/bcp.13177

Opioids and antidepressants that inhibit serotonin and norepinephrine reuptake (SNRI) are recognized as analgesics to treat severe and moderate pain, but their mechanisms of action in humans remain unclear. The present study aimed to explore how oxycodone (an opioid) and venlafaxine (an SNRI) modulate spinal and supraspinal sensory processing. Methods: Twenty

volunteers were included in a randomized, double-blinded, three-way (placebo, oxycodone, venlafaxine), crossover study. Spinal and full scalp cortical evoked potentials (EPs) to median nerve stimulation were recorded before and after 5 days of treatment. Assessment of the central effects of the three treatments involved: (i) amplitudes and latencies of spinal EPs (spinal level); (ii) amplitudes and latencies of the P14 potential (subcortical level); (iii) amplitudes and latencies of early and late cortical EPs (cortical level); (iv) brain sources underlying early cortical Eps; and (v) brain networks underlying the late cortical EPs. Results: In the venlafaxine arm, the spinal P11 and the late cortical N60-80 latencies were reduced by 1.8% [95% confidence interval (CI) 1.7%, 1.9%) and 5.7% (95% CI 5.3%, 6.1%), whereas the early cortical P25 amplitude was decreased by 7.1% (95%CI 6.1%, 8.7%). ***Oxycodone increased the subcortical P14 [+25% (95% CI 22.2%, 28.6%)], early cortical N30 [+12.9% (95% CI 12.5%, 13.2%)] amplitudes and the late cortical N60-80 latency [+2.9% (95% CI 1.9%, 4.0%)]. The brainstem and primary somatosensory cortex source strengths were increased by 66.7% (95% CI 62.5%, 75.0%) and 28.8% (95% CI 27.5%, 29.6%) in the oxycodone arm***, whereas the primary somatosensory cortex strength was decreased in the venlafaxine arm by 18.3% (95% CI 12.0%, 28.1%). Conclusions: Opioids and SNRI drugs exert different central effects. The present study contributed to the much-needed human models of the mechanisms of action of drugs with effects on the central nervous system.

Increased latency of N1 (ERP), anterior cingulate and insula moved caudally.

Nedergaard, R. B., Hansen, T. M., Mørch, C. D., Niesters, M., Dahan, A., & Drewes, A. M. (2022). *Influence of tapentadol and oxycodone on the spinal cord and brain using electrophysiology: a randomized, placebo-controlled trial*. British journal of clinical pharmacology, 88(12), 5307–5316. https://doi.org/10.1111/bcp.15453.

The aim of this study was to investigate the effects of tapentadol and oxycodone using the nociceptive withdrawal reflex and sensory evoked potentials. **Methods:** Twenty-one healthy volunteers completed a cross-over trial with oxycodone (10 mg), tapentadol (50 mg) extended-release tablets, or placebo treatment administered orally BID for 14 days. Electrical stimulations were delivered on the plantar side of the foot to evoke a nociceptive withdrawal reflex at baseline and post-interventions. Electromyography, recorded at tibialis anterior, and electroencephalography were recorded for analysis of: number of reflexes, latencies, and area under the curve of the nociceptive withdrawal reflex as well as latencies, amplitudes and dipole sources of the sensory-evoked potential. **Results:** Tapentadol decreased the odds ratio of eliciting nociceptive withdrawal reflex by -0.89 (P = .001, 95% confidence interval [CI] -1.46, -0.32), whereas ***oxycodone increased the latency of the N1 component of the sensory-evoked potential at the vertex by 12.5 ms (P = .003, 95% CI 3.35, 21.69). Dipole sources revealed that the anterior cingulate component moved caudally for all three interventions (all P < .02), and the insula components moved caudally in both the oxycodone and tapentadol arms (all P < .03)***. **Conclusion:** A decrease in the number of nociceptive withdrawal reflex was observed during tapentadol treatment, possibly relating to the noradrenaline reuptake inhibition effects on the spinal cord. Both oxycodone and tapentadol affected cortical measures possible due to μ-opioid receptor agonistic effects evident in the dipole sources, with the strongest effect being mediated by oxycodone. These findings could support the dual effect analgesic mechanisms of tapentadol in humans as previously shown in preclinical studies.

Decreased the spectral power in the delta and theta bands, increased power in the alpha1, alpha2 and beta1 band, and decreased activity of the temporal and limbic region in the delta band, and frontal lobe in the alpha2 and beta1 bands.

Nedergaard, R. B., Hansen, T. M., Nissen, T. D., Mark, E. B., Brock, C., & Drewes, A. M. (2021). *The effects of tapentadol and oxycodone on central processing of tonic pain*. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 132(10), 2342–2350. https://doi.org/10.1016/j.clinph.2021.07.021

The present study investigated differences between opioids to experimental tonic pain in healthy men. Twenty-one males participated in this cross-over-trial. Interventions twice daily were oxycodone (10 mg), tapentadol (50 mg) and placebo for 14 days. Tonic pain was induced on day 1, 4 and 14 by immersing the hand in 2 °C water for 120 s. Electroencephalography was recorded during test pain at baseline and after 14 days. Spectral analysis and source localization were investigated in predefined frequency bands. A decreased perception of pain on day 4 persisted throughout the 14 days compared to baseline ($p < 0.006$). ***Oxycodone decreased the electroencephalography spectral power in the delta and theta bands and increased power in the alpha1, alpha2 and beta1 bands ($p < 0.03$)***. Tapentadol increased spectral power in the alpha1 band ($p < 0.001$). Source localization revealed that ***oxycodone decreased activity of the temporal and limbic region in the delta band, and frontal lobe in the alpha2 and beta1 bands***, whereas tapentadol decreased alpha1 band activity in the temporal lobe compared to placebo. Oxycodone and tapentadol reduced pain perception and changed the central processing of tonic pain. Different mechanisms of action were involved, where oxycodone affected cortical structures more than tapentadol.

----- REMIFENTANIL (Ultiva) -----

DRUG FACTS

SYNOPSIS: Prescribed to relieve pain during and after surgery.

Increased delta band and decreased the theta in F1 and alpha band oscillations in C6.

Graversen, C., Malver, L. P., Kurita, G. P., Staahl, C., Christrup, L. L., Sjøgren, P., & Drewes, A. M. (2015). *Altered frequency distribution in the electroencephalogram is correlated to the analgesic effect of remifentanil*. Basic & clinical pharmacology & toxicology, 116(5), 414–422. https://doi.org/10.1111/bcpt.12330

Opioids alter resting state brain oscillations by multiple and complex factors, which are still to be elucidated. To increase our knowledge, multi-channel electroencephalography (EEG) was subjected to multivariate pattern analysis (MVPA), to identify the most descriptive frequency bands and scalp locations altered by remifentanil in healthy volunteers. Sixty-two channels of resting EEG followed by independent measures of pain scores to heat and bone pain were recorded in 21 healthy males before and during remifentanil infusion in a placebo-controlled, double-blind crossover study. EEG frequency distributions were extracted by a continuous wavelet transform and normalized into delta, theta, alpha, beta and gamma bands. Alterations relative to pre-treatment responses were calculated for all channels and used as input to the MVPA. Compared to placebo, ***remifentanil increased the delta band and decreased the theta***

and alpha band oscillations as a mean over all channels (all p ≤ 0.007). The most discriminative channels in these frequency bands were F1 in delta (83.33%, p = 0.0023) and theta bands (95.24%, p < 0.0001), and C6 in the alpha band (80.95%, p = 0.0054). These alterations were correlated to individual changes in heat pain in the delta (p = 0.045), theta (p = 0.038) and alpha (p = 0.039) bands and to bone pain in the alpha band (p = 0.0092). Hence, MVPA of multi-channel EEG was able to identify frequency bands and corresponding channels most sensitive to altered brain activity during remifentanil treatment. As the EEG alterations were correlated to the analgesic effect, the approach may prove to be a novel methodology for monitoring individual efficacy to opioids.

Increased neuronal activity around frontal, fronto-central and fronto-temporal brain regions including: insula (Brodmann area, BA13) for both delta and alpha bands, inferior frontal gyrus (BA47) for theta, inferior frontal gyrus (BA45) for beta1, and precentral gyrus (BA6) at frontal lobe for beta2 band, all on left hemisphere

Khodayari-Rostamabad, A., Graversen, C., Malver, L. P., Kurita, G. P., Christrup, L. L., Sjøgren, P., & Drewes, A. M. (2015). *A cortical source localization analysis of resting EEG data after remifentanil infusion*. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 126(5), 898–905. https://doi.org/10.1016/j.clinph.2014.08.006

Objective: To explore changes in current source density locations after remifentanil infusion in healthy volunteers using source localization of the electroencephalography (EEG). ***The effect of remifentanil on source localization was identified to be increased neuronal activity around frontal, fronto-central and fronto-temporal brain regions including: insula (Brodmann area, BA13) for both delta and alpha bands, inferior frontal gyrus (BA47) for theta, inferior frontal gyrus (BA45) for beta1, and precentral gyrus (BA6) at frontal lobe for beta2 band, all on left hemisphere***. The brain areas identified to be affected by remifentanil in this study are among the areas identified in several other EEG and imaging studies of analgesic drugs and cortical processing related to pain and cognitive processing. For example, similar to our findings, Schlünzen et al. (2004) used positron emission tomographic and EEG to show that sevoflurane (an anesthetic drug) caused cerebral blood flow changes in several brain areas including left insula. Besides, their EEG analysis revealed that high doses of sevoflurane caused increased delta, theta, alpha and beta power. Schlereth et al. (2003) observed left-hemisphere dominance (particularly on left frontal operculum and adjacent dorsal insula) of early sensorydiscriminative dimensions of nociceptive pain processing. Finally, Wang et al. (2012) found that patients with persistent cognitive impairment had altered activation of the left insular cortex compared to patients with late-life depression without persistent cognitive impairment. Interestingly, they also found a correlation between alterations in the left inferior parietal cortex and subsequent cognitive decline. This indicates that cognitive decline may be associated with alterations in the left hemisphere.

Altered alpha and low beta range (8 to 18 Hz).

Khodayari-Rostamabad, A., Olesen, S. S., Graversen, C., Malver, L. P., Kurita, G. P., Sjøgren, P., Christrup, L. L., & Drewes, A. M. (2015). *Disruption of cortical connectivity during remifentanil administration is associated with cognitive impairment but not with*

analgesia. Anesthesiology, 122(1), 140–149. https://doi.org/10.1097/ALN.0000000000000510

The authors investigated the effect of remifentanil administration on resting electroencephalography functional connectivity and its relationship to cognitive function and analgesia in healthy volunteers. Twenty-one healthy male adult subjects were enrolled in this placebo-controlled double-blind cross-over study. For each subject, 2.5 min of multichannel electroencephalography recording, a cognitive test of sustained attention (continuous reaction time), and experimental pain scores to bone-pressure and heat stimuli were collected before and after infusion of remifentanil or placebo. A coherence matrix was calculated from the electroencephalogram, and three graph-theoretical measures (characteristic path-length, mean clustering coefficient, and relative small-worldness) were extracted to characterize the overall cortical network properties. Compared to placebo, ***most graph-theoretical measures were significantly altered by remifentanil at the alpha and low beta range (8 to 18 Hz; all P < 0.001).*** Taken together, these alterations were characterized by an ***increase in the characteristic path-length (alpha 17% and low beta range 24%) and corresponding decrements in mean clustering coefficient (low beta range -25%) and relative small-worldness (alpha -17% and low beta range -42%).*** Changes in characteristic path-lengths after remifentanil infusion were correlated to the continuous reaction time index (r = -0.57; P = 0.009), while no significant correlations between graph-theoretical measures and experimental pain tests were seen***. Remifentanil disrupts the functional connectivity network properties of the electroencephalogram.*** The findings give new insight into how opioids interfere with the normal brain functions and have the potential to be biomarkers for the sedative effects of opioids in different clinical settings.

Increased the amplitude of the mismatch negativity (MMN) on F3 in females but not in males.

Quaedflieg, C. W., Münte, S., Kalso, E., & Sambeth, A. (2014*). Effects of remifentanil on processing of auditory stimuli: a combined MEG/EEG study.* Journal of psychopharmacology (Oxford, England), 28(1), 39–48. https://doi.org/10.1177/0269881113512036

Remifentanil (Ultiva®) is a potent ultra-short acting mu-opioid receptor agonist used for perioperative pain treatment and anaesthesia. The primary aim of the present study was to investigate the effects of remifentanil on auditory processing measured with a MMN paradigm consisting of six deviant stimuli using a within-subject design. Automatic auditory processing was quantified as the amplitude of the MMN(m) while controlled top-down auditory processing was quantified as the amplitude of the P3a(m) (Friedman et al., 2001; Näätänen et al., 2011; Polich, 2007). For the MMN a gender effect was found for the frequency stimuli. ***Remifentanil increased the amplitude of the MMN on F3 in females but not in males***. Again, no effect of treatment was found for the novel P3a, indicating that the top-down controlled switching of attention to the novel sound was not affected by remifentanil. Remifentanil resulted in an increase in the amplitude of the frequency MMN for females. This is in line with previous studies showing that remifentanil increased the bold response and regional cerebral blood flow in areas rich in MORs related to pain processing, for example the anterior cingulate and frontal cortex and in the temporal cortex involved in auditory processing (Leppa et al., 2006; Wagner et al., 2001). These findings disagree to some extent with the results of Haenggi et al. (2004), who

did not find any effect of remifentanil on the amplitude of the mismatch negativity. However, the sample in the study of Haenggi et al. (2004) consisted of only male participants. The female-specific effect found in this study might be explained by gender differences in the density and distribution of opioid receptors (Craft, 2003).

----- TAPENTADOL (Nucynta) -----

DRUG FACTS

SYNOPSIS: Prescribed to treat moderate to severe acute pain.

Decreased functional connectivity between bilateral thalamus and the anterior cingulate cortex.

Croosu, S. S., Frøkjaer, J. B., Drewes, A. M., & Hansen, T. M. (2021). *Tapentadol and oxycodone affect resting-state functional brain connectivity: A randomized, placebo-controlled trial.* Journal of neuroimaging : official journal of the American Society of Neuroimaging, 31(5), 956–961. https://doi.org/10.1111/jon.12902

The changes in functional brain connectivity induced by treatment with analgesics are poorly investigated. Unfortunately, results from clinical studies investigating treatments in patients with pain are often confounded by co-medication and comorbidity. Thalamus is central in sensory processing, and we hypothesized that functional connectivity between thalamus and other brain areas in healthy volunteers was different in treatment with oxycodone, representing a pure opioid, compared to treatment with tapentadol, which has a dual effect on the opioidergic and adrenergic systems. Methods: Twenty-one healthy male volunteers were included in a randomized, double-blind, three-armed, placebo-controlled, cross-over study. All received tapentadol (50 mg extended release), oxycodone (10 mg extended release), or placebo twice daily for 14 days. Resting-state functional magnetic resonance imaging data were obtained before and after treatment. Seed-based functional connectivity analyses were performed between thalamus and other brain regions. Results: Compared to placebo, tapentadol increased functional connectivity between left thalamus and precentral cortex (P = .048), whereas ***oxycodone decreased functional connectivity between bilateral thalamus and the anterior cingulate cortex (P ≤ .005).*** Conclusions: This study has shown that the functional connectivity between thalamus and other brain areas central in pain processing was different for the tapentadol and oxycodone treatments compared to placebo. This supports that the two treatments exert different mechanism of action. Further studies with larger sample sizes need to be carried out in order to validate this.

Reduced functional coupling between the dorsal ACC and bilateral anterior insula/putamen and the rostral ACC and right insula.

Gorka, S. M., Fitzgerald, D. A., de Wit, H., Angstadt, M., & Phan, K. L. (2014). *Opioid modulation of resting-state anterior cingulate cortex functional connectivity.* Journal of psychopharmacology (Oxford, England), 28(12), 1115–1124. https://doi.org/10.1177/0269881114548436

Individuals misuse oxycodone, a widely prescribed opioid analgesic, in part to self-medicate physical and emotional pain. Physical and emotional pain is thought to be represented in the

brain by a 'pain matrix,' consisting of the insula, thalamus, and somatosensory cortices, with processing of the affective dimension of pain in the dorsal and rostral anterior cingulate cortex (ACC). The current study examined oxycodone's effects on resting-state functional connectivity between the dorsal ACC, rostral ACC, and other regions of the pain matrix using functional magnetic resonance imaging (fMRI). In a within-subjects, randomized, double-blind, placebo-controlled, dose-response design, 14 healthy subjects completed a resting-state scan following ingestion of placebo, 10 mg, or 20 mg of oxycodone. Functional correlations between the dorsal and rostral ACC seed regions and the pain matrix were examined and compared across sessions. Both doses of ***oxycodone reduced functional coupling between the dorsal ACC and bilateral anterior insula/putamen and the rostral ACC and right insula relative to placebo*** (no differences between doses). The findings do not withstand correction for multiple comparisons, and thus should be considered preliminary. However, they are consistent with the idea that oxycodone may produce its physical and emotional 'analgesic' effects through disruption of ACC-insula and ACC-putamen connectivity.

Decreased functional connectivity between limbic structures and to supralimbic areas

Hansen, T. M., Lelic, D., Olesen, A. E., Drewes, A. M., & Frøkjaer, J. B. (2018). *Differential effects of oxycodone and venlafaxine on resting state functional connectivity-A randomized placebo-controlled magnetic resonance imaging study*. CNS neuroscience & therapeutics, 24(9), 820–827. https://doi.org/10.1111/cns.12827

Different mechanisms may be involved in the antinociceptive effects of oxycodone (opioid) and venlafaxine (serotonin-norepinephrine reuptake inhibitor), and the aim of this study was to investigate the effect of these drugs on brain functional connectivity. Methods: Resting state functional magnetic resonance imaging was acquired in 20 healthy volunteers before and after a 5-day treatment with oxycodone, venlafaxine, or placebo in a randomized, double-blind, crossover study. Functional connectivity analyses were performed between four predefined seeds (dorsal anterior cingulate cortex, rostral anterior cingulate cortex, posterior insula, and prefrontal cortex), and the whole brain. Results: The overall interpretation was that there were differences between the effects of oxycodone and venlafaxine on functional connectivity. ***Oxycodone mainly showed decreased functional connectivity between limbic structures and to supralimbic areas*** (all $P < 0.05$). Venlafaxine also showed decreased functional connectivity between limbic structures and to supralimbic areas, but increased functional connectivity to structures in the midbrain and brain stem was also found (all $P < 0.05$). Conclusions: Oxycodone and venlafaxine showed differential effects on resting-state functional connectivity as compared to placebo. This supports that the two drugs exert different mechanisms, and that the drugs in combination may exert additive effects and could potentially improve pain therapy.

Decreased glutamate/creating levels at anterior cingulate

Hansen, T. M., Frøkjaer, J. B., Mark, E. B., & Drewes, A. M. (2022). *Tapentadol and oxycodone reduce cingulate glutamate in healthy volunteers*. British journal of clinical pharmacology, 88(3), 1358–1364. https://doi.org/10.1111/bcp.15050

Tapentadol and oxycodone are commonly used analgesics. Preclinical studies have shown that oxycodone modulates brain metabolites related to opioid pathways, whereas tapentadol also affects noradrenergic activity. However, knowledge about the function of the medications in

the human brain is limited. The aim was to investigate effects of tapentadol and oxycodone on brain glutamate, the most important neurotransmitter in pain processing. Magnetic resonance spectroscopy was obtained in 21 healthy subjects from the anterior cingulate cortex, prefrontal cortex, and insula at baseline and after 14 days of treatment with either 50 mg tapentadol, 10 mg oxycodone (equipotent dose, both extended release) or placebo twice daily in a randomized double-blind cross-over study. ***Compared to baseline, decreased glutamate/creatine levels were identified in anterior cingulate cortex after tapentadol (1.26 ± 0.14 vs. 1.35 ± 0.18, P = .04) and oxycodone (1.26 ± 0.10 vs. 1.35 ± 0.12, P = .05) treatments, both with 7% reduction***. This indicates that both analgesics modulate the glutamatergic system at the supraspinal level in humans.

Decreased the odds ratio of eliciting nociceptive withdrawal reflex, anterior cingulate and insula components moved caudally.

Nedergaard, R. B., Hansen, T. M., Mørch, C. D., Niesters, M., Dahan, A., & Drewes, A. M. (2022). *Influence of tapentadol and oxycodone on the spinal cord and brain using electrophysiology: a randomized, placebo-controlled trial*. British journal of clinical pharmacology, 88(12), 5307–5316. https://doi.org/10.1111/bcp.15453.

The aim of this study was to investigate the effects of tapentadol and oxycodone using the nociceptive withdrawal reflex and sensory evoked potentials. **Methods:** Twenty-one healthy volunteers completed a cross-over trial with oxycodone (10 mg), tapentadol (50 mg) extended-release tablets, or placebo treatment administered orally BID for 14 days. Electrical stimulations were delivered on the plantar side of the foot to evoke a nociceptive withdrawal reflex at baseline and post-interventions. Electromyography, recorded at tibialis anterior, and electroencephalography were recorded for analysis of: number of reflexes, latencies, and area under the curve of the nociceptive withdrawal reflex as well as latencies, amplitudes and dipole sources of the sensory-evoked potential. **Results:** ***Tapentadol decreased the odds ratio of eliciting nociceptive withdrawal reflex*** by -0.89 (P = .001, 95% confidence interval [CI] -1.46, -0.32), whereas oxycodone increased the latency of the N1 component of the sensory-evoked potential at the vertex by 12.5 ms (P = .003, 95% CI 3.35, 21.69). ***Dipole sources revealed that the anterior cingulate component moved caudally for all three interventions (all P < .02), and the insula components moved caudally in both the oxycodone and tapentadol arms*** (all P < .03). **Conclusion:** A decrease in the number of nociceptive withdrawal reflex was observed during tapentadol treatment, possibly relating to the noradrenaline reuptake inhibition effects on the spinal cord. Both oxycodone and tapentadol affected cortical measures possible due to μ-opioid receptor agonistic effects evident in the dipole sources, with the strongest effect being mediated by oxycodone. These findings could support the dual effect analgesic mechanisms of tapentadol in humans as previously shown in preclinical studies.

Tapentadol increased spectral power in the alpha1 band and decreased alpha1 band activity in the temporal lobe.

Nedergaard, R. B., Hansen, T. M., Nissen, T. D., Mark, E. B., Brock, C., & Drewes, A. M. (2021). *The effects of tapentadol and oxycodone on central processing of tonic pain*. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 132(10), 2342–2350. https://doi.org/10.1016/j.clinph.2021.07.021

The present study investigated differences between opioids to experimental tonic pain in healthy men. Twenty-one males participated in this cross-over-trial. Interventions twice daily were oxycodone (10 mg), tapentadol (50 mg) and placebo for 14 days. Tonic pain was induced on day 1, 4 and 14 by immersing the hand in 2 °C water for 120 s. Electroencephalography was recorded during test pain at baseline and after 14 days. Spectral analysis and source localization were investigated in predefined frequency bands. A decreased perception of pain on day 4 persisted throughout the 14 days compared to baseline ($p < 0.006$*). Oxycodone decreased the electroencephalography spectral power in the delta and theta bands and increased power in the alpha1, alpha2 and beta1 bands ($p < 0.03$).* ***Tapentadol increased spectral power in the alpha1 band*** ($p < 0.001$). Source localization revealed that oxycodone decreased activity of the temporal and limbic region in the delta band, and frontal lobe in the alpha2 and beta1 bands, ***whereas tapentadol decreased alpha1 band activity in the temporal lobe*** compared to placebo. Oxycodone and tapentadol reduced pain perception and changed the central processing of tonic pain. Different mechanisms of action were involved, where oxycodone affected cortical structures more than tapentadol.

----- TRAMADOL () -----

DRUG FACTS

SYNOPSIS: Prescribed to relieve moderate to moderately severe pain.

Increased delta and gamma power and decreased alpha power

Koncz, S., Papp, N., Menczelesz, N., Pothorszki, D., & Bagdy, G. (2021). *EEG and Sleep Effects of Tramadol Suggest Potential Antidepressant Effects with Different Mechanisms of Action.* Pharmaceuticals (Basel, Switzerland), 14(5), 431. https://doi.org/10.3390/ph14050431.

Tramadol is a widely used, centrally acting, opioid analgesic compound, with additional inhibitory effects on the synaptic reuptake of serotonin and noradrenaline, as well as on the 5-HT2 and NMDA receptors. Preclinical and clinical evidence also suggests its therapeutic potential in the treatment of depression and anxiety. The effects of most widely used antidepressants on sleep and quantitative electroencephalogram (qEEG) are well characterized; however, such studies of tramadol are scarce. Our aim was to characterize the effects of tramadol on sleep architecture and qEEG in different sleep-wake stages. EEG-equipped Wistar rats were treated with tramadol (0, 5, 15 and 45 mg/kg) at the beginning of the passive phase, and EEG, electromyogram and motor activity were recorded. Tramadol dose-dependently reduced the time spent in rapid eye movement (REM) sleep and increased the REM onset latency. Lower doses of tramadol had wake-promoting effects in the first hours, while 45 mg/kg of tramadol promoted sleep first, but induced wakefulness thereafter. ***During non-REM sleep, tramadol (15 and 45 mg/kg) increased delta and decreased alpha power, while all doses increased gamma power***. In conclusion, the sleep-related and qEEG effects of tramadol suggest antidepressant-like properties, including specific beneficial effects in selected patient groups, and raise the possibility of a faster acting antidepressant action.

Peak amplitudes EO-EC smaller in the central theta, central beta, and parietal beta.

Zortea, M., Beltran, G., Alves, R. L., Vicuña, P., Torres, I. L. S., Fregni, F., & Caumo, W. (2021).

Spectral Power Density analysis of the resting-state as a marker of the central effects of opioid use in fibromyalgia. Scientific reports, 11(1), 22716. https://doi.org/10.1038/s41598-021-01982-0

This study showed two main findings related to FM patients in use of opioid analgesics associated to the variations between EO and EC states on the oscillations of SPD in frontal, central, and parietal regions at resting: First, the ***variation for peak amplitudes EO-EC was smaller in opioid users than non-opioid users in the central theta, central beta, and parietal beta. At the parietal region, the delta EO-EC variation was positive for the opioid users. This indicates that in EO the peak amplitude was larger than EC. However, the EO-EC variations in parietal delta were also negatively related to the disability due to pain, and central and parietal beta were positively correlated with sleep quality. Second, these variations in EO-EC states for central beta and parietal beta are likely suitable markers to discriminate opioid users over non-users***. In sum, these results give insights into generating testable hypotheses regarding the dynamics of resting-state brain activity that may disrupt opioid users. These results give a remarkable contribution to this field of knowledge, indicating that ***opioid users lack expected neural modulation between EO and EC states***. However, the exposure of opioid use has been assessed by self-reported, a factor that restricts us from making inferences about its relationship with dose or a specific drug. In contrast, the strength of these results is mainly because our primary outcome was evaluated by electrophysiological measures upon an experimental controlled condition, making them less prone to assessment biases. They are relevant to research and perhaps to the clinical setting, mainly to open an avenue to use the amplitude of EEG indexed by SPD as a marker to comprehend opioids' effect on cortical processing. Despite this contribution to the scientific field, we cannot isolate if these changes in the electrophysiological measures indicate a deteriorated cortical processing related to the severity of disease or consequence of opioids effects. In fact, recent findings suggest the severity of symptoms, including pain duration, anxiety and depression was negatively correlated with EEG wave power). However, we need to realize that these are aspects intrinsic of the condition of illness (i.e., severity of symptoms and analgesic demand), which we cannot change.

Another exciting result is that we found these associations in a sample of FM, in which the most frequent opioid used was tramadol. Recently, tramadol has been attributed some potential benefits over other opioids on treating pain symptoms in fibromyalgia. It is important to stress that there is no evidence about its effect based on clinical outcomes. Their theoretical benefits are associated with its pharmacodynamics properties, such as act a weak an um agonist mu, and efficacy is linked to action on serotonin reuptake inhibition and noradrenaline. Based on these pharmacological properties, its reputation is growing as a drug with a more favorable side effect profile, including lower constipation rates, overdose, and addiction. This way, these results based on neurophysiological measures are essential to understand the neural mechanisms responsible for its effect at the cortical level. Given there is growing evidence that excessive ***tramadol consumption causes significant changes in the prefrontal cortex's cognitive function***. Based on this data, it is plausible that tramadol use can increase the cortical dysfunction that leads to symptoms severity in fibromyalgia, which itself may induce the prescription of higher dose and more frequent analgesic. This way, the severity of pain can work as a trigger to use opioids, which on the other side contributes to change the cortical

dysfunction, forming a vicious cycle that self feeds back. From this perspective, the current findings contribute to revealing a neural substrate to comprehend the harmful role of the opioid on the cortical neural networks.

----- PSYCHEDELICS | HALLUCINOGENS -----

CLASS FACTS

SYNOPSIS: This class of drugs tends to desynchronize the EEG, possibly predominantly in the frontal cortex.

Decrease/desynchronization of EEG activity and disconnection within 1–40 Hz, localized on the large areas of the frontal and sensorimotor cortex

Vejmola, Č., Tylš, F., Piorecká, V. et al. P*silocin, LSD, mescaline, and DOB all induce broadband desynchronization of EEG and disconnection in rats with robust translational validity*. Transl Psychiatry 11, 506 (2021). https://doi.org/10.1038/s41398-021-01603-4

Serotonergic psychedelics are recently gaining a lot of attention as a potential treatment of several neuropsychiatric disorders. Broadband desynchronization of EEG activity and disconnection in humans have been repeatedly shown; however, translational data from animals are completely lacking. Therefore, the main aim of our study was to assess the effects of tryptamine and phenethylamine psychedelics (psilocin 4 mg/kg, LSD 0.2 mg/kg, mescaline 100 mg/kg, and DOB 5 mg/kg) on EEG in freely moving rats. A system consisting of 14 cortical EEG electrodes, co-registration of behavioral activity of animals with subsequent analysis only in segments corresponding to behavioral inactivity (resting-state-like EEG) was used in order to reach a high level of translational validity. ***Analyses of the mean power, topographic brain-mapping, and functional connectivity revealed that all of the psychedelics irrespective of the structural family induced overall and time-dependent global decrease/desynchronization of EEG activity and disconnection within 1–40 Hz. Major changes in activity were localized on the large areas of the frontal and sensorimotor cortex showing some subtle spatial patterns characterizing each substance.*** A rebound of occipital theta (4–8 Hz) activity was detected at later stages after treatment with mescaline and LSD. Connectivity analyses showed an overall decrease in global connectivity for both the components of cross-spectral and phase-lagged coherence. Since our results show almost identical effects to those known from human EEG/MEG studies, we conclude that our method has robust translational validity.

----- KETAMINE \ NMDA RECEPTOR ANTAGONISTS -----

DRUG FACTS

SYNOPSIS: This drug is a short-acting anesthetic that may adjust the thalamic generator with consequences in the DMN, Salience, and Executive networks. There is some indication that alpha and beta power increases relevant to dosage. Some types of NMDA receptor agonists may also decrease theta power.

Integral role in synaptic plasticity, a neuronal mechanism believed to be the basis of memory formation.

Jewett BE, Thapa B. *Physiology, NMDA Receptor*. [Updated 2021 Dec 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519495/

The N-methyl-D-aspartate (NMDA) receptor is a receptor of glutamate, the primary excitatory neurotransmitter in the human brain. ***It plays an integral role in synaptic plasticity, which is a neuronal mechanism believed to be the basis of memory formation.*** NMDA receptors also appear to have involvement in a process called excitotoxicity. Excitotoxicity may play a role in the pathophysiology of a variety of diseases such as epilepsy or Alzheimer disease. Many drugs inhibit NMDA receptors, including ketamine and phencyclidine, two common drugs of abuse.

Thalamus Alpha Generator: Ketamine

Zorumski CF, Izumi Y, Mennerick S. *Ketamine: NMDA Receptors and Beyond*. J Neurosci. 2016 Nov 2;36(44):11158-11164. doi: 10.1523/JNEUROSCI.1547-16.2016. PMID: 27807158; PMCID: PMC5148235.

Human studies examining the effects of the dissociative anesthetic ketamine as a model for psychosis and as a rapidly acting antidepressant have spurred great interest in understanding ketamine's actions at molecular, cellular, and network levels. Although ketamine has unequivocal uncompetitive inhibitory effects on N-methyl-d-aspartate receptors (NMDARs) and may preferentially alter the function of NMDARs on interneurons, recent work has questioned whether block of NMDARs is critical for its mood enhancing actions. In this viewpoint, we examine the evolving literature on ketamine supporting NMDARs as important triggers for certain psychiatric effects and the possibility that the antidepressant trigger is unrelated to NMDARs. The rapidly evolving story of ketamine offers great hope for untangling and treating the biology of both depressive and psychotic illnesses.

The task of elucidating the network and pharmacological mechanisms that underlie schizophrenia is extremely challenging, and it is important to seek converging hints using multiple approaches. We have described in our Perspectives article converging evidence that ***the psychotogenic action of ketamine may result from preferential inhibition of GluN2C-containing NMDARs and that the critical site of action may be the thalamus, where the inhibition evokes δ frequency oscillations (Zhang et al., 2012). Such oscillations may be transmitted to cortex and hippocampus and produce psychotogenic effects. Related processes could cause the elevated δ power in the EEG of patients with schizophrenia (Lehmann et al., 2014).*** Understanding these processes may be key to developing treatments for the disease.

DMN, Salience, Central Executive Networks, Ketamine

de la Salle, S., Choueiry, J., Shah, D., Bowers, H., McIntosh, J., Ilivitsky, V., & Knott, V. (2016). *Effects of Ketamine on Resting-State EEG Activity and Their Relationship to Perceptual/Dissociative Symptoms in Healthy Humans*. *Frontiers in Pharmacology*, *7*. https://www.frontiersin.org/articles/10.3389/fphar.2016.00348

N-methyl-D-aspartate (NMDA) receptor antagonists administered to healthy humans results in schizophrenia-like symptoms, which preclinical research suggests are due to glutamatergically altered brain oscillations. Here, we examined resting-state electroencephalographic activity in 21 healthy volunteers assessed in a placebo-controlled, double-blind, randomized study involving administration of either a saline infusion or a sub-anesthetic dose of ketamine, an NMDA receptor antagonist. ***Frequency-specific current source density (CSD) was assessed at sensor-level and source-level using eLORETA within regions of interest of a triple network model of schizophrenia (this model posits a dysfunctional switching between large-scale***

Default Mode and Central Executive networks by the monitor-controlling Salience Network). These CSDs were measured in each session along with subjective symptoms as indexed with the Clinician Administered Dissociative States Scale. Ketamine-induced CSD reductions in slow (delta/theta and alpha) and increases in fast (gamma) frequencies at scalp electrode sites were paralleled by frequency-specific CSD changes in the Default Mode, Central Executive, and Salience networks. Subjective symptoms scores were increased with ketamine and ratings of depersonalization in particular were associated with alpha CSD reductions in general and in specific regions of interest in each of the three networks. These results tentatively support the hypothesis that pathological brain oscillations associated with hypofunctional NMDA receptor activity may contribute to the emergence of the perceptual/dissociate symptoms of schizophrenia.

EEG Gamma Power Changes Following Administration of NMDA Receptor Antagonists

Maninder Chopra, Michael Quirk, Ray Rothstein, John Roberts, Mary J Bock, Ed Christian, Russell Bialecki and Carlos Fonck Neuroscience Biology, Safety Assessment, DMPK, Astrazeneca R&D, Wilmington, DE. *EEG Gamma Power Changes Following Administration of NMDA Receptor Antagonists*. PPT

Quantitative EEG (qEEG) offers an opportunity to provide a pharmaco-dynamic, mechanistic, and potentially translatable biomarker for various drug-induced and disease states.
RESULTS: Changes in electroencephalogram (EEG) gamma band power, defined as frequencies ranging between 30 and 80 Hz, have been linked in humans to enhanced cognitive function, but also to pathological states such as schizophrenia, drug- induced hallucinations, epilepsy, and Alzheimer's disease.
Thus, the ability to pharmacologically modulate gamma power may be of therapeutic interest. The EEG provides temporal resolution in the milliseconds range, and the ability to detect both excitatory and inhibitory neuronal activity. Here we study effects of NMDA receptor blockers on mouse EEG, with an overall aim to develop a useful biomarker for this compound class, with a potential for forward and back- translation.
Non-selective NMDA receptor open channel blockers ketamine and remacemide increased beta and alpha power in dose- and exposure-dependent manner. In contract, traxoprodil, an NR2b specific allosteric antagonist showed a small decrease on theta power. Differences in the effects on EEG theta power caused by the O types of NMDA receptor agonists may be explained by differences in blocking mechanisms.

Gamma and theta in resting state network in schizophrenia

Curic, S., Andreou, C., Nolte, G., Steinmann, S., Thiebes, S., Polomac, N., Haaf, M., Rauh, J., Leicht, G., & Mulert, C. (2021). Ketamine Alters Functional Gamma and Theta Resting-State Connectivity in Healthy Humans: Implications for Schizophrenia Treatment Targeting the Glutamate System. *Frontiers in psychiatry*, *12*, 671007. https://doi.org/10.3389/fpsyt.2021.671007

Disturbed functional connectivity is assumed to cause neurocognitive deficits in patients suffering from schizophrenia. A Glutamate N-methyl-D-aspartate receptor (NMDAR) dysfunction has been suggested as a possible mechanism underlying altered connectivity in schizophrenia, especially in the gamma- and theta-frequency range. The present study aimed to

investigate the effects of the NMDAR-antagonist ketamine on resting-state power, functional connectivity, and schizophrenia-like psychopathological changes in healthy volunteers. In a placebo-controlled crossover design, 25 healthy subjects were recorded using resting-state 64-channel-electroencephalography (EEG) (eyes closed). The imaginary coherence-based Multivariate Interaction Measure (MIM) was used to measure gamma and theta connectivity across 80 cortical regions. The network-based statistic was applied to identify involved networks under ketamine. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) and the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC). Ketamine caused an increase in all PANSS ($p < 0.001$) as well as 5D-ASC scores ($p < 0.01$). Significant increases in resting-state gamma and theta power were observed under ketamine compared to placebo ($p < 0.05$). The source-space analysis revealed two distinct networks with an increased mean functional gamma- or theta-band connectivity during the ketamine session. ***The gamma-network consisted of midline regions, the cuneus, the precuneus, and the bilateral posterior cingulate cortices, while the theta-band network involved the Heschl gyrus, midline regions, the insula, and the middle cingulate cortex. The current source density (CSD) within the gamma-band correlated negatively with the PANSS negative symptom score, and the activity within the gamma-band network correlated negatively with the subjective changed meaning of percepts subscale of the 5D-ASC. These results are in line with resting-state patterns seen in people who have schizophrenia and argue for a crucial role of the glutamate system in mediating dysfunctional gamma- and theta-band-connectivity in schizophrenia. Resting-state networks could serve as biomarkers for the response to glutamatergic drugs or drug development efforts within the glutamate system***.

Reduced auditory evoked gamma-band response and schizophrenia-like clinical symptoms under subanesthetic ketamine

Curic, S., Leicht, G., Thiebes, S., Andreou, C., Polomac, N., Eichler, I. C., Eichler, L., Zöllner, C., Gallinat, J., Steinmann, S., & Mulert, C. (2019). *Reduced auditory evoked gamma-band response and schizophrenia-like clinical symptoms under subanesthetic ketamine*. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 44(7), 1239–1246. https://doi.org/10.1038/s41386-019-0328-5

Abnormal gamma-band oscillations (GBO) have been frequently associated with the pathophysiology of schizophrenia. GBO are modulated by glutamate, a neurotransmitter, which is continuously discussed to shape the complex symptom spectrum in schizophrenia. The current study examined the effects of ketamine, a glutamate N-methyl-D-aspartate receptor (NMDAR) antagonist, on the auditory-evoked gamma-band response (aeGBR) and psychopathological outcomes in healthy volunteers to investigate neuronal mechanisms of psychotic behavior. In a placebo-controlled, randomized crossover design, the aeGBR power, phase-locking factor (PLF) during a choice reaction task, the Positive and Negative Syndrome Scale (PANSS) and the Altered State of Consciousness (5D-ASC) Rating Scale were assessed in 25 healthy subjects. Ketamine was applied in a subanaesthetic dose. ***Low-resolution brain electromagnetic tomography was used for EEG source localization. Significant reductions of the aeGBR power and PLF were identified under ketamine administration compared to***

placebo (p < 0.01). Source-space analysis of aeGBR generators revealed significantly reduced current source density (CSD) within the anterior cingulate cortex during ketamine administration. Ketamine induced an increase in all PANSS (p < 0.001) as well as 5D-ASC scores (p < 0.01) and increased response times (p < 0.001) and error rates (p < 0.01). Only negative symptoms were significantly associated with an aeGBR power decrease (p = 0.033) as revealed by multiple linear regression. These findings argue for a substantial role of the glutamate system in the mediation of dysfunctional gamma band responses and negative symptomatology of schizophrenia and are compatible with the NMDAR hypofunction hypothesis of schizophrenia.

Ketamine increased basal power in the gamma band and decreased the evoked power in the theta band.

Ehrlichman, R. S., Gandal, M. J., Maxwell, C. R., Lazarewicz, M. T., Finkel, L. H., Contreras, D., Turetsky, B. I., & Siegel, S. J. (2009). *N-methyl-d-aspartic acid receptor antagonist-induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia.* Neuroscience, 158(2), 705–712. https://doi.org/10.1016/j.neuroscience.2008.10.031

Introduction: Electrophysiological responses to auditory stimuli have provided a useful means of elucidating mechanisms and evaluating treatments in psychiatric disorders. Deficits in gating during paired-click tasks and lack of mismatch negativity following deviant stimuli have been well characterized in patients with schizophrenia. Recently, analyses of basal, induced, and evoked frequency oscillations have gained support as additional measures of cognitive processing in patients and animal models. The purpose of this study is to examine frequency oscillations in mice across the theta (4-7.5 Hz) and gamma (31-61 Hz) bands in the context of N-methyl-d-aspartic acid receptor (NMDAR) hypofunction and dopaminergic hyperactivity, both of which are thought to serve as pharmacological models of schizophrenia. **Experimental procedures:** Electroencephalograms (EEG) were recorded from mice in five treatment groups that consisted of haloperidol, risperidone, amphetamine, ketamine, or ketamine plus haloperidol during an auditory task. Basal, induced and evoked powers in both frequencies were calculated. **Results:** ***Ketamine increased basal power in the gamma band and decreased the evoked power in the theta band. The increase in basal gamma was not blocked by treatment with a conventional antipsychotic. No other treatment group was able to fully reproduce this pattern in the mice***. **Conclusions:** Ketamine-induced alterations in EEG power spectra are consistent with abnormalities in the theta and gamma frequency ranges reported in patients with schizophrenia. Our findings support the hypothesis that NMDAR hypofunction contributes to the deficits in schizophrenia and that the dopaminergic pathways alone may not account for these changes.

Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine.

Hong, L. E., Summerfelt, A., Buchanan, R. W., O'Donnell, P., Thaker, G. K., Weiler, M. A., & Lahti, A. C. (2010). *Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine*. Neuropsychopharmacology : official

publication of the American College of Neuropsychopharmacology, 35(3), 632–640. https://doi.org/10.1038/npp.2009.168

Several electrical neural oscillatory abnormalities have been associated with schizophrenia, although the underlying mechanisms of these oscillatory problems are unclear. Animal studies suggest that one of the key mechanisms of neural oscillations is through glutamatergic regulation; therefore, neural oscillations may provide a valuable animal-clinical interface on studying glutamatergic dysfunction in schizophrenia. To identify glutamatergic control of neural oscillation relevant to human subjects, we studied the effects of ketamine, an N-methyl-D-aspartate antagonist that can mimic some clinical aspects of schizophrenia, on auditory-evoked neural oscillations using a paired-click paradigm. This was a double-blind, placebo-controlled, crossover study of ketamine vs saline infusion on 10 healthy subjects. Clinically, infusion of ketamine in subanesthetic dose significantly increased thought disorder, withdrawal-retardation, and dissociative symptoms. ***Ketamine significantly augmented high-frequency oscillations (gamma band at 40-85 Hz, p=0.006) and reduced low-frequency oscillations (delta band at 1-5 Hz, p<0.001) compared with placebo. Importantly, the combined effect of increased gamma and reduced delta frequency oscillations was significantly associated with more withdrawal-retardation symptoms experienced during ketamine administration (p=0.02). Ketamine also reduced gating of the theta-alpha (5-12 Hz) range oscillation, an effect that mimics previously described deficits in schizophrenia patients and their first-degree relatives. In conclusion, acute ketamine appeared to mimic some aspects of neural oscillatory deficits in schizophrenia, and showed an opposite effect on scalp-recorded gamma vs low-frequency oscillations***. These electrical oscillatory indexes of subanesthetic ketamine can be potentially used to cross-examine glutamatergic pharmacological effects in translational animal and human studies.

Ketamine enhanced the low-gamma-band (30-60 Hz) and dampened the beta-band (13-30 Hz).

Ma, L., Skoblenick, K., Johnston, K., & Everling, S. (2018). *Ketamine Alters Lateral Prefrontal Oscillations in a Rule-Based Working Memory Task*. The Journal of neuroscience : the official journal of the Society for Neuroscience, 38(10), 2482–2494. https://doi.org/10.1523/JNEUROSCI.2659-17.2018

Acute administration of N-methyl-D-aspartate receptor (NMDAR) antagonists in healthy humans and animals produces working memory deficits similar to those observed in schizophrenia. However, it is unclear whether they also lead to altered low-frequency (≤60 Hz) neural oscillatory activities similar to those associated with schizophrenia during working memory processes. Here, we recorded local field potentials (LFPs) and single-unit activity from the lateral prefrontal cortex (LPFC) of three male rhesus macaque monkeys while they performed a rule-based prosaccade and antisaccade working memory task both before and after systemic injections of a subanesthetic dose (≤0.7 mg/kg) of ketamine. ***Accompanying working-memory impairment, ketamine enhanced the low-gamma-band (30-60 Hz) and dampened the beta-band (13-30 Hz) oscillatory activities in the LPFC during both delay periods and intertrial intervals. It also increased task-related alpha-band activities, likely reflecting compromised attention. Beta-band oscillations may be especially relevant to working memory processes because stronger beta power weakly but significantly predicted***

shorter saccadic reaction time. Also in beta band, ketamine reduced the performance-related oscillation as well as the rule information encoded in the spectral power. Ketamine also reduced rule information in the spike field phase consistency in almost all frequencies up to 60 Hz. Our findings support NMDAR antagonists in nonhuman primates as a meaningful model for altered neural oscillations and synchrony, which reflect a disorganized network underlying the working memory deficits in schizophrenia. SIGNIFICANCE STATEMENT Low doses of ketamine, an NMDAR blocker, produce working memory deficits similar to those observed in schizophrenia. In the lateral prefrontal cortex, a key brain region for working memory, we found that ketamine altered neural oscillatory activities in similar ways that differentiate schizophrenic patients and healthy subjects during both task and nontask periods. Ketamine induced stronger gamma (30-60 Hz) and weaker beta (13-30 Hz) oscillations, reflecting local hyperactivity and reduced long-range communications. Furthermore, ketamine reduced performance-related oscillatory activities, as well as the rule information encoded in the oscillations and in the synchrony between single-cell activities and oscillations. The ketamine model helps link the molecular and cellular basis of neural oscillatory changes to the working memory deficit in schizophrenia.

Ketamine increased gamma-power while beta-band activity was decreased.

Rivolta, D., Heidegger, T., Scheller, B., Sauer, A., Schaum, M., Birkner, K., Singer, W., Wibral, M., & Uhlhaas, P. J. (2015). *Ketamine Dysregulates the Amplitude and Connectivity of High-Frequency Oscillations in Cortical-Subcortical Networks in Humans: Evidence From Resting-State Magnetoencephalography-Recordings.* Schizophrenia bulletin, 41(5), 1105–1114. https://doi.org/10.1093/schbul/sbv051

Hypofunctioning of the N-methyl-D-aspartate receptor (NMDA-R) has been prominently implicated in the pathophysiology of schizophrenia (ScZ). The current study tested the effects of ketamine, a dissociative anesthetic and NMDA-R antagonist, on resting-state activity recorded with magnetoencephalography (MEG) in healthy volunteers. In a single-blind cross-over design, each participant (n = 12) received, on 2 different sessions, a subanesthetic dose of S-ketamine (0.006 mg/Kg) and saline injection. MEG-data were analyzed at sensor- and source-level in the beta (13-30 Hz) and gamma (30-90 Hz) frequency ranges. In addition, connectivity analysis at source-level was performed using transfer entropy (TE). ***Ketamine increased gamma-power while beta-band activity was decreased. Specifically, elevated 30-90 Hz activity was pronounced in subcortical (thalamus and hippocampus) and cortical (frontal and temporal cortex) regions, whilst reductions in beta-band power were localized to the precuneus, cerebellum, anterior cingulate, temporal and visual cortex. TE analysis demonstrated increased information transfer in a thalamo-cortical network after ketamine administration***. The findings are consistent with the pronounced dysregulation of high-frequency oscillations following the inhibition of NMDA-R in animal models of ScZ as well as with evidence from electroencephalogram-data in ScZ-patients and increased functional connectivity during early illness stages. Moreover, our data highlight the potential contribution of thalamo-cortical connectivity patterns towards ketamine-induced neuronal dysregulation, which may be relevant for the understanding of ScZ as a disorder of disinhibition of neural circuits.

Cortical Connectivity Moderators of Antidepressant vs Placebo Treatment Response in Major Depressive Disorder: Secondary Analysis of a Randomized Clinical Trial

Rolle, C. E., Fonzo, G. A., Wu, W., Toll, R., Jha, M. K., Cooper, C., Chin-Fatt, C., Pizzagalli, D. A., Trombello, J. M., Deckersbach, T., Fava, M., Weissman, M. M., Trivedi, M. H., & Etkin, A. (2020). *Cortical Connectivity Moderators of Antidepressant vs Placebo Treatment Response in Major Depressive Disorder: Secondary Analysis of a Randomized Clinical Trial*. JAMA psychiatry, 77(4), 397–408. https://doi.org/10.1001/jamapsychiatry.2019.3867

Objective: To determine whether EEG connectivity could reveal neural moderators of antidepressant treatment. Design, setting, and participants: In this nonprespecified secondary analysis, data were analyzed from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinic Care study, a placebo-controlled, double-blinded randomized clinical trial. Recruitment began July 29, 2011, and was completed December 15, 2015. A random sample of 221 outpatients with depression aged 18 to 65 years who were not taking medication for depression was recruited and assessed at 4 clinical sites. Analysis was performed on an intent-to-treat basis. Statistical analysis was performed from November 16, 2018, to May 23, 2019. Interventions: Patients received either the selective serotonin reuptake inhibitor sertraline hydrochloride or placebo for 8 weeks. **Main outcomes and measures**: Electroencephalographic orthogonalized power envelope connectivity analyses were applied to resting-state EEG data. Intent-to-treat prediction linear mixed models were used to determine which pretreatment connectivity patterns were associated with response to sertraline vs placebo. The primary clinical outcome was the total score on the 17-item Hamilton Rating Scale for Depression, administered at each study visit. **Results:** ***Of the participants recruited, 9 withdrew after first dose owing to reported adverse effects, and 221 participants (150 women; mean [SD] age, 37.8 [12.7] years) underwent EEG recordings and had high-quality pretreatment EEG data. After correction for multiple comparisons, connectome-wide analyses revealed moderation by connections within and between widespread cortical regions-most prominently parietal-for both the antidepressant and placebo groups. Greater alpha-band and lower gamma-band connectivity predicted better placebo outcomes and worse antidepressant outcomes. Lower connectivity levels in these moderating connections were associated with higher levels of anhedonia. Connectivity features that moderate treatment response differentially by treatment group were distinct from connectivity features that change from baseline to 1 week into treatment.*** The group mean (SD) score on the 17-item Hamilton Rating Scale for Depression was 18.35 (4.58) at baseline and 26.14 (30.37) across all time points. **Conclusions and relevance**: These findings establish the utility of EEG-based network functional connectivity analyses for differentiating between responses to an antidepressant vs placebo. A role emerged for parietal cortical regions in predicting placebo outcome. From a treatment perspective, capitalizing on the therapeutic components leading to placebo response differentially from antidepressant response should provide an alternative direction toward establishing a placebo signature in clinical trials, thereby enhancing the signal detection in randomized clinical trials.

Shift of energy to slow (delta, theta) and fast (gamma) wave frequencies in the ketamine condition.

Zacharias, N., Musso, F., Müller, F., Lammers, F., Saleh, A., London, M., de Boer, P., & Winterer, G. (2020). *Ketamine effects on default mode network activity and vigilance: A randomized, placebo-controlled crossover simultaneous fMRI/EEG study.* Human brain mapping, 41(1), 107–119. https://doi.org/10.1002/hbm.24791

In resting-state functional connectivity experiments, a steady state (of consciousness) is commonly supposed. However, recent research has shown that the resting state is a rather dynamic than a steady state. In particular, changes of vigilance appear to play a prominent role. Accordingly, it is critical to assess the state of vigilance when conducting pharmacodynamic studies with resting-state functional magnetic resonance imaging (fMRI) using drugs that are known to affect vigilance such as (subanesthetic) ketamine. In this study, we sought to clarify whether the previously described ketamine-induced prefrontal decrease of functional connectivity is related to diminished vigilance as assessed by electroencephalography (EEG). We conducted a randomized, double-blind, placebo-controlled crossover study with subanesthetic S-Ketamine in N = 24 healthy, young subjects by simultaneous acquisition of resting-state fMRI and EEG data. ***We conducted seed-based default mode network functional connectivity and EEG power spectrum analyses. After ketamine administration, decreased functional connectivity was found in medial prefrontal cortex whereas increased connectivities were observed in intraparietal cortices. In EEG, a shift of energy to slow (delta, theta) and fast (gamma) wave frequencies was seen in the ketamine condition. Frontal connectivity is negatively related to EEG gamma and theta activity while a positive relationship is found for parietal connectivity and EEG delta power. Our results suggest a direct relationship between ketamine-induced functional connectivity changes and the concomitant decrease of vigilance in EEG. The observed functional changes after ketamine administration may serve as surrogate end points and provide a neurophysiological framework, for example, for the antidepressant action of ketamine*** (trial name: 29JN1556, EudraCT Number: 2009-012399-28).

----- THC -----

DRUG FACTS

SYNOPSIS: It has been shown that THC has differing effects on the EEG based upon mechanism of intake and type of THC compound. Relatively quickly, higher inhaled doses will lower iAPF and over time its effect will be on faster frequencies. The CNV is affected by dose as well. THC may induce neural noise – a phenomenon that is indicated in schizophrenia and involves increased interruption and confusion of the EEG.

Significant decrease in the peak power of the alpha rhythm and an increase in auditory evoked-response latency.

Low, M. D., Klonoff, H., & Marcus, A. (1973). *The neurophysiological basis of the marijuana experience*. Canadian Medical Association journal, 108(2), 157–165.

Experiments were done with 75 healthy young adults to explore the neurophysiological basis of the acute marijuana intoxication state. Tests included recording the scalp EEG, visual and auditory cerebral evoked-potentials, the CNV, cerebral slow potentials related to certainty of response correctness in auditory discrimination tasks, heart rate, respiration and the galvanic

skin response. All variables were recorded over 45 minutes before and 45 minutes after smoking a marijuana cigarette containing either 4.8, 9.1 or less than 0.01 mg. Delta (9)-THC. ***High doses of marijuana induced a significant decrease in the peak power of the alpha rhythm and an increase in auditory evoked-response latency.*** The CNV increased in amplitude after smoking marijuana in low doses and sequential CNVs showed changes consistent with sustained attention but decreased certainty about performance following either low or high dose. Marijuana interfered significantly with performance of the discrimination task itself.

Neural noise

Cortes-Briones, J. A., Cahill, J. D., Skosnik, P. D., Mathalon, D. H., Williams, A., Sewell, R. A., Roach, B. J., Ford, J. M., Ranganathan, M., & D'Souza, D. C. (2015). *The psychosis-like effects of Δ(9)-tetrahydrocannabinol are associated with increased cortical noise in healthy humans*. Biological Psychiatry (1969), 78(11), 805–813. https://doi.org/10.1016/j.biopsych.2015.03.023

Drugs that induce psychosis may do so by increasing the level of task-irrelevant random neural activity or neural noise. Increased levels of neural noise have been demonstrated in psychotic disorders. We tested the hypothesis that neural noise could also be involved in the psychotomimetic effects of delta-9-tetrahydrocannabinol (Δ(9)-THC), the principal active constituent of cannabis. Neural noise was indexed by measuring the level of randomness in the electroencephalogram during the prestimulus baseline period of an oddball task using Lempel-Ziv complexity, a nonlinear measure of signal randomness. The acute, dose-related effects of Δ(9)-THC on Lempel-Ziv complexity and signal power were studied in humans (n = 24) who completed 3 test days during which they received intravenous Δ(9)-THC (placebo, .015 and .03 mg/kg) in a double-blind, randomized, crossover, and counterbalanced design. Δ(9)-THC increased neural noise in a dose-related manner. Furthermore, ***there was a strong positive relationship between neural noise and the psychosis-like positive and disorganization symptoms induced by Δ(9)-THC, which was independent of total signal power.*** Instead, there was no relationship between noise and negative-like symptoms. In addition, Δ(9)-THC reduced total signal power during both active drug conditions compared with placebo, but no relationship was detected between signal power and psychosis-like symptoms. At doses that produced psychosis-like effects, Δ(9)-THC increased neural noise in humans in a dose-dependent manner. Furthermore, increases in neural noise were related with increases in Δ(9)-THC-induced psychosis-like symptoms but not negative-like symptoms. **These findings suggest that increases in neural noise may contribute to the psychotomimetic effects of Δ(9)-THC.**

Immediate and long-term changes in EEG with 3 types of THC

Uchiyama, N., Kikura-Hanajiri, R., Matsumoto, N., Huang, Z.-L., Goda, Y., & Urade, Y. (2012). *Effects of synthetic cannabinoids on electroencephalogram power spectra in rats. Forensic Science International*, 215(1), 179–183. https://doi.org/10.1016/j.forsciint.2011.05.005

Several synthetic cannabinoids have recently been distributed as psychoactive adulterants in many herbal products on the illegal drug market around the world. However, there is little information on pharmacology and toxicology of such compounds. Although Δ9 -tetrahydrocannabinol (Δ9 -THC), a psychoactive cannabinoid of marijuana, was reported to

affect electroencephalograms (EEG) of rats, the effects of synthetic cannabinoids are unknown. We examined the pharmacological activities of three synthetic cannabinoids; cannabicyclohexanol (CCH), CP-47,497 and JWH-018; by analyzing EEG power spectra and locomotor activity after intraperitoneal administration to rats and compared them with those of Δ9 -THC. **The three compounds significantly increased the EEG power in the frequency range of 5.0–6.0 Hz for the first 3 h, while Δ9 -THC decreased the power spectra in the wide range of 7.0–20.0 Hz during the first hour. These results indicate that the effect of the three compounds on EEG is different from that of Δ9 -THC.** Additionally, CCH, CP-47,497 and JWH-018 significantly decreased the locomotor activity for 11.5 h, 11 h and 4.5 h, respectively, after administration which was longer than that of Δ9 -THC (3.5 h). Furthermore, all three compounds significantly reduced the total amounts of locomotor activity during a 3-h, 6-h and 12-h period after injection, whereas no statistical difference was observed for the Δ9 -THC injection. Among the three compounds, CCH and CP-47,497 exerted a longer duration of the change in the EEG power spectra and suppression of the locomotor activity than JWH-018.

----- PCP (Phencyclidine) -----

DRUG FACTS

SYNOPSIS: mPFC tends to have the largest impact from intake of PCP.

Long-lasting activation of medial prefrontal cortex (mPFC) neurons

Katayama, T., Jodo, E., Suzuki, Y., Hoshino, K.-Y., Takeuchi, S., & Kayama, Y. (2007). *Activation of medial prefrontal cortex neurons by phencyclidine is mediated via AMPA/kainate glutamate receptors in anesthetized rats*. Neuroscience, 150(2), 442–448. https://doi.org/10.1016/j.neuroscience.2007.09.007

Abstract Phencyclidine (PCP) is a psychotomimetic drug that elicits schizophrenia-like symptoms in healthy individuals, and animals administered PCP are now considered a reliable pharmacological model of schizophrenia. ***Recent studies have shown that systemically administered PCP produces long-lasting activation of medial prefrontal cortex (mPFC) neurons, and that hyperactivation of mPFC neurons plays a critically important role in the development of PCP-induced behavioral abnormalities.*** However, the receptors mediating this mPFC activation have not been clearly determined. Here, we examined the effects of local application of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), an AMPA/kainate glutamate receptor antagonist, scopolamine, a muscarinic acetylcholine receptor antagonist, and mecamylamine, a nicotinic acetylcholine receptor antagonist, on the increase in firing rate of mPFC neurons induced by systemic PCP in anesthetized rats. After tonic activation of mPFC neurons by PCP had been established, CNQX, scopolamine, or mecamylamine was iontophoretically applied or pressure-ejected on the recorded neuron. CNQX suppressed PCP-induced elevation of firing rate to baseline level, though scopolamine and mecamylamine each induced little change in firing rate. These findings suggest that PCP-induced activation of mPFC neurons is mediated primarily via AMPA/kainate glutamate receptors.

----- AYAHUASCA -----

DRUG FACTS

SYNOPSIS: This recreational and ceremonious drug is taken orally and is believed to also have medicinal value. Overall reduction in EEG power has been noted. Lower frequencies are reduced as time increases from ingestion. Hemispheric effects are found in the alpha and gamma bands.

Absolute power decreased in all frequency bands, most prominently in the theta band.

Riba, J., Anderer, P., Morte, A., Urbano, G., Jane, F., Saletu, B., & Barbanoj, M. J. (2002). *Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers*. British Journal of Clinical Pharmacology, 53(6), 613–628. https://doi.org/10.1046/j.1365-2125.2002.01609.x

Aims: Ayahuasca is a traditional South American psychoactive beverage used in Amazonian shamanism, and in the religious ceremonies of Brazilian-based syncretic religious groups with followers in the US and several European countries. This tea contains measurable amounts of the psychotropic indole N,N-dimethyltryptamine (DMT), and β-carboline alkaloids with MAO-inhibiting properties. In a previous report we described a profile of stimulant and psychedelic effects for ayahuasca as measured by subjective report self-assessment instruments. In the present study the cerebral bioavailability and time-course of effects of ayahuasca were assessed in humans by means of topographic quantitative-electroencephalography (q-EEG), a noninvasive method measuring drug-induced variations in brain electrical activity. Methods: Two doses (one low and one high) of encapsulated freeze-dried ayahuasca, equivalent to 0.6 and 0.85 mg DMT kg−1 body weight, were administered to 18 healthy volunteers with previous experience in psychedelic drug use in a double-blind crossover placebo-controlled clinical trial. Nineteen-lead recordings were undertaken from baseline to 8 h after administration. Subjective effects were measured by means of the Hallucinogen Rating Scale (HRS). Results: Ayahuasca induced a pattern of psychoactive effects which resulted in significant dose-dependent increases in all subscales of the HRS, and in significant and dose-dependent modifications of brain electrical activity. ***Absolute power decreased in all frequency bands, most prominently in the theta band. Mean absolute power decreases (95% CI) at a representative lead (P3) 90 min after the high dose were −20.20±15.23 μV2 and −2.70±2.21 μV2 for total power and theta power, respectively. Relative power decreased in the delta (−1.20±1.31% after 120 min at P3) and theta (−3.30±2.59% after 120 min at P3) bands, and increased in the beta band, most prominently in the faster beta-3 (1.00±0.88% after 90 min at P3) and beta-4 (0.30±0.24% after 90 min at P3) subbands. Finally, an increase was also seen for the centroid of the total activity and its deviation. EEG modifications began as early as 15-30 min, reached a peak between 45 and 120 min and decreased thereafter to return to baseline levels at 4-6 h after administration.*** Conclusions: The central effects of ayahuasca could be objectively measured by means of q-EEG, showing a time pattern which closely paralleled that of previously reported subjective effects. The modifications seen for the individual q-EEG variables were in line with those previously described for other serotonergic psychedelics and share some features with the profile of effects shown by pro-serotonergic and pro-dopaminergic drugs. The q-EEG profile supports the role of 5-HT2 and dopamine D2-receptor agonism in mediating the effects of ayahuasca on the central nervous system.

EEG power changes during ayahuasca intake

Schenberg, E. E., Alexandre, J. F. M., Filev, R., Cravo, A. M., Sato, J. R., Muthukumaraswamy, S. D., Yonamine, M., Waguespack, M., Lomnicka, I., Barker, S. A., & da Silveira, D. X. (2015). *Acute Biphasic Effects of Ayahuasca*. PloS One, 10(9), e0137202–. https://doi.org/10.1371/journal.pone.0137202

Ritual use of ayahuasca, an Amazonian Amerindian medicine turned sacrament in syncretic religions in Brazil, is rapidly growing around the world. Because of this internationalization, a comprehensive understanding of the pharmacological mechanisms of action of the brew and the neural correlates of the modified states of consciousness it induces is important. Employing a combination of electroencephalogram (EEG) recordings and quantification of ayahuasca's compounds and their metabolites in the systemic circulation we found ayahuasca to induce a biphasic effect in the brain. This effect was composed of reduced power in the alpha band (8-13 Hz) after 50 minutes from ingestion of the brew and increased slow- and fast-gamma power (30-50 and 50-100 Hz, respectively) between 75 and 125 minutes. ***Alpha power reductions were mostly located at left parieto-occipital cortex, slow-gamma power increase was observed at left centro-parieto-occipital, left fronto-temporal and right frontal cortices while fast-gamma increases were significant at left centro-parieto-occipital, left fronto-temporal, right frontal and right parieto-occipital cortices. These effects were significantly associated with circulating levels of ayahuasca's chemical compounds, mostly N,N-dimethyltryptamine (DMT), harmine, harmaline and tetrahydroharmine and some of their metabolites*.** An interpretation based on a cognitive and emotional framework relevant to the ritual use of ayahuasca, as well as it's potential therapeutic effects is offered.

----- PSILOCYBIN -----

DRUG FACTS

SYNOPSIS: Psilocybin is a compound produced from fungi in South America taken for recreational use. Cingulate areas and parahippocampal structures are most noted to have changes and may be related to the spiritual effect associated with this drug.

Current source and lagged coherence during psilocybin use

Kometer, Michael, et al. *Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations.* Psychopharmacology, vol. 232, no. 19, Oct. 2015, pp. 3663+. Gale OneFile: Nursing and Allied Health, link.gale.com/apps/doc/A427857125/PPNU?u=dall6191&sid=bookmark-PPNU&xid=fa1a5e01. Accessed 7 Mar. 2023.

Rationale: During the last years, considerable progress has been made toward understanding the neuronal basis of consciousness by using sophisticated behavioral tasks, brain-imaging techniques, and various psychoactive drugs. Nevertheless, the neuronal mechanisms underlying some of the most intriguing states of consciousness, including spiritual experiences, remain unknown. Objectives: To elucidate state of consciousness-related neuronal mechanisms, human subjects were given psilocybin, a naturally occurring serotonergic agonist and hallucinogen that has been used for centuries to induce spiritual experiences in religious and medical rituals. Methods: In this double-blind, placebo-controlled study, 50 healthy human

volunteers received a moderate dose of psilocybin, while high-density electroencephalogram (EEG) recordings were taken during eyes-open and eyes-closed resting states. The current source density and the lagged phase synchronization of neuronal oscillations across distributed brain regions were computed and correlated with psilocybin-induced altered states of consciousness. Results: ***Psilocybin decreased the current source density of neuronal oscillations at 1.5-20 Hz within a neural network comprising the anterior and posterior cingulate cortices and the parahippocampal regions. Most intriguingly, the intensity levels of psilocybin-induced spiritual experience and insightfulness correlated with the lagged phase synchronization of delta oscillations (1.5-4 Hz) between the retrosplenial cortex, the parahippocampus, and the lateral orbitofrontal area.*** Conclusions: These results provide systematic evidence for the direct association of a specific spatiotemporal neuronal mechanism with spiritual experiences and enhanced insight into life and existence. The identified mechanism may constitute a pathway for modulating mental health, as spiritual experiences can promote sustained well-being and psychological resilience.

----- LSD -----

DRUG FACTS

SYNOPSIS: LSD is a recreational drug taken orally. It can cause hallucinations, which may be due to its effect on the brain stem. It's effects include decreases in overall EEG power, but also increases of the low alpha band. Changes in ERPs include increased amplitude of the P300 and N170 components and increased P100 latency.

EEG alerting of the hallucinogens in the lower brainstem region.

Schweigerdt, A. K., Stewart, A. H., & Himwich, H. E. (1966). *An electrographic study of lysergic acid diethylamide and nine congeners.* Journal of Pharmacology and Experimental Therapeutics, 151(3), 353. http://jpet.aspetjournals.org/content/151/3/353.abstract

Ninety-six rabbits were used for an electrographic analysis of d-lysergic acid diethylamide (LSD) and 9 congeners. Experiments performed on the groups of intact animals showed that sustained drug-induced EEG arousal patterns were obtained with LSD, d-lysergic acidmonoethylamide (LAE), d-lysergic acid morpholide (LSM), d-1-methyl-lysergic acid diethylamide (MLD) and d-lysergic acid dimethylamide (DAM), but not with 1-methyl-3-lysergic acid butanolamide (UML), d-isolysergic acid diethylamide (d-iso-LSD), l-lysergic acid diethylamide (l-LSD) and 2-brom-d-lysergic acid diethylamide (BOL). All drugs which produced EEG activation were psychotomimetic, but the reverse did not necessarily hold true. One hallucinogen, d-lysergic acid amide, failed to elicit EEG arousal. In order to ascertain a site of EEG alerting, a series of transections consisting of sections above the midbrain, below the midbrain and at the level of the first cervical vertebra were made. Cervical transection neither abolished the evoked activation when LSD was given previous to the section nor inhibited the appearance of EEG arousal in rabbits transected prior to the administration of the drug. However, the arousal reaction was abolished by transections caudal to the midbrain, indicating an effective locus for LSD between these planes. Even though LSM, MLD and DAM evoked EEG alerting in animals with intact brain, the drug-induced arousal could be neither initiated nor maintained following cervical transection. In contrast, LAE elicited activation following transections posterior to the midbrain whereas sections above the midbrain abolished the

drug-induced pattern. ***These results indicate effective loci for EEG alerting of the hallucinogens in the lower brainstem region.*** In general, our results show that those psychotomimetic compounds containing the N-diethyl configuration exhibited loci of action in the lower brainstem. Furthermore, it has been suggested that the indole group and the N-diethyl or N-dimethyl configuration are important in producing changes in the site of EEG activation as well as in psychotomimetic behavior.

Increases in alpha-1 power in the hippocampus and striatum.

Dimpfel, W., Spüler, M., & Borbe, H. O. (1988). *Monitoring of the effects of antidepressant drugs in the freely moving rat by radioelectroencephalography (tele-stereo-EEG*). Neuropsychobiology, 19(2), 116–120. https://doi.org/10.1159/000118445

Chronic implantation of four bipolar concentric electrodes into frontal cortex, hippocampus, striatum and reticular formation of the rat allows continuous recording of bioelectric potentials during the action of various drugs. Frequency analysis of the potentials serves to quantify EEG changes over longer periods of time. Segmentation of the spectra into six frequency bands and integration of their power provides parameters by which the different drugs can be differentiated from each other. The action of classic tricyclic antidepressants like amitriptyline and imipramine as well as the effect of doxepine is characterized by a general decrease in power with respect to all frequency bands and all brain areas. Amitriptylinoxide can be distinguished from them by its lack of decrease in beta-2 power and a smaller decrease in alpha-1 power. Amphetamine lacks decreases in alpha-1 frequencies in the striatum and the reticular formation. Both diazepam and haloperidol show increases in beta-2 power; haloperidol increases alpha-1 power, whereas diazepam diminishes it. ***LSD can be differentiated from amphetamine by its increases in alpha-1 power in the hippocampus and striatum***. Thus, all antidepressants show very similar changes with respect to the frequency patterns obtained after drug injection, whereas drugs used for other indications can be well distinguished from each other and also from antidepressants.

Reduced oscillatory power across delta, theta, alpha, beta, and gamma frequency bands. Reduced ERP amplitudes for P300 and N170 components and increased P100 latencies.

Murray, C. H., Tare, I., Perry, C. M., Malina, M., Lee, R., & de Wit, H. (2022). *Low doses of LSD reduce broadband oscillatory power and modulate event-related potentials in healthy adults.* Psychopharmacology, 239(6), 1735–1747. https://doi.org/10.1007/s00213-021-05991-9

Rationale: Classical psychedelics, including psilocybin and lysergic acid diethylamide (LSD), are under investigation as potential therapeutic agents in psychiatry. Whereas most studies utilize relatively high doses, there are also reports of beneficial effects of "microdosing," or repeated use of very low doses of these drugs. The behavioral and neural effects of these low doses are not fully understood.

Objectives: To examine the effects of LSD (13 μg and 26 μg) versus placebo on resting-state electroencephalography (EEG) and event-related potential (ERP) responses in healthy adults.

Methods: Twenty-two healthy men and women, 18 to 35 years old, participated in 3 EEG sessions in which they received placebo or LSD (13 μg and 26 μg) under double-blind conditions. During each session, participants completed drug effect and mood questionnaires at

hourly intervals, and physiological measures were recorded. ***During expected peak drug effect, EEG recordings were obtained, including resting-state neural oscillations in scalp electrodes over default mode network (DMN) regions and P300, N170, and P100 ERPs evoked during a visual oddball paradigm.***
Results: LSD dose-dependently reduced oscillatory power across delta, theta, alpha, beta, and gamma frequency bands during both eyes closed and eyes open resting conditions. During the oddball task, LSD dose-dependently reduced ERP amplitudes for P300 and N170 components and increased P100 latency. LSD also produced dose-related increases in positive mood, elation, energy, and anxiety and increased heart rate and blood pressure. On a measure of altered states of consciousness, LSD dose-dependently increased Blissful State, but not other indices of perceptual or sensory effects typical of psychedelic drugs. The subjective effects of the drug were not correlated with the EEG measures.
Conclusions: Low doses of LSD produced broadband cortical desynchronization over the DMN during resting state and reduced P300 and N170 amplitudes, patterns similar to those reported with higher doses of psychedelics. Notably, these neurophysiological effects raise the possibility that very low doses of LSD may produce subtle behavioral and perhaps therapeutic effects that do not rely on the full psychedelic experience.

----- COCAINE -----

DRUG FACTS

SYNOPSIS: Cocaine is a recreational drug, generally snorted, favored for its effects on dopamine pathways, leading to euphoria, reward experience, and alertness. This translated into higher power during a cue-driven ERP study and in another study, the possibility of delta-driven dopamine pathways. Blood perfusion and metabolism measures may provide insight into treatment success.

EEG cordance may be a value for treatment

Venneman, S., Leuchter, A., Bartzokis, G., Beckson, M., Simon, S. L., Schaefer, M., Rawson, R., Newton, T., Cook, I. A., Uijtdehaage, S., & Ling, W. (2006). *Variation in Neurophysiological Function and Evidence of Quantitative Electroencephalogram Discordance: Predicting Cocaine-Dependent Treatment Attrition.* The Journal of Neuropsychiatry and Clinical Neurosciences, 18(2), 208–216. https://doi.org/10.1176/jnp.2006.18.2.208

Cocaine treatment trials suffer from a high rate of attrition. We examined pretreatment neurophysiological factors to identify participants at greatest risk. Twenty-five participants were divided into concordant and discordant groups following electroencephalogram (EEG) measures recorded prior to a double-blind, placebo-controlled treatment trial. Three possible outcomes were examined: successful completion, dropout, and removal. Concordant (high perfusion correlate) participants had an 85% rate of successful completion, while discordant participants had a 15% rate of successful completion. Twenty-five percent of dropouts and 50% of participants removed were discordant (low perfusion correlate), while only 25% of those who completed were discordant. ***Failure to complete the trial was not explained by depression, craving, benzoylecgonine levels or quantitative electroencephalogram (QEEG)***

power; thus, cordance may help identify attrition risk. However, previous electroencephalogram (EEG) studies have not demonstrated an association between QEEG power measurements and treatment outcome. In this study, we examined cocaine-dependent participants using QEEG cordance, a measure that has moderately strong associations with cerebral perfusion and metabolism measured with positron emission tomography (PET) or single photon emission computed tomography (SPECT).

Cocaine and ERPs

Moscon, J. A., Conti, C. L., & Nakamura-Palacios, E. M. (2016). *Increased electroencephalographic activity in crack-cocaine users visualizing crack cues.* Journal of Psychiatric Research, 83, 137–139. https://doi.org/10.1016/j.jpsychires.2016.08.016

Abstract: This study aimed to examine electrophysiologically the cerebral function under visual cue-reactivity paradigm in crack-cocaine users. This was an exploratory open trial in which young crack-cocaine-users and non-users were clinically examined. The participants' brain activity was analyzed by an event-related potentials procedure under a cue-reactivity paradigm with the random visual presentation of crack-related and neutral images. Nine young male crack-cocaine users and nine age-matched male healthy subjects from research center's neighborhood volunteered themselves to participate in this study. We demonstrated through electrophysiological tools that crack-cocaine users are more likely to show higher brain activity, notably in the frontal lobe region, when processing crack-related images. Though imaging studies have already showed increased brain activity in this paradigm, this data shows that event-related potentials can be an effective tool for brain evaluation in addiction.

From the manuscript: ***Moreover, cocaine addicts watching cocaine-cue videotapes had regional brain activations that were not present in healthy subjects watching the same tapes and that were not present in either cocaine addicts or healthy subjects when watching tapes that evoked happy or sad feelings, strengthening the idea that these activations are associated with the drug-taking experiences in drug-addicted subjects (Wexler et al., 2001). These results support the assumption that addiction is characterized and maintained through the sensitization of the mesolimbic dopaminergic system along with the incentive salience of drug and drug-related cues*** (Goldstein and Volkow, 2002, Dunning et al., 2011).

Significant influence on delta power.

Alper K. R. (1999). *The EEG and cocaine sensitization: a hypothesis. The Journal of neuropsychiatry and clinical neurosciences*, 11(2), 209–221. https://doi.org/10.1176/jnp.11.2.209

The author presents the hypothesis that reduced delta EEG power observed in cocaine withdrawal is related to changes in dopamine (DA) transmission related to cocaine sensitization. Evidence for this hypothesis includes the topographic anatomical correspondence between the putative site of delta generation and the cortical terminal field of the mesotelencephalic DA system, as well as the laminar distribution and ultrastructural features of DA terminals in frontal cortex that appear to be adapted to the modulation of the delta rhythm, a global forebrain EEG mode. ***The effect of DA on membrane conductance of individual pyramidal neurons also suggests that DA exerts a significant influence on delta power by modulating the transition between global and local EEG modes***. Access to a neural correlate of

sensitization via noninvasive EEG methodology could be useful in investigating the relationship of stimulant sensitization to the clinical syndrome of cocaine dependence.

----- MDMA (Ecstasy) -----

DRUG FACTS

SYNOPSYS: Ecstasy is a stimulant that targets the NMDA receptor for the excitatory neurotransmitter glutamate. It is a mood and metabolism enhancer. It will decrease coherence, and delta and theta power and increase beta power. There are conflicting findings regarding alpha power.

MDMA, THC, and alcohol interactions

Lansbergen, M., Dumont, G. J., Gerven, J. M. van, Buitelaar, J., & Verkes, R. . (2011). *Acute effects of MDMA (3,4-methylenedioxymethamphetamine) on EEG oscillations: alone and in combination with ethanol or THC (delta-9-tetrahydrocannabinol).* Psychopharmacologia, 213(4), 745–756. https://doi.org/10.1007/s00213-010-2031-4

RATIONALE: Typical users of 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") are polydrug users, combining MDMA with alcohol or cannabis [most active compound: delta-9-tetrahydrocannabinol (THC)]. OBJECTIVES: The aim of the present study was to investigate whether co-administration of alcohol or THC with MDMA differentially affects ongoing electroencephalogram (EEG) oscillations compared to the administration of each drug alone. METHODS: In two separate experiments, 16 volunteers received four different drug conditions: (1) MDMA (100 mg); (2) alcohol clamp (blood alcohol concentration = 0.6 per thousand) or THC (inhalation of 4, 6 and 6 mg, interval of 1.5 h); (3) MDMA in combination with alcohol or THC; and (4) placebo. Before and after drug administration, electroencephalography was recorded during an eyes closed resting state. RESULTS: Theta and alpha power increased after alcohol intake compared to placebo and reduced after MDMA intake. No interaction between alcohol and MDMA was found. Significant MDMA x THC effects for theta and lower-1-alpha power indicated that the power attenuation after the combined intake of MDMA and THC was less than the sum of each drug alone. For the lower-2-alpha band, the intake of MDMA or THC alone did not significantly affect power, but the intake of combined MDMA and THC significantly decreased lower-2-alpha power. CONCLUSIONS: ***The present findings indicate that the combined intake of MDMA and THC, but not of MDMA and alcohol, affects ongoing EEG oscillations differently than the sum of either one drug alone. Changes in ongoing EEG oscillations may be related to the impaired task performance that has often been reported after drug intake.***

Positively correlated with absolute power in the alpha (8-12 Hz) and beta (12-20 Hz) frequency bands.

Dafters, R. I., Duffy, F., O'donnell, P. J., & Bouquet, C. (1999). *Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence.* Psychopharmacologia, 145(1), 82–90. https://doi.org/10.1007/s002130051035

Despite animal studies implicating 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in serotonergic neurotoxicity, there is little direct evidence of changes in neural function in humans who use MDMA as a recreational drug. The present study investigated whether there is a correlation between quantitative EEG variables (spectral power and coherence) and cognitive/mood variables, and level of prior use of MDMA. Twenty-three recreational MDMA users were studied. Resting EEG was recorded with eyes closed, using a 128-electrode geodesic net system, from which spectral power, peak frequency and coherence levels were calculated. Tests of intelligence (NART), immediate and delayed memory, frontal function (card sort task), and mood (BDI and PANAS scales) were also administered. Pearson correlation analyses were used to examine the relationship between these measures and the subject's consumption of MDMA during the previous 12-month period. Partial correlation was used to control for the use of other recreational drugs. ***MDMA use was positively correlated with absolute power in the alpha (8-12 Hz) and beta (12-20 Hz) frequency bands, but not with the delta (1-3 Hz) or theta (4-7 Hz) bands. MDMA use was negatively correlated with EEG coherence, a measure of synchrony between paired cortical locations, in posterior brain sites thought to overly the main visual association pathways of the occipito-parietal region.*** MDMA use did not correlate significantly with any of the mood/cognitive measures except the card sort task, with which it was weakly negatively correlated. ***Alpha power has been shown to be inversely related to mental function and has been used as an indirect measure of brain activation in both normal and abnormal states. Reduced coherence levels have been associated with dysfunctional connectivity in the brain in disorders such as dementia, white-matter disease, and normal aging.*** Our results may indicate altered brain function correlated with prior MDMA use and show that electroencephalography may be a cheap and effective tool for examining neurotoxic effects of MDMA and other drugs.

Widespread decrease of slow and medium frequency activity and an increase of fast frequency activity in the anterior temporal and posterior orbital cortex.

Frei, E., Gamma, A., Pascual-Marqui, R., Lehmann, D., Hell, D., & Vollenweider, F. X. (2001). *Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA)*. Human Brain Mapping, 14(3), 152–165. https://doi.org/10.1002/hbm.1049

3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy') is a psychostimulant drug producing heightened mood and facilitated social communication. In animal studies, MDMA effects are primarily mediated by serotonin (5-HT), but also by dopamine (DA) and possibly noradrenaline (NA). In humans, however, the neurochemical and neurophysiological basis of acute MDMA effects remains unknown. The distribution of active neuronal populations after administration of a single dose of MDMA (1.7 mg/kg) or placebo was studied in 16 healthy, MDMA-naïve volunteers. Thirty-one-channel scalp EEGs during resting with open and closed eyes was analyzed in the different EEG frequency bands. Scalp maps of power showed significant, global differences between MDMA and placebo in both eye conditions and all frequency bands. ***Low resolution brain electromagnetic tomography (LORETA) was used to compute 3D, functional images of electric neuronal activity from the scalp EEG data. MDMA produced a widespread decrease of slow and medium frequency activity and an increase of fast frequency activity in the anterior temporal and posterior orbital cortex, concomitant with a marked enhancement***

of mood, emotional arousal and increased extraversion. This activation of frontotemporal areas indicates that the observed enhancement of mood and possibly the increased extroversion rely on modulation of limbic orbitofrontal and anterotemporal structures known to be involved in emotional processes. Comparison of the MDMA-specific EEG pattern with that of various 5-HT, DA, and NA agonists indicates that serotonin, noradrenaline, and, to a lesser degree, dopamine, contribute to the effects of MDMA on EEG, and possibly also on mood and behavior.

Delta and alpha2 power increase

Herning, R. I., Better, W., Tate, K., & Cadet, J. L. (2005). *Neuropsychiatric alterations in MDMA users: preliminary findings.* Annals of the New York Academy of Sciences, 1053, 20–27. https://doi.org/10.1196/annals.1344.003

The use of marijuana is rampant among 3,4-methylenedioxymethamphetamine (MDMA) users. The co-occurrence of abuse of these two drugs has made it difficult to assess the specific residual effects of MDMA alone. As a first step toward identifying the effects of long-term MDMA use, we studied 8 MDMA abusers, 8 marijuana/MDMA abusers, 15 marijuana abusers (matched in marijuana use without MDMA use), and 17 control subjects. EEG, cerebral blood velocity by pulsed transcranial Doppler (TCD), and psychological measures were collected. Three-minute resting eyes-closed EEG recordings were obtained from 16 electrodes. The EEG was converted to 6 frequency bands (delta, theta, alpha-1, alpha-2, beta-1, and beta-2) using a fast Fourier transformation. Blood flow velocity was determined using a temporal window for the right and left middle cerebral arteries using TCD. ***Absolute log delta power in the EEG of MDMA abusers at central electrode sites was significantly higher than that of the MDMA/marijuana, marijuana abusers, and control subjects. There were also increases in alpha-2 EEG power observed only in marijuana abusers.*** The blood flow measure, diastolic velocity, was increased in MDMA abusers whether they used marijuana or not. Because increases in delta power and perfusion deficits are associated with some chronic disorders, our findings in these ecstasy abusers suggest that MDMA use may be associated with a drug-induced neuropathological state. More research is necessary to test these ideas.