Indiana Neurological Society

Functional Neurological Disorders: They're Not Fake News

Friday, November 3, 2023
Wyndham Indianapolis West Hotel

PROGRAM AGENDA

8:00 AM – 9:20 AM: Registration and Exhibits

9:20 AM – 9:30 AM: Welcome and Introductory Remarks
Laurie Gutmann, MD; President, INS; Chair, Dept. of Neurology, Indiana Univesity School of Medicine

9:30 AM – 10:30 AM: *"Epidemiology, Etiology, and Pathophysiology of Functional Neurological Disorders."*
Mark Hallett, MD; NINDS, NIH

10:30 AM – 11:30 AM: *"Functional Movement Disorders."*
Sarah Lidstone, MD, PhD; University of Toronto Temerty Faculty of Medicine

11:30 AM – 1:00 PM: Lunch
11:45 AM – 12:30 PM: INS Business Meeting
11:45 AM – 1:00 PM: Exhibits

1:00 PM – 2:00 PM: *"Persistent Postural-Perceptual Dizziness and Other Functional Vestibular Disorders"*
Jeffrey Staab, MD; Mayo Clinic College of Medicine and Science

2:00 PM – 3:00 PM: *"Advances in Evaluation and Management of Psychogenic Nonepileptic Seizures."*
W. Curt LaFrance, MD, MPH; Brown University Warren Alpert Medical School

3:00 PM – 3:30 PM: Break and Exhibits

3:30 PM – 4:30 PM: *"Differential Diagnosis and Potential Pitfalls in the Evaluation of Functional Neurological Disorders."*
Sara Finkelstein, MD, MSc; Harvard Medical School

4:30 PM – 5:30 PM: *"Managing Functional Neurological Disorders in the Emergency Department"*
Barbara Dworetzky, MD; Harvard Medical School

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PROGRAM FACULTY

Mark Hallett, MD, FAAN
Distinguished Investigator Emeritus
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Functional Neurological Disorder Society

Sarah Lidstone, MD, PhD
Director, Integrated Movement Disorders Program, Toronto Rehabilitation Institute, University Health Network
Assistant Professor of Neurology, University of Toronto

Jeffrey P Staab, MD, MS
Chair, Department of Psychiatry and Psychology, Mayo Clinic
Consultant, Departments of Psychiatry & Psychology & Otorhinolaryngology
Professor of Psychiatry, Mayo Clinic College of Medicine and Science

W. Curt LaFrance Jr., MD, MPH, FAAN, FANPA, DFAPA
Director, Neuropsychiatry and Behavioral Neurology, Rhode Island Hospital
Director, VA Mind Brain Program, Providence Veterans Affairs Medical Center
Professor of Psychiatry and Neurology, Brown University Warren Alpert Medical School

Sara A Finkelstein, MD, FRCPC
Neurologist, Massachusetts General Hospital
Instructor, Harvard University Medical School

Barbara A Dworetzky, MD, FAAN
Chief, Division of Epilepsy & EEG
Director, Edward B. Bromfield Comprehensive Epilepsy Program
Brigham and Women's Hospital
Professor of Neurology, Harvard University Medical School

2023 INS FALL MEETING CME INFORMATION

CME Accreditation

This live activity has been planned and implemented in accordance with the accreditation requirements and policies of the Indiana State Medical Association through the joint providership of the Indiana Association of Pathologists and the Indiana Neurological Society. The Indiana Association of Pathologists is accredited by the Indiana State Medical Association (ISMA) to provide continuing medical education for physicians.

Designation Statement

The IAP designates this live activity for 6.0 *AMA PRA Category* 1 *credits*™. Physicians should only claim credit commensurate with their participation in the activity.

Faculty Disclosure Statement

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by the Indiana Association of Pathologists (IAP) must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, and planning committee members participating in an IAP-sponsored activity are required to disclose any relevant financial interest or other relationship with any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients that are discussed in an educational activity. The INS planning committee and those in a position to control the content of this activity have disclosed the relationships displayed in the table on the following page:

Note

While it offers CME credits, this activity is not intended to provide extensive training or certification in the field.

Name of individual	Individual's role in activity	Name of ineligible company	Nature of relationship	Mechanism(s) implemented to mitigate relevant financial relationships
Mark Hallett, MD	Faculty Presenter	VoxNeuro; QuantalX; Janssen Pharmaceutical	Consultant	Independent review: no conflict
Sarah Lidstone, MD, PhD	Faculty Presenter	No relationships		
Jeffrey Staab, MD	Faculty Presenter	Sleep Number Corporation	Grant/Research Support as Co-investigator	Independent review. No conflict
W. Curt LaFrance, MD, MPH	Faculty Presenter	No relationships		
Sara Finkelstein, MD, MSc	Faculty Presenter	No relationships		
Barbara Dworetzky, MD	Faculty Presenter	No relationships		
Robert Flint, MD	Planner/ Course Director/Reviewer	No relationships		
Norma Erickson, IAP CME Staff	Reviewer	No relationships		

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PROGRAM OBJECTIVES

Title: "Epidemiology, Etiology, and Pathophysiology of Functional Neurological Disorders."

1. The participant will be able to discuss the evolution of understanding concerning the underlying mechanism of functional neurologic disorders.
2. The participant will be able to describe the potential causes and risks for the development of functional neurologic disorders.
3. The participant will be able to differentiate between functional and factitious neurologic disorders.

Title: "Functional Movement Disorders."

1. The participant will be able to conduct an appropriate evaluation for functional movement disorders.
2. The participant will be able to communicate the diagnosis for functional movement disorders confidently.
3. The participant will be able to formulate an initial treatment plan for a patient with a functional movement disorder.

Title: "Persistent Postural-Perceptual Dizziness and Other Functional Vestibular Disorders"

1. The participant will be able to describe key features of the two currently defined functional vestibular disorders.
2. The participant will be able to initiate an evaluation of a patient with suspected functional dizziness.
3. The participant will be able to develop a management plan for a patient diagnosed with functional dizziness.

Title: "Advances in Evaluation and Management of Psychogenic Nonepileptic Seizures."

1. The participant will be able to list the risk factors for the development of psychogenic nonepileptic seizures.
2. The participant will be able to initiate an appropriate evaluation for psychogenic nonepileptic seizures.
3. The participant will be able to develop a treatment plan for psychogenic nonepileptic seizures.

Title: "Differential Diagnosis and Potential Pitfalls in the Evaluation of Functional Neurological Disorders."

1. The participant will be able to develop a differential diagnosis for functional neurologic disorders.
2. The participant will be able to describe diagnostic pitfalls to be aware of when considering a diagnosis of functional neurologic disorders.
3. The participant will be able to develop a rational diagnostic workup for a patient with a potential functional neurologic disorder.

Title: "Managing Functional Neurological Disorders in the Emergency Department"

1. The participant will be able to describe the approach to diagnosis of functional neurologic disorders using positive "rule in" signs.
2. The participant will be able to discuss initial management of functional neurologic disorders in the ED.
3. The participant will be able to discuss the challenges/pitfalls of identifying and managing functional neurologic disorders in the ED.

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PROGRAM EXHIBITORS*

Abbvie - Migraine

Abbvie – Parkinson's Disease

Acadia

Alexion

Amneal Pharmaceuticals

Axsome Therapeutics

Argenx

Catalyst Pharma -Epilepsy

Catalyst Pharma - LEMS

EMD Serono

Genentech/Roche

Harmony Biosciences

Horizon Therapeutics –NMOSD

Horizon Therapeutics - TED

Jazz Pharmaceuticals

LivaNova

Lundbeck

Mallinckrodt Pharmaceuticals

Novartis

NS Pharma

Sandoz

Sanofi Genzyme - Rare Diseases

SK Life Sciences

TG Therapeutics

UCB

**The aforementioned companies, providing exhibits, had no influence on the development, planning, or execution of any part of this program. The compensation from these companies, for their exhibits, is not being used to reimburse any of the expenses directly related to this accredited educational program.*

The Indiana Neurological Society wishes to gratefully acknowledge these organizations for their generous support.

Epidemiology, Etiology, and Pathophysiology of Functional Neurological Disorders

Mark Hallett, MD, FAAN

Functional Neurological Disorders
Epidemiology, Etiology, Pathophysiology

Mark Hallett, M.D.
Human Motor Control Section, NINDS, Bethesda

National Institute of Neurological Disorders and Stroke

Disclosures

- I have no *relevant* disclosures

- *Irrelevant* disclosures
  - I am one of the inventors of an NIH patent for a “Coil for Magnetic Stimulation and methods for using the same (H-coil)” and receive a share of license fee payments from the NIH (coming from Brainsway).
  - Member of the Medical Advisory Boards of Brainsway, QuantalX, and VoxNeuro.
  - Consultant Janssen Pharmaceutical

Functional Neurological Disorders

AKA

- Psychogenic neurological disorders
- Hysteria
- Conversion disorders
- Dissociative disorders

Functional Neurological Disorders

(my definition)

- A neurological disorder, characterized by almost any type of neurological symptom,
- not voluntarily produced,
- caused by a brain network dysfunction that does not exclude the possibility of normal function,
- sometimes due in part to a psychological cause, and
- not explained by other neurological pathology that may or may not be present.
- Symptoms may be inconsistent (variable) or incompatible (incongruent) with other known neurological disorders or human anatomy and physiology.

Somatic Symptom & Related Disorders

DSM-5-TR

- Somatic Symptom Disorder
- Illness Anxiety Disorder
- Functional Neurological Symptom Disorder (Conversion Disorder)
- Psychological Factors Affecting Other Medical Conditions
- Factitious Disorder
- Other Specified Somatic Symptom & Related Disorder
- Unspecified Somatic Symptom & Related Disorder

Somatic Symptom & Related Disorders

DSM-5-TR

- Somatic Symptom Disorder
- Illness Anxiety Disorder
- Functional Neurological Symptom Disorder (Conversion Disorder)
- Psychological Factors Affecting Other Medical Conditions
- Factitious Disorder
- Other Specified Somatic Symptom & Related Disorder
- Unspecified Somatic Symptom & Related Disorder
- (Malingering) – not a condition on this list

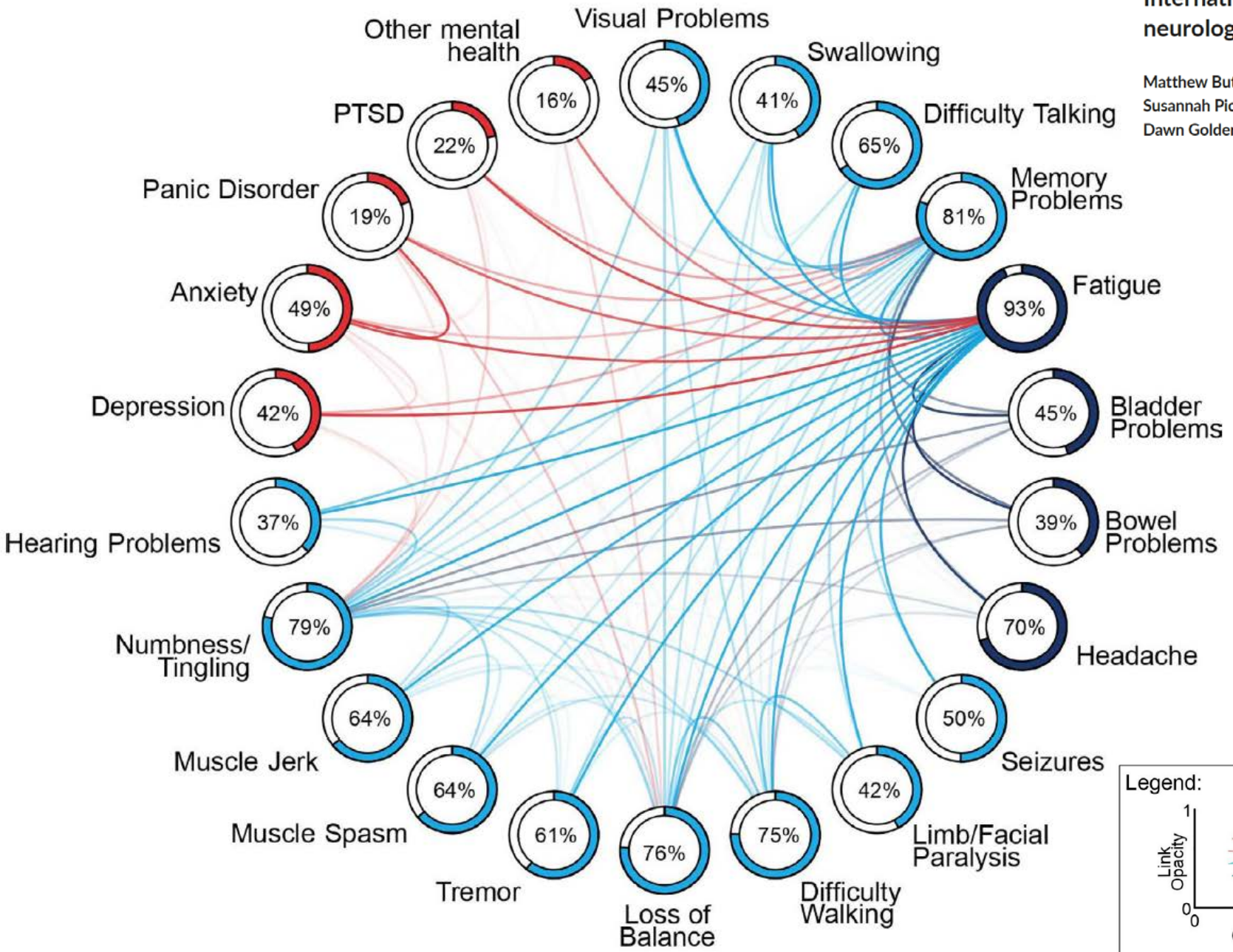
Types of FNDs

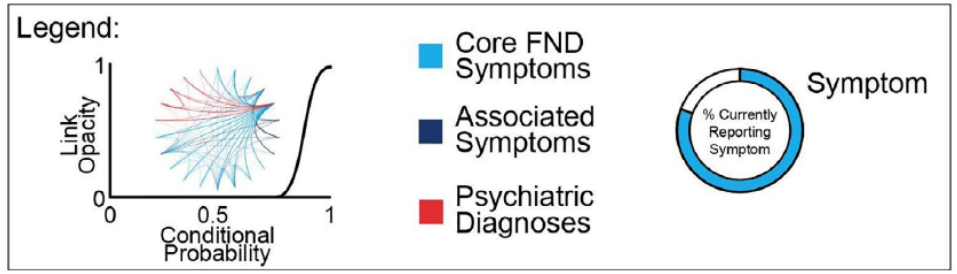
- (Psychogenic) Nonepileptic Seizures (PNES)
- Functional Movement (Motor) Disorders
- Functional Sensory Symptoms
- Functional coma
- Functional visual loss, auditory disorders
- Functional eye movement disorders
- Functional speech disorders
- Functional memory disorders
- Functional dizziness (PPPD)
- Functional urologic symptoms
- Functional disorders of swallowing

Epidemiology

- Incidence: FND 4-12/100,000; FMD 4-5/100,000
- Prevalence: 50/100,000
- Neurology Hospital admissions 9% (Beharry et al. 2021)
- Neurology Clinics (Stone et al. 2010)
  - 5.4% had a primary diagnosis of FND
  - 30% FND was a part of the diagnosis
- Women are 60-75% of patient population

- Data as summarized in Espay et al. 2018 *JAMA Neurology* and O'Mahony et al. *2023 Neurology*



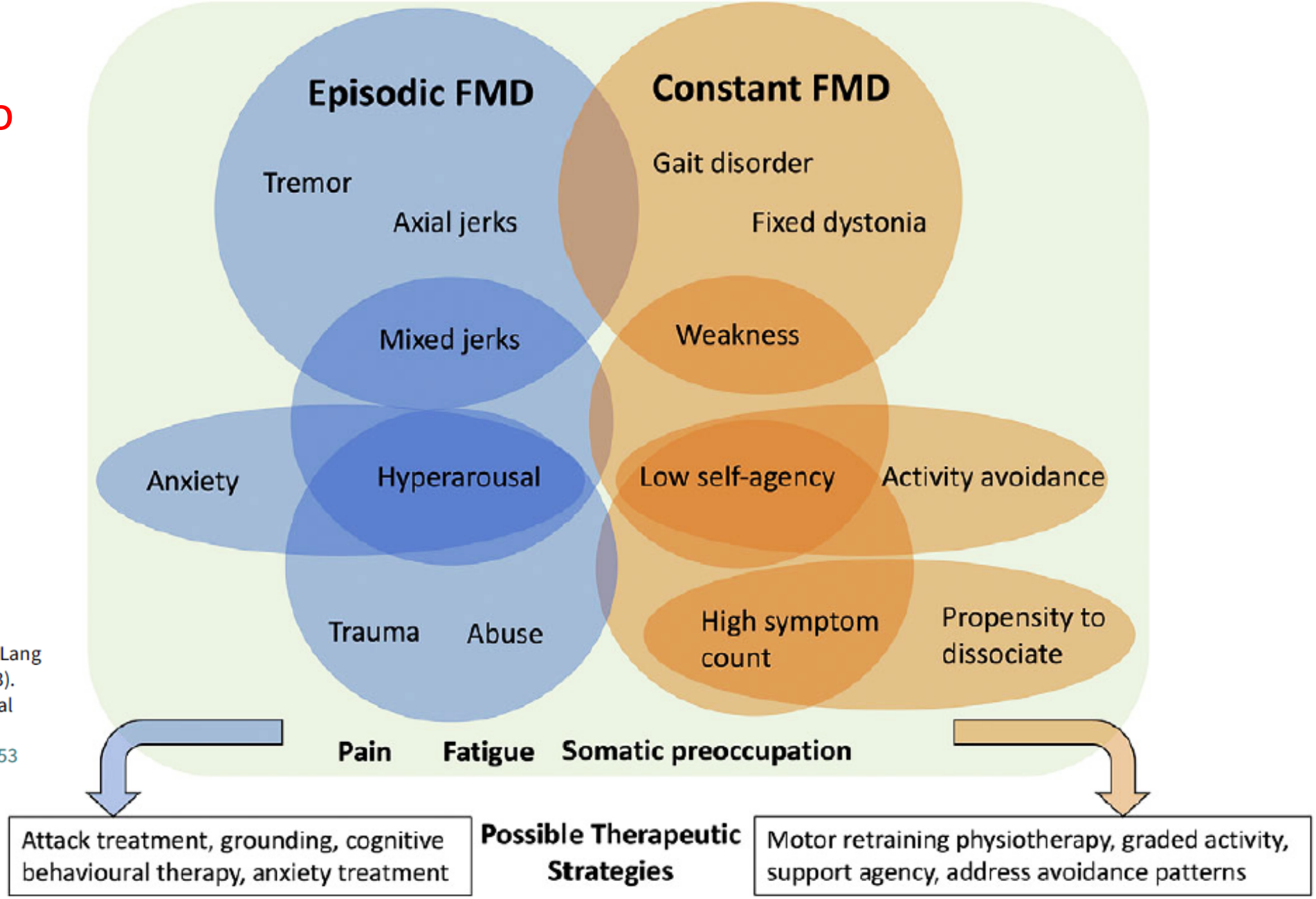


International online survey of 1048 individuals with functional neurological disorder

Matthew Butler[1] | Oliver Shipston-Sharman[2] | Mathieu Seynaeve[1] | Jianan Bao[1] | Susannah Pick[1] | Abigail Bradley-Westguard[3] | Eveliina Ilola[1] | Bridget Mildon[4] | Dawn Golder[5] | James Rucker[1] | Jon Stone[6] | Timothy Nicholson[1]

Eur J Neurol. 2021;28:3591–3602.

Can FMD be clustered into subtypes?



Cite this article: Gilmour GS, Langer LK, Lang AE, MacGillivray L, and Lidstone SC (2023). Neuropsychiatric phenotypes in functional movement disorder. *CNS Spectrums* https://doi.org/10.1017/S1092852923002353

Impact on disability & QOL

Anderson et al. 2007

- 66 patients with PMD compared with 704 patients with PD
- Similar levels of disability on the OARS
- Similar level of physical health QOL
- Worse level of mental health QOL
- Higher levels of distress, anxiety, depression and somatization

Mortality in patients with psychogenic nonepileptic seizures

Russell Nightscales, BSc(Hons), Lara McCartney, MBBS, Clarissa Auvrez, MD, Gerard Tao, MD, Sarah Barnard, MIPH, Charles B. Malpas, PhD, Piero Perucca, MD, PhD, Anne McIntosh, PhD, Zhibin Chen, MBiostat, PhD, Shobi Sivathamboo, PhD, Sophia Ignatiadis, MSc, Simon Jones, MBBS, Sophia Adams, MBBS, PhD, Mark J. Cook, MD, Patrick Kwan, MD, PhD, Dennis Velakoulis, MBBS, Wendyl D'Souza, MBChB, PhD,* Samuel F. Berkovic, MD,* and Terence J. O'Brien, MD*

Neurology® 2020;95:e643-e652. doi:10.1212/WNL.0000000000009855

- 5508 patients with video-EEG
  - PNES 674, epilepsy 3064, both 175
- Standardized mortality ratio for PNES was 2.5
  - No difference among groups
- 20% of deaths due to suicide in those <50 years of age

DOI: 10.1111/epi.17752

RESEARCH ARTICLE

Epilepsia™ 2023;00:1–17

Prevalence of ictal injuries in functional (psychogenic nonepileptic) seizures: A systematic review and meta-analysis

Adriana Boschi Moreira[1] | André Enoch Knochenhauer[1] | Giullia Victória Froehner[1] | Marcelo Liborio Schwarzbold[1] | Ali Akbar Asadi-Pooya[2,3] | Izabel Galhardo Demarchi[1] | Francesco Brigo[4,5] | Katia Lin[1]

Key Points

- Over a lifetime, 25% of individuals were injured due to an FS
- During a VEEG examination, .7% of individuals were injured due to an FS
- Only .1% of the functional seizures that occurred during a VEEG examination caused an injury; they were exclusively oral injuries

Note Combinations

- Multiple types of movement disorders
- Combination with other neurological disorders, examples:
  - Multiple sclerosis
  - Parkinson disease

JAMA Neurology | Original Investigation

JAMA Neurol. 2021;78(1):88-101. doi:10.1001/jamaneurol.2020.3753

Assessment of Emergency Department and Inpatient Use and Costs in Adult and Pediatric Functional Neurological Disorders

Christopher D. Stephen, MB ChB, MRCP(UK), MS; Vicki Fung, PhD; Codrin I. Lungu, MD; Alberto J. Espay, MD, MSc

The annual cost is more than $1.2 billion dollars….comparable to ALS, MS, epilepsy

Economic Cost of Functional Neurologic Disorders

A Systematic Review

Brian O'Mahony, MB BCh, BAO, Glenn Nielsen, BSc, PhD, Sallie Baxendale, PhD, Mark J. Edwards, MBBS, BSc, PhD, FRCP, FEAN, and Mahinda Yogarajah, MD

Correspondence
Dr. Yogarajah
mahinda.yogarajah@nhs.net

Neurology® 2023;101:e202-e214. doi:10.1212/WNL.0000000000207388

The annual cost per person ranged from $4,964–$86,722 in 2021 US dollars

Current Neurology and Neuroscience Reports
https://doi.org/10.1007/s11910-023-01298-8

Published online: 11 September 2023

REVIEW

The Financial Burden of Functional Neurological Disorders

Meagan Watson[1] · Jared Woodward[1] · Laura A. Strom[1]

Review of the issues.

Frequency of Types of FMD

Predominant movement feature	No.	Percent
Tremor	467	37.5
Dystonia	365	29.3
Myoclonus	146	11.7
Gait disorder	114	9.2
Parkinsonism	60	4.8
Tics	29	2.3
Other	64	5.1
Total	**1245**	**100**

Table from Jankovic et al. 2021; Data from Lang in Hallett et al 2006

Understanding disease

Biopsychosocial Model

- Etiology of FMD is multifactorial

- Basic biology—genetics, stress responsivity
- Psychologic factors—depression, anxiety
- Social factors—physical and emotional trauma; childhood abuse

Biopsychosocial Model

- The factors can interact
- For example:
  - Early childhood trauma can lead to changes in the developing brain, such as a larger size of the amygdala and epigenetic changes of specific genotypes, that will lead to less resilience to stress in later life and propensity to anxiety and depression, as well as the development of an FND

Movement disorders

ORIGINAL RESEARCH

Effects of *TPH2* gene variation and childhood trauma on the clinical and circuit-level phenotype of functional movement disorders

Primavera A Spagnolo [1], Gina Norato,[2] Carine W Maurer,[3] David Goldman,[4] Colin Hodgkinson,[4] Silvina Horovitz,[1] Mark Hallett [1]

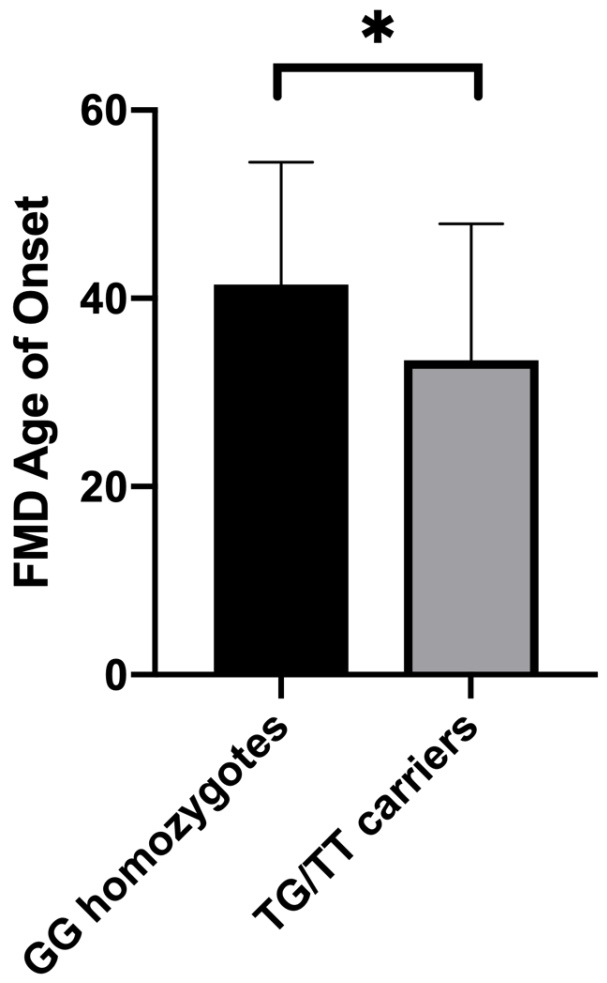
J Neurol Neurosurg Psychiatry 2020;**0**:1–8. doi:10.1136/jnnp-2019-322636

- Sixty-eight patients with a diagnosis of FMD
- Subjects were predominantly female (73%) and Caucasian (89%), with a mean age of 46.7 years ± 8.3 [range 21–60]
- 53% reported exposure to childhood trauma

- TPH2 is tryptophan hydroxylase-2 (rs4570625)
  - Gene is relevant for serotonin synthesis

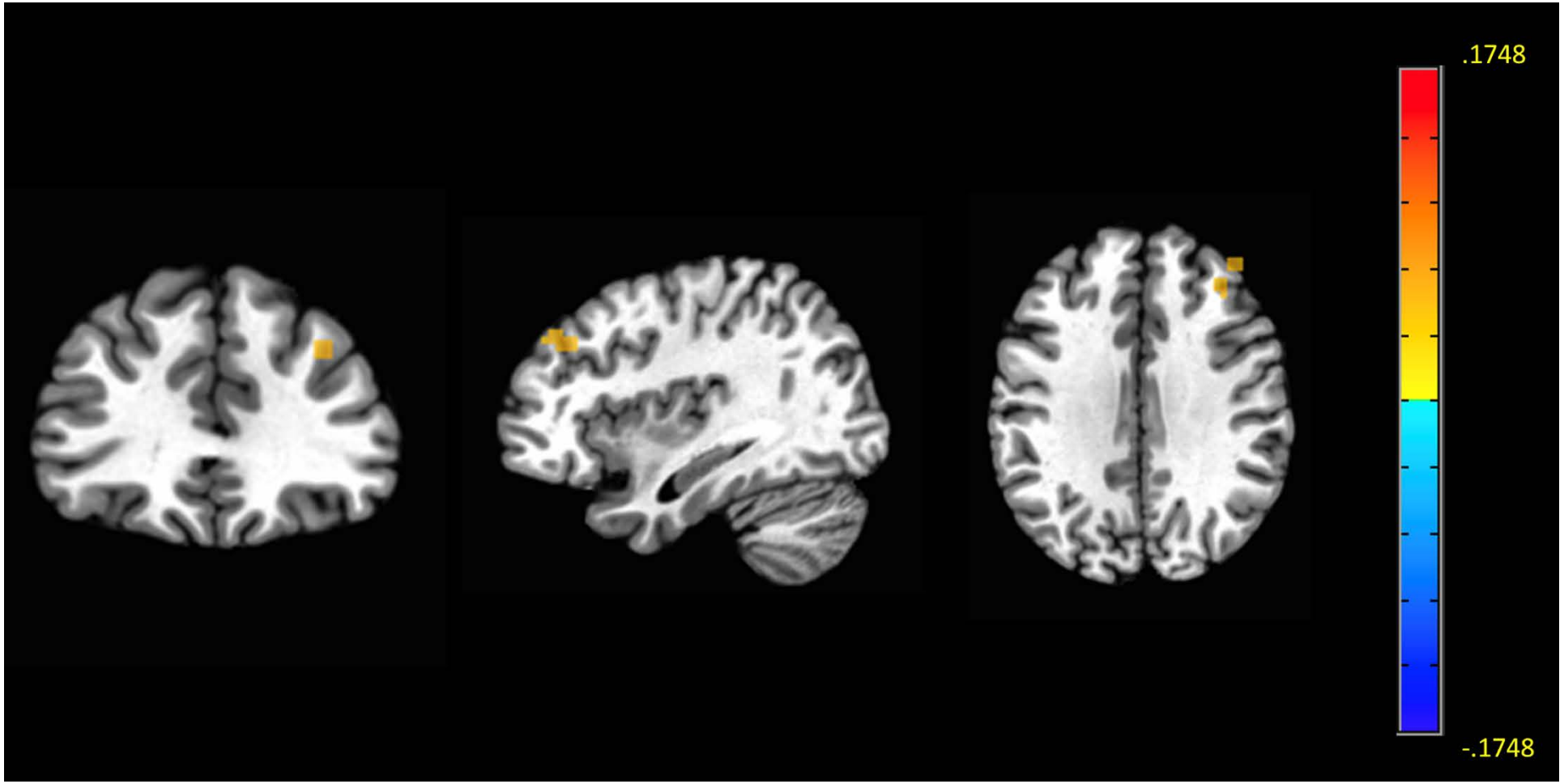
Results

The G-703T polymorphism in *TPH2* was a significant predictor of FMD age of onset



Results

T carriers exhibited decreased resting state functional connectivity between the R amygdala and the R middle frontal gyrus (uncinate fasciculus)



Epigenetics

- Spagnolo, Johnson, Hodgkinson, Goldman, Hallett (2023) Progress in Neuropsychopharmacology & Biological Psychiatry (in press)
- Study of the methylome in FMD patients
- Affected genetic pathways related to childhood abuse and sex
  - Stress
  - Pain

Psychopathology and Psychogenic Movement Disorders

Movement Disorders 2011:26:1844

Sarah Kranick, MD,[1] Vindhya Ekanayake, BA,[2] Valeria Martinez, MS,[1] Rezvan Ameli, PhD,[3] Mark Hallett, MD,[1] and Valerie Voon, MD, PhD[1,4]*

TABLE 3. Psychiatric disorders, depression, and anxiety

	PMD	HVs	FHD	Chi-square or *F*	*P* value
SCID (%)					
Major depression (lifetime)	37.1%		33.3%	0.2	.83
Generalized anxiety disorder	20.0%		15.3%	0.4	.61
Phobia	14.3%		12.8%	0.03	1.0
Panic disorder	2.9%		2.6%	0.03	1.0
Beck Depression Inventory	10.7 (8.4, 57)	4.0 (4.7, 38)	6.4 (5.6, 28)	11.6	< .0001
Beck Anxiety Inventory	14.6 (9.8, 58)	2.6 (3.9, 38)	6.1 (6.8, 28)	31.7	< .0001

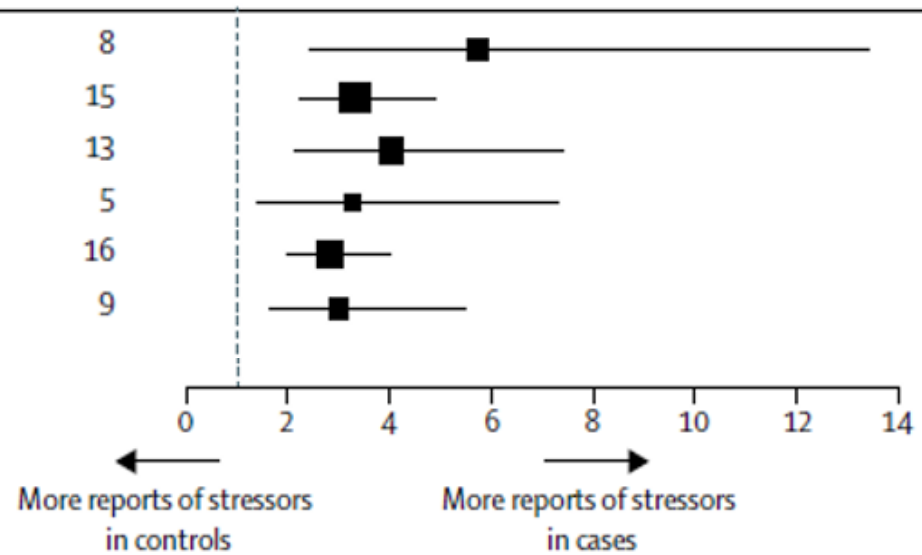
Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies

Lancet Psychiatry 2018

Published Online
March 8, 2018
http://dx.doi.org/10.1016/
S2215-0366(18)30051-8

Lea Ludwig, Joëlle A Pasman, Timothy Nicholson, Selma Aybek, Anthony S David, Sharon Tuck, Richard A Kanaan, Karin Roelofs, Alan Carson, Jon Stone

	Case (n)	Control (n)	Studies (n)	OR (95% CI; random effect)	I^{2*} (95% CI)
Childhood emotional neglect	421	391	8	5·6 (2·4–13·1)	86·3% (73·9–91·3)
Childhood sexual abuse	1375	708	15	3·3 (2·2–4·8)	40·9% (0–66·6)
Childhood physical abuse	612	636	13	3·9 (2·2–7·2)	74·6% (51·8–84·0)
Adulthood emotional neglect	223	204	5	3·2 (1·4–7·2)	68·2% (0–85·6)
Adulthood sexual abuse	775	771	16	2·8 (2·0–3·9)	41·8% (0–66·5)
Adulthood physical abuse	363	343	9	2·9 (1·6–5·4)	44·0% (0–72·5)



Journal of Neurology
https://doi.org/10.1007/s00415-021-10943-6

ORIGINAL COMMUNICATION

Gender disparity and abuse in functional movement disorders: a multi-center case-control study

Isaiah Kletenik[1,2,3] · Samantha K. Holden[2,3,4] · Stefan H. Sillau[2] · Nicola O'Connell[5] · Lindsey MacGillivray[6] · Joel Mack[7,8] · Beatrix Haddock[9] · M. Ashworth Dirac[9,10] · Anthony S. David[11] · Timothy R. Nicholson[12] · Sanaz N. Attaripour Isfahani[13] · Carine W. Maurer[14] · Sarah C. Lidstone[15] · Mark Hallett[16] · Kathrin LaFaver[17,18] · Brian D. Berman[2,4,19] · Jon Stone[20]

696 subjects (512 women); 141 controls (98 women) + population controls

	Subjects		Controls	
	Women	**Men**	**Women**	**Men**
Sexual abuse	35.3%	11.5%	10.6%	5.6%

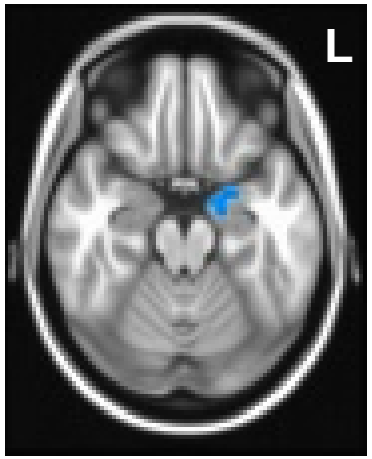
For Women (only)

Likelihood of FMD with sexual abuse: 4.57 (95% confidence limits 2.31 – 9.07)

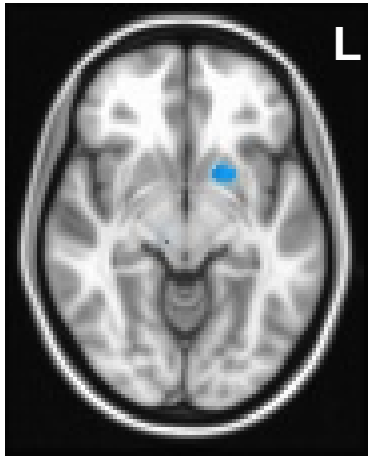
Population attributable fraction from sexual abuse: 0.12 (95% confidence limits 0.05 – 0.19)

VBM in FMD

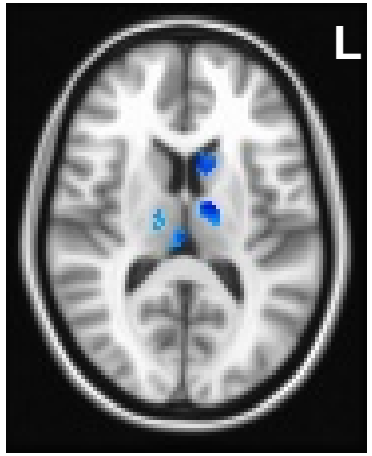
Gray Matter Increases Associated with FMD



L amygdala



L putamen



L caudate; bilateral thalami

n = 48 FMD
n = 55 HV

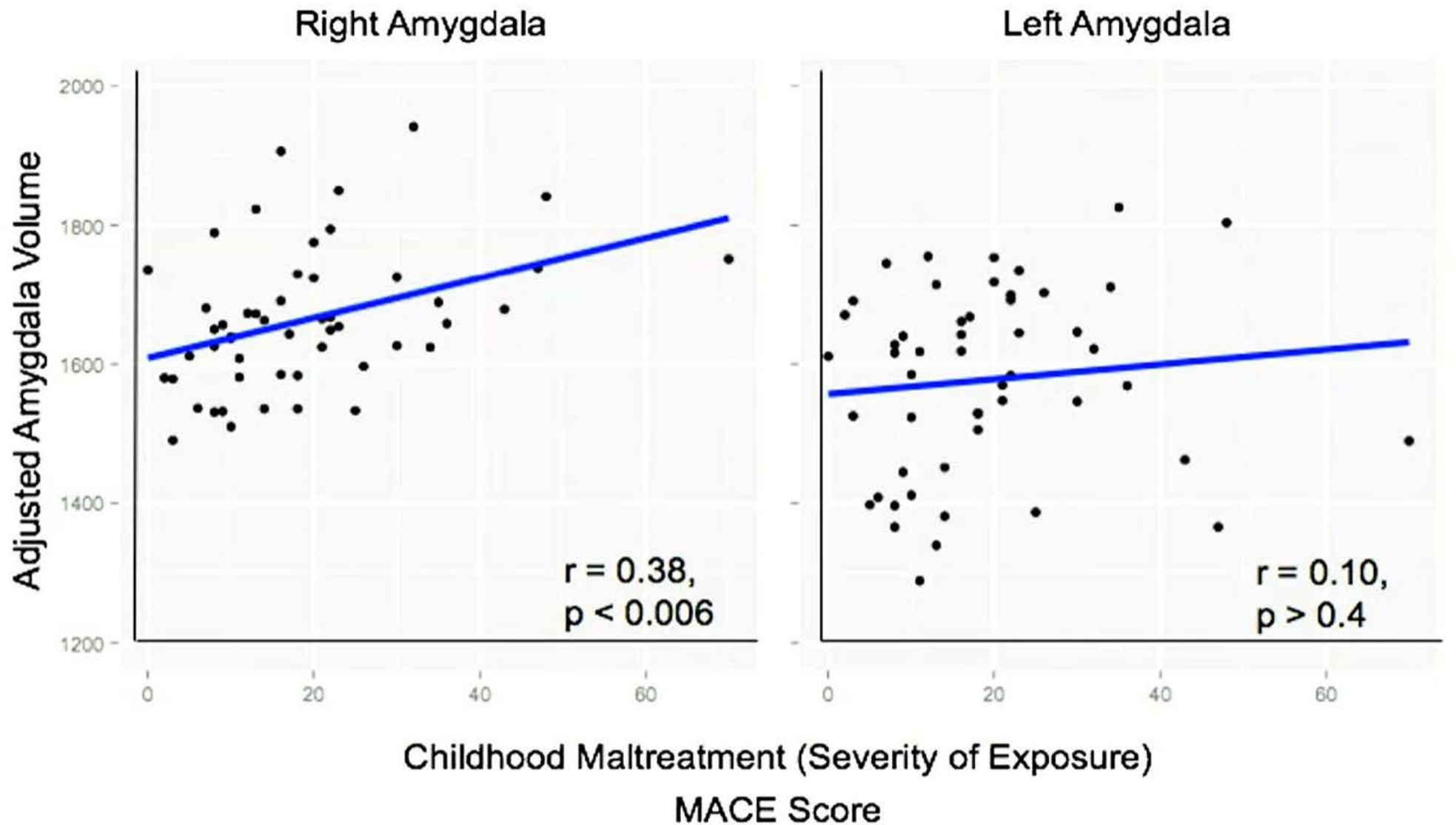
$p < 0.05$ (whole brain corrected)

Maurer et al. *Neurology* 2018

Sensitive periods of amygdala development: The role of maltreatment in preadolescence

NeuroImage 97 (2014) 236–244

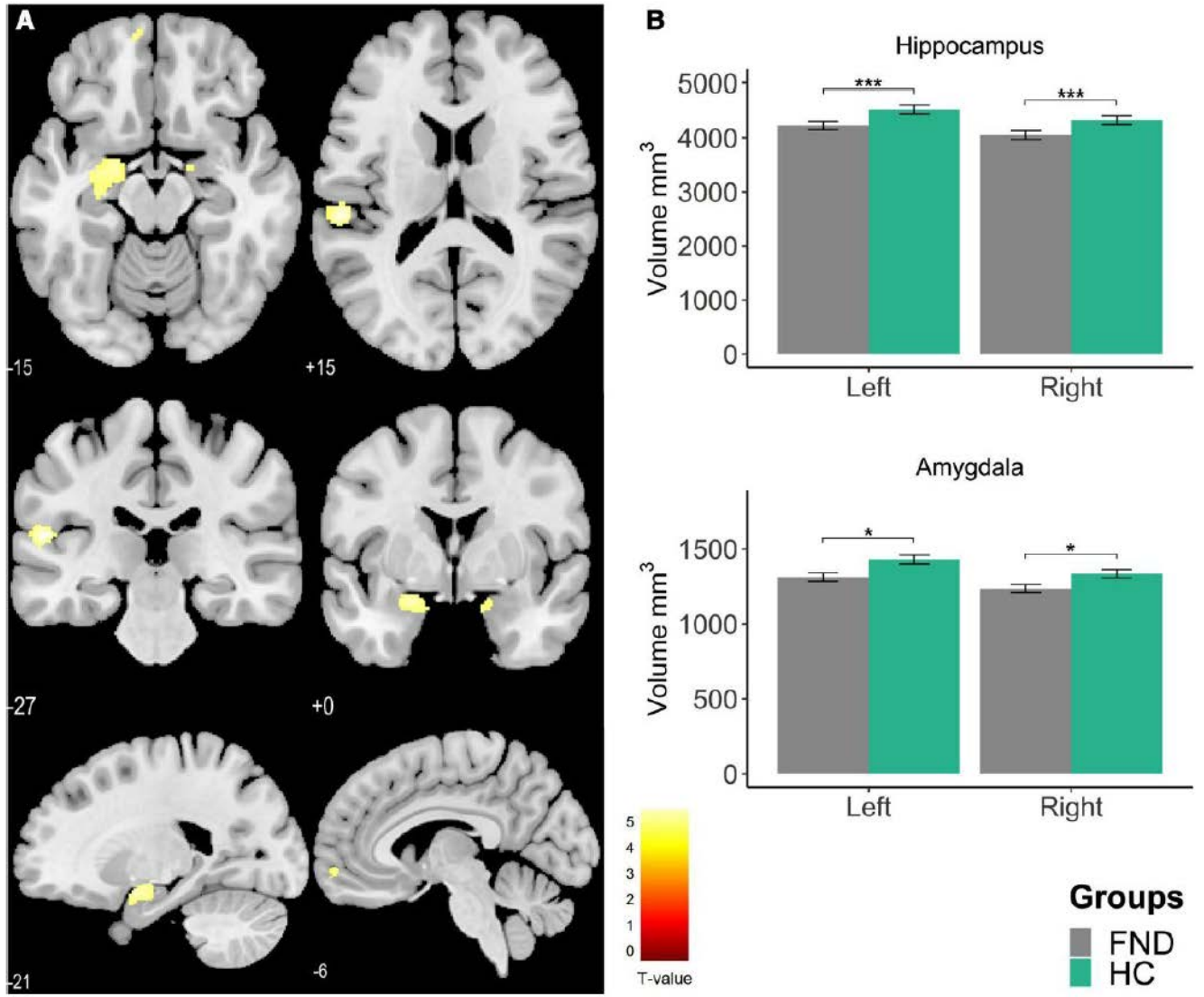
Pia Pechtel [a,e,*], Karlen Lyons-Ruth [b,e], Carl M. Anderson [c,d,e], Martin H. Teicher [c,e]



Identification of biopsychological trait markers in functional neurological disorders

BRAIN 2023: 146; 2627–2641

Samantha Weber,[1,2,3] Janine Bühler,[1,2,4] Giorgio Vanini,[1] Serafeim Loukas,[1,5,6] Rupert Bruckmaier[7] and Selma Aybek[1,2]



Reactivation of Early-Life Stress-Sensitive Neuronal Ensembles Contributes to Lifelong Stress Hypersensitivity

Julie-Anne Balouek, Christabel A. Mclain, Adelaide R. Minerva, Rebekah L. Rashford, Shannon N. Bennett, Forrest D. Rogers, and Catherine Jensen Peña

The Journal of Neuroscience, August 23, 2023 • 43(34):5996–6009

- In mice, early life stress activates neuronal ensembles in nucleus accumbens and medial prefrontal cortex (mPFC)
- Inhibition of these neurons, when mice are adult, reduces social avoidance behavior following chronic social defeat

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Sex-Specific Timelines for Adaptations of Prefrontal Parvalbumin Neurons in Response to Stress and Changes in Anxiety- and Depressive-Like Behaviors

Emma Woodward,[1,*] Claudia Rangel-Barajas,[3,*] Amanda Ringland,[2] Marian L. Logrip,[3,4] and Laurence Coutellier[1,2]

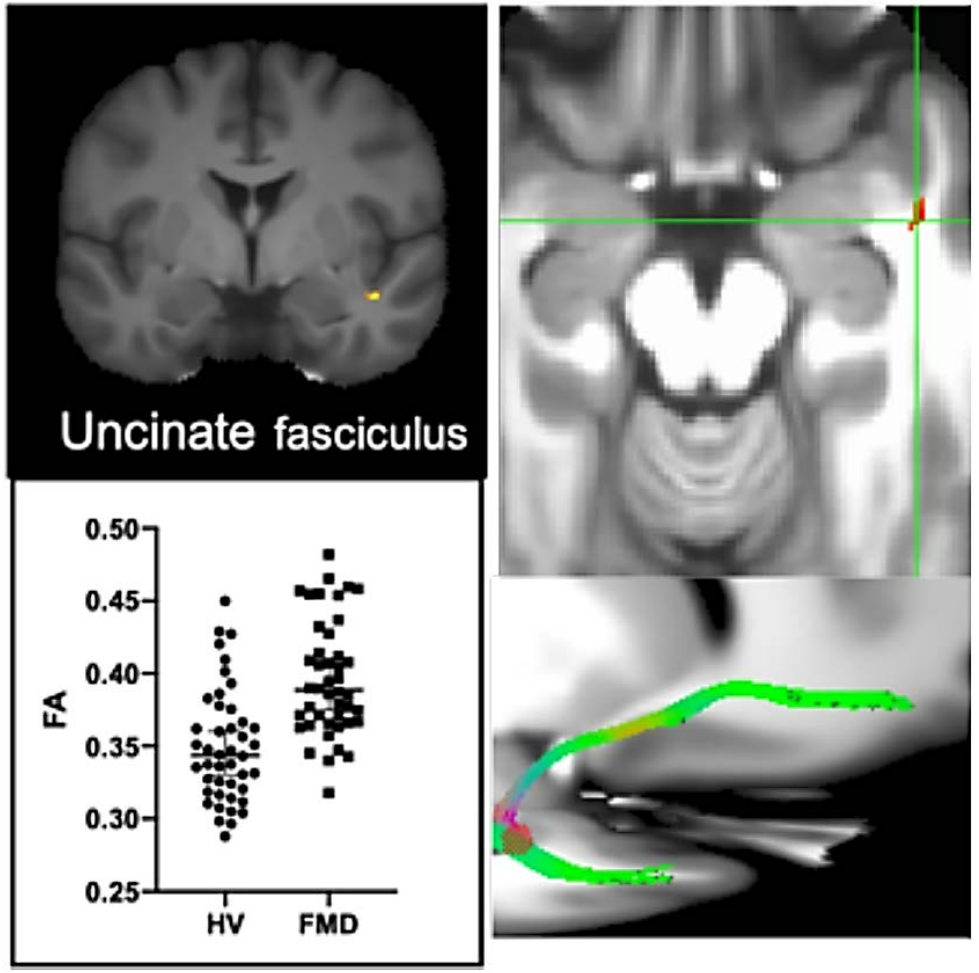
March 2023, 10(3) ENEURO.0300-22.2023 1–19

- In mice, chronic mild stress increases activity of parvalbumin interneurons in mPFC
- This is more in females than males

DTI in FMD

White Matter Changes Associated with FMD

Right uncinate fasciculus

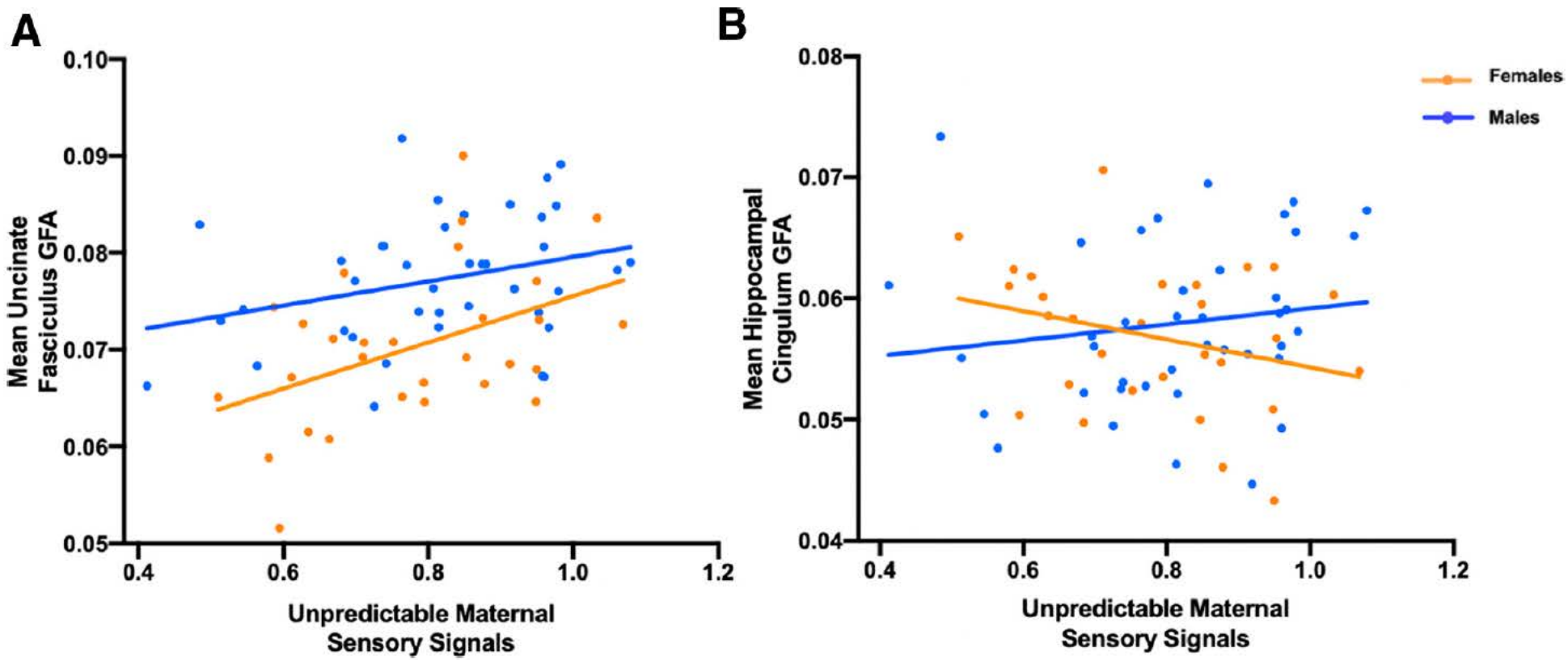


(in preparation)

Aberrant Maturation of the Uncinate Fasciculus Follows Exposure to Unpredictable Patterns of Maternal Signals

The Journal of Neuroscience, February 10, 2021 • 41(6):1242–1250

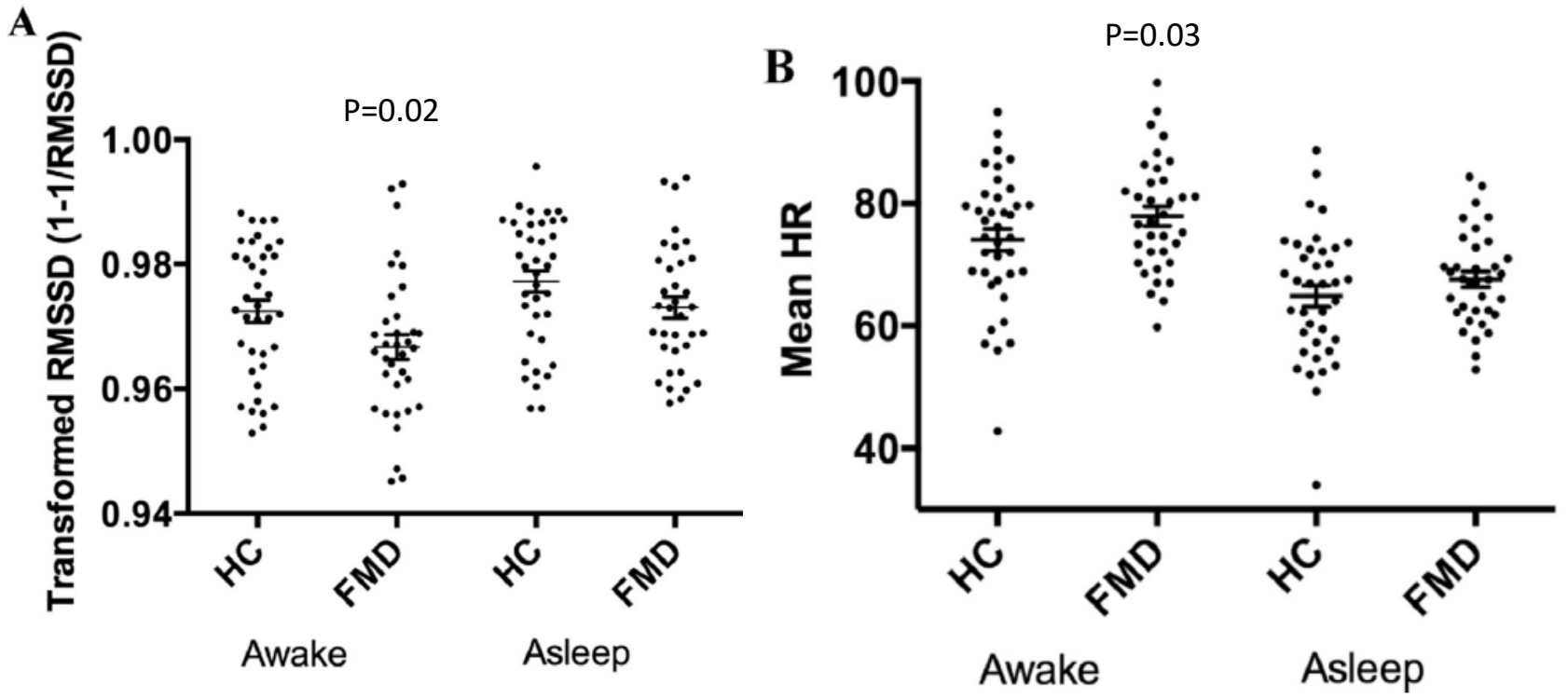
Steven J. Granger,[1,2] Laura M. Glynn,[3] Curt A. Sandman,[4] Steven L. Small,[5] Andre Obenaus,[6] David B. Keator,[4] Tallie Z. Baram,[1,6,7] Hal Stern,[8] Michael A. Yassa,[1,2,4] and Elysia Poggi Davis[4,9]



Impaired resting vagal tone in patients with functional movement disorders

Carine W. Maurer [a, *], Victoria D. Liu [a], Kathrin LaFaver [a, b], Rezvan Ameli [c], Tianxia Wu [d], Ryan Toledo [a], Steven A. Epstein [e], Mark Hallett [a]

Parkinsonism and Related Disorders 30 (2016) 18–22



RMSSD = root mean square of successive differences between adjacent NN intervals

Impaired resting state vagal tone may reflect increased stress vulnerability

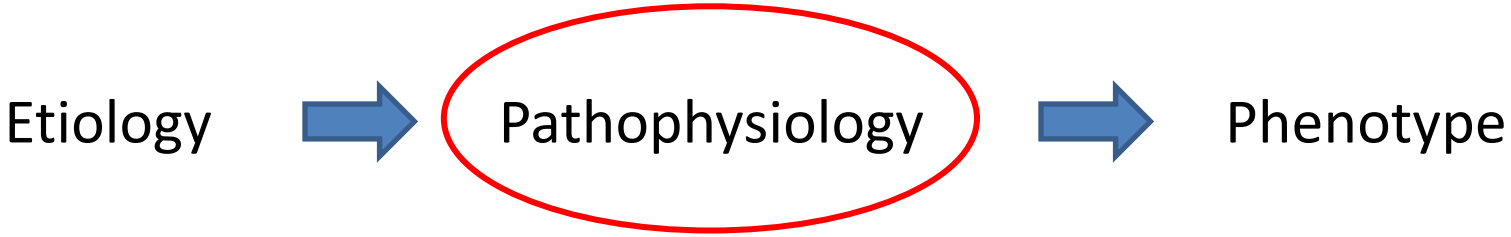
Biopsychosocial Model

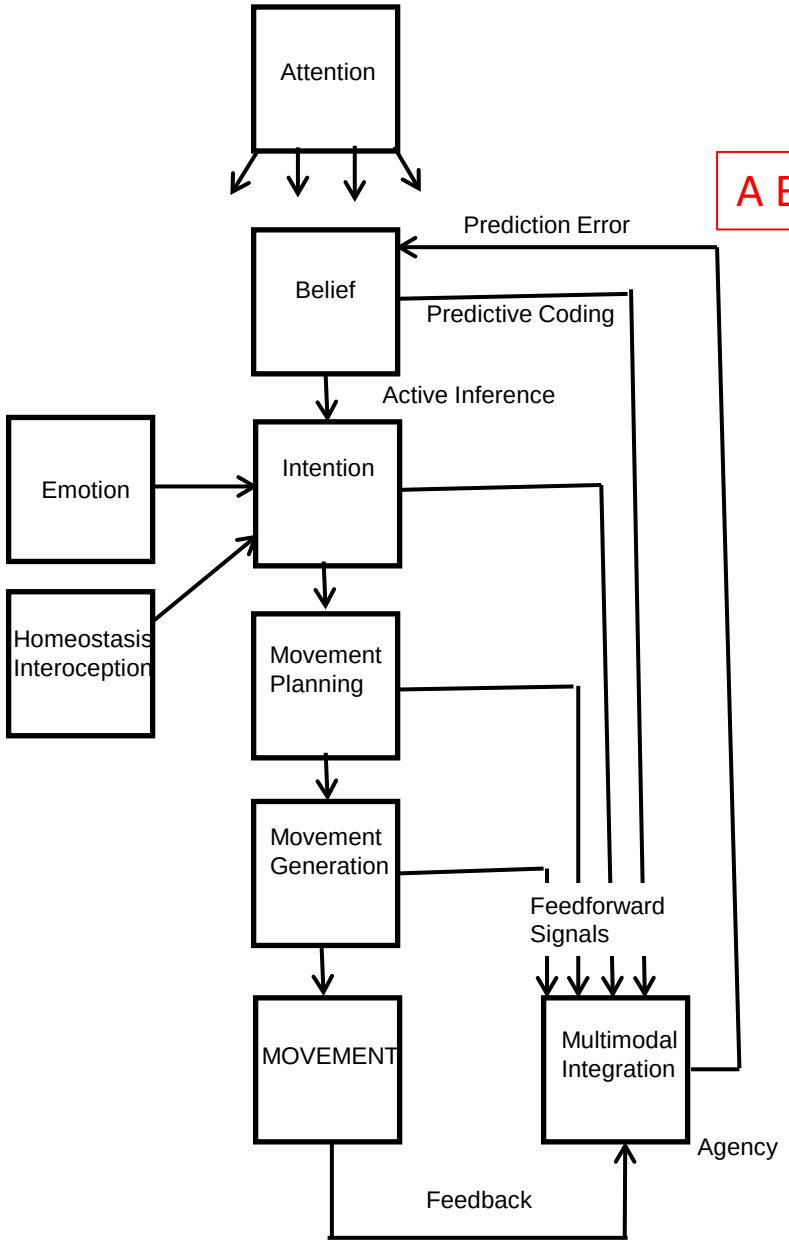
- Etiology of FMD is multifactorial

- Basic biology—genetics, stress responsivity
- Psychologic factors—depression, anxiety
- Social factors—physical and emotional trauma; childhood abuse

- One apparent result is overactivity of the limbic system

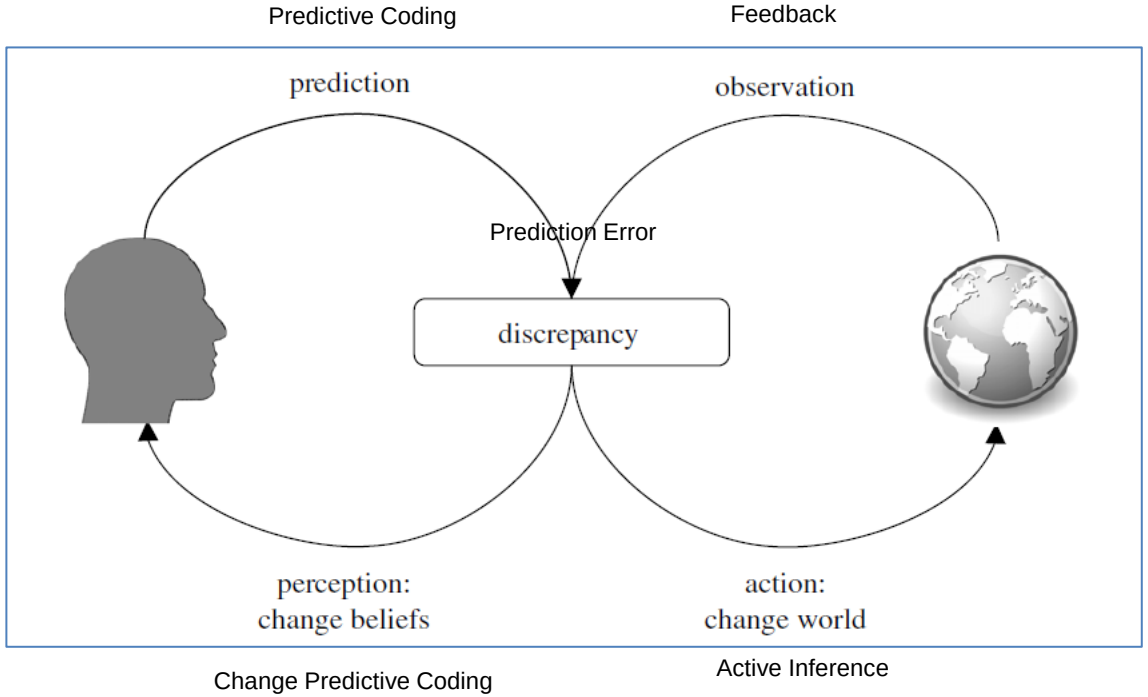
Understanding disease



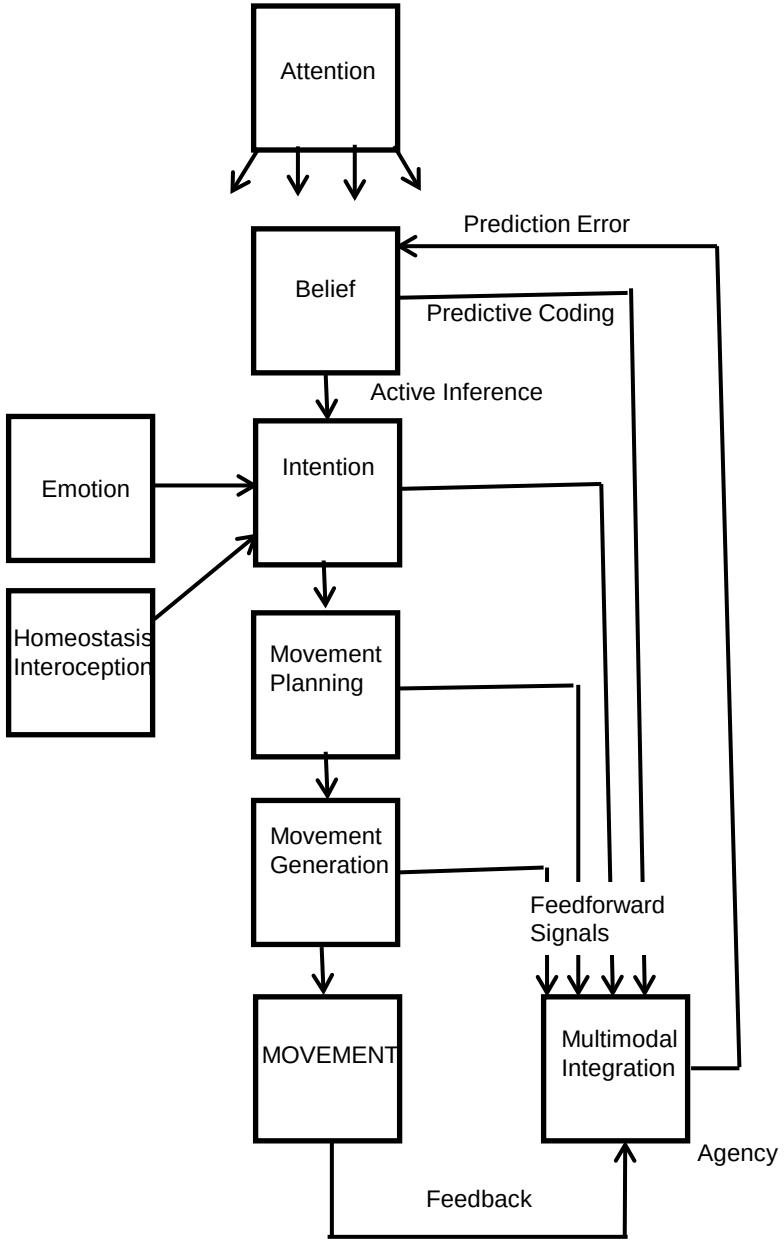


A Bayesian network

Pezzulo et al. 2021 Phil Trans R Soc B 377: 20200531



Neural correlate of belief may be in the insula and associated parts of frontal cortex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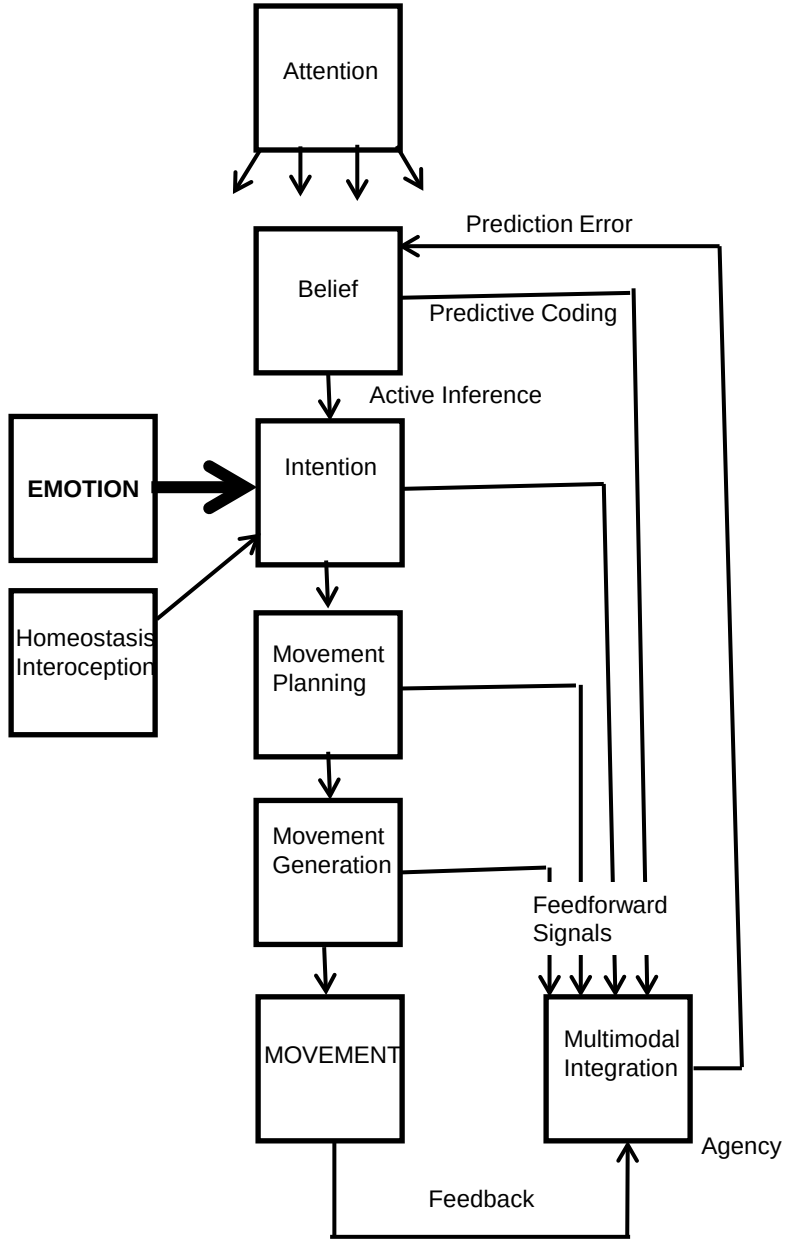
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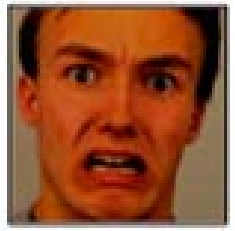
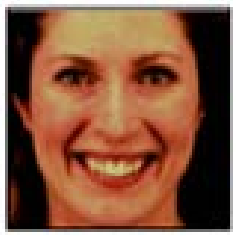
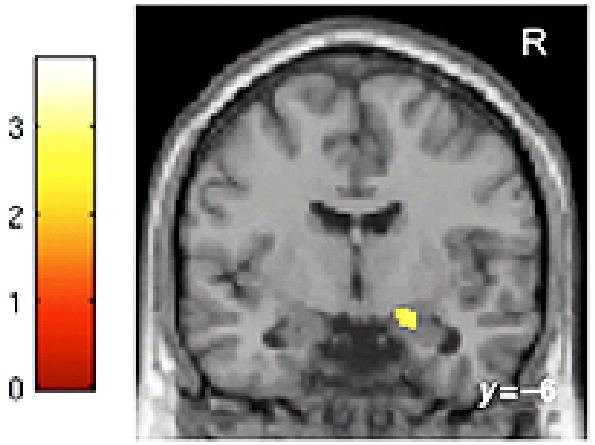
Affect processing and the right amygdala in FMD

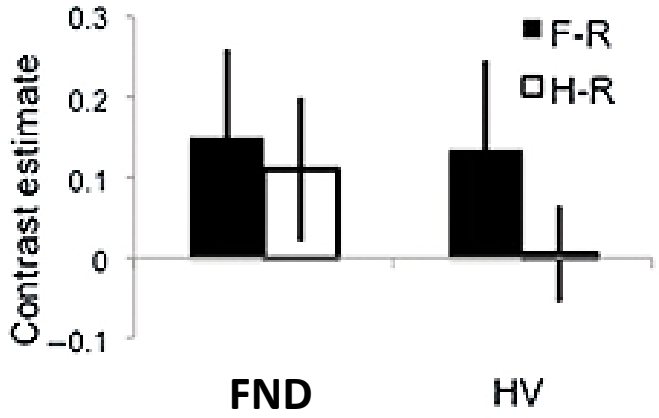


Fearful face



Happy face





Voon, V. et al. *Brain* 2010 133:1526-1536; doi:10.1093/brain/awq054

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BRAIN A JOURNAL OF NEUROLOGY

Aybek S, Nicholson TR, O'Daly O, Zelaya F, Kanaan RA, et al. (2015)
Emotion-Motion Interactions in Conversion Disorder: An fMRI Study.
PLOS ONE 10(4): e0123273. https://doi.org/10.1371/journal.pone.0123273

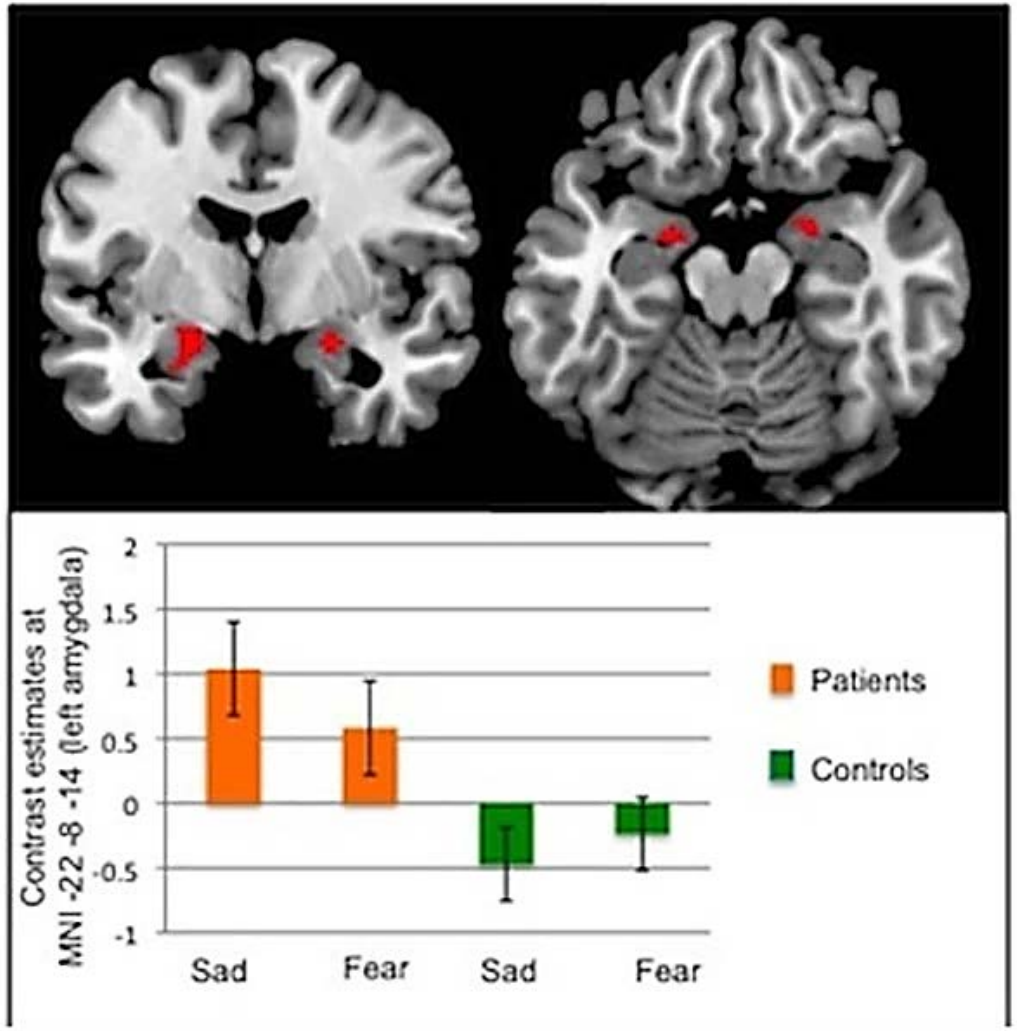
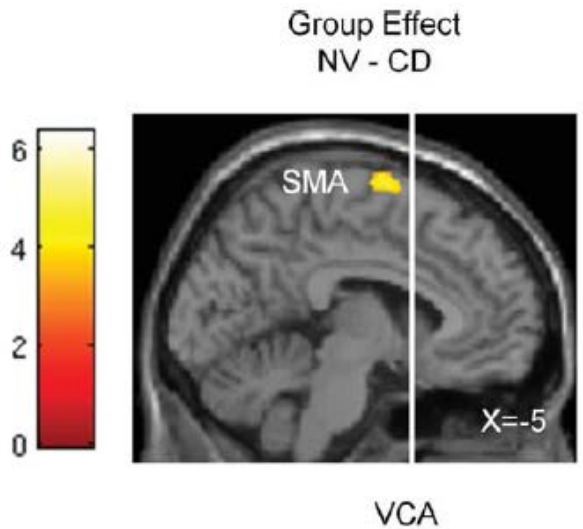


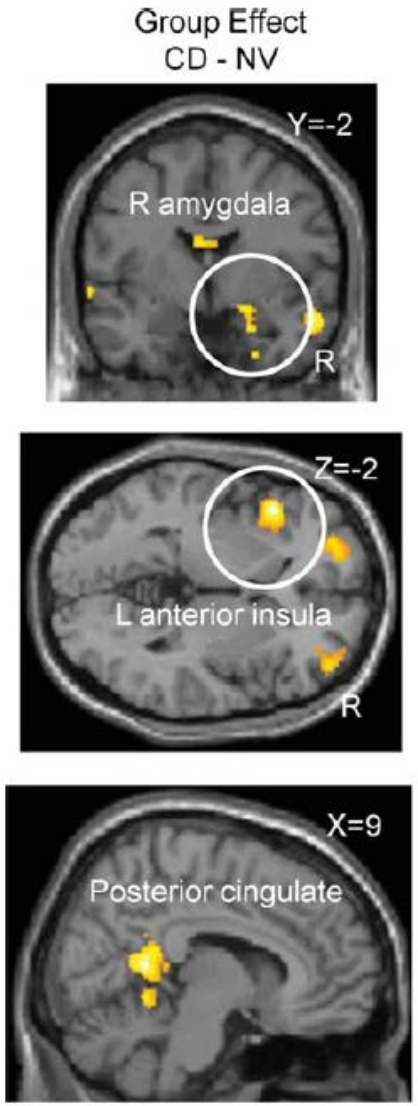
Fig 1. ROI analysis: Group effect in the Emotion Model.

Aberrant Supplementary Motor Complex and Limbic Activity During Motor Preparation in Motor Conversion Disorder

Valerie Voon, MD PhD,[1]* Christina Brezing, MD,[2] Cecile Gallea, PhD,[2] and Mark Hallett, MD[2]

Movement Disorders, Vol. 26, No. 13, 2011

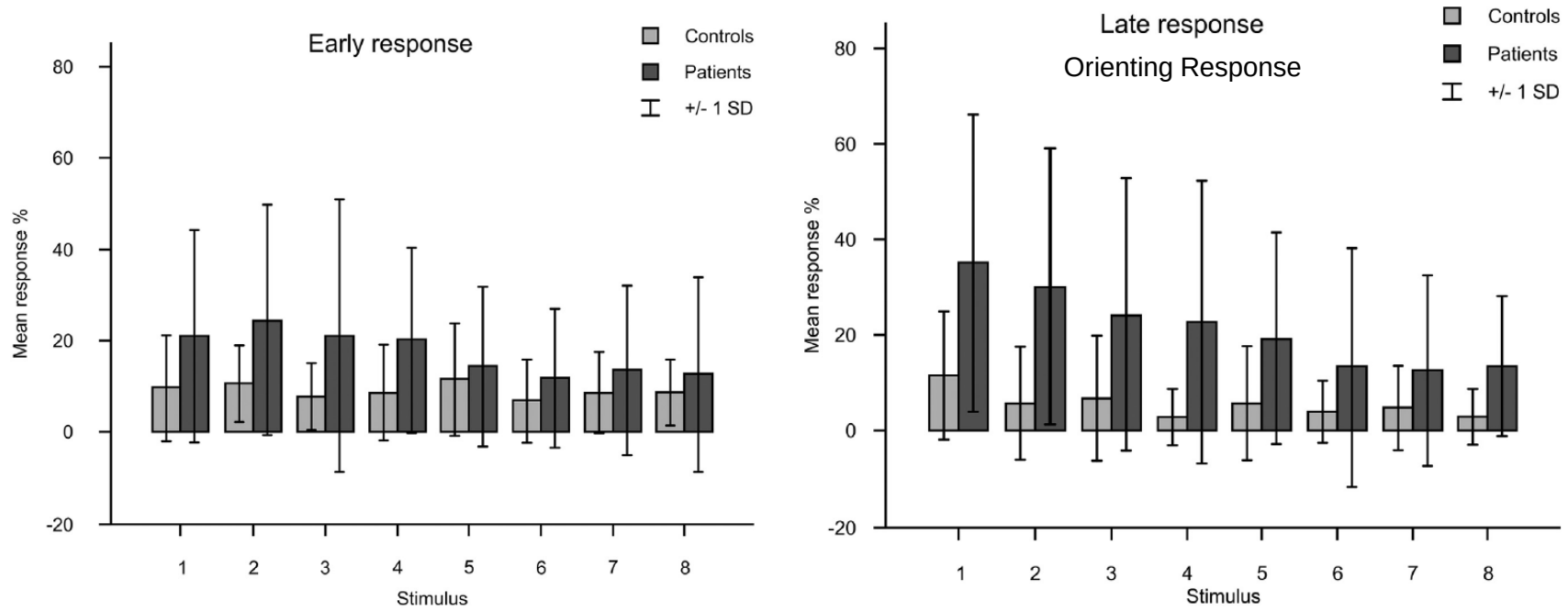




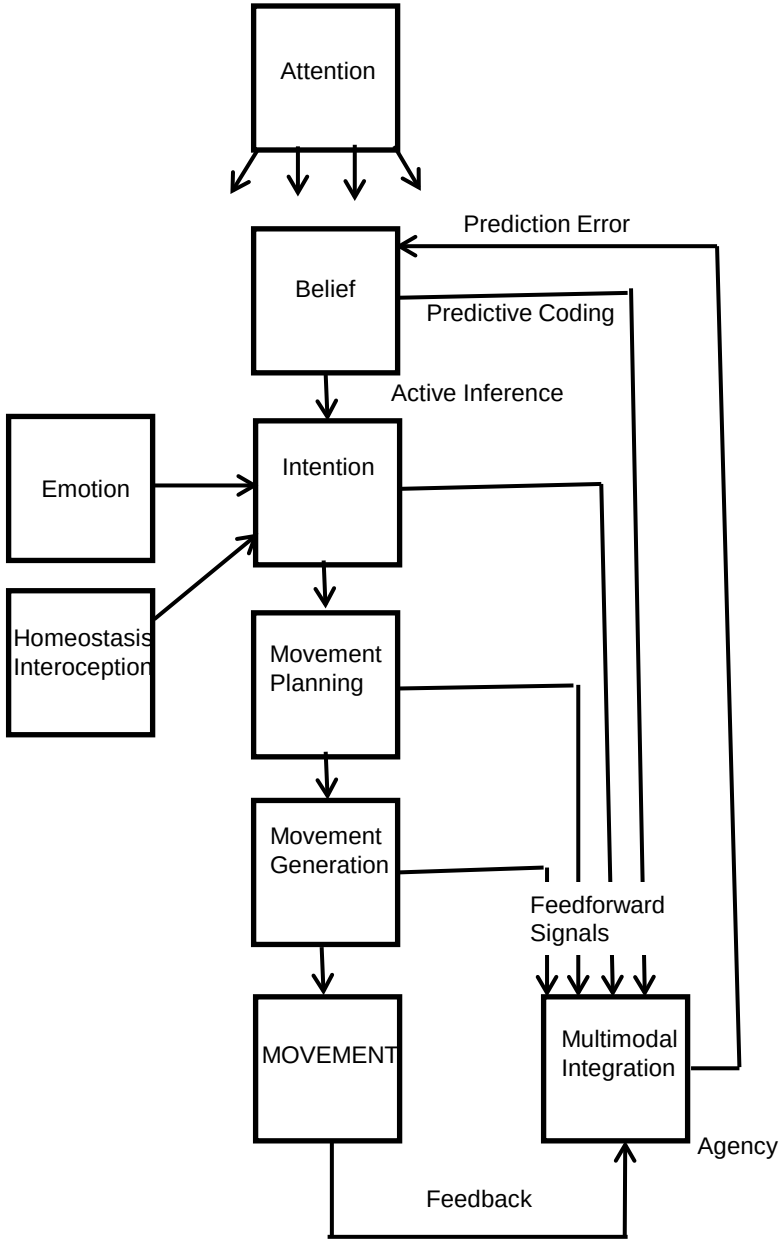
Startle responses in functional jerky movement disorders are increased but have a normal pattern

Parkinsonism and Related Disorders 40 (2017) 27–32

Y.E.M. Dreissen, MD [a], T. Boeree [a], J.H.T.M. Koelman, MD, PhD [a], M.A.J. Tijssen, Prof [b, *]



Exaggerated startle responses may arise from overactive limbic system (amygdala)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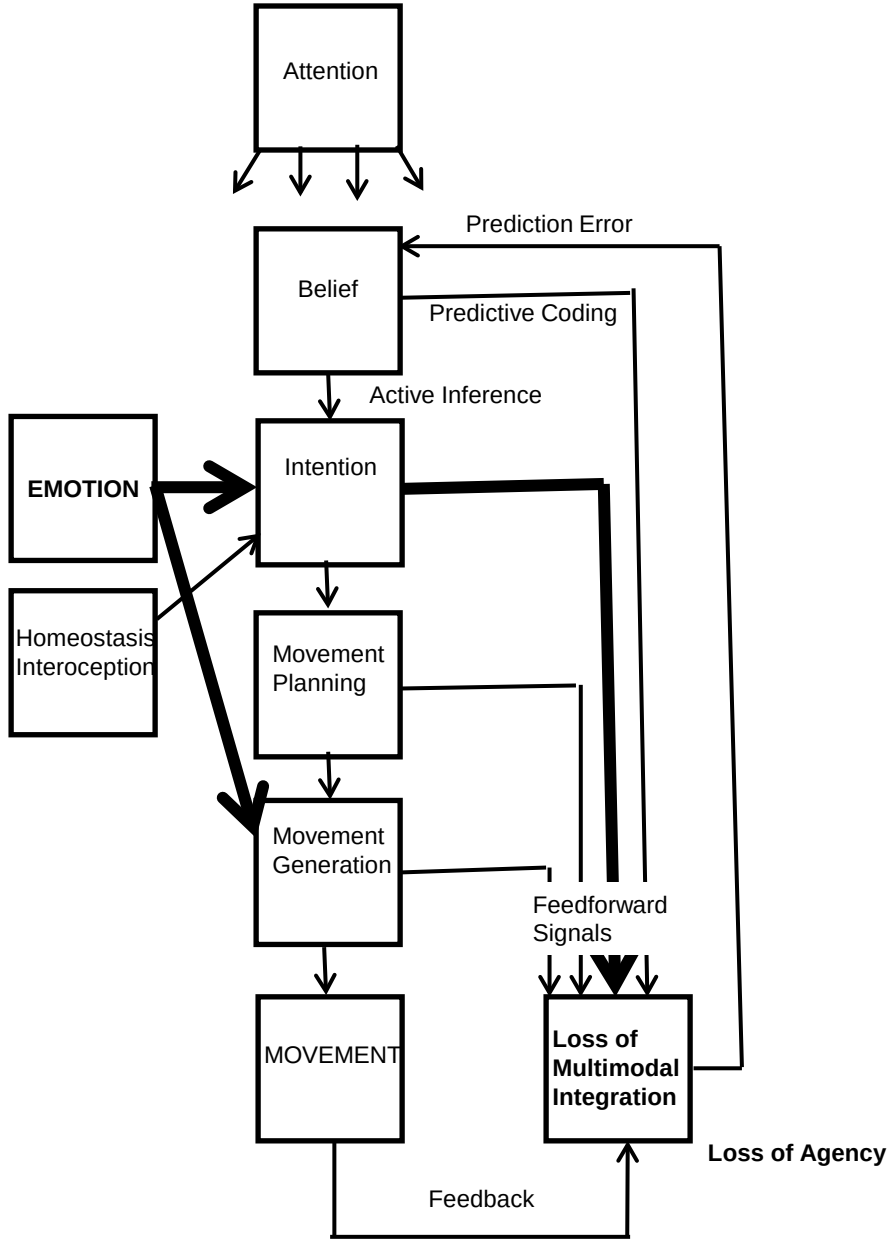
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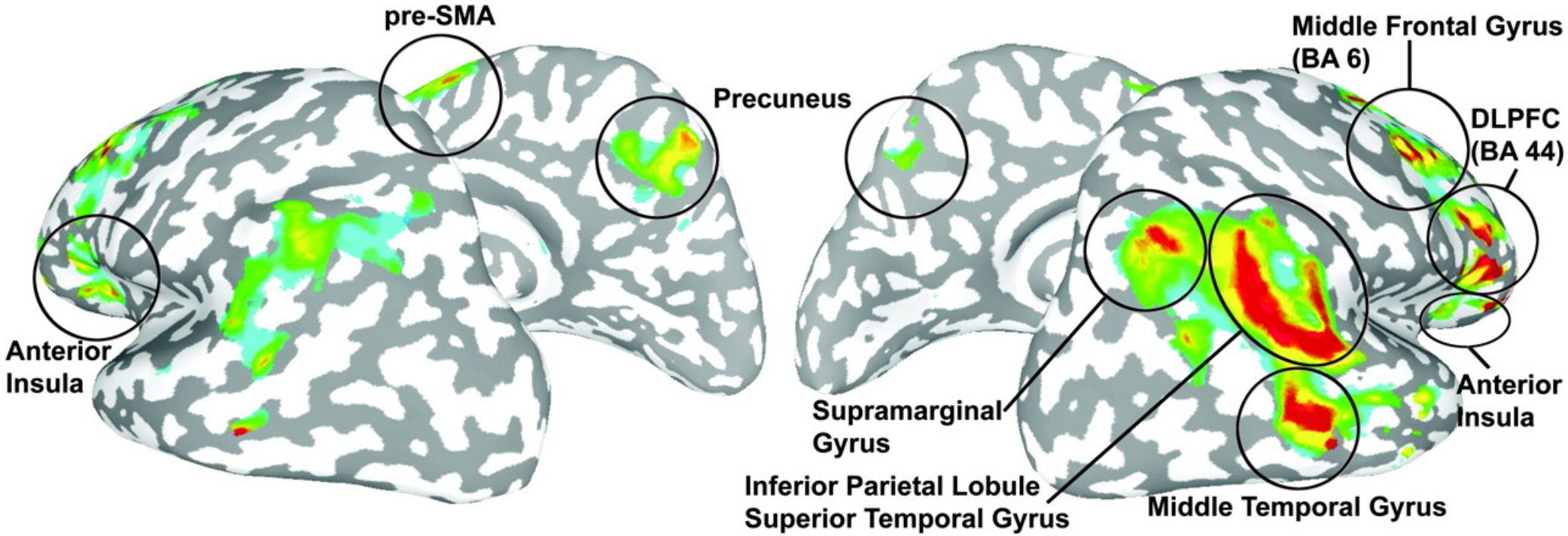
Regions responding proportionally to the loss of self-agency



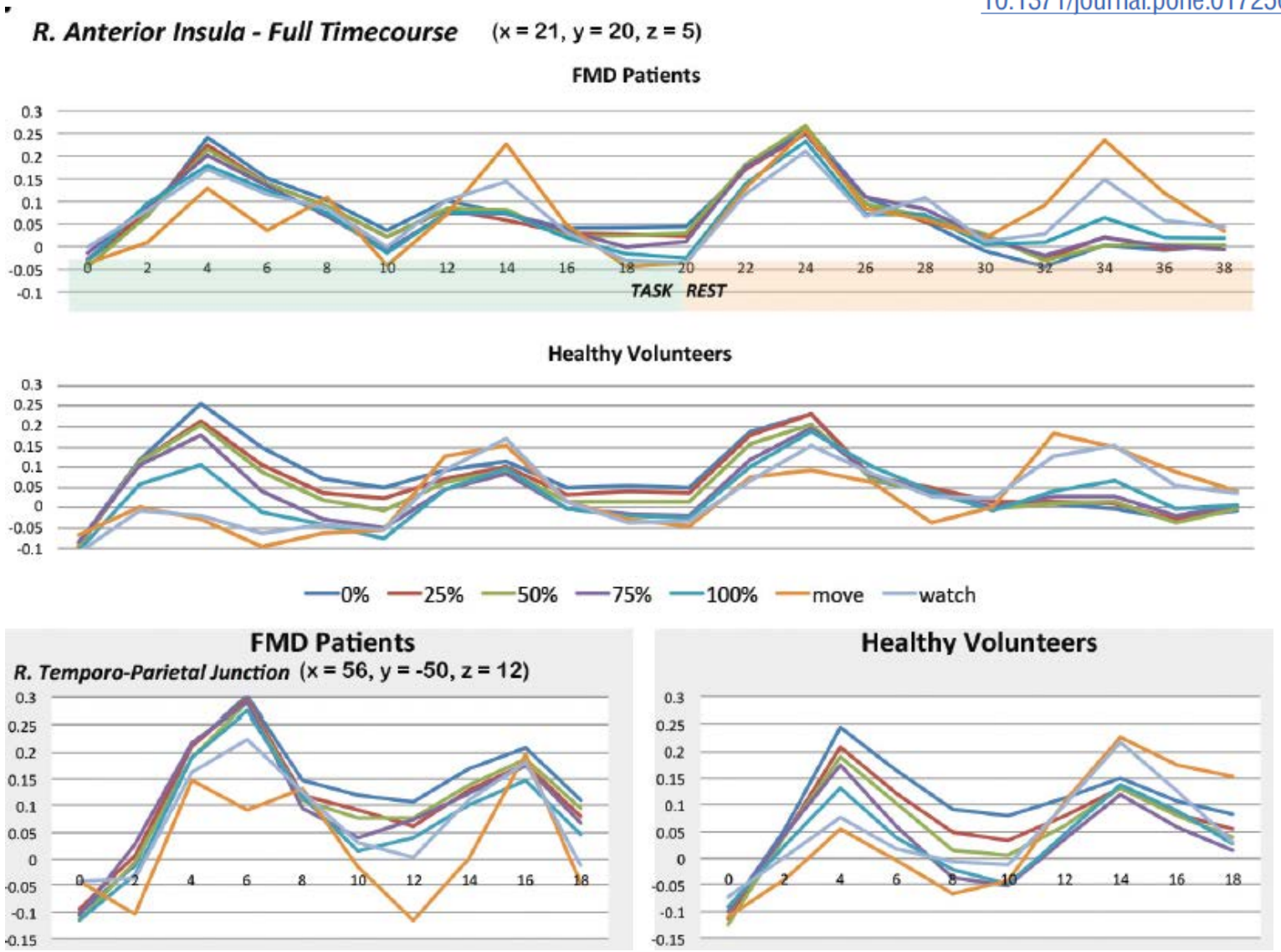
Nahab F B et al. Cereb. Cortex 2011;21:48-55

Published by Oxford University Press 2010.

Cerebral CORTEX

Less modulation of self-agency in patients with FMD

Citation: Nahab FB, Kundu P, Maurer C, Shen Q, Hallett M (2017) Impaired sense of agency in functional movement disorders: An fMRI study. PLoS ONE 12(4): e0172502. https://doi.org/10.1371/journal.pone.0172502



Arrow: R TPJ

Area of hypoactivity with functional tremor compared with voluntary mimic

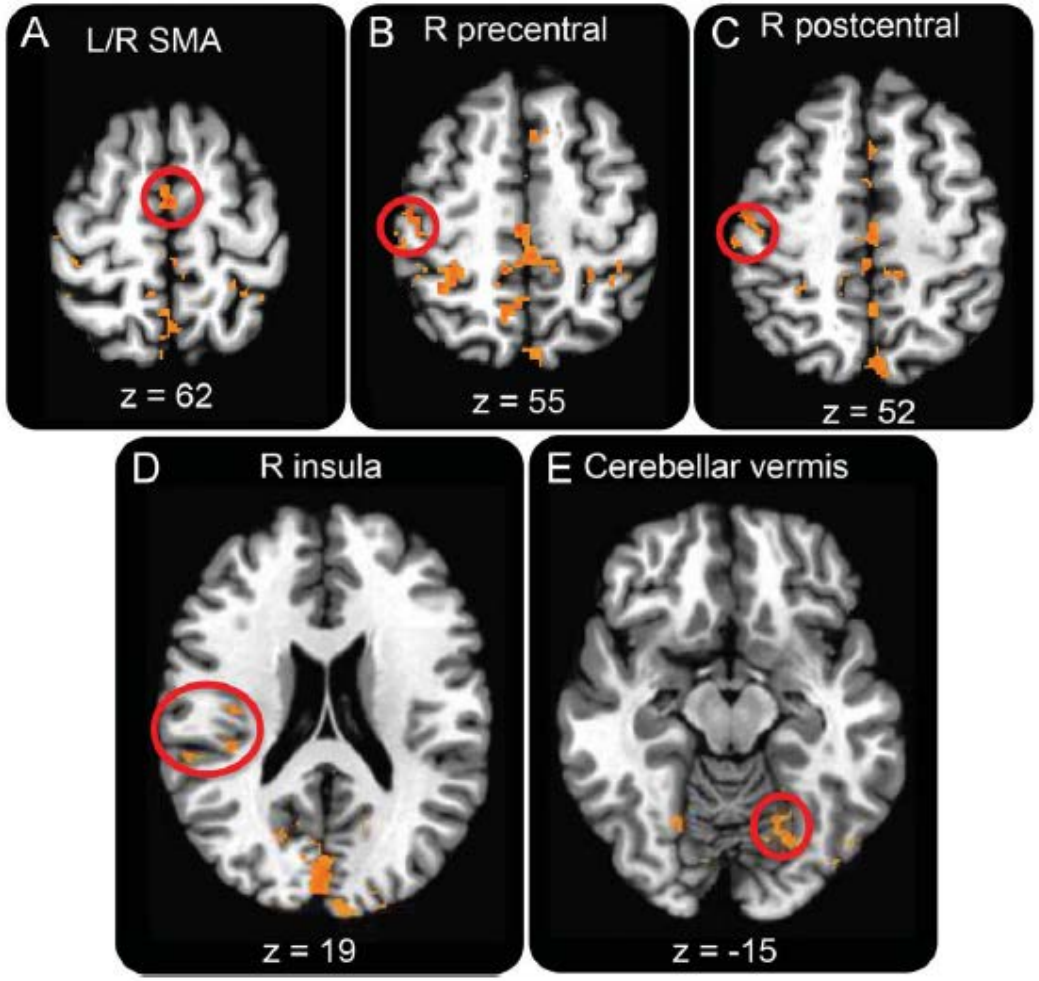
TPJ = temporoparietal junction

And decreased connectivity of the R TPJ to the sensorimotor cortex & ventral anterior cingulate

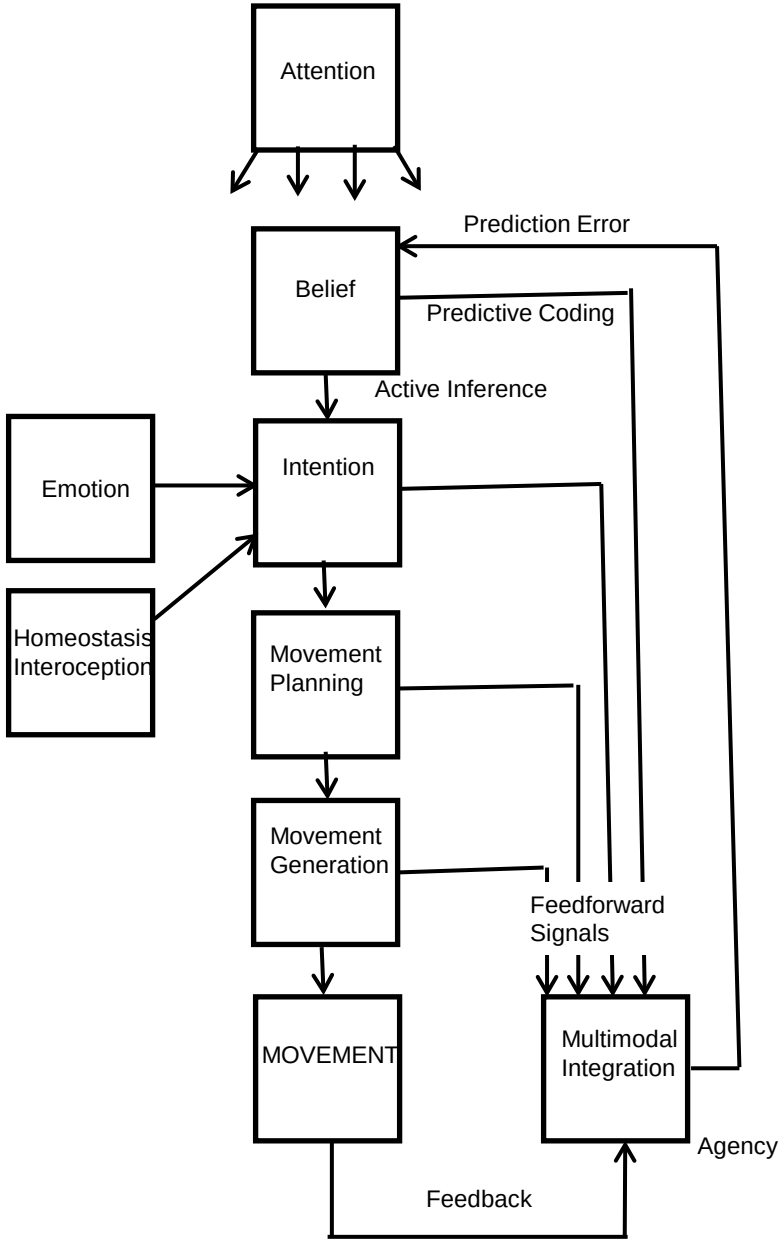
Voon et al. *Neurology* 2010;74:223-228

Resting state fMRI

Figure 1 Decreased functional connectivity (FC) between the right temporo-parietal junction (rTPJ) and bilateral sensorimotor regions in patients with functional movement disorders (FMD)



Maurer et al. *Neurology* 2016;87:564-70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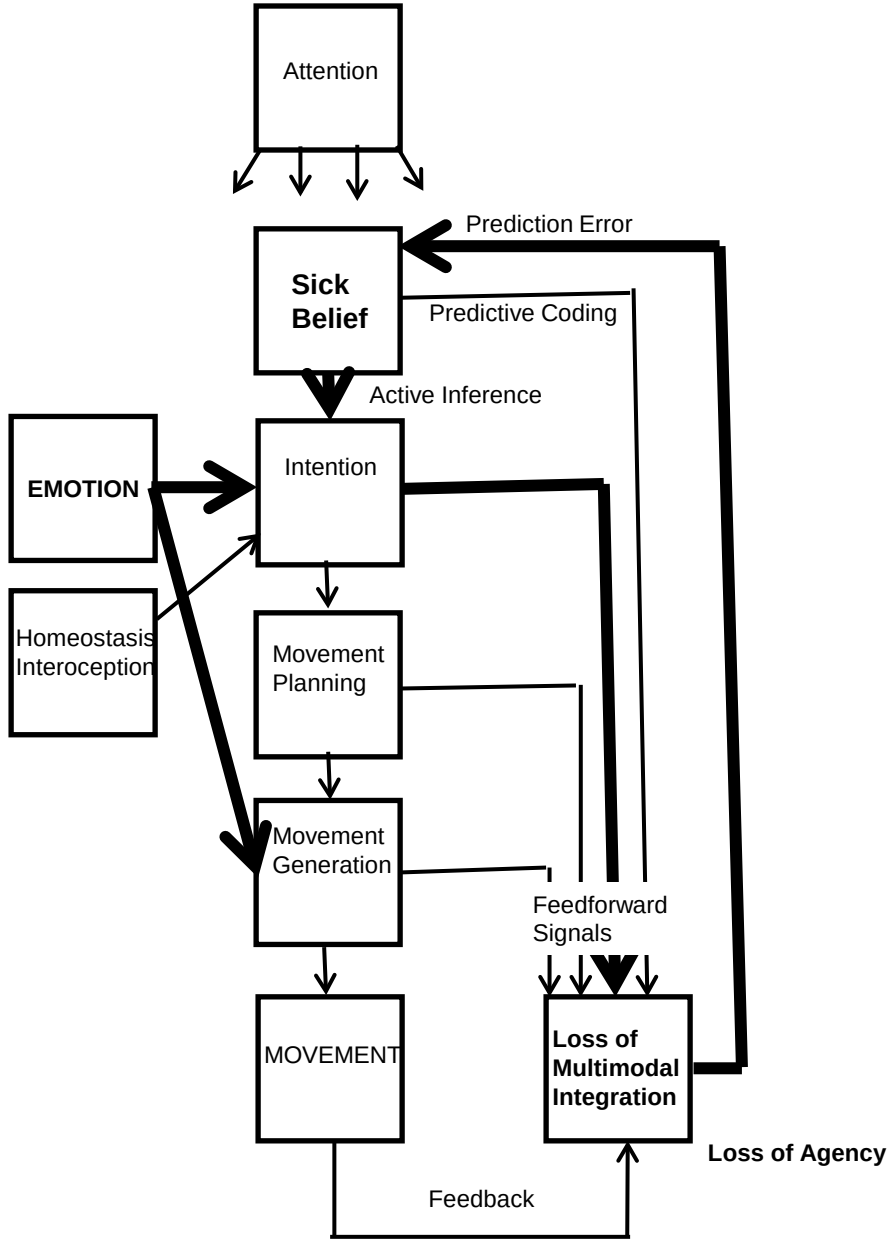
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How can active inference cause functional movements?

Compare tics…

doi:10.1093/brain/awl050 Brain (2006), 129, 2029–2037

Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study

S. Bohlhalter, A. Goldfine,* S. Matteson,* G. Garraux, T. Hanakawa, K. Kansaku,
R. Wurzman and M. Hallett

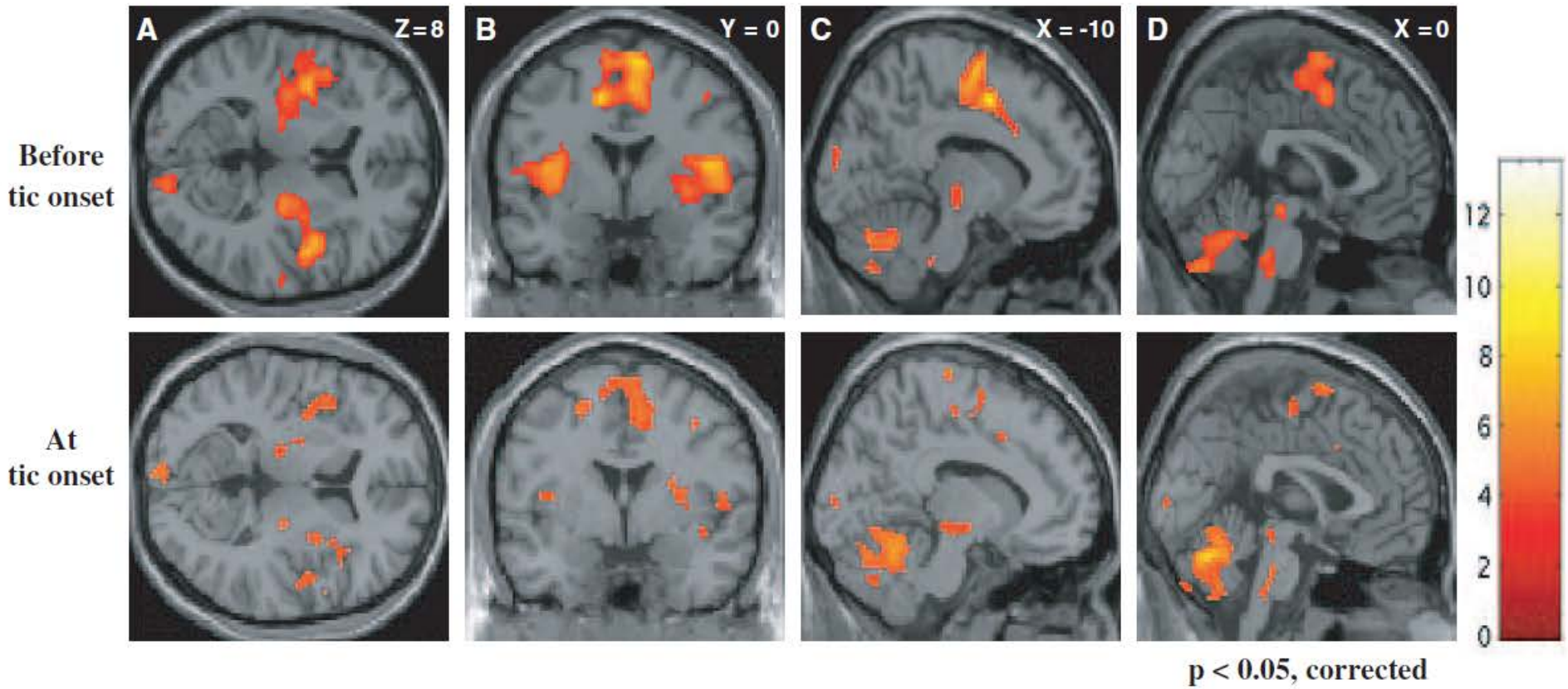
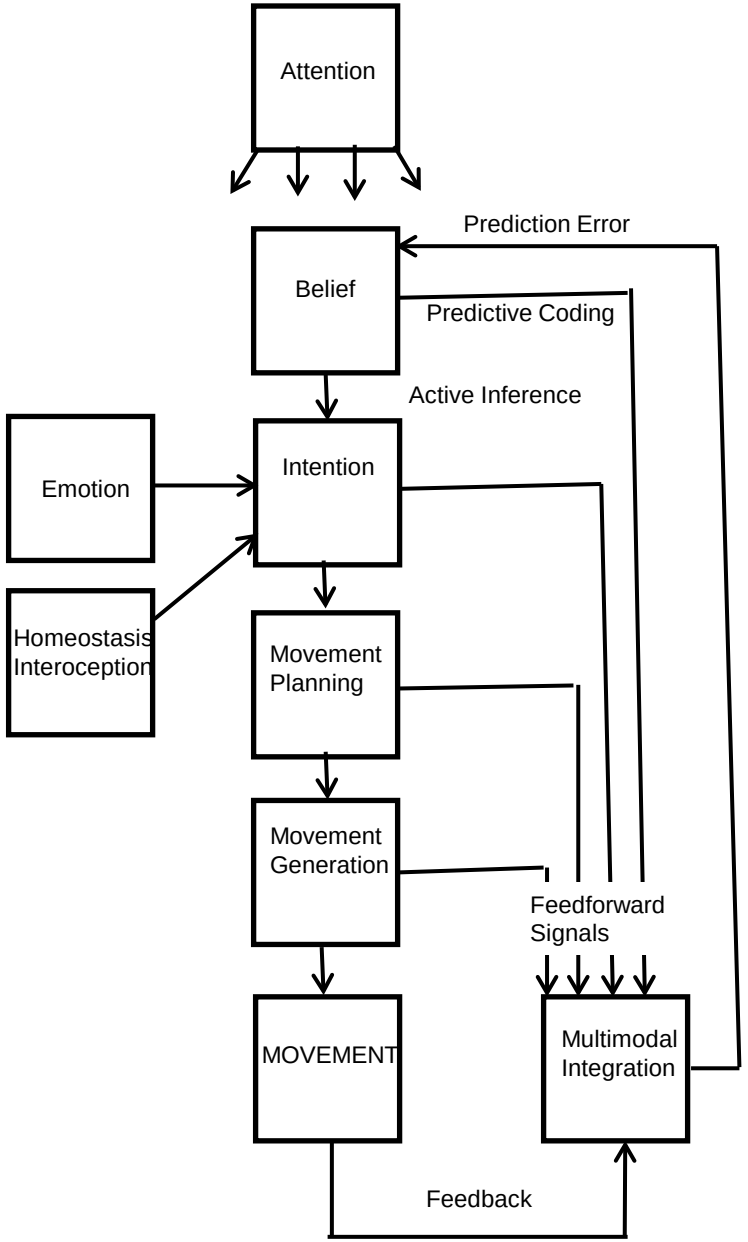


Fig. 2 Statistical parametric maps superimposed on axial (**A**), coronal (**B**) and sagittal (**C** and **D**) views are shown. The upper row shows significant activations ($P < 0.05$, corrected for multiple comparisons) of paralimbic areas (ACC and insular region bilaterally) before tic onset; these activations were much less prominent at tic onset (lower row).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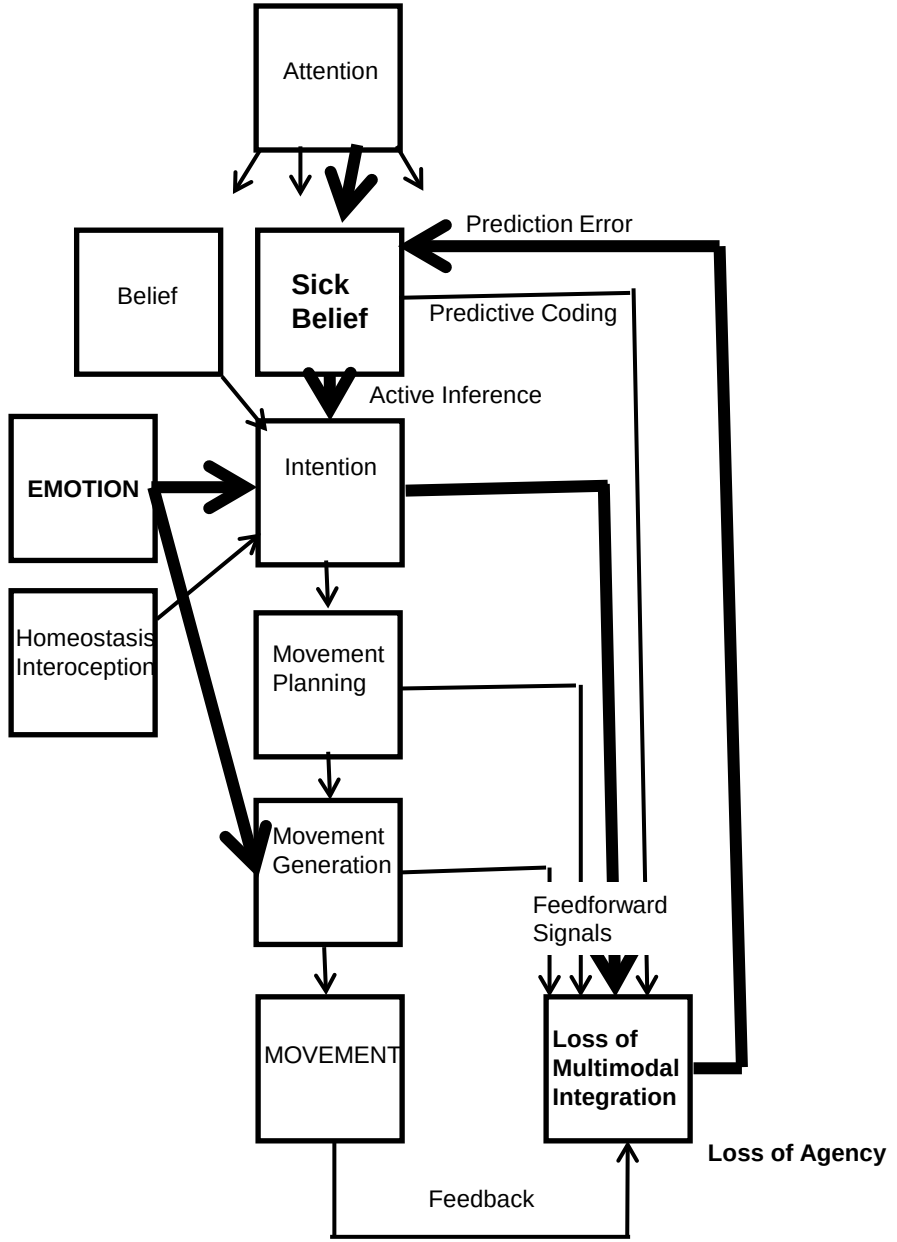
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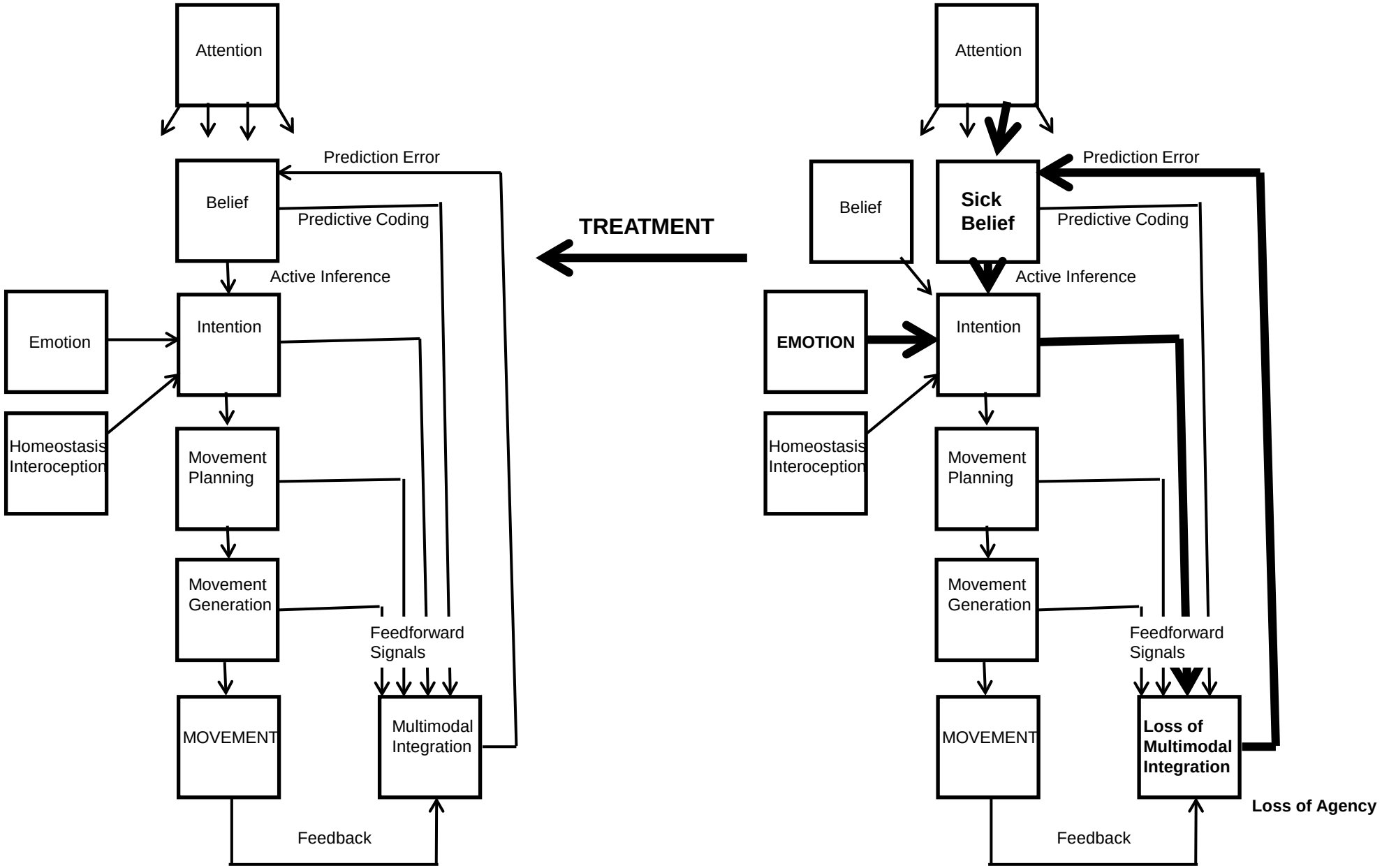
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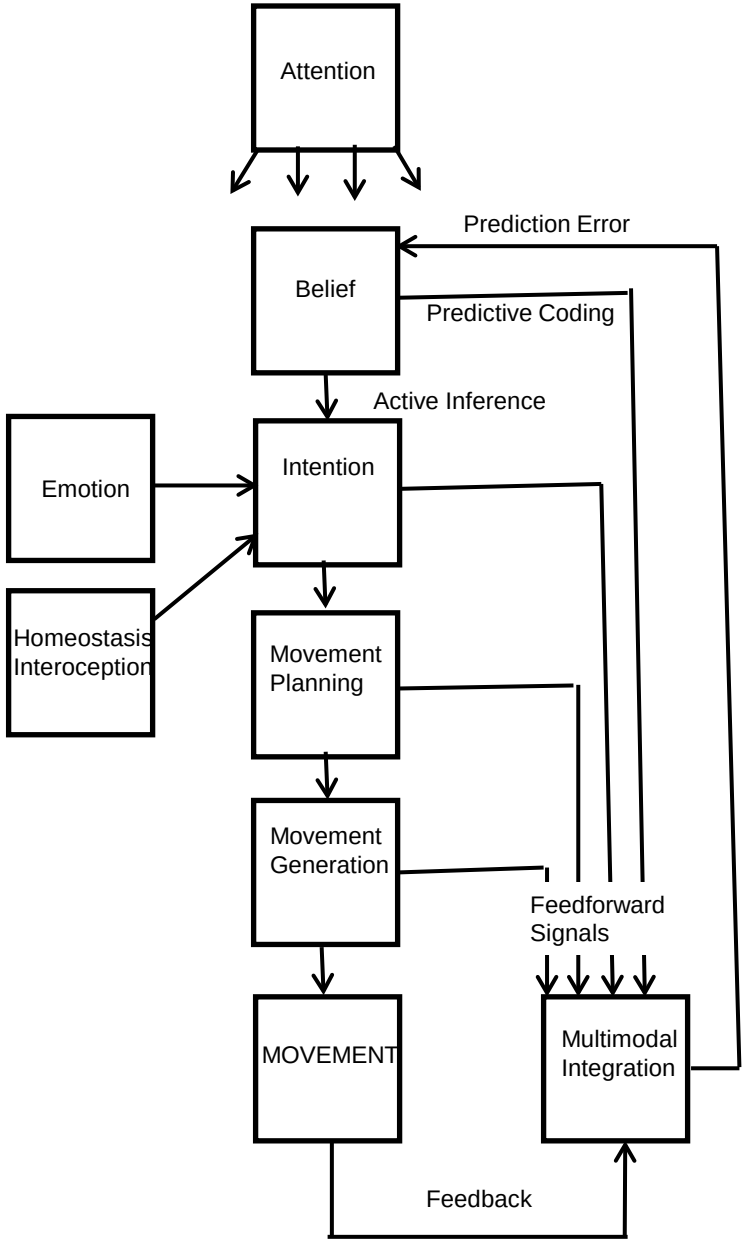
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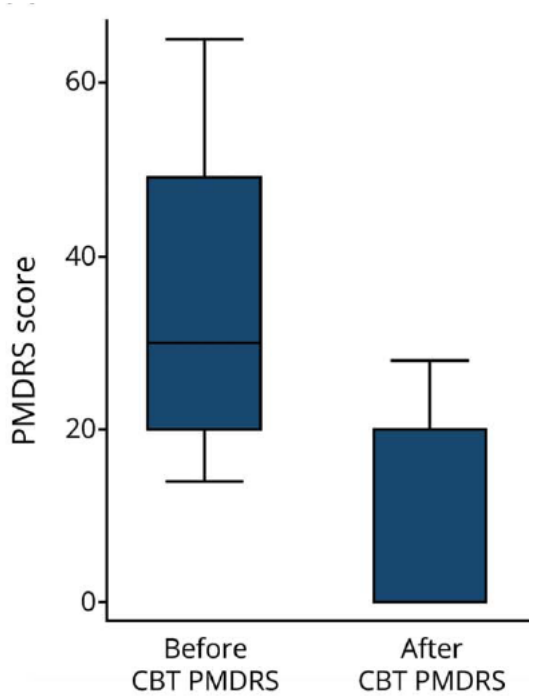
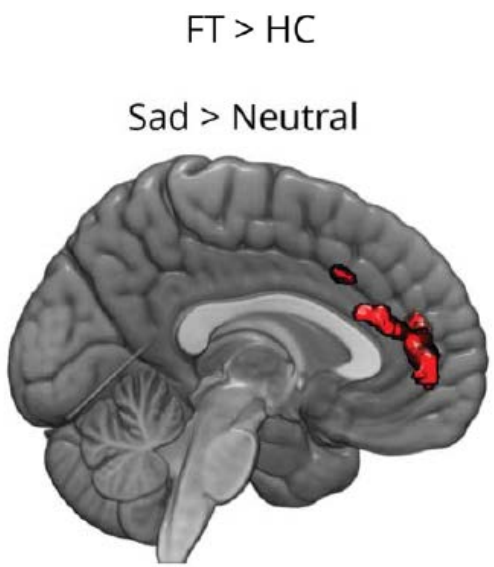
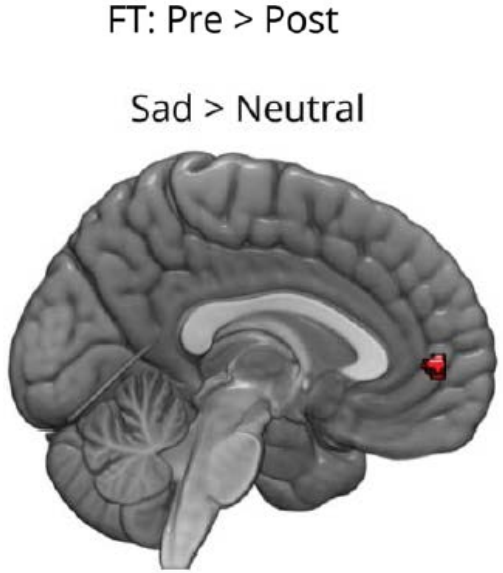
Clinical and neural responses to cognitive behavioral therapy for functional tremor

Alberto J. Espay, MD, MSc, Scott Ries, LISW, Thomas Maloney, MS, Jennifer Vannest, PhD, Erin Neefus, BS, CCRP, Alok K. Dwivedi, PhD, Jane B. Allendorfer, PhD, Lawson R. Wulsin, MD, W. Curt LaFrance, Jr, MD, MPH, Anthony E. Lang, MD, FRCPC, and Jerzy P. Szaflarski, MD, PhD

Neurology® 2019;93:e1787-e1798. doi:10.1212/WNL.0000000000008442







Amygdala and Insula Connectivity Changes Following Psychotherapy for Posttraumatic Stress Disorder: A Randomized Clinical Trial

Gregory A. Fonzo, Madeleine S. Goodkind, Desmond J. Oathes, Yevgeniya V. Zaiko, Meredith Harvey, Kathy K. Peng, M. Elizabeth Weiss, Allison L. Thompson, Sanno E. Zack, Steven E. Lindley, Bruce A. Arnow, Booil Jo, Barbara O. Rothbaum, and Amit Etkin

Biological Psychiatry May 1, 2021; 89:857–867

Simple summary

- FNDs are common, disabling, and expensive.
- FNDs are multifactorial in etiology, best understood by the biopsychosocial model
- FNDs are involuntary
- Pathophysiology, triggered by limbic overactivity, may arise from abnormal belief driving a feedforward-feedback (Bayesian) network

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Functional Movement Disorders

Sarah Lidstone, MD, PhD

Functional Movement Disorders: clinical presentations and treatment approaches

November 3, 2023

Sarah C. Lidstone M.D., Ph.D.

Director, Integrated Movement Disorders Program, Toronto Rehabilitation Institute

Movement Disorders Neurologist, University Health Network

Assistant Professor, University of Toronto

Affiliate Scientist, KITE, Toronto Rehabilitation Institute

Sarah.Lidstone@uhnresearch.ca, @sarahlidstone

Disclosures

- Royalties from UptoDate article “Functional Movement Disorder”

Outline

- Part 1: Review of FMD positive signs and phenotypes
- Part 2: 5 lessons about FMD relevant for treatment
- Part 3: Practical tips and therapy approaches for the neurologist

Please no recording.
Patients shown have provided consent for videos to be used for educational purposes, only.

Part 1: Review of FMD positive signs and phenotypes

FMD phenotype frequency

Original research

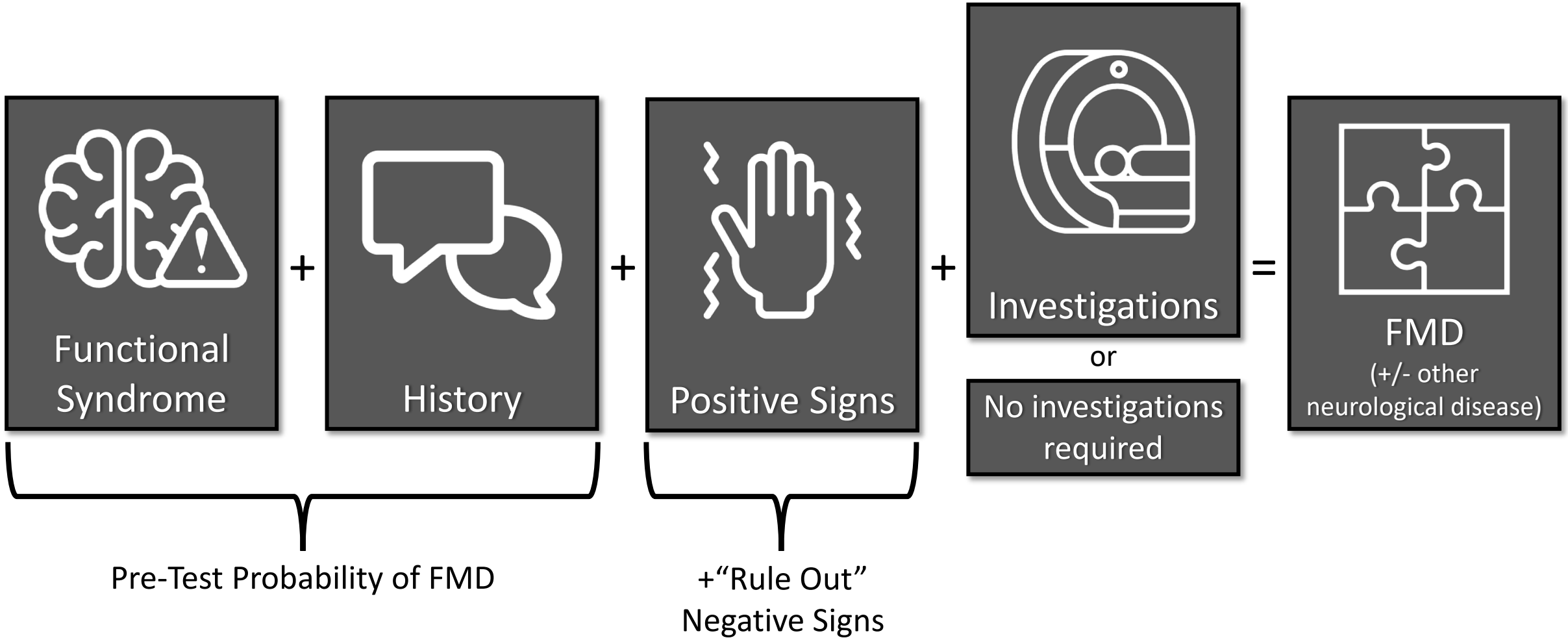
Functional movement disorder gender, age and phenotype study: a systematic review and individual patient meta-analysis of 4905 cases

Sarah C. Lidstone [1,2] Michael Costa-Parke,[1] Emily J. Robinson,[3,4] Tommaso Ercoli [5] Jon Stone [6] FMD GAP Study Group

Table 1 Descriptive summary statistics and one-stage individual patient data meta-analysis mixed-effects linear regression model for age of symptom onset, with 'tremor' and 'female' as the reference categories

	n (%)	Age of onset Mean (SD)	Gender Women (%)	Coefficient (95% CI)	Standardised effect size (95% CI)	P value
Gender						
Women	3558 (72.5)	39.1 (15.9)	–	–	–	–
Men	1347 (27.5)	41.0 (16.5)	–	1.66 (0.71 to 2.62)	0.10 (0.04 to 0.16)	0.001*
Phenotype						
Mixed	1127 (23.0)	42.1 (16.3)	848 (75.2)	0.32 (–1.05 to 1.69)	0.02 (–0.07 to 0.10)	0.649
Tremor	1056 (21.6)	40.7 (16.6)	752 (71.2)	–	–	–
Weakness	887 (18.1)	36.4 (13.4)	647 (72.9)	–3.74 (–5.35 to 2.14)	–0.23 (–0.33 to to 0.13)	<0.001*
Dystonia	578 (11.8)	34.5 (14.8)	453 (78.4)	–4.31 (–5.98 to 2.65)	–0.27 (–0.37 to to 0.16)	<0.001*
Gait	405 (8.3)	43.2 (18.4)	284 (70.1)	3.21 (1.39 to 5.03)	0.20 (0.09 to 0.31)	0.001*
Jerks/myoclonus	223 (4.5)	39.8 (18.7)	142 (63.7)	1.03 (–1.19 to 3.25)	0.06 (–0.07 to 0.20)	0.363
Parkinsonism†	83 (1.7)	44.6 (12.9)	43 (51.8)	–	–	–
Facial symptoms†	67 (1.4)	37.3 (12.6)	56 (83.6)	–	–	–
Other/unknown	479 (9.8)	40.3 (15.8)	333 (69.5)	–1.11 (–3.19 to 0.98)	–0.07 (–0.20 to 0.06)	0.298
Total sample	4905 (100.0)	39.7 (16.1)				

Coefficients are to be interpreted in terms of age at onset in years; and standardised coefficients are interpreted in SD. Positive coefficient means that the variable was associated with a later age of onset and negative coefficient with an earlier age of onset.
*Statistically significant at the p<0.05 level.
†Not inputted into linear regression model.


Functional Syndrome
+
History
+
Positive Signs
+
Investigations
or
No investigations required
=
FMD
(+/- other neurological disease)
Pre-Test Probability of FMD
+"Rule Out" Negative Signs

Variability
Inconsistency
Distractibility
Incongruency

Functional tremor

Co-contraction

"Whack-a-mole"

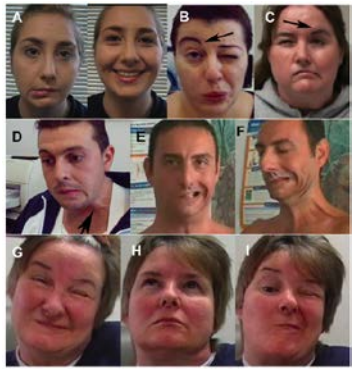
Entrainment

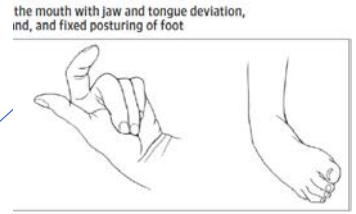
Coherence

Contralateral ballistic movement

Functional dystonia

Resistance to passive ROM

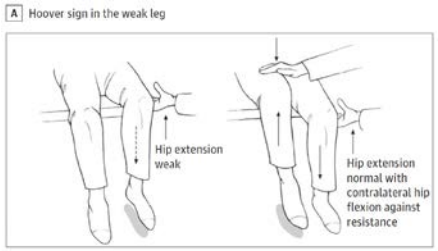


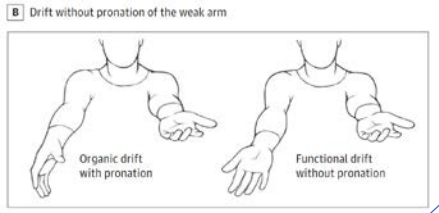


Functional weakness

Hip abductor sign

Collapsing weakness





Functional gait disorder

Astasia-abasia

Uneconomical gait

Knee buckling

Tight-rope

Walking on ice

Leg dragging

Excessive slowness

Functional jerks

Entrainment

Axial/facial distribution

Functional tics

Self-injury

Adult onset

Wide repertoire, lack of stereotype

Lack of urge*

Not suppressible

Functional "parkinsonism"

Slowness without decrement

Paratonia

Preserved speed

Automatic tasks

Espay et al. 2018; Fasano et al. 2012; Gilmour, Lidstone, Lang, 2022

Variability

Changing patterns of the abnormal movements over time

- Distribution
- Amplitude
- Frequency
- Phenomenology

Inconsistency

Movement impaired at some times and preserved in others; inconsistent performance on examination and times when the patient is not being actively examined

Distractibility

Abnormal movements resolve during cognitive or motor tasks*

*the patient must be truly distracted

Enhancement with attention

Abnormal movement worsens/emerges when attention is drawn to it

Incongruency

Clinical picture is incompatible with other neurological diseases

Entrainment

Tremor/jerks take the same frequency of an externally cued rhythmic movement

Co-contraction

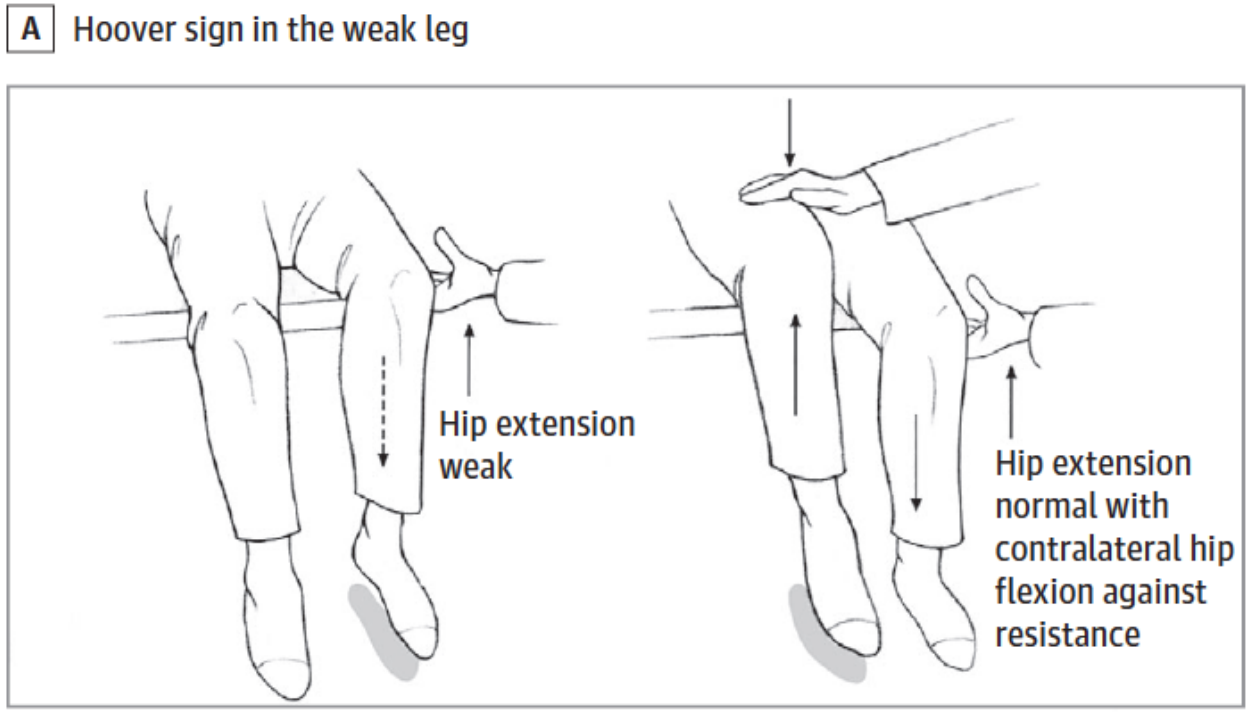
Simultaneous contraction of agonist and antagonist muscles resulting in little movement +/- tremor

“Whack-a-mole” sign

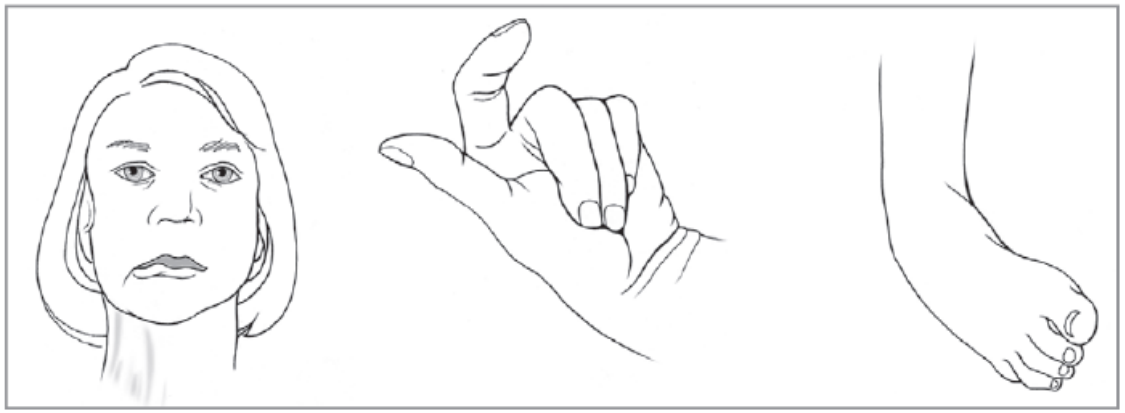
Emergence or worsening of an involuntary movement in a separate body part when initially affected body part is restrained by examiner

Hoover sign

- Most useful in asymmetrical leg weakness
- May be present in patients not complaining of weakness
- Hip abduction hoover sign useful if bed bound or bilateral leg weakness
- If present is extremely useful for explaining the diagnosis to the patient



Functional Dystonia



Exploratory Neuropsychiatric Phenotypes: Movement Disorder

Table 5. Logistic Regression Models Examining Relationships between Functional Movement Disorder Phenotype and Episodic vs. Constant Symptoms

	Episodic phenotype			Constant phenotype		
Independent variables	OR	95% CI	P	OR	95% CI	P
Gait disorder	0.35	0.15-0.84	.019	7.32	3.07-17.48	<.0001
Tremor	5.41	2.14-13.72	.0004	0.83	0.36-1.95	.673
Weakness	0.70	0.24-2.07	.522	4.88	1.76-13.53	.002
Appendicular jerks	11.32	4.12-31.14	<.0001	0.32	0.12-0.78	.013
Fixed dystonia	1.01	0.17-6.16	.989	12.36	1.89-80.94	.009
Axial jerks	20.86	2.33-187.09	.007	0.45	0.08-2.56	.369
Facial movements	2.88	0.78-10.57	.112	1.33	0.40-4.43	.647
Parkinsonism	2.02	0.22-18.78	.538	0.40	0.05-3.33	.398

Abbreviations: CI, confidence interval; OR, odds ratio.

FMD-Relevant Factors

- Recurrent, observable **behavioural patterns** noted in patients with FMD
- Factors are drawn from psychiatry literature and clinical experience
  - Some have been previously associated with FMD, others are recognized phenomena in psychiatry
- May not be routinely assessed by neurologists or psychiatrists
- **Not inherently pathological or etiological for FMD** → May contribute to the expression of FMD acting as predisposing or precipitating factors

Activity Avoidance: Limiting activities due to fear of symptom exacerbation either during or after activity

Propensity to Dissociate: Tendency towards disconnections from one's thoughts, feelings, actions and sense of self. May be directly observed or described from patient experience

Emotional Avoidance: Tendency to avoid experiencing or expressing uncomfortable emotions, either directly expressed by patient, evident as a pattern or clearly visible during clini

Somatic Preoccupation/Health Anxiety: Preoccupation and excessive worry/attention to bodily symptoms, time and energy spent on symptoms, worry

This list is not exhaustive!

"Go-Go-Go" Coping Style: keeping busy, highly productive and discomfort with free time when not attending to a goal

rder Traits: Not diagnosed with a personality disorder, but with overlapping traits including emotional dysregulation, help-seeking-help-lf-image and relationships

These are not pathological!

Hyperarousal: Elevated an activation, hyper-talkativeness, diffuse hyperreflexia without upper motor neuron signs, diaphoresis, visible muscle tension, fidgeting, fist clenching

Pleasing: Self-reported strong urge to attend to others' needs and wants at the expense of their own, high responsibility taking

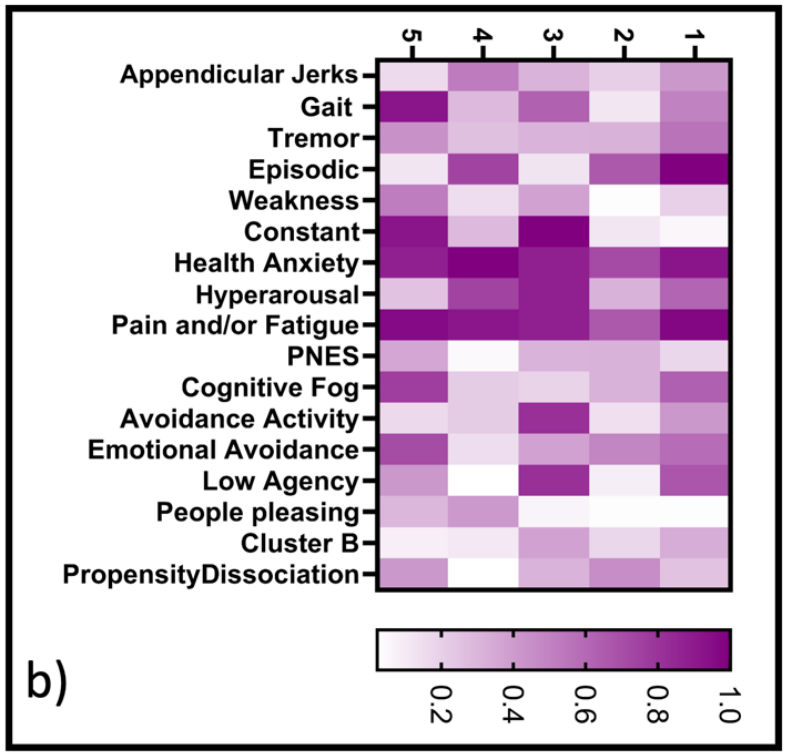
Low Self-Agency: Feeling a lack of control over self or environment, tendency to allow others to provide care needs, tendency to attribute success/failure to others, evident by historical patterns

Tendency Toward Perfectionism: Self-reported striving for perfection, critical self-evaluation, pressure to achieve unrealistic goals

Neuropsychiatric phenotypes in functional movement disorder

Gabriela S. Gilmour[1,2], Laura K. Langer[3], Anthony E. Lang[1,2], Lindsey MacGillivray[4,5,6] and Sarah C. Lidstone[2,3,4]

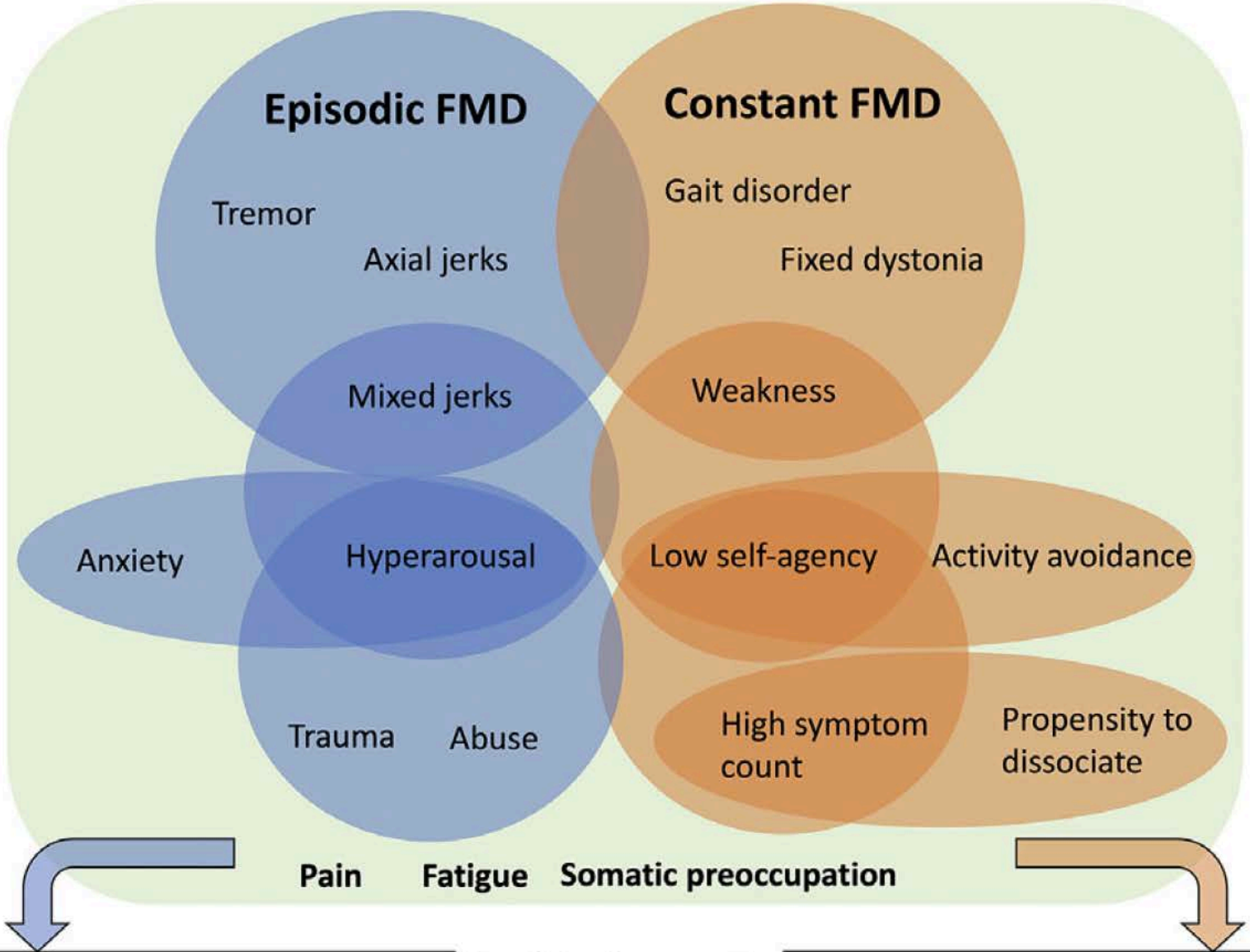
N=160 consecutive FMD patients
Movement disorders evaluation at 2 time points
Psychiatric FND evaluation



Depression ⟷ Gait Disorder

Low Self-Agency ⟷ Weakness

Hyperarousal ⟷ Appendicular Jerks/ Myoclonus



Gilmour et al. 2023

Episodic FMD

Movement: hyperkinetic motor symptoms

FMD Factors: anxiety, hyperarousal, history of trauma

39-year-old man, history IBS

- Onset: 6 months prior
- Primary symptoms: **episodic axial jerks** originating from area of abnormal sensation on back, stuttering speech
- FMD-Relevant Factors: **anxiety, hyperarousal**, emotional avoidance
- Experienced chronic adversity with ex-wife

Constant FMD

Movement: gait disorder, weakness, fixed dystonia

FMD Factors: activity avoidance, low self-agency

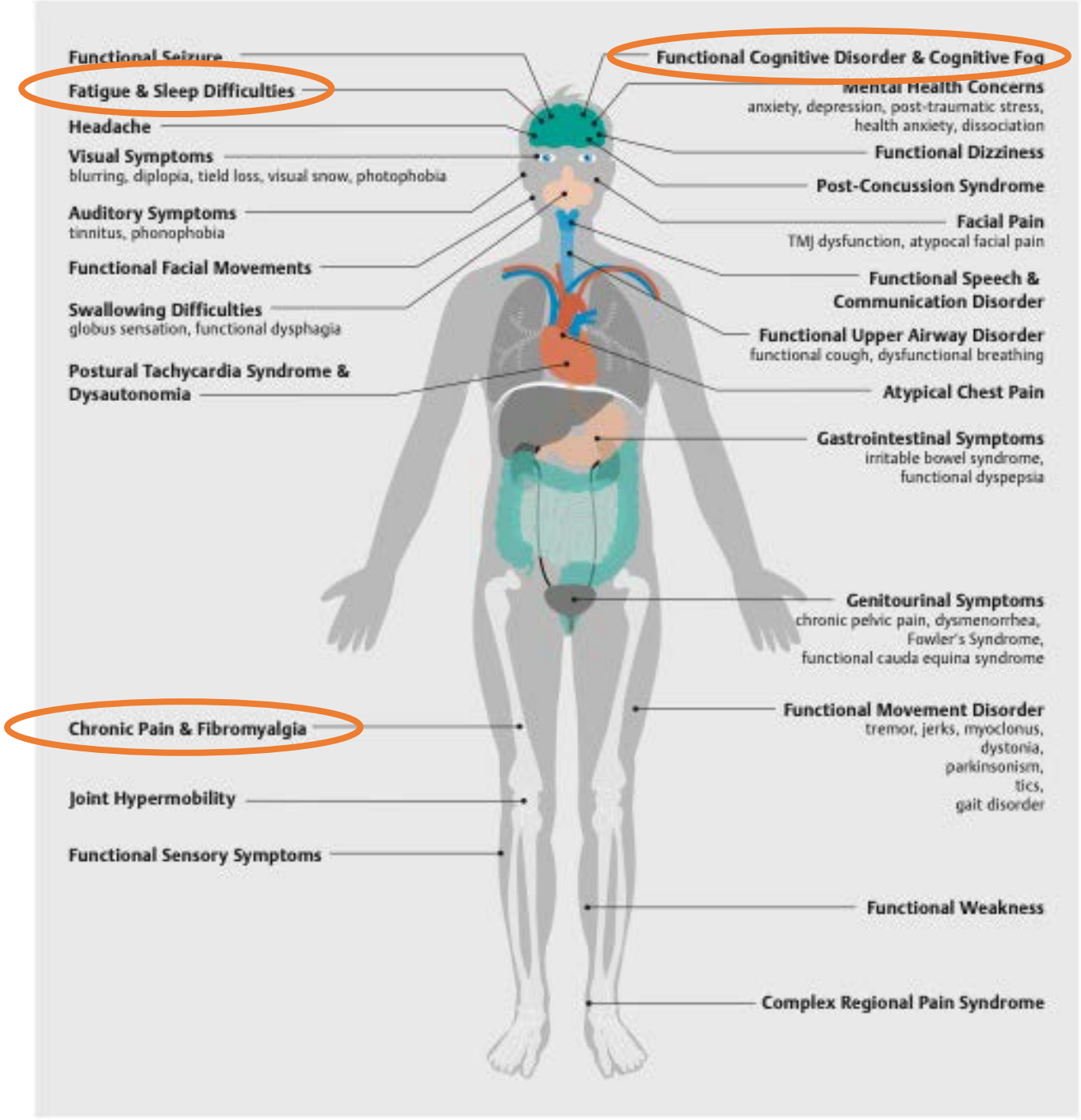
20-year-old woman

- Onset: 2 years ago, after suspected viral encephalitis
- Primary symptoms: **constant** generalized weakness, fatigue, cognitive fog
- FMD-Relevant Factors: **activity avoidance**, **low self-agency**, propensity to **dissociate**, perfectionism

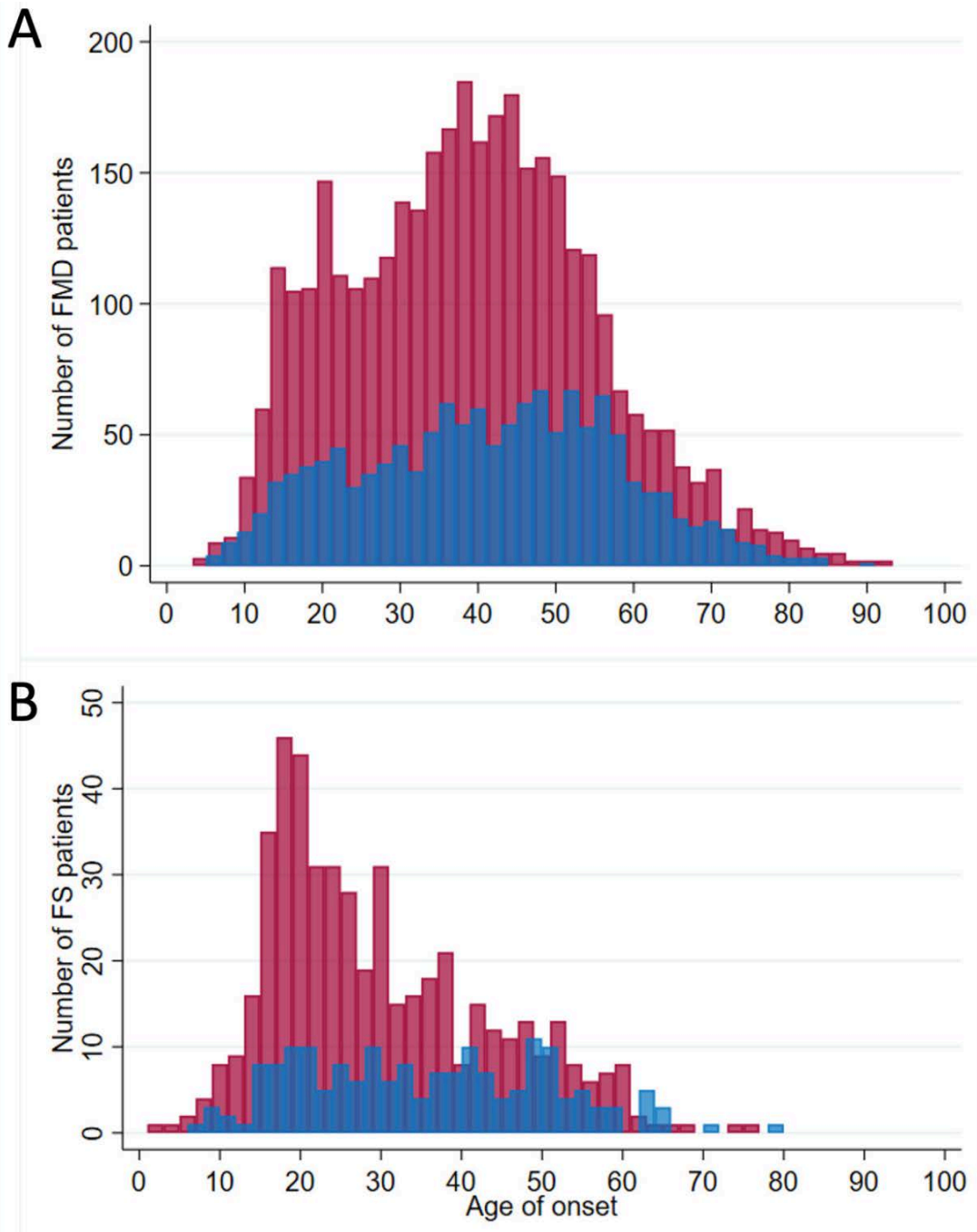
Part 2: 5 lessons about FMD relevant for treatment

1. FMD is a syndrome beyond the movement disorder

FMD is a syndrome



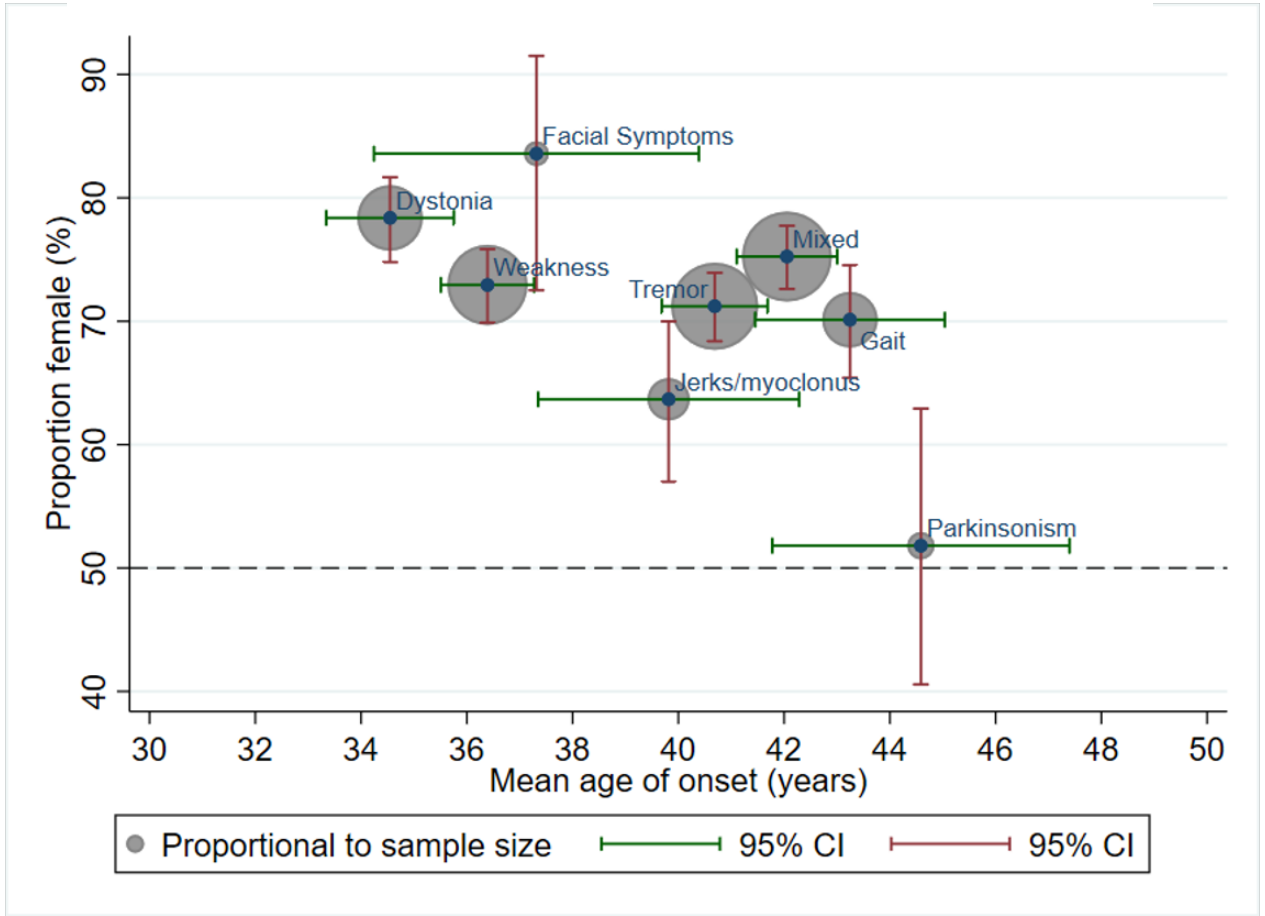
Gilmour and Lidstone in press



Original research

Functional movement disorder gender, age and phenotype study: a systematic review and individual patient meta-analysis of 4905 cases

Sarah C. Lidstone [1,2] Michael Costa-Parke,[1] Emily J. Robinson,[3,4] Tommaso Ercoli [5] Jon Stone [6] FMD GAP Study Group



Lidstone et al. 2022 JNNP

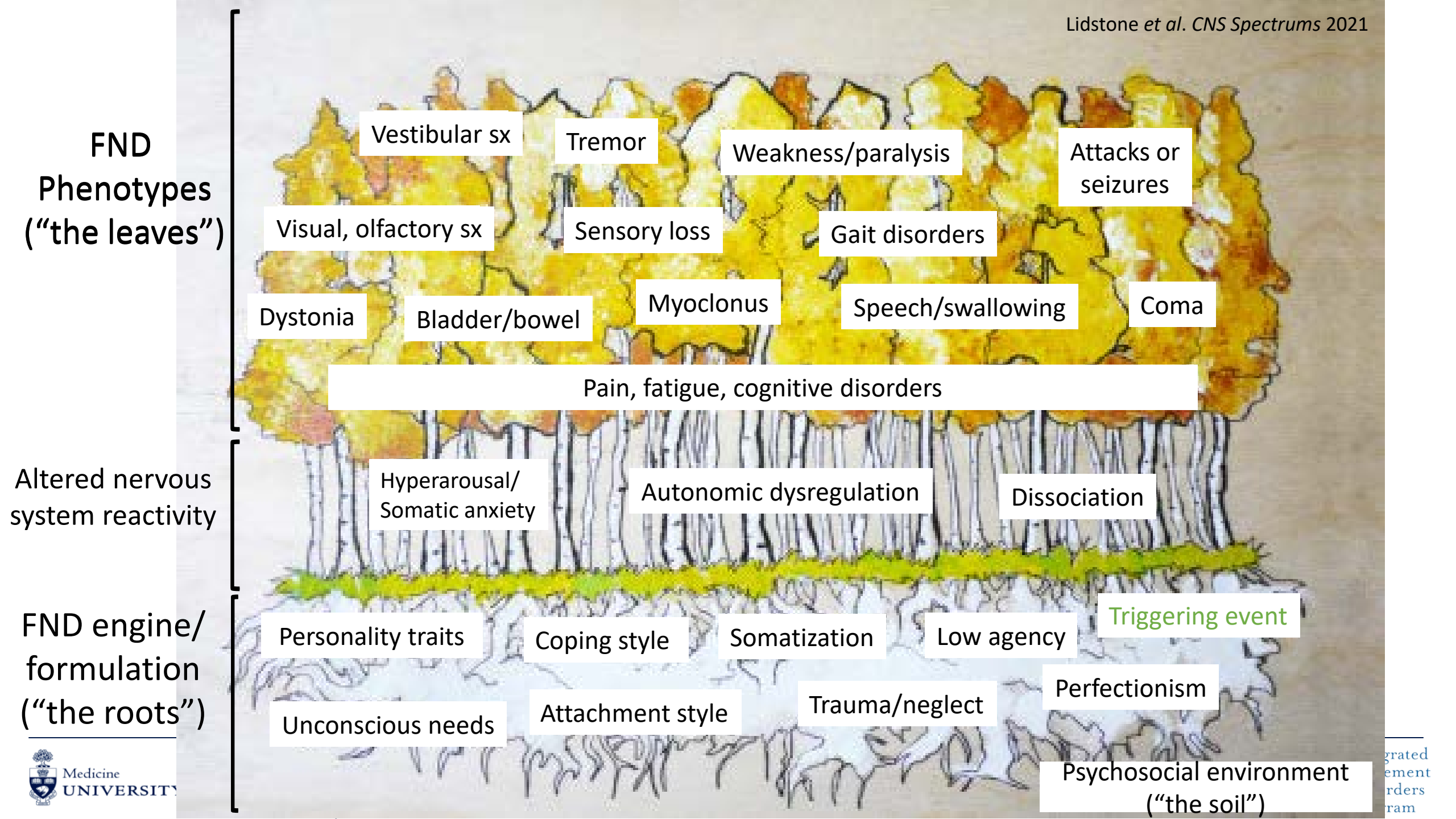
UHN Integrated Movement Disorders Program

Motor phenotype changes in 40% of patients

Supplemental Table 1. Functional movement disorder phenotypic change between assessments

Phenotype	Change			No change
	Any change	Gained	Lost	
All phenotypes (n = 139)	58 (42%)	33 (24%)	45 (32%)	81 (58%)
Movement phenotype				
Appendicular jerks	19 (33%)	9 (16%)	10 (17%)	39 (67%)
Gait	18 (26%)	6 (9%)	12 (17%)	52 (74%)
Weakness	13 (35%)	2 (5%)	11 (30%)	24 (65%)
Tremor	10 (17%)	4 (7%)	6 (10%)	50 (83%)
Facial	7 (29%)	5 (21%)	2 (8%)	17 (71%)
Fixed dystonia	4 (36%)	1 (9%)	3 (27%)	7 (64%)
Parkinsonism	3 (43%)	0	3 (43%)	4 (57%)
Tics	2 (40%)	1 (20%)	1 (20%)	3 (60%)
Axial jerks	1 (8%)	1 (8%)	0	11 (92%)
Episodic/constant symptoms				
Episodic	21 (21%)	11 (11%)	10 (10%)	78 (79%)
Constant	17 (28%)	4 (7%)	13 (21%)	44 (72%)

Not associated with duration between appointments (p = 0.58)


Lidstone *et al*. *CNS Spectrums* 2021
FND Phenotypes ("the leaves")
Vestibular sx
Tremor
Weakness/paralysis
Attacks or seizures
Visual, olfactory sx
Sensory loss
Gait disorders
Dystonia
Bladder/bowel
Myoclonus
Speech/swallowing
Coma
Pain, fatigue, cognitive disorders
Altered nervous system reactivity
Hyperarousal/ Somatic anxiety
Autonomic dysregulation
Dissociation
FND engine/ formulation ("the roots")
Personality traits
Coping style
Somatization
Low agency
Triggering event
Unconscious needs
Attachment style
Trauma/neglect
Perfectionism
Psychosocial environment ("the soil")

2. Functional and structural symptoms coexist

Throw out the dualism

- Neurological symptoms/disease is the largest risk factor for FND
- Functional/dissociative seizures and epilepsy comorbidity is 30%
- Functional tremor or parkinsonism can occur in prodromal Parkinson's disease
- Chronic illness of any kind is a risk factor for functional symptoms

The big idea: should we drop the distinction between mental and physical health?

The current false dichotomy holds back research and stigmatises patients

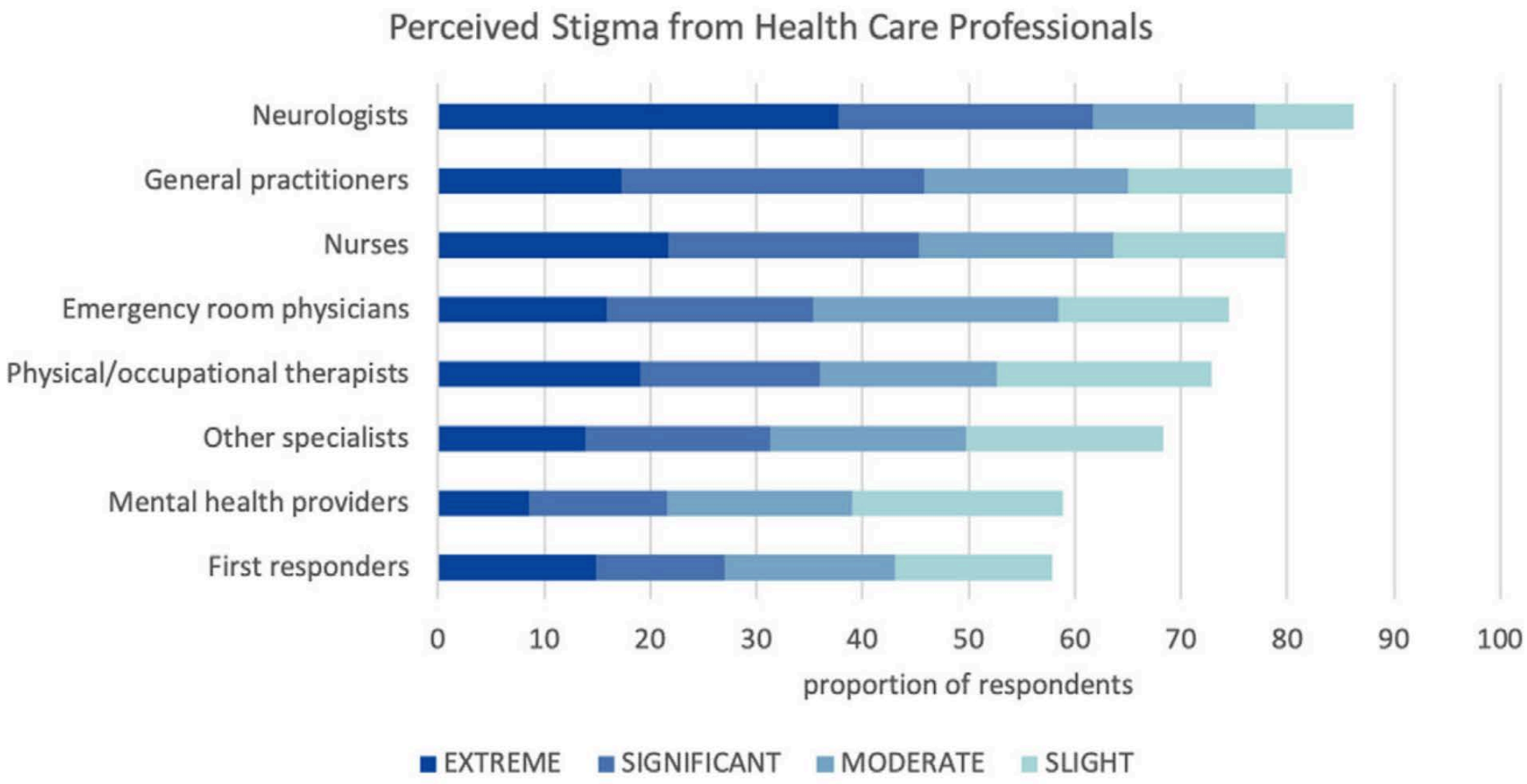
Illustration: Elia Barbieri

Search | International ed

The Guardian

News website of the year

“Your symptoms are very real…to you”



Impact of stigma in the clinical encounter in FND

1. Patient with functional symptoms seek help

↓

2. Provider explains symptoms are "not real"

↓

3. Patient feels invalidated/angry/confused

↓

4. Communication suffers, trust is broken

↙ Provider categorizes encounter as "difficult" and does not learn from it (**return to 2**)

↘ Patient does not benefit from encounter and seeks help from different provider (**return to 1**)

3. FMD is treatable*

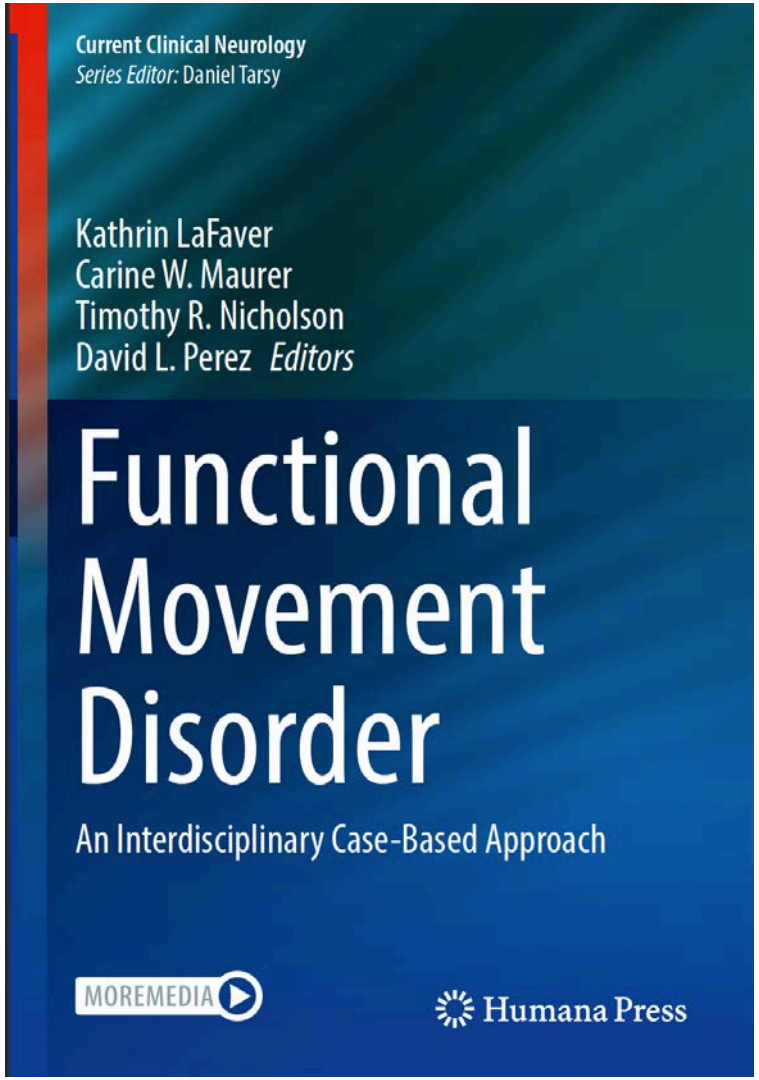
*but not for everyone at that time

FND treatment is opt in

- Therapy cannot be done TO the patient
- Successful outcomes depend on:
  - Active engagement by the patient
  - Realistic and specific goals for improvement
  - Diagnostic agreement
  - Minimizing barriers to rehabilitation (e.g. pain, fatigue, cognitive)
  - Alignment of patient goals with skill set of the team

FMD treatment options

- Diagnosis and education
- Motor retraining physiotherapy
- Mind-body therapies
- Psychotherapy
  - Adapted Cognitive Behavioural Therapy
  - Psychodynamic psychotherapy (intensive, short- or long-term)
- Multidisciplinary rehabilitation
- Treat comorbid conditions (anxiety, chronic pain, trauma therapy, etc.)



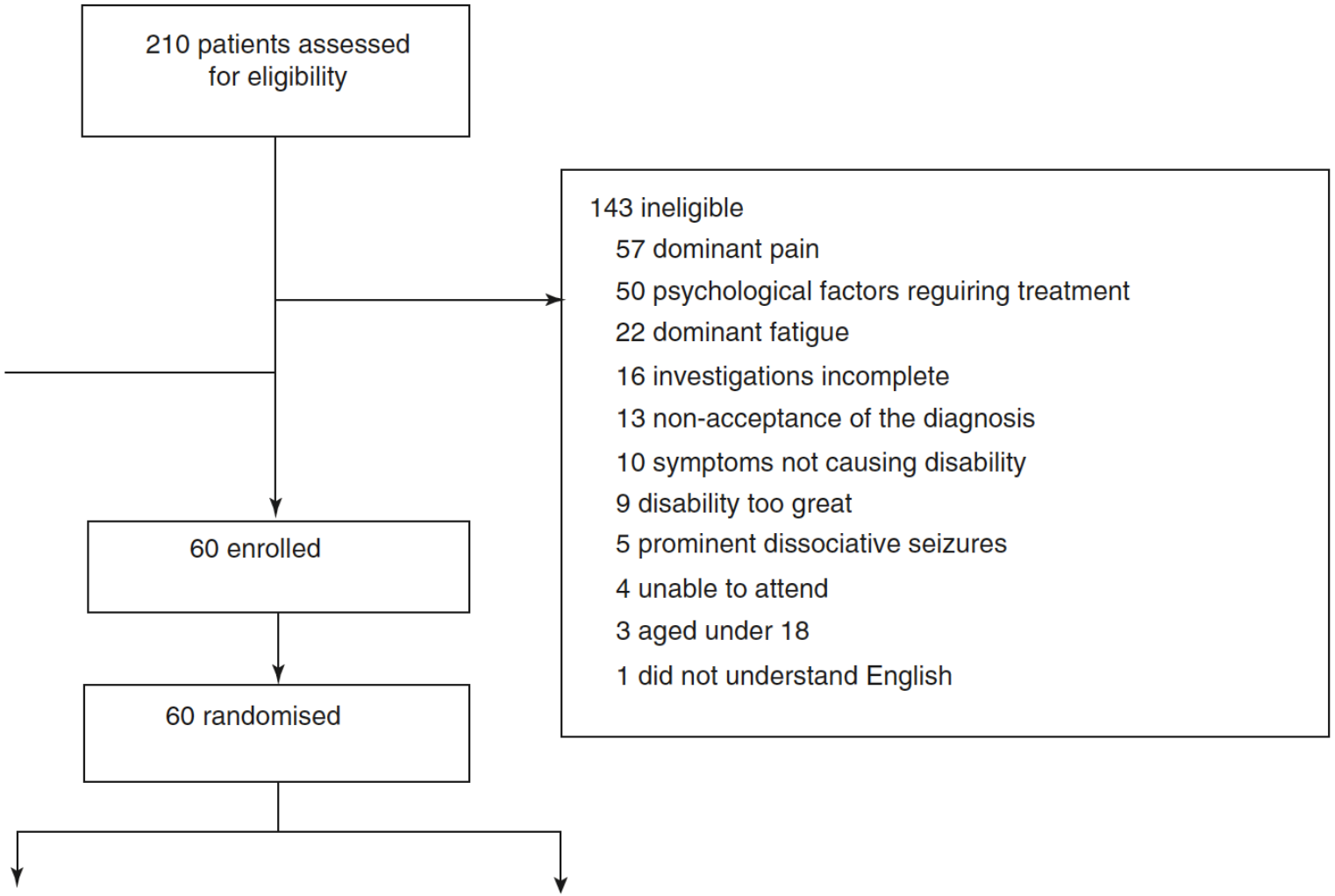


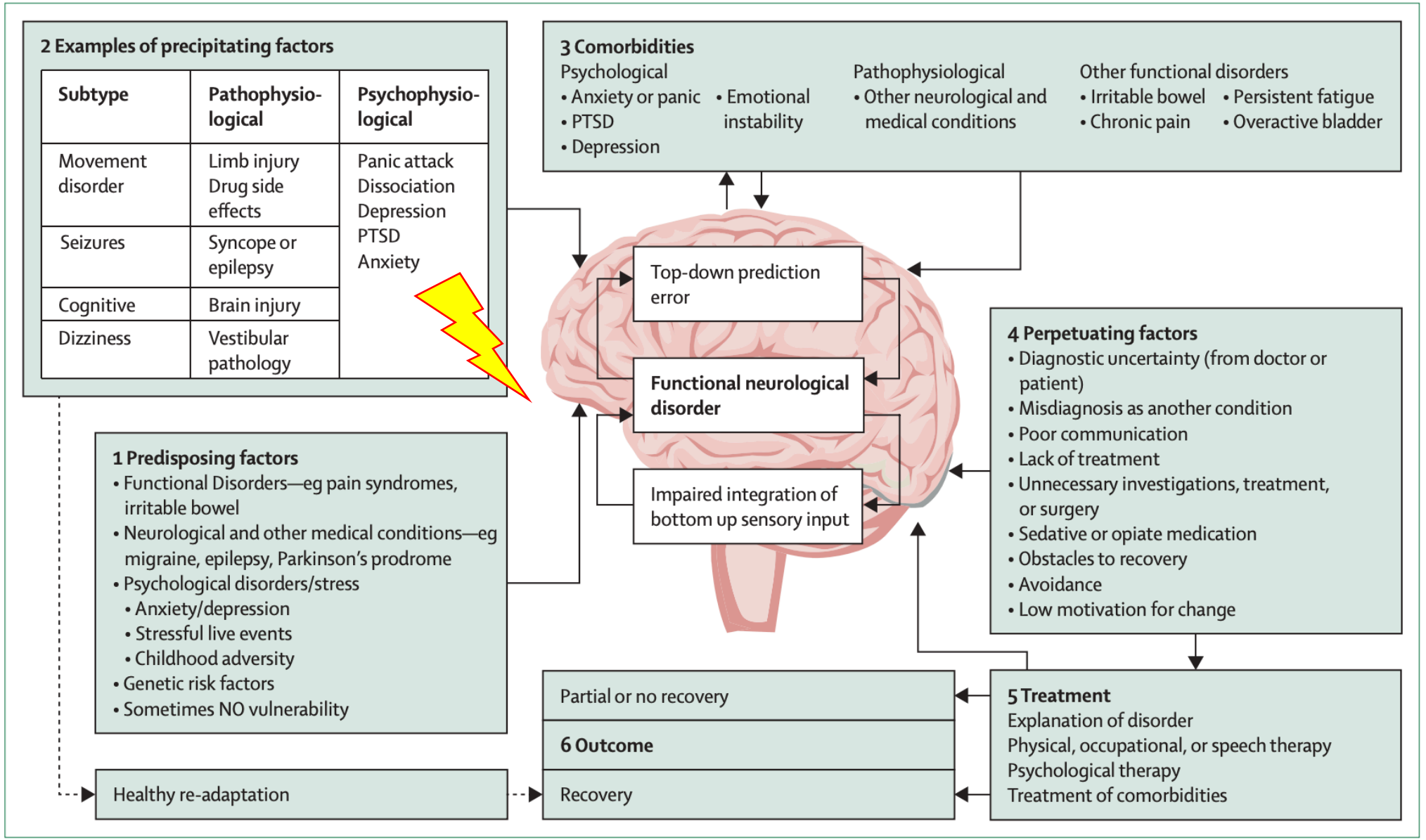
Fig. 20.2 Example of patient triage into specialist physiotherapy for patients with functional movement disorder (Diagram adopted with permission from Nielsen et al. 2017)

Red flags for rehab: not the time

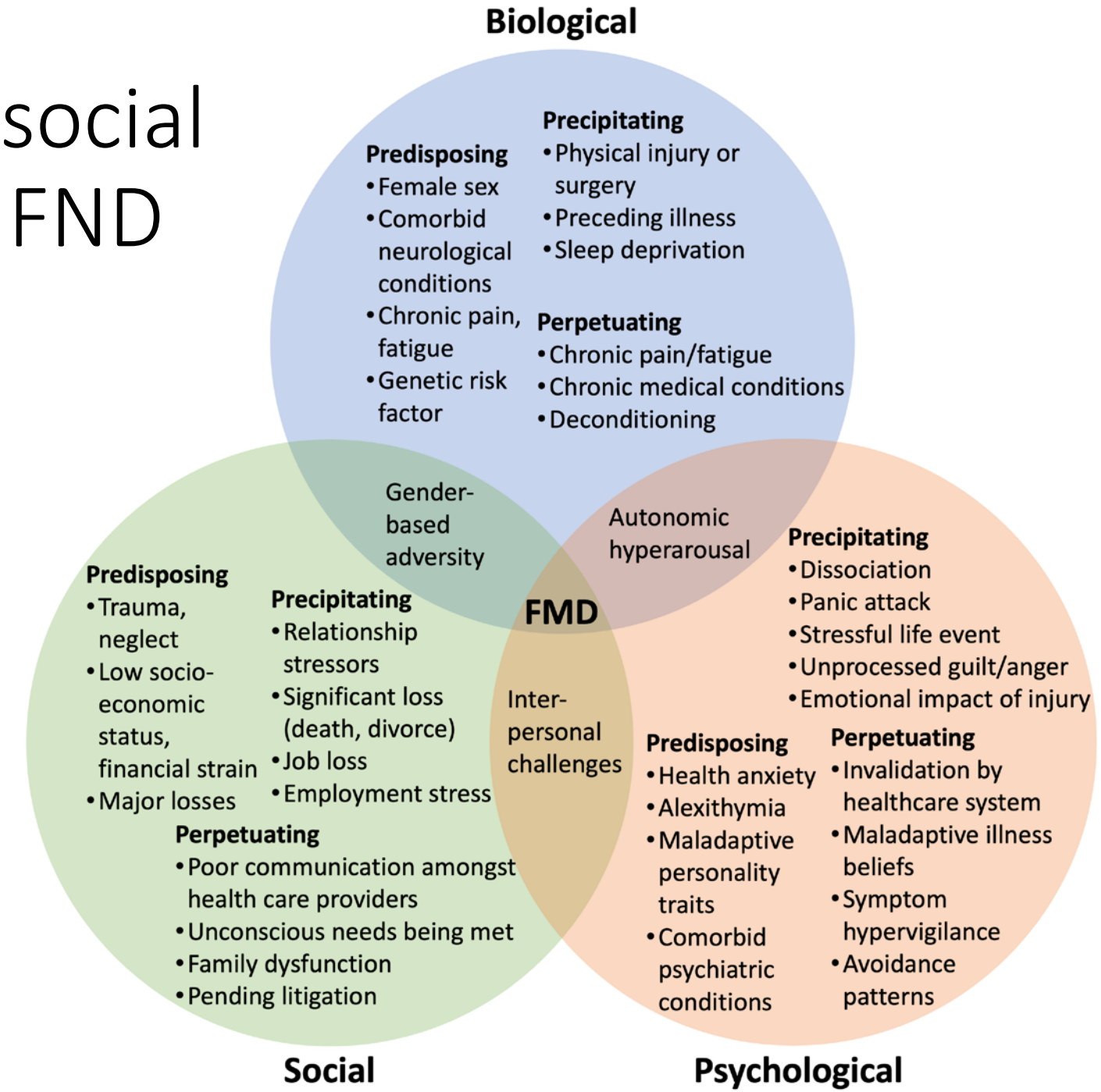
- Unable to notice inconsistency or positive signs when shown
- “What will you do to fix me?” = low agency
- “I will do anything to get better”+ many failed Tx’s = help seek, help reject pattern (cluster B trait)
- Polysymptomatic functional syndrome = somatization (i.e. not FMD)
- Chronic and coping -> can be destabilized by a new illness model
- Negative syndrome (weakness/fatigue/wheelchair) = avoidance
- Facial symptoms = unexpressed anger
- Active litigation

Before treatment

4. Recovery potential is determined by perpetuating factors


2 Examples of precipitating factors
Subtype
Pathophysio-logical
Psychophysio-logical
Movement disorder
Limb injury
Drug side effects
Panic attack
Dissociation
Depression
PTSD
Anxiety
Seizures
Syncope or epilepsy
Cognitive
Brain injury
Dizziness
Vestibular pathology
3 Comorbidities
Psychological
• Anxiety or panic
• PTSD
• Depression
• Emotional instability
Pathophysiological
• Other neurological and medical conditions
Other functional disorders
• Irritable bowel
• Chronic pain
• Persistent fatigue
• Overactive bladder
Top-down prediction error
Functional neurological disorder
Impaired integration of bottom up sensory input
4 Perpetuating factors
• Diagnostic uncertainty (from doctor or patient)
• Misdiagnosis as another condition
• Poor communication
• Lack of treatment
• Unnecessary investigations, treatment, or surgery
• Sedative or opiate medication
• Obstacles to recovery
• Avoidance
• Low motivation for change
1 Predisposing factors
• Functional Disorders—eg pain syndromes, irritable bowel
• Neurological and other medical conditions—eg migraine, epilepsy, Parkinson's prodrome
• Psychological disorders/stress
• Anxiety/depression
• Stressful live events
• Childhood adversity
• Genetic risk factors
• Sometimes NO vulnerability
Partial or no recovery
6 Outcome
Recovery
5 Treatment
Explanation of disorder
Physical, occupational, or speech therapy
Psychological therapy
Treatment of comorbidities
Healthy re-adaptation

Biopsychosocial model for FND



Gilmour and Lidstone In press

MacGillivray and Li

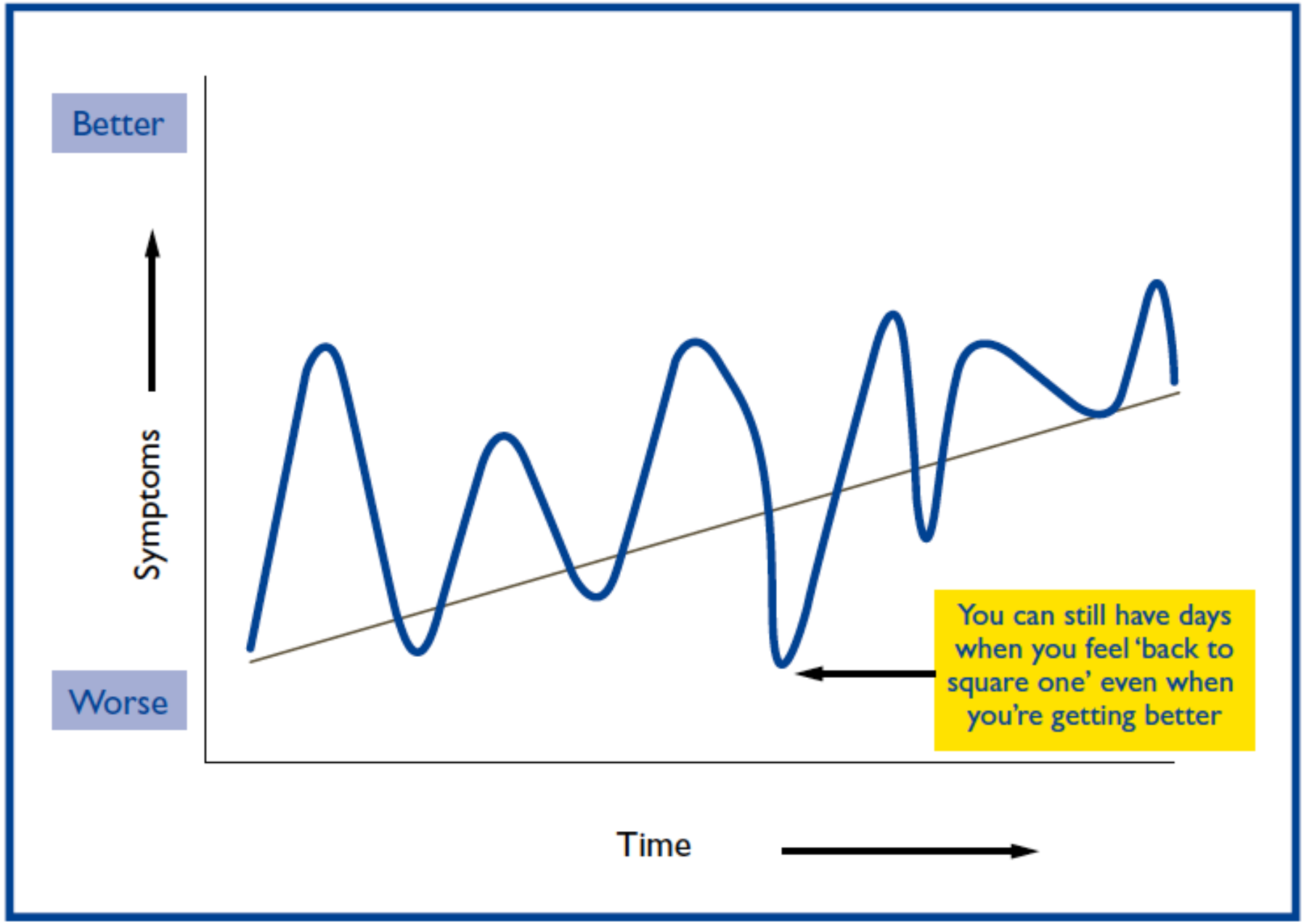
Chronic FMD

- 40% of patients with FMD remain with similar or worse symptoms in the long-term
- Numerous reasons patients become “stuck”
  - Implicit needs are being met through illness
  - Maladaptive personality style/coping mechanisms
  - Low/no agency, external locus of control, victimized stance
  - High resistance e.g. persistent unexpressed anger, profound self-stigma
- With earlier diagnosis, better diagnostic explanation and rapid access to appropriate evidence-based treatments, most patients can achieve long-lasting improvement

Diagnostic disagreement

- Your job is not to convince the patient they have FMD
- Not everyone will agree with you – that's ok!
- An accurate diagnosis, empathy, and validation can counteract previous invalidating health care experiences
- Persistent/entrenched diagnostic resistance usually indicates deeper perpetuating factors

5. Recovery is self-management, not the absence of symptoms



Courtesy of G. Nielsen

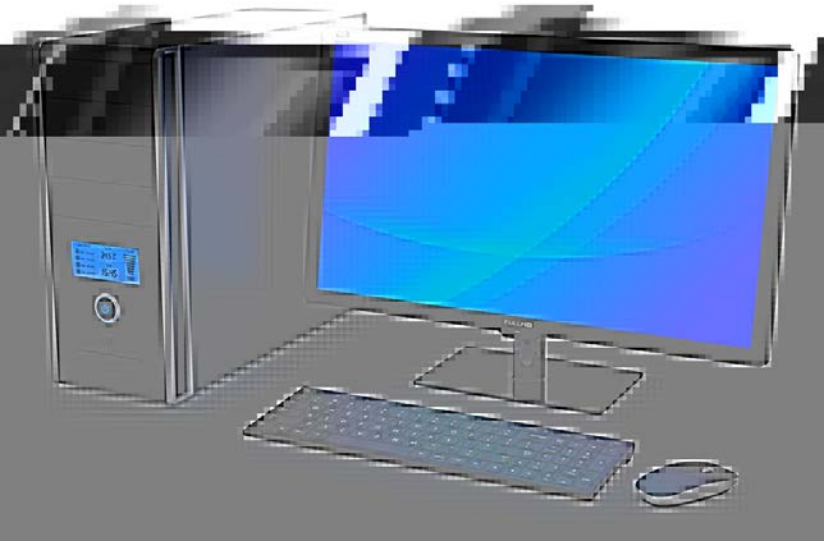
What recovery looks like

Part 3: Practical tips and therapy approaches for neurologists

Bedside treatment tips

- Noticing when movement is better during automatic movements
  - Incorporate these into the assessment, e.g. taking on/off shoes, putting phone away in purse, moving pillow on the exam bed
- Self-distraction
  - Teach the patient how distraction improves symptoms and attention makes them worse
- Incorporate body relaxation techniques into the neurological exam and point out how the symptoms change
  - Especially useful for hyperkinetic patients

Hardware-software and distractibility

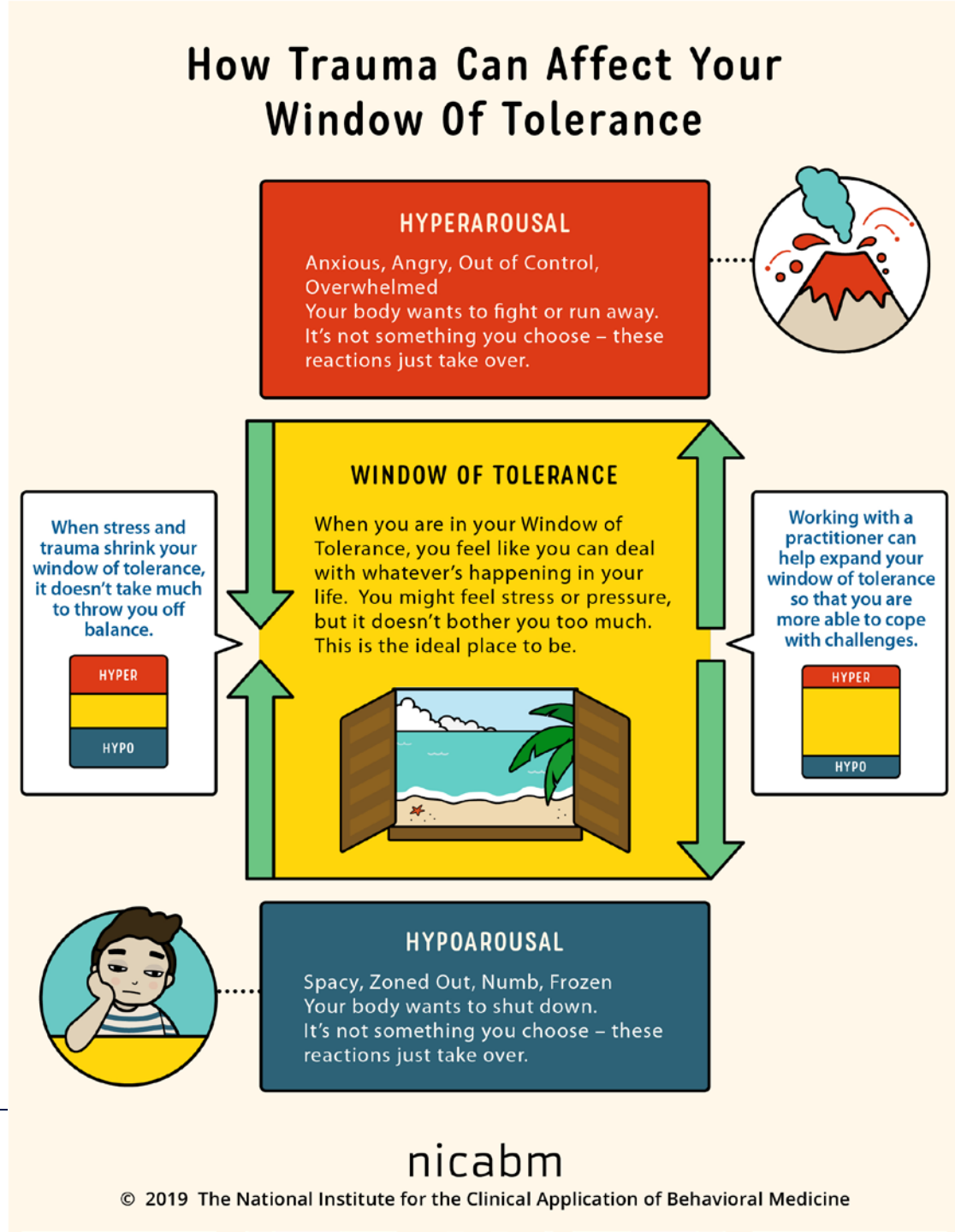


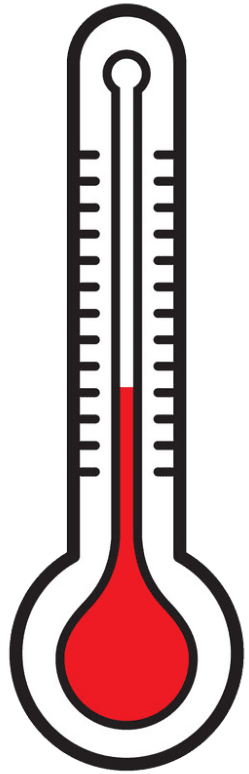
Automatic Motor Programs

Rehab approach: learned automatic movements

Nervous system overflow

Nervous system reset





Rehab approach: nervous system “reset”

Take home points

- FMD is a syndrome with an underlying engine
- Risk and triggering factors are responsible for symptom onset, perpetuating factors are responsible for symptom maintenence
- A good diagnosis and education is the first step in treating FMD and is the role of the neurologist
- FMD is treatable, and treatment needs to be carefully triaged for suitable patients
  - Patient engagement is paramount
- Recovery from FMD is self-management
- Some patients will remain chronic which needs to be considered for resource allocation


8-11 June 2024
Verona, Italy
FUNCTIONAL NEUROLOGICAL DISORDER SOCIETY
fndsociety.org
5th International Conference on Functional Neurological Disorder

Our patients for their consent to share their videos with you.

Integrated Movement Disorders Program

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Haseel Bhatt MSc, MScPT
Keschey Marcelle RN, MA, MSc
Dr. Darcy O'Brien
Sarine Willis-O'Connor
Julie Racioppa
Swati Kumar

- Anonymous donation for Neuromodulation and Multidisciplinary Care

Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic

Dr. Tony Lang
Dr. Gabriela Gilmour

Toronto Rehabilitation Institute

Dr. Mark Bayley
Laura Langer

FNDS

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Persistent Postural-Perceptual Dizziness and Other Functional Vestibular Disorders

Jeffrey P Staab, MD, MS

Indiana Neurological Society
2023 Fall Conference

Persistent Postural-Perceptual Dizziness (PPPD) and other functional causes of dizziness

Jeffrey P. Staab, MD, MS
Professor and Chair, Department of Psychiatry and Psychology

Consultant, Departments of Psychiatry and Psychology and Otorhinolaryngology – Head and Neck Surgery

Mayo Clinic, Rochester, MN USA

MAYO CLINIC

03 November 2023

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Disclosures

- Commercial interests
  - None
- Recommendations for off-label use of medications
  - SSRIs/SNRIs for persistent postural perceptual dizziness (PPPD)
  - SSRIs/SNRIs and benzodiazepines for mal de debarquement syndrome (MdDS)
- Discussion of off-label use of neuromodulation
  - Vagal nerve stimulation and transcranial magnetic stimulation for PPPD
  - Transcranial magnetic stimulation for MdDS
- Grant funding
  - U.S. National Institute on Deafness and Other Communication Disorders
  - U.S. Department of Defense via the Congressionally Directed Medical Research Program
  - Mayo Clinic

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Overview

1. Persistent postural perceptual dizziness (PPPD)
    1. History
    2. Diagnostic criteria
    3. Clinical epidemiology
    4. Case examples
    5. Pathophysiologic model
    6. Treatment
2. Mal de debarquement syndrome (MdDS)
    1. Diagnostic criteria
    2. Pathophysiologic model
    3. Treatment
3. Chronic dizziness in somatic symptom disorder
    1. Diagnostic criteria
    2. Treatment

Our focus will be on functional and somatic symptom disorders that manifest vestibular and balance symptoms.

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History – precursor of PPPD

Die Agoraphobie (fear of marketplace)
"Patients find it impossible to cross open squares and walk along certain streets. Fear restricts their **mobility**, [but] they insist that they are not aware of any reasons for their **anxiety**. It seems to arise as an alien force as soon as a square is crossed or approached. With the anxiety, as part of **one process**, occurs the **thought** of not being able to cross and a **perception** of an enormous expanse of space."

Carl Westphal, 1871

Kuch and Swinson, Can J Psychiatry, 1992

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PPPD – new-ish, but really not new at all

- 1870 – Platzschwindel (Benedikt)
- 1871 – Die Agoraphobie (Westphal)
- 1872 – Platzangst (Cordes)

Psychogenic dizziness

- 1975-1985 – Supermarket syndrome, space phobia, etc.
- 1986 – Phobic postural vertigo (PPV)
- 1993 – Space-motion discomfort (SMD)
- 1995 – Visual vertigo (VID)
- 2004 – Chronic subjective dizziness (CSD)
- 2017 – Persistent postural-perceptual dizziness (PPPD)

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PPPD: International Classification of Vestibular Disorders (ICVD)

A. Dizziness, unsteadiness, or non-spinning vertigo present on most days for 3 months or more.
   - Symptoms must be present for prolonged (hours-long) periods but need not be continuous throughout the entire day.

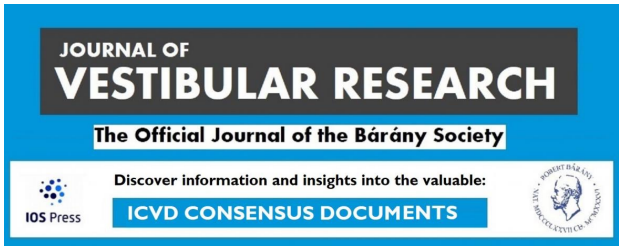
B. Persistent symptoms are present without specific provocation, but are exacerbated by 3 factors:
   - Upright posture, active or passive motion, and exposure to moving visual stimuli or complex visual patterns.

C. The disorder is triggered by events that cause vertigo, unsteadiness, dizziness, or problems with balance:
   - Acute, episodic, or chronic vestibular syndromes, other neurologic or medical illnesses, and psychological distress.

D. Symptoms cause significant distress or functional impairment.

E. Symptoms are not better accounted for by another disease or disorder.

PPPD is not a diagnosis of exclusion.



Staab, et al., J Vestib Res, 2017; https://jvr-web.org/icvd#icvdpapers

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PPPD: International Classification of Diseases, 11th edition (ICD-11)

ICD-11 for Mortality and Morbidity Statistics (Version : 02/2022)

EN

Search persistent postural [Advanced Search]

Browse | Coding Tool | Special Views | Info

- **10** Diseases of the ear or mastoid process
  - Diseases of external ear
  - Diseases of middle ear or mastoid
  - Diseases of inner ear
    - **AB30** Acute vestibular syndrome
    - **AB31** Episodic vestibular syndrome
    - **AB32** Chronic vestibular syndrome
      - **AB32.0** Persistent Postural-Perceptual Dizziness
      - **AB32.1** Chronic unilateral idiopathic vestibulopathy
      - **AB32.2** Persistent unilateral vestibulopathy after vestibular neuronitis

Foundation URI : http://id.who.int/icd/entity/2005792829

AB32.0 Persistent Postural-Perceptual Dizziness

Parent

AB32 Chronic vestibular syndrome

Show all ancestors

Description

Persistent non-vertiginous dizziness, unsteadiness, or both lasting three months or more. Symptoms are present most days, often increasing throughout the day, but may wax and wane. Momentary flares may occur spontaneously or with sudden movement. Affected individuals feel worst when upright, exposed to moving or complex visual stimuli, and during active or passive head motion. These situations may not be equally provocative. Typically, the disorder follows occurrences of acute or episodic vestibular or balance-related problems. Symptoms may begin intermittently, and then consolidate. Gradual onset is uncommon.

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Clinical epidemiology of PPPD

Location	Point Prevalence of PPPD (Patients with dizziness)	Demographics
Primary care	14%	Sex – 66% F Age – 55 yrs
Neurology clinic	20%	
Specialty dizziness center	10% sole Dx 45% co-existing Dx	
Pediatric balance center	7%	Sex – 83% F Age – 15 yrs

PPPD is the most common cause of chronic vestibular symptoms in all of these clinical settings.

MAYO CLINIC

Xue H, et al., 2018; Staibano P, et al., 2019; Adamec I, et al., 2020; Kim H-J, et al., 2020; Wang, et al., 2021

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Precipitants (also differential diagnosis)	Philadelphia CSD N=345	Rochester, MN CSD N=103	Munich PPPD N=356	Boston (children) PPPD N=53
Acute and episodic vestibular syndromes	25%	21%	24%	70%
Anxiety disorders	25%	22%	20%	4%
Neurologic Illnesses				
- migraine	16%	25%	11%	56%
- traumatic brain injury	15%	10%	3%	15%
- autonomic dysregulation	7%	6%	1%	4%
Other Medical Conditions				
- dysrhythmias, metabolic disorders	7%	3%	6%	Structural ear disease 8%

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Staab & Ruckenstein, 2007; Staab, in press; Habs et al., 2020; Wang, et al., 2021

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Case example #1

- 44 yo M awoke with spinning vertigo and gait unsteadiness
  - Not positional or postural
  - No hearing changes, headache, focal neurologic symptoms
  - Vertiginous symptoms gradually improved over 2-4 weeks
  - Now 4 years of swaying/rocking unsteadiness (↑↓)
    - Increased with his own movement, better recumbent
    - Increased in stores, busy social gatherings, traffic
    - Increased using mobile phone, computer

Acute vestibular syndrome

Chronic vestibular syndrome

1. Vestibular testing – 54% right peripheral deficit, otherwise normal
   - Acute unilateral vestibulopathy (compensated), then PPPD

2. History of continued brief motion-induced vertigo
   Vestibular testing – 54% right peripheral deficit, positive head impulse test, positive head shake test
   - Acute unilateral vestibulopathy (uncompensated) and PPPD

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Case example #2

- 48 yo F described a 5-year history of recurrent attacks of spinning vertigo lasting hours
  - Attacks occur spontaneously 1-2/month, unsure about triggers (maybe poor sleep)
  - Mild aural fullness and occasional tinnitus, either ear, sometimes bilateral
  - 75% of attacks are followed by a severe headache + photophobia and nausea
  - For the first 2 years, she felt completely normal between attacks
  - Then, dizziness began to linger between attacks, gradually became constant (↑↓)
    - Increased with her own movement
    - Increased in her busy open office, on train, in stores
    - Increased using mobile phone and tablet

Episodic vestibular syndrome

Chronic vestibular syndrome

1. Audiogram and vestibular testing – normal (not strictly needed)
2. MRI including IACs, and CT of temporal bone – normal (not strictly needed)
   - Vestibular migraine and PPPD

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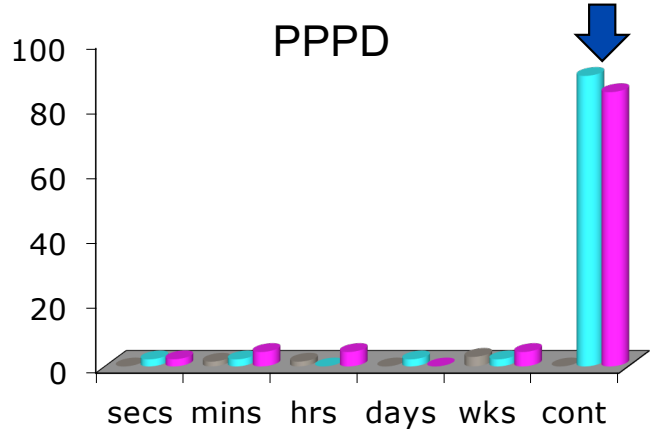
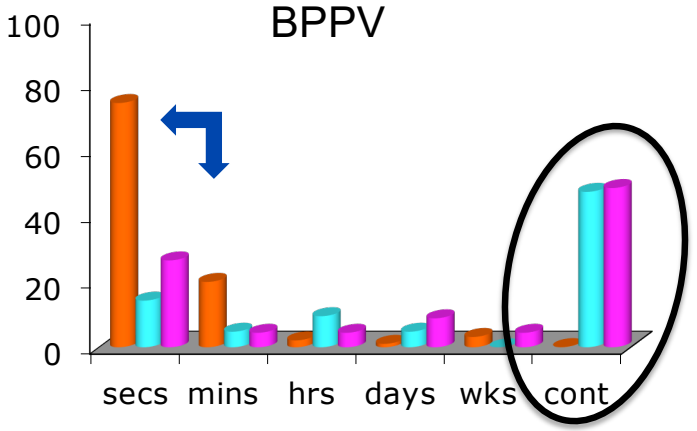
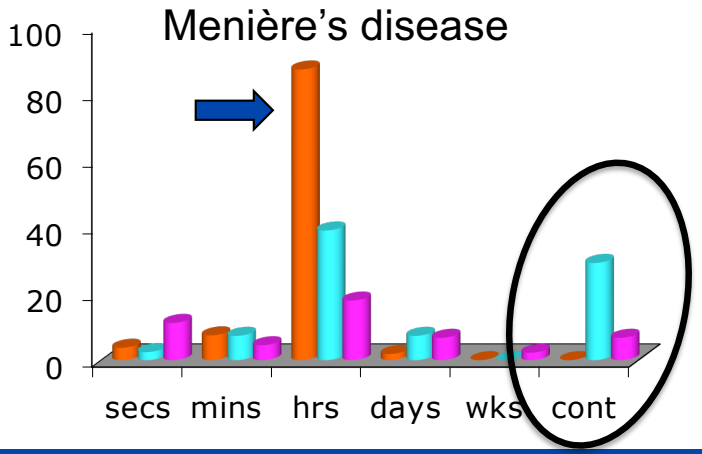
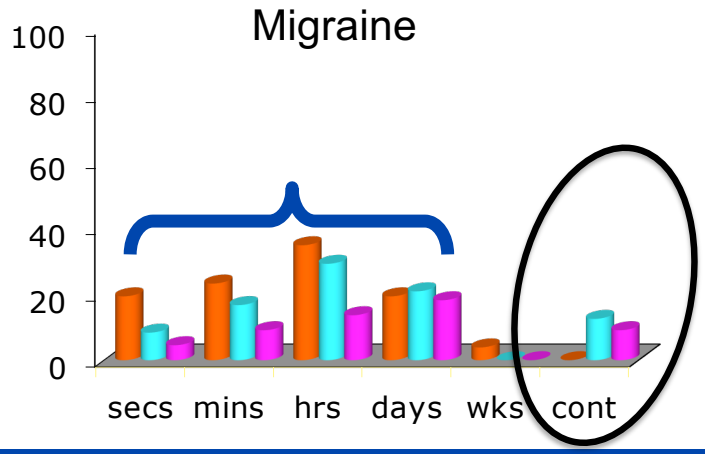
Illness Profiles: Vertigo, Unsteadiness, Dizziness (N=410)









Sensitivity >85%

Specificity >85%

Staab, et al., 2010

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Diagnostic aids

- Self-report questionnaires
  - Early screening (within 90 days of symptom onset) – Retrospective study (N=155)
    - **Niigata PPPD Questionnaire (NPQ)** – total score ≥27
      - Sensitivity = 0.88; Specificity = 0.52
  - Late screening (patients with chronic symptoms) – Two retrospective studies (N=85; N=292)
    - **Dizziness Handicap Inventory (DHI)** – total score >60
      - Specificity = 0.88: functional disorders (mostly PPPD) or psychiatric illness
- Vestibular laboratory tests and neuroimaging
  - The diagnosis of PPPD is based on clinical history.
    - Core symptoms (criterion A) and responses to exacerbating factors (criterion B).
  - Lab testing and imaging may be needed to work through the differential diagnosis.
    - To evaluate the clinical state of precipitants (criterion C).
    - To consider co-existing conditions (criterion E).

Kabaya, et al., 2022; Yagi, et al., 2019 Graham, et al., 2021; Staibano, et al., 2019

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Red Flags that it's Not PPPD

- Indistinct onset, slowly progressive symptoms
  - Neurodegenerative disorder
    - Peripheral neuropathy, progressive vestibular loss
    - Cerebellar degeneration, Parkinson's disease
  - Generalized anxiety disorder and dysautonomias may have a indistinct starts
- Falls – gait disturbance is not part of PPPD
  - Peripheral or central neurotologic disorder
  - Cardiovascular or autonomic disorder
  - Functional gait disorder
- Constant symptoms – regardless of provocative factors
  - Accompanied by other physical complaints (fatigue, pain)
    - Somatic symptom disorder

Staab et al., J Vest Res, 2017

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Key concepts in the pathophysiologic model of PPPD

- Vestibular relativity and motion priors
- Optimal control
  - Top down vs bottom up neural processing
- Misperception of motion
  - Resets movement priorities

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From bottom-up determinism to top-down relativity

Common beliefs

- Vestibular, visual, and proprioceptive inputs are transmitted from end organs to cortex.
- Perception of motion = conscious awareness of multi-sensory integration (deterministic).
- Perception of motion is the end result of bottom-up transmission of multi-sensory data.
- Basic vestibular reflexes (e.g., VOR and VSR) have fixed dynamics.
- Perception of motion
- Learned motor behaviors
- Vestibular reflex actions
- Autonomic responses
- Emotional reactions

} are congruent

Emerging concepts

- Sensory inputs are highly processed and yield **context-dependent estimates** of space & motion.
- Perception of motion = conscious awareness of context-dependent estimates **(vestibular relativity).**
- **Perception of motion** and context sits at the apex of **top-down control** of movement.
- **Top-down control tunes system functioning** via optimal sets of commands that embody priorities and constraints **(cost functions and priors).**
- Each action has its own dynamics (partially linked). Perception of motion (+ context and illness) may be **dissociated** from other responses to space and motion stimuli **(normally and to our benefit).**

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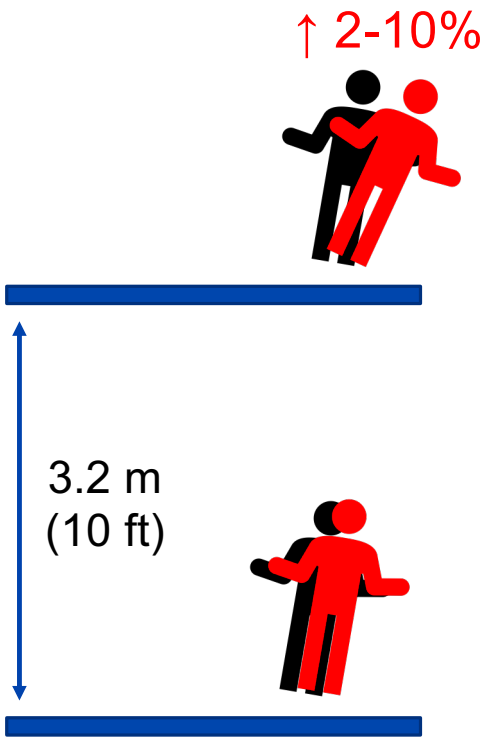
Effects of context of external threat (normal individuals)



Changes at height

1. Psychology – ↑ anxiety and fear
   - balance confidence ↓
   - autonomic arousal (sweating) ↑
2. Physiology – ↑ postural stiffness
   - Soleus reflexes ↑ ~10%
   - Natural sway ↓
3. **Perception** – ↑ sensation of motion
   - Forward lean, side-to-side sway ↑ 2-10%

Cleworth TW, et al., Gait & Posture, 2018; Neuroscience, 2019

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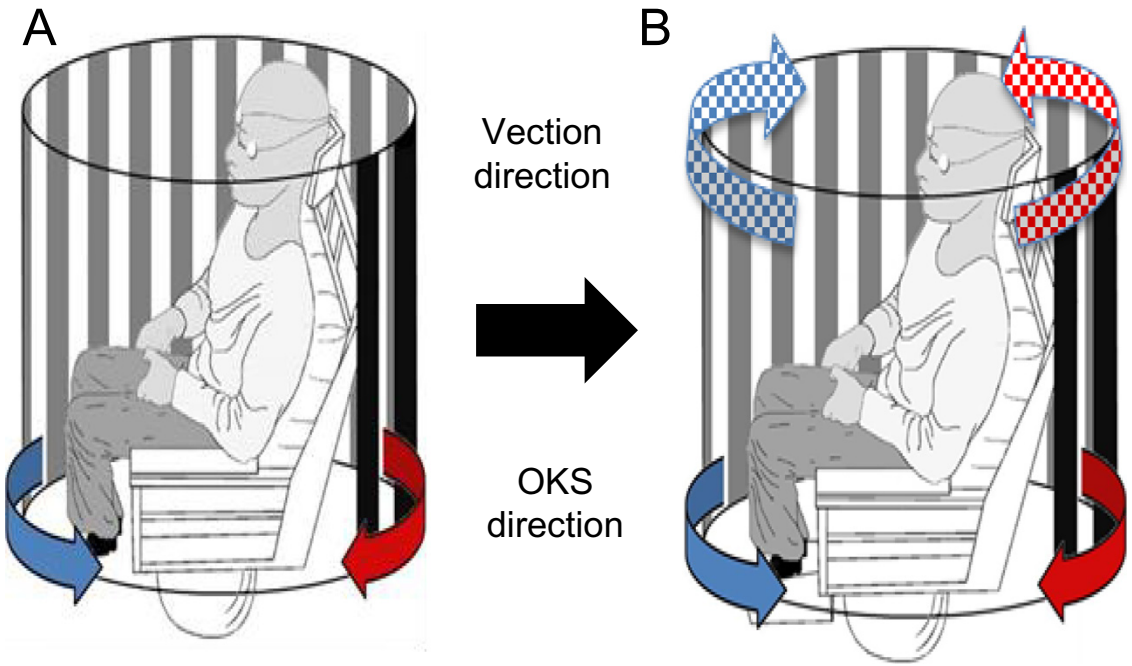
Perception *is an optimized solution to sensory inputs in context.*
It is relative (not absolute) and can shift dramatically ***(vestibular relativity)***.



Illusion of vection

The powerful effect of priors (experience & expectations) on perception.

Qadeer Arshad et al. / Neuroscience 408 (2019) 378–387

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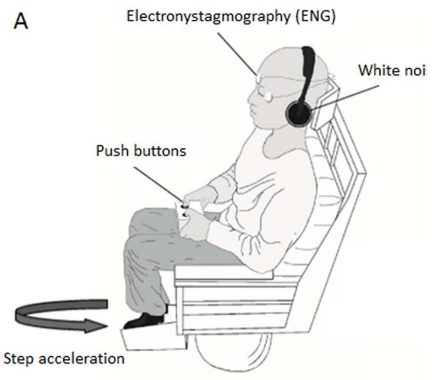
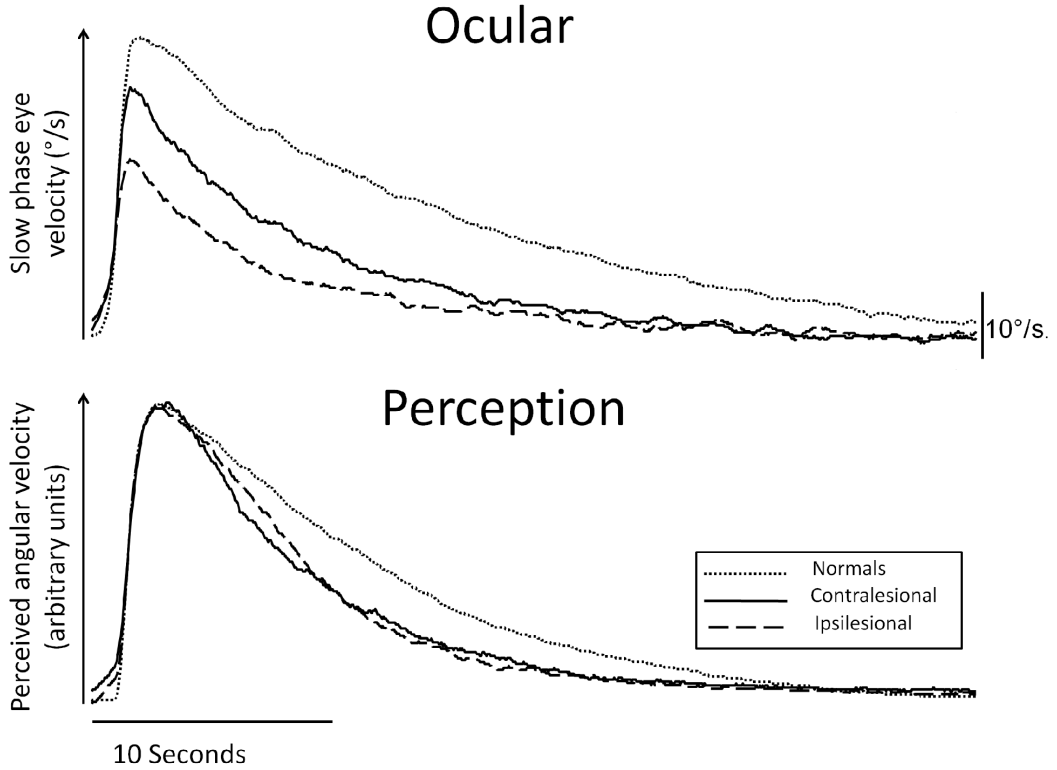
Perception *may promote recovery.*

It is a best estimate, not a direct reflection of structural integrity.





*Perception of rotation & VOR **two days** after onset of vestibular neuritis.*

Cousins, et al., 2013

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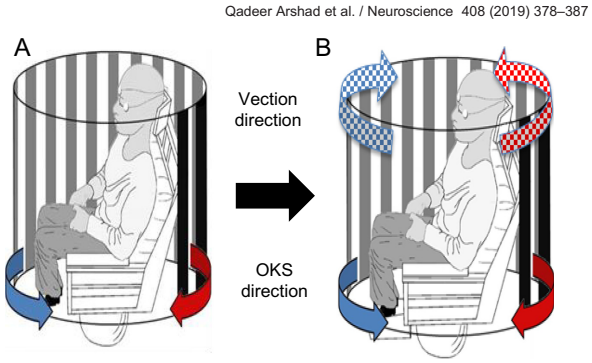
Estimates and priors offer solutions to common ambiguities.



Motion of self versus world

Active versus passive motion

Translation versus tilt

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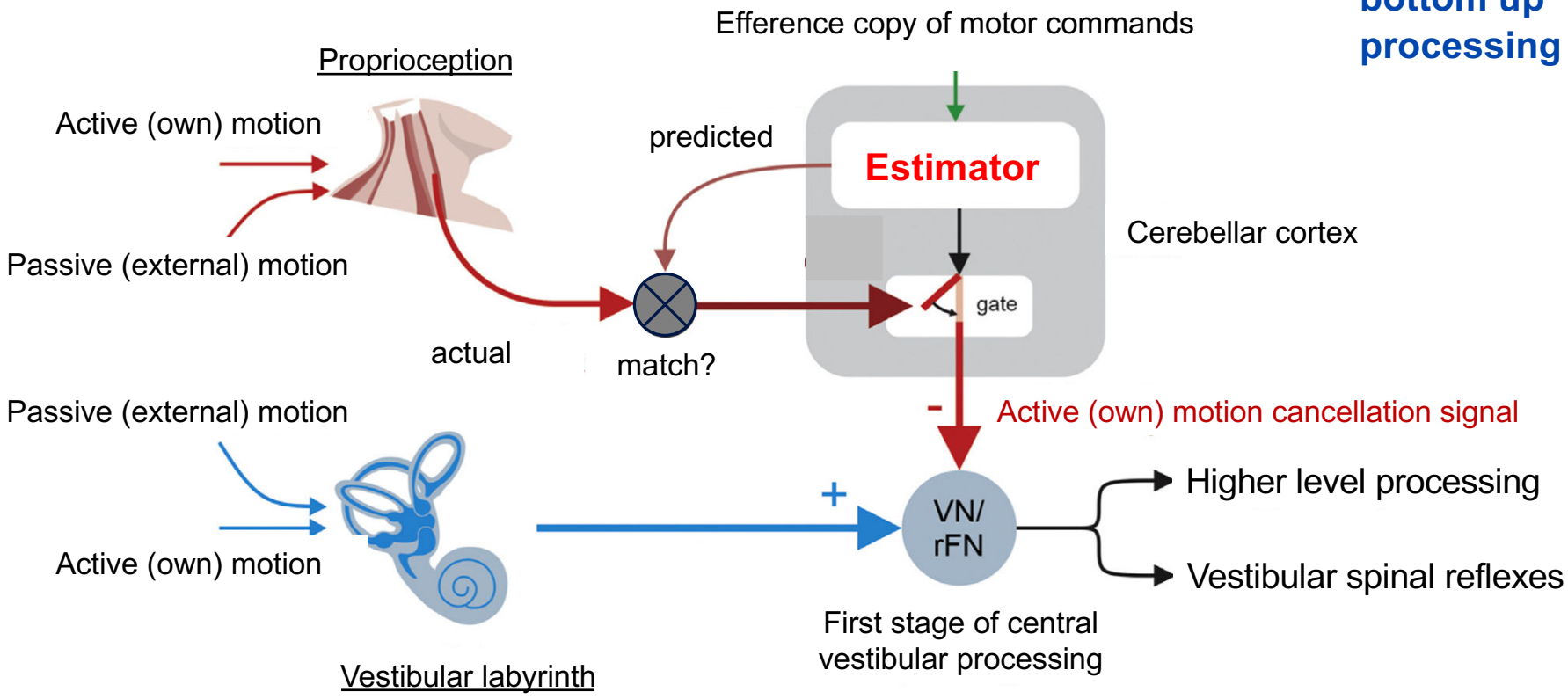
Proprioception and the predictive sensing of active self-motion

Kathleen E Cullen[1,2,3,4], **Omid A Zobeiri**[5]

Curr Opin Physiol. 2021 April ; 20: 29–38.

Top down effect on bottom up processing



VN/rFN – vestibular nuclei; thalamus; rostral fastigial nuclei

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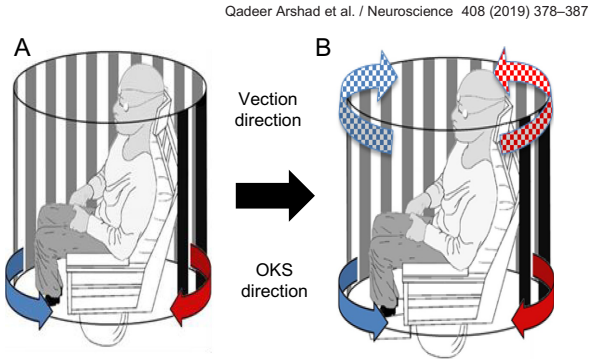
Estimates and priors offer solutions to common ambiguities.

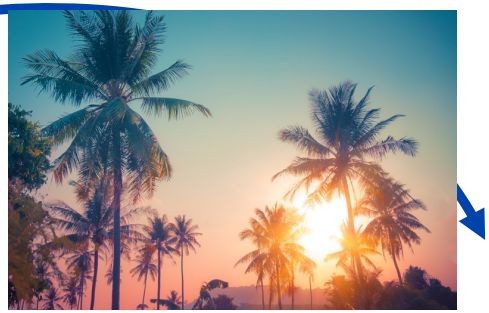


Motion of self versus world

Active versus passive motion

Visual tracking

Translation versus tilt



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Understanding of gravity:

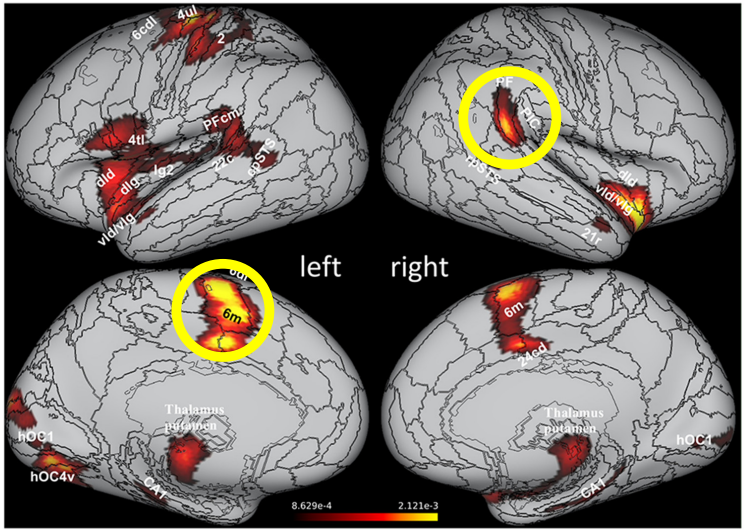
An essential prior

Watching the Effects of Gravity. Vestibular Cortex and the Neural Representation of "Visual" Gravity

Sergio Delle Monache[1,2], Iole Indovina[2,3], Myrka Zago[2,4,5], Elena Daprati[2,4,6], Francesco Lacquaniti[2,4,6] and Gianfranco Bosco[2,4,6]**

Effect of gravity on motion of objects in the visual field

Supplemental motor area



Posterior insular cortex

Front. Integr. Neurosci. 15:793634. doi: 10.3389/fnint.2021.793634

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A conceptual dilemma

- IF:
  - Perception is relative (based on context-dependent estimates)
    - and it relies on internal estimates
    - and it sometimes overrides “reality”
    - for our own good (e.g., to allow functioning with structural damage)
- THEN:
  - We need a new concept to replace our largely “bottom up” deterministic one.

A conceptual solution

- In complex systems:
  - Internal estimates offer robust control (estimate, observe, adjust).
  - Priors drive efficiency (experience offers a library of ready-made solutions).
  - Top down (master) controller chooses from optimal solutions (shifts sets).

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Comparison of cost functions for postural stability versus fluid locomotion

Variable	Standing (low risk)		Walking smoothly
Constraints (on movement)	• Sway path constrained at limits of stability. • Specific path not relevant.		Path optimized: • To reach target or • Maintain desired trajectory and • Avoid obstacles
Set point or target (spatial orientation)	• Gravity (static)		• Trajectory (dynamic)
Data streams and weighting (sensory inputs)	• Internal data are adequate (vestibular, proprioceptive)		• External data are required (primarily visual)
Operating envelope (environment)	• Support surface (narrow)		• Path and destination (wide)
Tolerance for error (trigger for input from controller)	• High		• Variable
Duration	• Not constrained		• Not constrained
Energy expenditure	• Minimized		• Minimized, adjusted to demand • Constrained by physical fitness

MAYO CLINIC

Staab JP, Neuro Clin, 2023

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Comparison of cost functions for postural stability versus fluid locomotion

Variable	Standing (low risk)	Standing (high risk)	Walking smoothly
Constraints (on movement)	• Sway path constrained at limits of stability. • Specific path not relevant.	• Sway path constrained within narrower (safer) limits. • Specific path not relevant.	Path optimized: • To reach target or • Maintain desired trajectory and • Avoid obstacles
Set point or target (spatial orientation)	• Gravity (static)	• Gravity (static)	• Trajectory (dynamic)
Data streams and weighting (sensory inputs)	• Internal data are adequate (vestibular, proprioceptive)	• Internal data are adequate (vestibular, proprioceptive) • External data are desired (primarily visual - overweighted)	• External data are required (primarily visual)
Operating envelope (environment)	• Support surface (narrow)	• Support surface (narrow)	• Path and destination (wide)
Tolerance for error (trigger for input from controller)	• High	• **Low**	• Variable
Duration	• Not constrained	• Transient (typically momentary)	• Not constrained
Energy expenditure	• Minimized	• Constrained by physical fitness	• Minimized, adjusted to demand • Constrained by physical fitness

MAYO CLINIC

What if the dominant prior is high risk and estimates of motion are too high?

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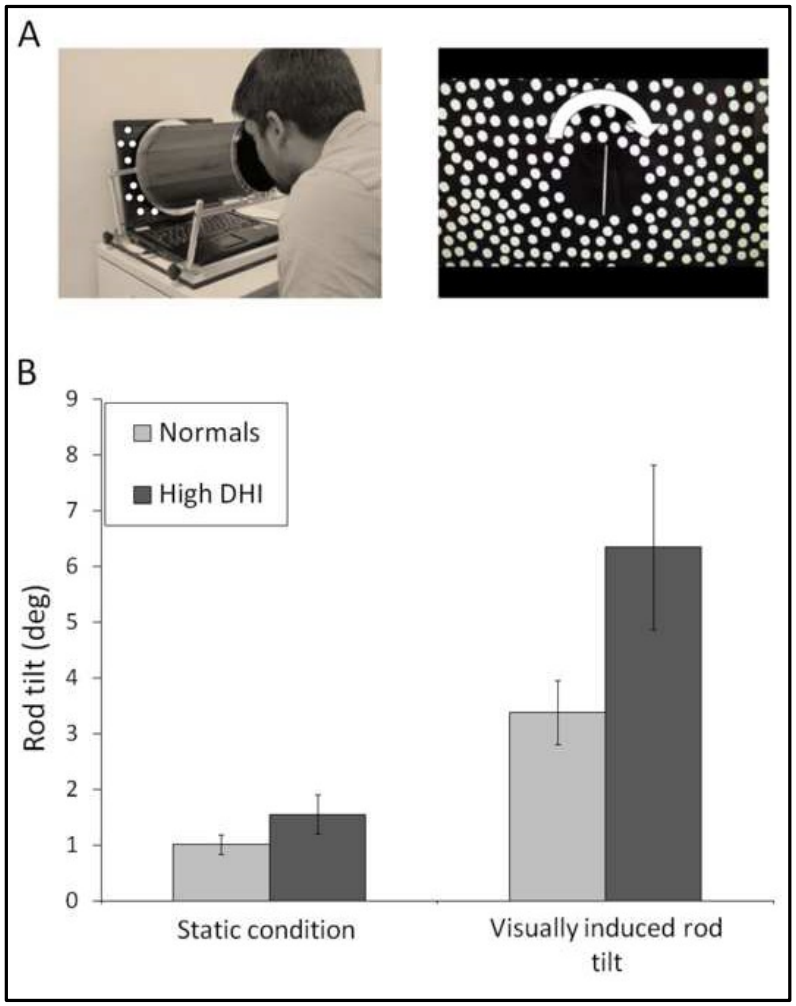
Transition from acute to chronic dizziness

Predictors of 6-month outcomes following acute vestibular neuritis

High risk assessment
Acute anxiety in the form of increased body vigilance and negative illness perceptions

+

Visual dependence
Over-weighting of visual cues for spatial orientation



Cousins, et al., PLoS 2014; Cousins, et al., Ann Clin Trans Neuro, 2017

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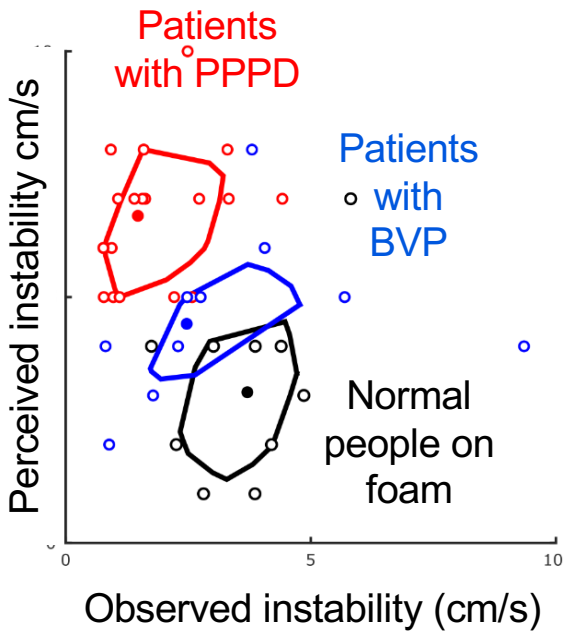
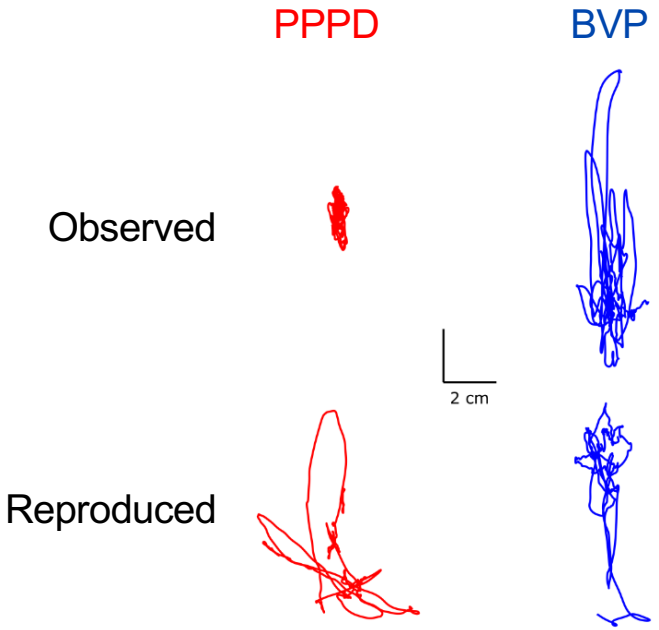
Misperception of motion in patients with PPPD

Patients with PPPD vs. normal controls

1. Misperceive (overestimate) postural sway
2. Misperceive (overestimate) roll/tilt of the head

Perceived vs. observed motion in patients with PPPD vs. BVP vs. Control (on foam)





San Pedro Murillo E, et al., 2023 ; Yagi, et al., 2021

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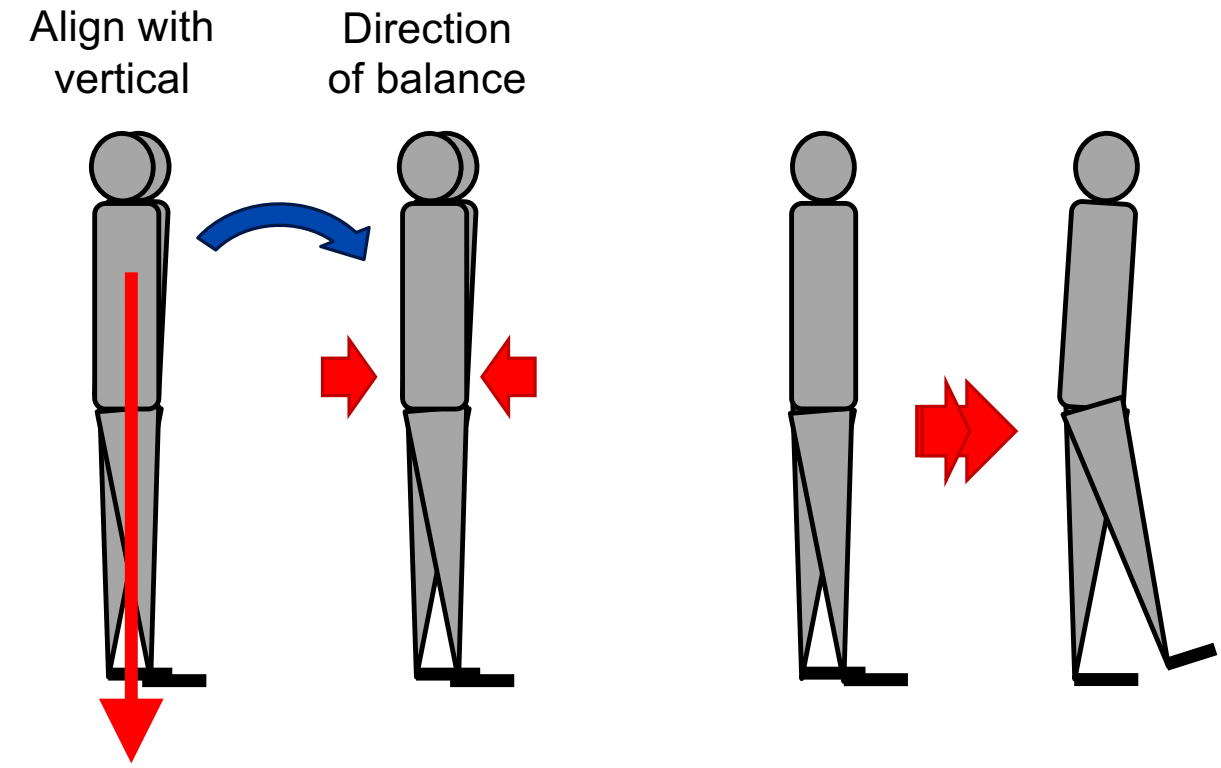
Control of stance and gait – less than optimal



During locomotion, static postural control must be inhibited or it would generate counterproductive stabilizing commands.

What if the dominant prior is high risk and estimates of motion are too high?

MAYO CLINIC
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Pathophysiologic model of the development of PPPD

Precipitants
1. Vestibular crisis
2. Medical event
3. Acute anxiety

threat

Acute Adaptation
1. ***Perception of increased motion***
2. ***Use of high-risk postural control strategies***
3. ***Visual*-somatosensory *dependence***

excessive body vigilance

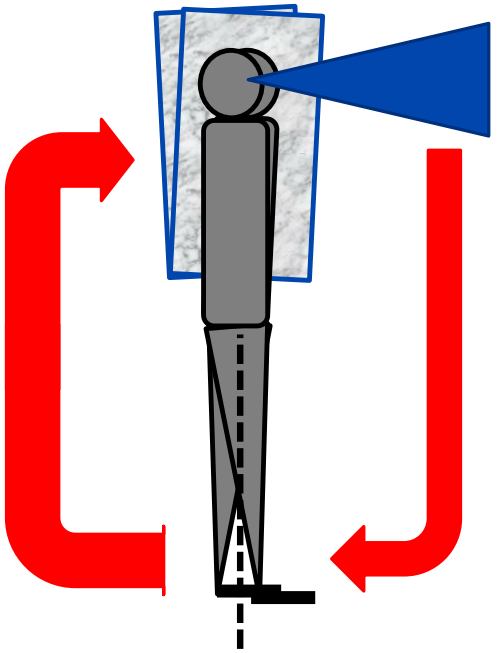
Chronic misperception of motion

Shift in priorities: from mobility to stability

Conscious attention to postural stability
over directing navigation through space

Reduced thresholds for:
- Motion detection
- Initiating closed loop feedback

↑ *control effort*



Overcontrolled gaze
↓ *speed of gaze shifts*
↑ *gaze oscillations*

Visual dependence
Vulnerability to disorienting visual stimuli

Stiffened control of posture and gait
↑ *motor effort*, ↓ *range of stability*

Recovery
1. Neurotologic
2. Medical
3. Behavioral

Staab JP, Neuro Clin, 2023

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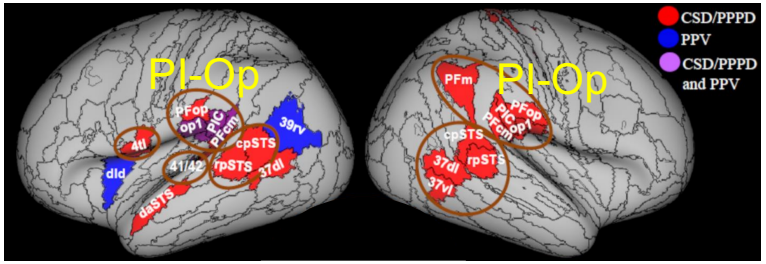
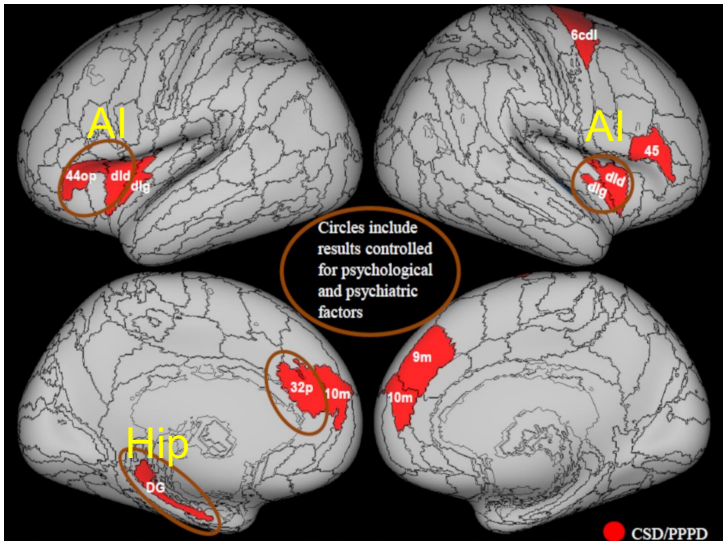
Neuroimaging Indovina, et al., 2021

Consolidated images from 13 studies of PPPD and its predecessors (PPV, SMD, CSD, VID).

Decreased cortical volume & folding



Decreased cortical activity

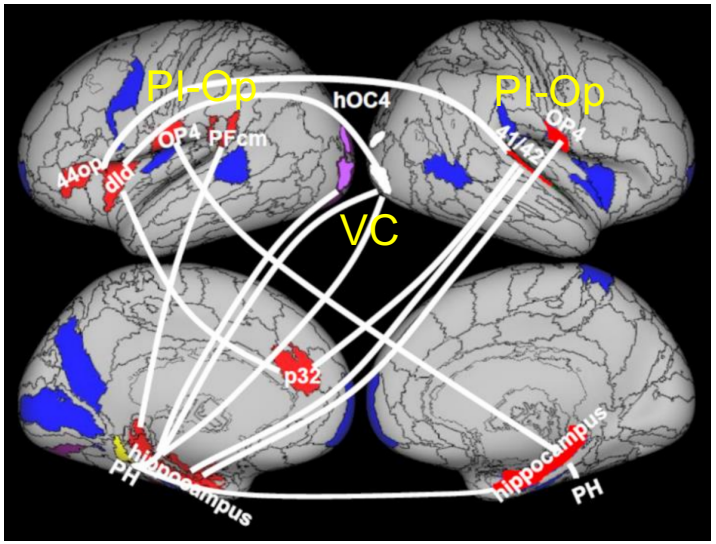


L hemisphere R hemisphere

Convexity (external) view

Mid-sagittal (internal) view

Decreased cortical connectivity



L hemisphere R hemisphere

AI – anterior insula; Hip – hippocampus; PI-Op – posterior insula / parietal operculum; VC – visual cortex

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Treatment of PPPD

- Three options
  1. Vestibular rehabilitation
  2. Serotonergic medications (SSRIs/SNRIs)
  3. Psychotherapy

- Often used in combination

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Physical Therapy

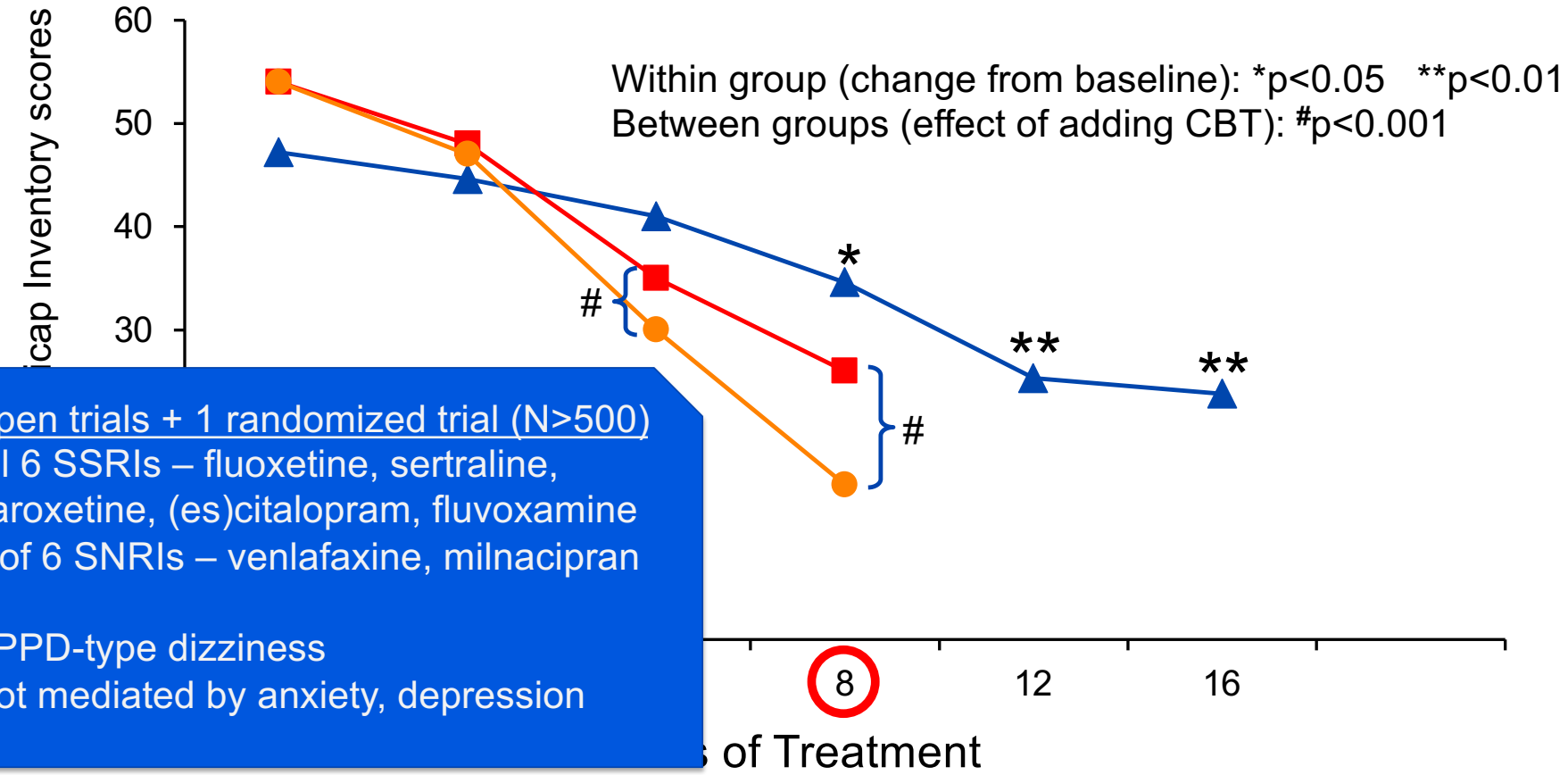
1. Normalize stance and gait
   - Promote relaxed stance, normal weight distribution, reshape functional changes
2. Improve tolerance for own motion
   - Head/eye movement ➤ body movement – habituation, not compensation
3. Improve tolerance for visual stimuli
   - Complex patterns, moving stimuli – This can be the most difficult rehab task.

Pacing and persistence are the keys to success.

Make it boring!

Pavlou, et al., J Vest Rehab, 2015; Thompson, et al., J Vest Res, 2015
Nada, et al., Annals Otol Rhinol Laryngol, 2019

Sertraline with and without CBT



8 open trials + 1 randomized trial (N>500)

- All 6 SSRIs – fluoxetine, sertraline, paroxetine, (es)citalopram, fluvoxamine
- 2 of 6 SNRIs – venlafaxine, milnacipran

- PPPD-type dizziness
- Not mediated by anxiety, depression

Staab et al., Laryngoscope, 2004; Yu, et al., 2018; Min, et al., 2021

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Medication dosing strategies

	Starting dose (1-2 weeks)	Titration increment (2-4 week intervals)	Final dose range (maintenance therapy 1+ years)
Sertraline	25 mg daily	25-50 mg	50-200 mg daily
Escitalopram	5 mg daily	5 mg	10-20 mg daily
Venlafaxine XR	37.5 mg daily	37.5-75 mg	75-225 mg daily

Staab JP, 2020; 2023

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Psychotherapy

Randomized controlled trials

- Cognitive Behavior Therapy (CBT)
- Acceptance and Commitment Therapy (ACT)

Goals

1. Reduce body vigilance
2. Reduce negative illness perceptions
3. Reduce anticipatory anxiety and avoidance of provocative stimuli.

Mahoney, et al., Am J Otolaryn, 2013; Toshishige, et al., Acta Oto-Laryngologica ,2020
Kuwabara, et al., Am J Otolaryngol, 2020; Yu, et al., Biomed Res Int, 2018

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Treatments for PPPD - comparison of outcomes		Pre-Tx DHI	Post-Tx DHI	Change MCID=18
Vestibular therapy				
Nada, 2019	6 weeks individualized exercises (N=60)	58	36	**22**
Teh, 2022	12 weeks in-clinic (N=15) vs. at-home (N=15)	50 (all patients)	34 (all patients)	**18** (clinic) 14 (home)
Herdman, 2022 (INVEST)	6 sessions psychologically-informed (N=20) vs standard VRT (N=20)	64 (INVEST) 65 (standard)	37 (INVEST) 49 (standard)	**27** (INVEST) 16 (standard)
Medication				
Yu, 2018	8 weeks, sertraline alone (N=45) vs. sertraline + CBT (N=46)	54 (sert alone) 54 (sert + CBT)	26 (sert alone) 15 (sert + CBT)	**28** (sert alone) **39** (sert + CBT)
Min, 2021	Chart review (N=197) -- SSRIs (escitalopram) + BZD (clonazepam)	50	65% much/very much improved	
Psychotherapy				
Waterston, 2022	Chart review (N=150) -- CBT	50	24	**26**
Kuwabara, 2020	6 wks, Acceptance and Commitment Therapy + VRT (N=27)	49	26 (at 6 months)	**23**

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Emerging therapeutics – *not ready for prime time*

Neuromodulation – early trials

- Non-invasive vagal nerve stimulation (nVNS)
  - 4 weeks – positive effect on dizziness, postural sway, quality of life
- Transcranial direct current stimulation (tDCS) – active vs. sham treatment
  - 15 sessions over 3 weeks – no benefit
- Repetitive transcranial magnetic stimulation (rTMS) – active vs. sham treatment
  - 4 weeks, daily sessions – results forthcoming

Eren, et al., 2018; Im, et al., 2022

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ICVD definition of Mal de debarquement syndrome (MdDS)

A. Non-spinning vertigo characterized by an oscillatory perception ('rocking,' 'bobbing,' or 'swaying') present continuously or for most of the day.

B. Onset occurs within 48 hours after the end of exposure to passive motion.

C. Symptoms temporarily reduce with exposure to passive motion.

D. Symptoms continue for >48 hours.

   D.0. MdDS in evolution – symptoms are ongoing, but the observation period has been less than 1 month

   D.1 Transient MdDS – symptoms resolve at or before 1 month and the observation period extends at least to the resolution point

   D.2 Persistent MdDS – symptoms last for more than 1 month

E. Symptoms are not better accounted for by another disease or disorder.

Cha YH, et al., J Vestib Res, 2020

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Frequency of postural sway in patients with MdDS

Sway (perceived and observed) is thought to reflect entrainment of precipitating motion.

A necessary **prior** that fails to reset.

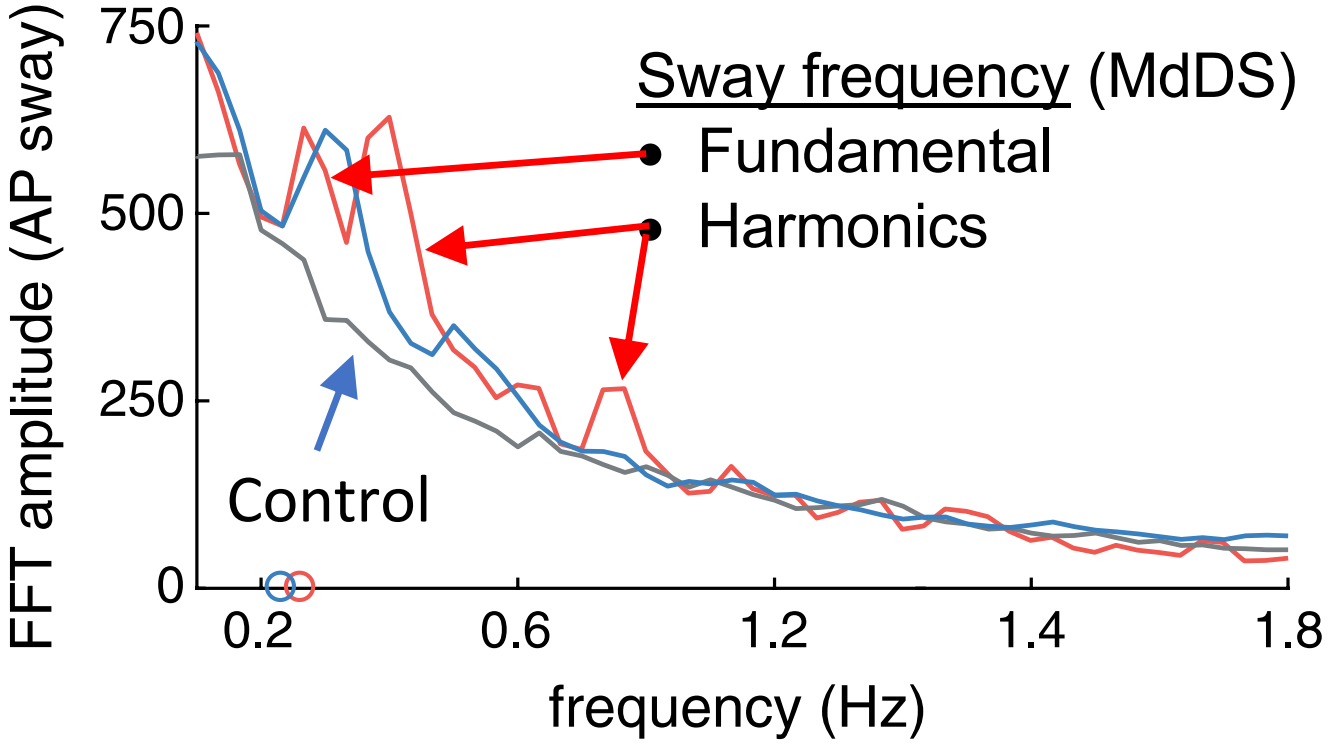

Figure 2. Low frequency sway in MdDS[16]

Schepermann A, et al., J Neurol, 2019; Dai, M, et al., Front Neurol, 2017

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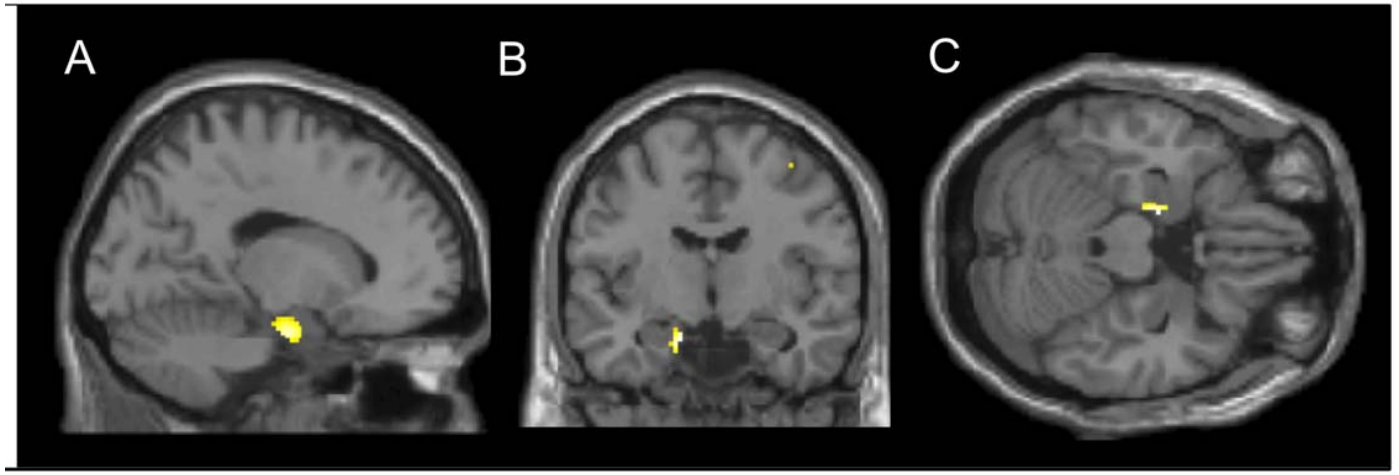
MdDS – hypermetabolism of the entorhinal cortex



Entorhinal cortex → Left hippocampus

Grid cells
(Spatial location, heading and speed)

(Egocentric spatial navigation)

Cha, et al., PLoS ONE, 2012

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Treatment of MdDS – usually partial benefit

- Patient education
- Medications (clinical experience, online patient survey)
  - SSRIs and SNRIs – especially venlafaxine (same dosing as for PPPD)
  - Benzodiazepines – standing dose or prn
- Velocity storage reprogramming – “Mount Sinai (Dai) protocol”
- Physical therapy – routine vestibular rehabilitation does not seem to be effective
- Psychotherapy – for psychiatric comorbidity

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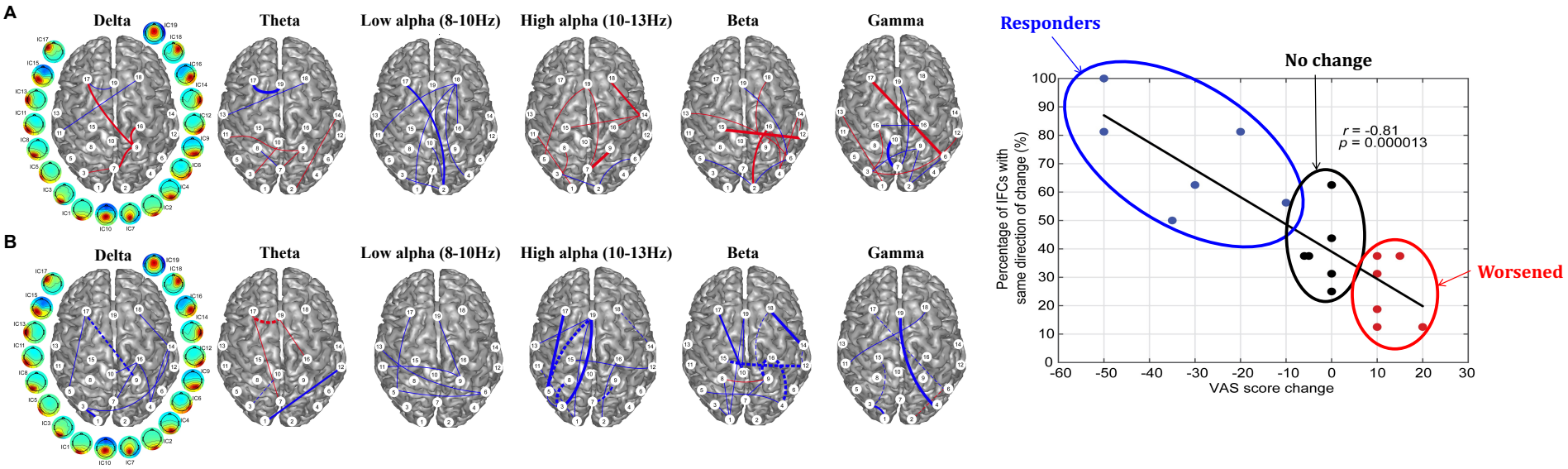
Treatment of MdDS – neuromodulation (still experimental)

Transcranial magnetic stimulation over the dorsolateral prefrontal cortex



Cha et al., Brain Topogr, 2018; Front Neurol, 2021

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Chronic dizziness as part of somatic symptom disorder

Somatic symptom disorder (DSM-5 definition)

A. 1+ somatic symptoms that are distressing or disrupt daily life
B. Illness- related thoughts, feelings, behaviors
    1. Thoughts about seriousness of symptoms
    2. High level of worry about symptoms (esp. about consequences)
    3. Aberrant health-seeking behaviors (too much or too little)
C. Symptoms present for 6+ months

- Mechanism is unknown – central sensitization + altered cognitions & behaviors??
- Chronic dizziness often co-exists with chronic pain (headache, fibromyalgia), chronic fatigue, and chronic non-specific cognitive complaints (brain fog).
    - May resemble PPPD (meeting criteria A-C)
    - Responds poorly to outpatient treatment
    - Clinical experience strongly supports multi-disciplinary rehabilitation programs
        - Intensive outpatient or inpatient – 2-4 weeks (pain rehab programs)

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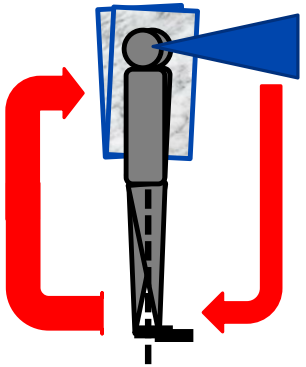
Conclusions

- PPPD is the most common cause of chronic vestibular and balance symptoms
  - One of the top three diagnoses in neuro-otology (with BPPV and vestibular migraine)
- Established diagnostic criteria
  - ICVD – Bárány Society; ICD-11 – World Health Organization
- Pathophysiologic mechanisms
  - Misperception of motion drives a top-down shift from smooth locomotion to postural stability
- Treatment
  - Individualized vestibular rehabilitation
  - Serotonergic medication (SSRIs and SNRIs)
  - Cognitive behavior therapy

} *Sequentially or in combination*



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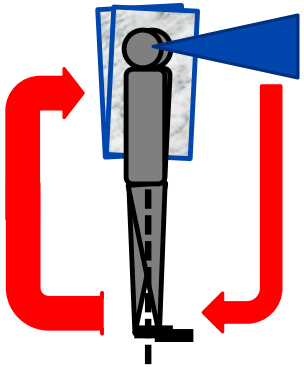
Conclusions

- MdDS is often overlooked or misdiagnosed
  - Prevalence of transient disembarkment symptoms is common, prevalence of MdDS ??
- Established diagnostic criteria
  - ICVD – Bárány Society
- Pathophysiologic mechanisms
  - Entrainment of inciting motion stimulus
- Treatment
  - Specialized vestibular reprogramming
  - SSRIs/SNRIs or benzodiazepines



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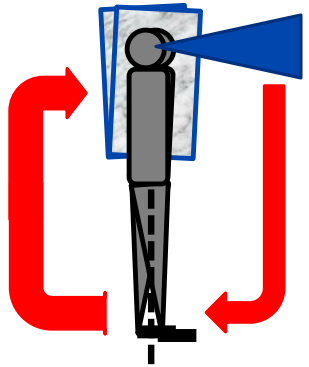
Conclusions

- Somatic symptom disorder is often overlooked
  - Focus on individual symptoms rather than overall somatic burden; prevalence ??
- Established diagnostic criteria
  - DSM-5
- Pathophysiologic mechanisms (unknown)
  - Central sensitization and aberrant illness-related anxieties, beliefs, and behaviors ??
- Treatment
  - Multi-disciplinary rehab programs



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Thank you for your attention.

Questions & Discussion

Staab.Jeffrey@mayo.edu

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References – citations in this presentation and additional resources

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Advances in Evaluation and Management of Psychogenic Nonepileptic Seizures

W. Curt LaFrance Jr., MD, MPH, FAAN, FANPA, DFAPA

Differential Diagnosis and Potential Pitfalls in the Evaluation of Functional Neurological Disorders

Sara A Finkelstein, MD, FRCPC

Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL

Differential Diagnosis and Potential Pitfalls in the Evaluation of Functional Neurological Disorder

INS Conference
Nov 3, 2023

Sara Finkelstein, MD MSc FRCPC
Functional Neurological Disorder Unit, Dept. of Neurology
Massachusetts General Hospital, Boston, MA
safinkelstein@mgh.harvard.edu

Objectives

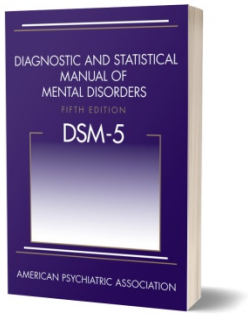
Develop a differential diagnosis for functional neurological disorder.

Describe diagnostic pitfalls to be aware of when considering a diagnosis of functional neurological disorder.

Develop a rational diagnostic workup for functional neurological disorder.

FUNCTIONAL NEUROLOGICAL DISORDER SOCIETY

What is FND?



- A neuropsychiatric disorder in which neurological symptoms are caused by a problem of brain networks
- Diagnosis based on POSITIVE SIGNS or SEMIOLOGICAL FEATURES typical of FND:

showing **INCONSISTENCY / REVERSIBILITY** of symptoms

- *No longer a diagnosis of exclusion*
- *No longer need stressor preceding to make diagnosis*

General pitfalls to be aware of

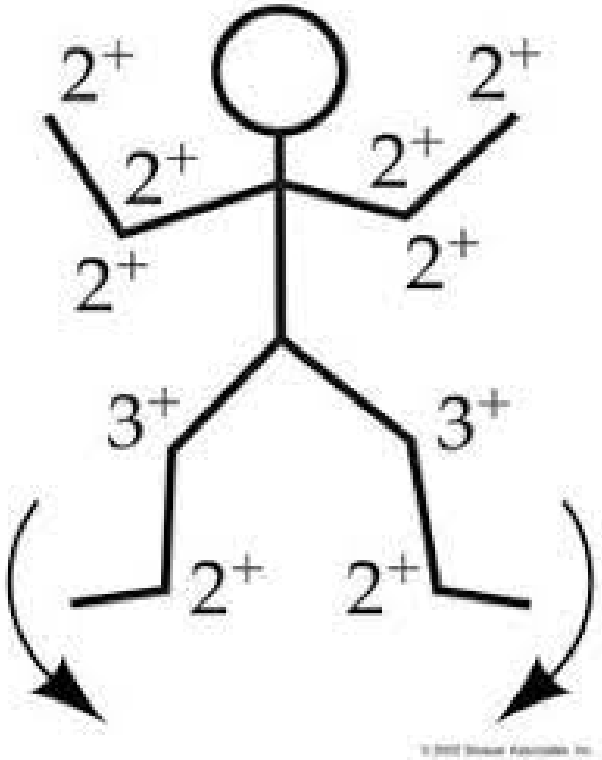
1. Excluding diagnosis based on demographic factors
2. Including/excluding diagnosis based on personality factors
3. Basing diagnosis on history of psychiatric comorbidity
4. Basing diagnosis on preceding stressor

Vignette: 27F with weakness

- Walking into work when started having trouble moving and feeling her legs, worse on right
- Progressive worsening over 3 hours, to a point where she was having trouble moving and feeling both her arms as well as legs

Exam in clinic several weeks later

- In wheelchair
- Motor: UE mild global weakness. LE R 2/5, L 3/5 in flexors and extensors
- Sensation: Decreased to pinprick arms and legs
- Gait: Able to ambulate around the room without aid. Slow, wide-based, hesitant.
- Positive Hoover sign and hip abductor sign on right



Limb Weakness

Drift without pronation

So-so reliability

Fig. 18.5. Drift without pronation sign: **(A)** hand drift and pronation in organic pyramidal arm weakness; **(B)** hand drift without pronation in functional arm weakness.

From Stone and Aybek, Handbook of Clinical Neurology Ch. 18, 2016

From Stone and Aybek, Handbook of Clinical Neurology Ch. 18, 2016

Hip Abductor sign

High reliability

Functional Neurological Disorder (FND) – An Introduction, iTZiT productions
https://www.youtube.com/watch?v=w4lqr4Mo32M

Other useful signs

Global weakness

So-so reliability

Collapsing weakness

Good reliability

Motor inconsistency

- < 3/5 strength supine but able to walk
- Able to stand on tiptoes or heels, but poor ankle strength when supine
- “Pseudo waxy flexibility” - unable to make antigravity movement but can hold limb antigravity when positioned there

So-so reliability

2 Cases

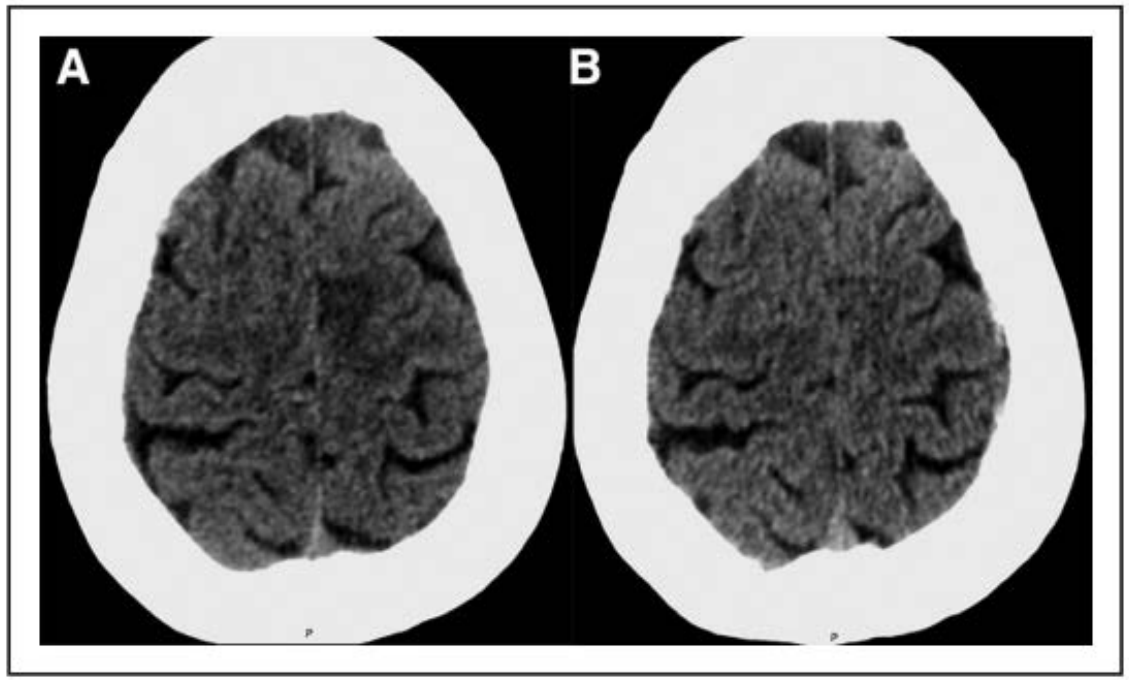
- 59M with dense right hemiplegia
- PMHx: MI
- Strength in leg 2/5, arm 1-2/5
- Hoover sign positive
- Able to reach for water with weak hand when offered
- Unaware of this discrepancy

Mathew et al 2018 *Stroke*

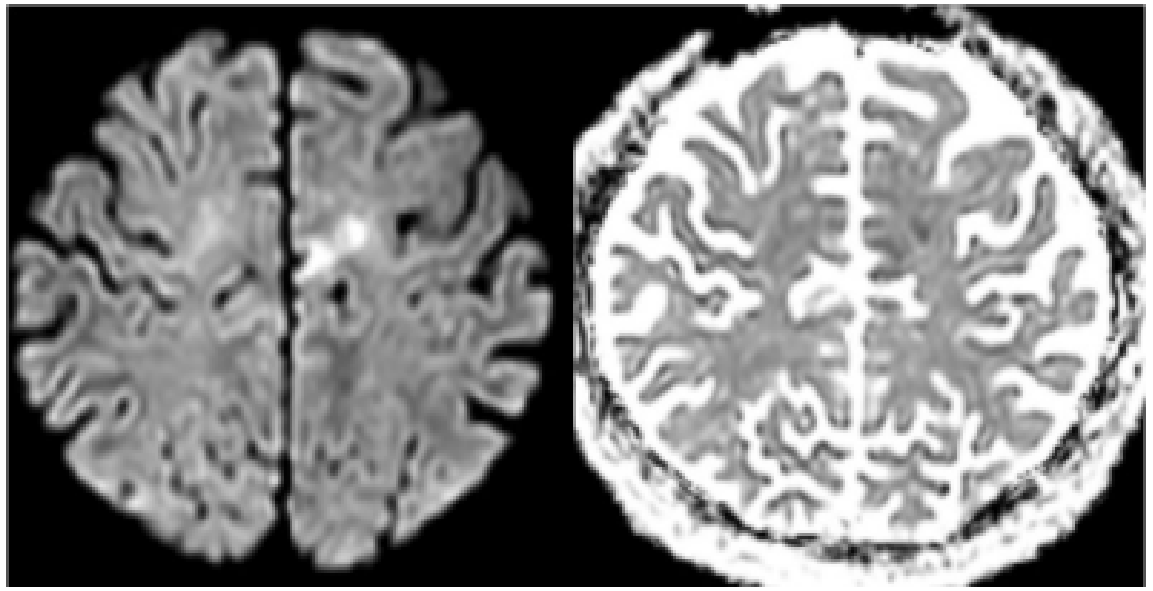
- 52F with dense right hemiplegia, mild right facial droop
- PMHx: non-ischemic cardiomyopathy, polymorphic VT with ICD
- Strength 0/5 arm and leg, decreased sensation leg
- Able to bear weight, positive Hoover sign

Mohebi et al 2019 *J Neurology*

False positive Hoover sign and reversibility of weakness reported in Supplementary Motor Area (SMA) stroke



Mathew et al 2018 *Stroke*



Mohebi et al 2019 *J Neurology*

Movement Disorders CLINICAL PRACTICE
Official Journal of the International Parkinson and Movement Disorder Society

CLINICAL VIGNETTE | Free Access

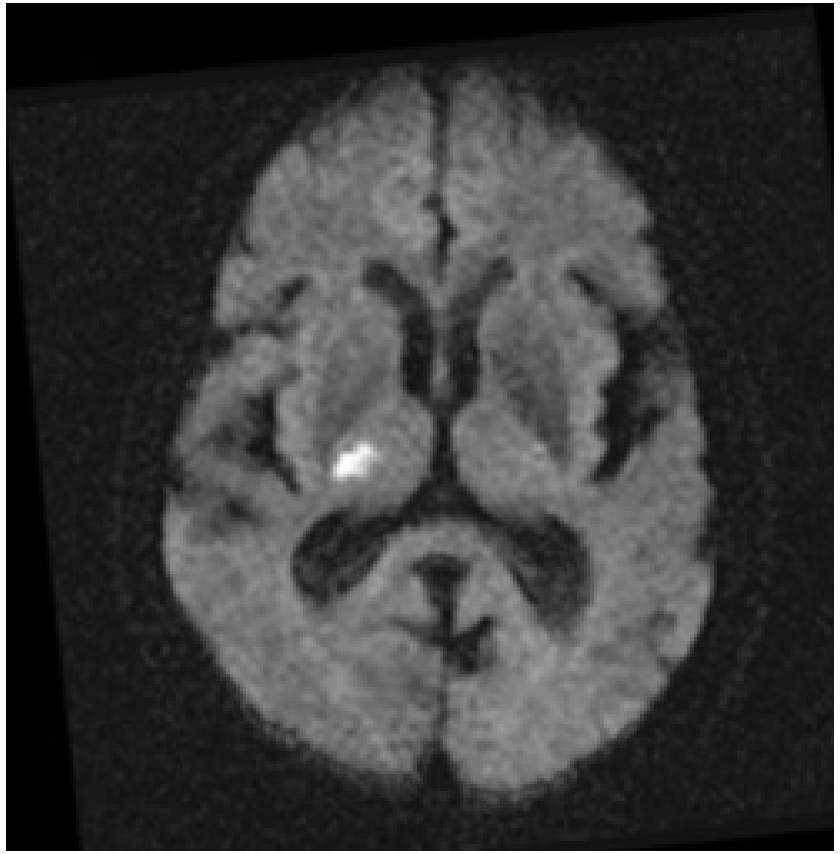
False Positive Hoover's Sign in Apraxia

Tommaso Ercoli MD, Jon Stone MB, ChB, FRCP, PhD

- 90F with 5 year history of not being to move left arm and leg properly
- Able to walk and use arm better with distraction
- Positive Hoover and hip abductor signs
- Marked rigidity, dystonia, and apraxia of right arm and leg
- Diagnosed with corticobasal syndrome

It can always localize to the thalamus…

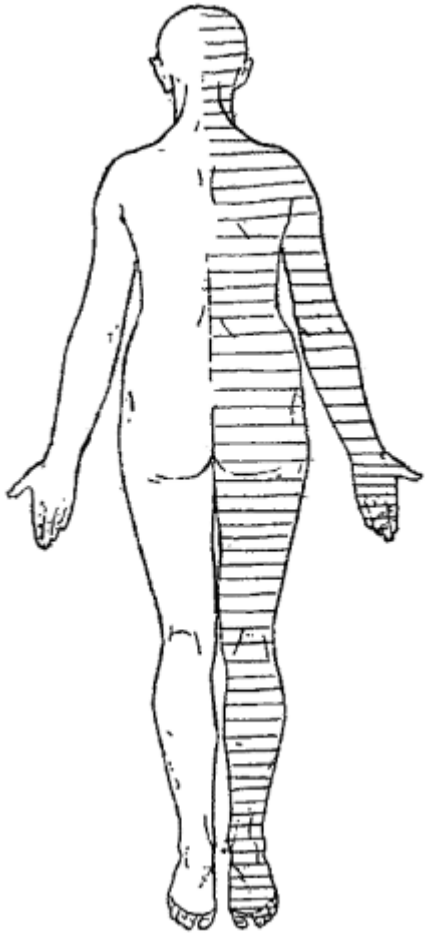
- 76F with postural instability
- Sitting relatively stable, unable to stand unassisted
- Lots of swaying back and forth while standing, with collapse when support withdrawn
- Strength and appendicular coordination testing showed mild dysmetria in left hand only



Lee et al 2005 *EJN*

What about sensory symptoms?

- Midline splitting or splitting of vibration sense have low discriminatory power
- “Non-anatomic” sensory distributions (e.g., glove pattern on single hand) can be found in small cortical stroke



Multiple Sclerosis and FND

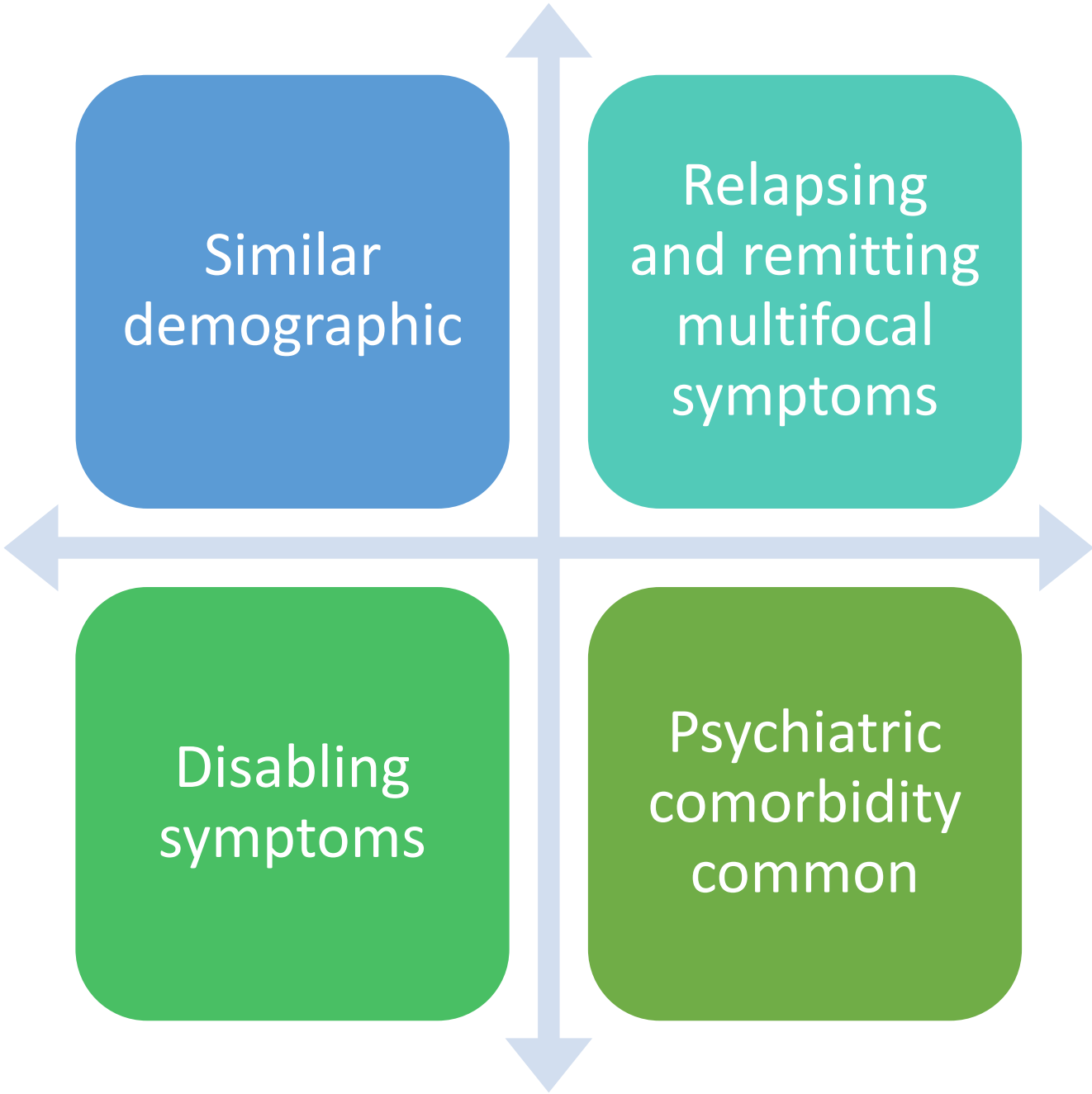
Journal of Neurology (2022) 269:654–663
https://doi.org/10.1007/s00415-021-10436-6

REVIEW

Functional neurological disorder and multiple sclerosis: a systematic review of misdiagnosis and clinical overlap

Dennis Walzl[1] · Andrew J. Solomon[2] · Jon Stone[1]

MS and FND Overlap



MS and FND Overlap

Front. Neurol., 11 April 2023
Sec. Multiple Sclerosis and Neuroimmunology
Volume 14 - 2023 | https://doi.org/10.3389/fneur.2023.1077838

Functional neurological symptoms are a frequent and relevant comorbidity in patients with multiple sclerosis

Katya Piliavska[1*] Michael Dantlgraber[2] Christian Dettmers[1,3] Michael Jöbges[1,3]
Joachim Liepert[1,4] Roger Schmidt[1,5]

Functional Limb Weakness Diagnostic Pitfalls

- Over-reliance on mildly positive or single rule-in sign
- Overlooking minor concomitant symptoms that are not functional
- Bias due to psychiatric history or stressor preceding symptom onset
- Failure to consider pain

Finkelstein et al 2021 FND in the ED *Acad Emerg Med*

Approach to Diagnostic Testing:

1) Stroke work-up is appropriate for sudden onset neurological symptoms of unknown etiology

2) MRI brain + spine typically appropriate for functional limb weakness workup

Alteration of Consciousness or Awareness

Functional Seizures: Diagnosis is based on typical semiological features

See Espay *et al.* JAMA Neurology 2018; Aybek and Perez BMJ 2022

Exam signs with good reliability for: functional seizures

Eye closure/resistance to opening

Duration > 2 minutes

Stopping and starting

Asynchronous limb movements

Maintained awareness during a generalized event

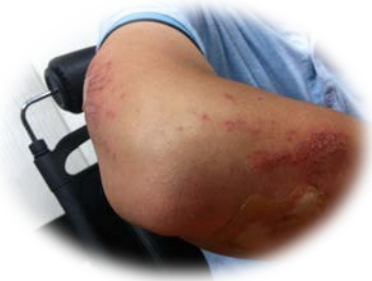
Ictal weeping

Aybek and Perez BMJ 2022

Unhelpful or Common to Both

Tongue biting
& incontinence

Aura or
post-ictal
confusion



Injury (bumps,
bruises)

Sympathetic
activation or
dissociation

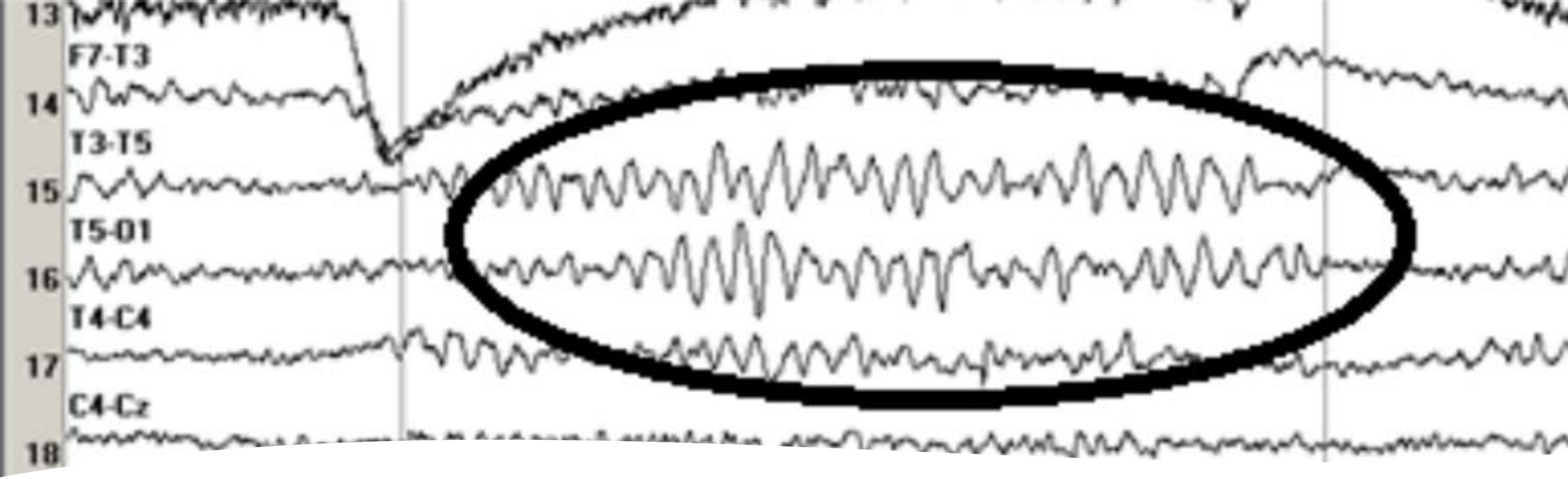
Attack out
of (non-EEG
confirmed)
'sleep'

No
witnesses

Recent meta-analysis:
Muthusamy et al. *Neurol Clin Pract* 2022

Not all non-epileptic events are functional seizures

https://www.youtube.com/watch?v=SOsNeUg1iGA

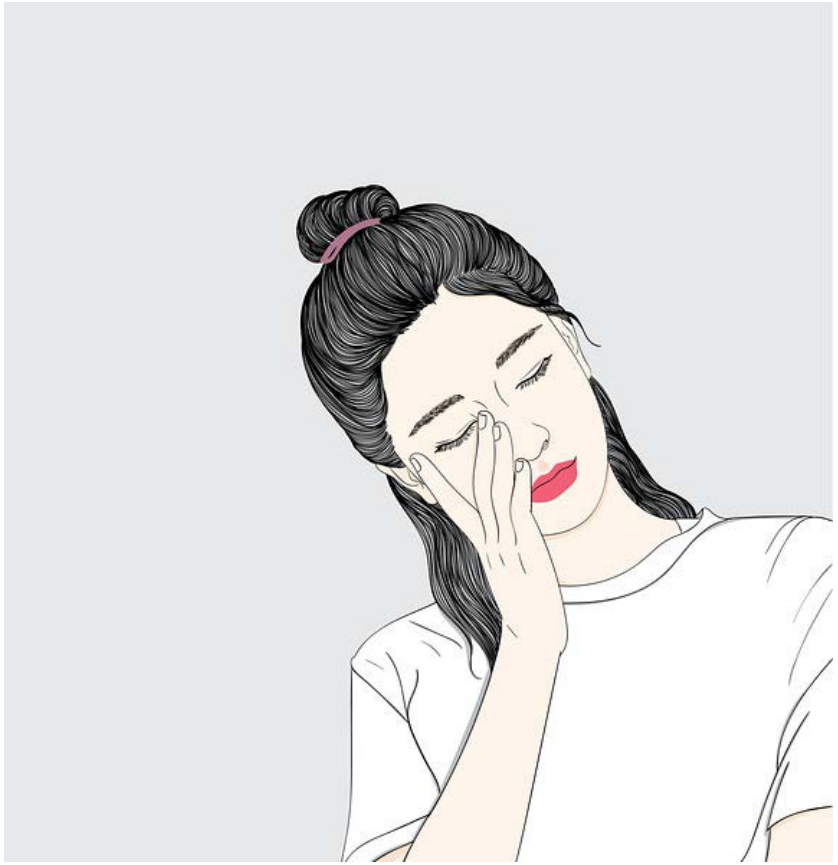


EEG

- Normal variants can be mistaken for abnormalities - e.g., wicket spikes,
- Non-specific EEG changes common in patients with functional seizures
- Deep seizure foci may not demonstrate scalp EEG changes

36F with episodes of déjà vu

- Disoriented for a few seconds
- May have a brief visual hallucination
- Other associated symptoms have variably included: tingling, fatigue, feeling like she is underwater or heavy, feeling limp, presyncope, photophobia, difficulty opening her eyes
- Can respond throughout, doesn't always remember episode well
- Afterwards, gets a throbbing, moderate-severe headache, associated with photophobia
- Other PMHx: migraine, panic attacks, PTSD, ADHD



Differential diagnosis?

Is this a functional seizure, migraine with complex aura, dissociation related to PTSD or anxiety diagnosis?

A combination of some of the above?

DDx: Autonomic or dissociative symptoms

- Can precede epileptic or functional seizures
- PTSD and anxiety/panic can have a high degree of sympathetic activation or dissociation
- Can cause ‘staring spells’/low responsiveness, paresthesias, dizziness, cognitive symptoms (attention, memory)
- Might not have an associated emotional valence (e.g., ‘panic without panic’)

Possible interactions between FND and migraine

- Migraine/aura as a somatic trigger for FND symptoms
- Migraine causing some dissociation or fatigue, in which FND symptoms are more likely to occur
- Migraine and FND tend to occur in similar demographics and appear to co-occur at elevated rates (Khoja et al 2020)
- Migraine worsening FND symptoms that are already present

From Stone and Evans 2011 *Headache*

Approach to Diagnostic Testing:

1) MRI and EEG generally appropriate for seizure-like episodes

2) Importance of capturing event on EEG depends on how consistent semiology is with functional seizure

Failure to consider to the psychiatric differential…

Incomplete diagnosis: not factoring in active psychiatric concerns into a biopsychosocial formulation for the patient

Wrong diagnosis: psychiatric disorders can mimic FND

Movement Disorders

Video Vignette:

55yo M, otherwise healthy, presenting with sudden onset severe tremor in the hands

From Roper et al Practical Neurology 2013

Tremor – Potential Pitfalls

- Amplitude can vary in PD, ET, and functional tremor
- Putting an overemphasis on importance of stress worsening symptoms: most tremor types get worse with stress
- Irregular amplitude and frequency can be seen with dystonic tremor

Video Vignette: 24yo M with new onset problems walking, no history of trauma

Functional gait disorders: A sign-based approach. Jorik Nonnekes et al. Neurology 2020, 94 (24) 1093-1099.

Video vignette: Patient with reversible foot dystonia

Functional gait disorders: A sign-based approach. Jorik Nonnekes et al. Neurology 2020, 94 (24) 1093-1099.

Video vignette: 40M with bizarre gait

Functional gait disorders: A sign-based approach. Jorik Nonnekes et al. Neurology 2020, 94 (24) 1093-1099.

Functional Gait Disorder – Potential Pitfalls

No single pathognomonic pattern

Bizarre ≠ functional

Dystonic gait can improve with alternate motor pattern or be inconsistent over time

Functional Dystonia

Fixed dystonic posturing, with plantar flexion & inversion of foot

Fixed dystonic posturing, with toe curling

Functional hand dystonia, with preserved pincer function

Complex regional pain syndrome and functional neurological disorders: time for reconciliation

Stoyan Popkirov,[1] Ingrid Hoeritzauer,[2] Lesley Colvin,[3] Alan J Carson,[2] Jon Stone[2]

. *J Neurol Neurosurg Psychiatry* 2018;**0**:1–7

Schmerler & Espay, 2016
Popkirov et al., 2018
Frucht et al., 2021

Dystonia: Features in favor of FND

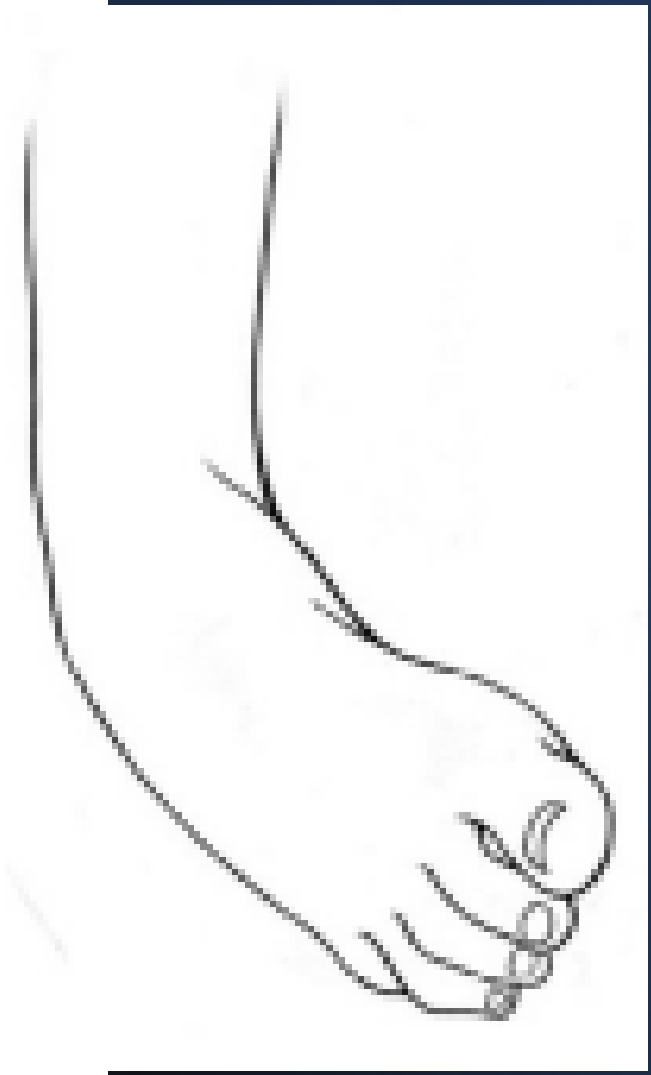
- Abrupt onset
- Fixed posture at onset
- Pain in affected body part
- Resistance to passive movements
- Varying in distribution & severity spontaneously

Functional Neurological Disorder (FND) – An Introduction, iTZiT productions
https://www.youtube.com/watch?v=w4lqr4Mo32M

Functional Dystonia - Potential Pitfalls

Several features can be common to both functional and other causes of dystonia:

- Change with alternate motor pattern
- Abnormal posturing
- Associated tremor
- Variability



Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

Viewpoint | Open Access

Rapid Onset Functional Tic-Like Behaviors in Young Females During the COVID-19 Pandemic

Tamara Pringsheim MD, Christos Ganos MD, PhD, Joseph F. McGuire Phd, Tammy Hedderly MBBS, Douglas Woods Phd, Donald L. Gilbert MD, John Piacentini PhD ... See all authors

First published: 13 August 2021 | https://doi.org/10.1002/mds.28778 | Citations: 57

Functional Tics: Pitfalls

- Several features can be common to both functional tics and other causes of tics:
- Triggered by stimulus
- Warning/build-up beforehand
- Suggestibility/worsening with attention
- Suppressibility

Vignette: 72F with parkinsonism

- 6 years ago developed tremor in her leg, shuffling gait
- Initially seemed to respond to Sinemet, followed by poor response with escalating doses
- Now has severe symptoms of fatigue, slackness of lower facial muscles, drooling, difficulty walking, shuffling, leg tremor
- ‘Off’ symptoms occur very rapidly

Vignette: 72F with parkinsonism

- Initially noted to have no parkinsonism other than slight rigidity at one wrist
- On repeat exam during ‘off’ period, noted:
  - Increased respiratory rate
  - Blank stare, slackness of lower face/jaw – muscles still strong to activation
  - No increase in rigidity or bradykinesia
  - Tremor alternating between left and right leg that was distractible
  - Gait slow, short stride length, normal turn, no freezing
  - Negative pullback test

FND symptoms may precede onset of or co-occur with Parkinson's disease

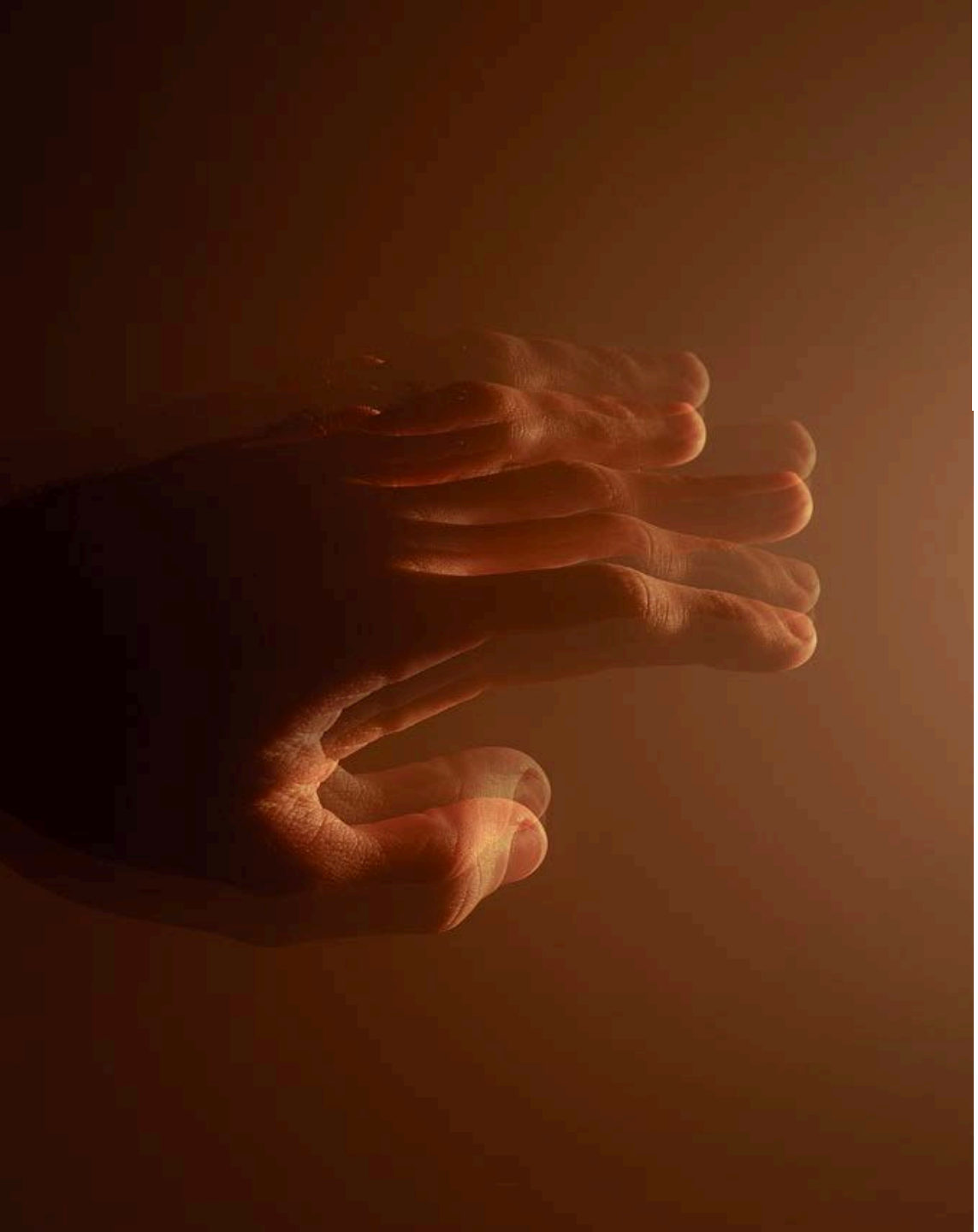
Functional neurological disorders in Parkinson disease

Wissel BD, *et al. J Neurol Neurosurg Psychiatry* 2018;**89**:566–571. doi:10.1136/jnnp-2017-317378

Functional Motor Symptoms in Parkinson's Disease and Functional Parkinsonism: A Systematic Review

Marine Ambar Akkaoui, M.D., Pierre A. Geoffroy, M.D., Ph.D., Emmanuel Roze, M.D., Ph.D., Bertrand Degos, M.D., Ph.D., Béatrice Garcin, M.D., Ph.D.

J Neuropsychiatry Clin Neurosci 32:1, Winter 2020



Functional Parkinsonism – Potential Pitfalls

- If rest tremor present, look for other signs of functional tremor
- Rigidity in FND due to paratonia and should improve with distraction
- Movements may be slow in both PD and FND – look for decrement
- Gait may be slow, difficult to initiate for both

Approach to Diagnostic Testing:

1) Many types of movement disorders rest upon a clinical diagnosis

2) Consider DAT-scan for parkinsonism

3) Diagnosis requires a high degree of familiarity with broad spectrum of MDs

Cognitive symptoms

Vignette: 63F with worsening memory

- Word-finding difficulty and forgets what she is saying in the middle of a sentence
- Reports having to ask her daughter to repeat things
- Trouble with concentration
- Husband died last year
- Sleeping poorly – waking up at 4 am and can’t get back to sleep
- Eating less

Depression

Can have a number of symptoms that overlap with FND

Fatigue, pain, problems with sleep

Cognitive symptoms can include memory and attention problems

Vignette: 21M with cognitive concerns

- Struggling more in school - A/Bs to barely passing
- 3 month history of high degree of somatic symptoms including paresthesias, feeling like his veins were very prominent, pain reported in jaw & right elbow, some blurring of vision, sensation of difficulty swallowing
- Reports some worsening of mood; affect blunted on exam
- Parents note he has become socially withdrawn and isolated

Psychotic Spectrum Disorders

- Rarely overlap with FND
- However, psychotic prodrome can often have a number of overlap features with FND:
  - Unusual body sensations or sensory abnormalities
  - Somatic preoccupations
  - Cognitive difficulties
  - Problems with communication
  - Impaired stress tolerance

Approach to Diagnostic Testing:

1) Consider MRI brain for new / worsening cognitive symptoms – particularly if middle-late age

2) Neuropsychological testing can be helpful in interpreting cognitive changes in context of psychiatric symptoms, baseline IQ, etc.

3) Consider possible psychiatric differential – engage psychiatry/neuropsychiatry colleagues as needed

Take Home Messages

- Diagnosis of FND is based on rule-in signs
- Signs for functional limb weakness can rarely have false positives
- There are both neurological and psychiatric considerations for DDX of periods of altered awareness and cognitive symptoms
- Be aware of overlap of functional movement disorder features with other MD diagnoses
- Diagnostic testing will depend on FND symptom subtype of degree of concern for alternative etiologies based on exam

Thank you! Questions?

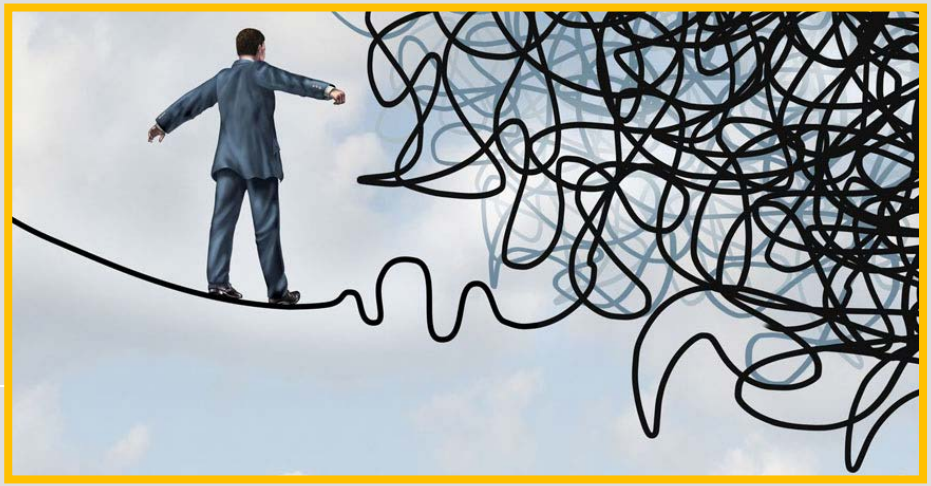
safinkelstein@mgh.Harvard.edu

Further reference: Finkelstein and Popkirov 2023 *Neurologic Clinics*

Managing Functional Neurological Disorders in the Emergency Department

Barbara A Dworetzky, MD, FAAN

FUNCTIONAL NEUROLOGIC DISORDER AND THE EMERGENCY DEPARTMENT (ED)



Barbara Dworetzky, MD

Professor of Neurology, Harvard Medical School

Chief, Epilepsy

Director, Bromfield Epilepsy Center

Program Dir., Clinical Neurophysiology Fellowship

Brigham and Women's Hospital/MGB

Brigham & Women's Hospital

Peter Bent Brigham Hospital

Building for Transformation of Medicine

Harvard Medical School, Boston

Mass General Brigham

Disclosures

- Founding member; President-Elect, Functional Neurological Disorders Society (FNDS)
- PAB, Epilepsy Foundation New England


Braves
13

Functional disorders are ubiquitous…

- GI: IBS
- Urology: OAB
- Rheumatology: FBM
- Infectious disease:CFS
- Immunology: multiple chemical sensitivities
- *Cardiology: Atypical CP, syncope

- *Pulmonary: SOB
- *ENT: Globus
- Gyn: pelvic pain
- Ophthalmology: blindness
- **Neuro: seizures/attacks; weakness, movement, sensory, cognitive/speech problems; dizziness**

FND

The Burden is High…

- **FND** Health Care Utilization (HCU) is very costly (meds, tests, admissions, amb, **ED, ICU visits**)[1,2,3], ~1.2 bill. (adults); 88 mill.(peds)[4]
- Lower rates of employment[5]
- ↓QOL (<= other neuro disorders)[6]
- Stigma worse [7]
- Caregiver burden similar [8,9]
- **Increased risk of injury,**[10] **death** (**SMR 2.5x gen. pop**)[11-13]

1. Martin et al, Seizure 1998; 2. Seneviratne et al, Epilepsia 2019; 3. O'Mahony et al, Neurology 2023; 4. Stephen et al, JAMA 2021; 5. Jennum et al, E and B, 2019; 6. Szaflarski and Szaflarski, Epilepsy and Beh 2004; 7. Robson et al, Seizure 2018; 8. Karakis et al, Seizure 2014; 9. Tsamakis et al, Epileptic Dis, 2023; 10. Moreira et al, Epilepsia 2023; 11. Nightscales et al, Neurology 2020; 12. LeZhang et al, JNNP, 2022; 13. Gelauff et al, Brain, 2019;

Prognosis is generally unfavorable* *Gelauff, Stone 2016*

- 71-75% adults w/FND continue to have symptoms[1-3]
- 56% are on disability
- Only 18% adults become sx free, able to work[3]
- Comorbid neuro/psych d/o,[4,5] receiving state disability,[6] social deprivation,[7] other somatic sx? → worse outcomes
- Children more likely resolve FND[8] but not school and family dysfunction[9]

1. Reuber, Pukrop, Bauer et al, Ann Neurol 2003; 2.Lancman, Brotherton et al, Seizure 1993; 3. Walczak, Papcostas et al, Epilepsia 1995; 4. Meierkord et al., 1991; 5. Gelauff, Stone 2016; 6. Duncan et al, 2014; 7. Goldstein et al, Epilepsia 2019; 8. Raper et al, 2019; 9. Dworetzky, Epilepsy Currents, 2015.

Why are outcomes poor?*

1. Rawlings, Reuber 2018; Barnett et al, 2022

- Health care providers are confused, fearful, challenged, avoidant[1,2]
- ?Clinicians don't believe it is a real disorder; Lack of: follow up, ownership of care?
  - Continue to order consults, tests, medications adding to confusion
  - FND is often not documented or considered in the medical record
- Disorder begins years before "diagnosis" (long delay)
- Lack of funding to study it? No drugs to treat it→ No pharma $$
- Limited evidence-based treatment (starting to change ☺)
- Secondary gain (perpetuating factors)
- ED and Internists→ **"biased to malingering"** as cause *Kilic et al, 2021*

- **Repeated ED visits are common w/ FND**
- **Decreased ED reattendance linked to**:
  - Documented FND in chart (p<.004)
  - Referral to treatment (p<.04)
  - Outpt neuro follow up (p<.001)

Williams et al, To emergency room and back: circular healthcare pathways for acute FND J. Neurolog Sci, 2022

***We don't know why but FND has been neglected and we need to do better!**

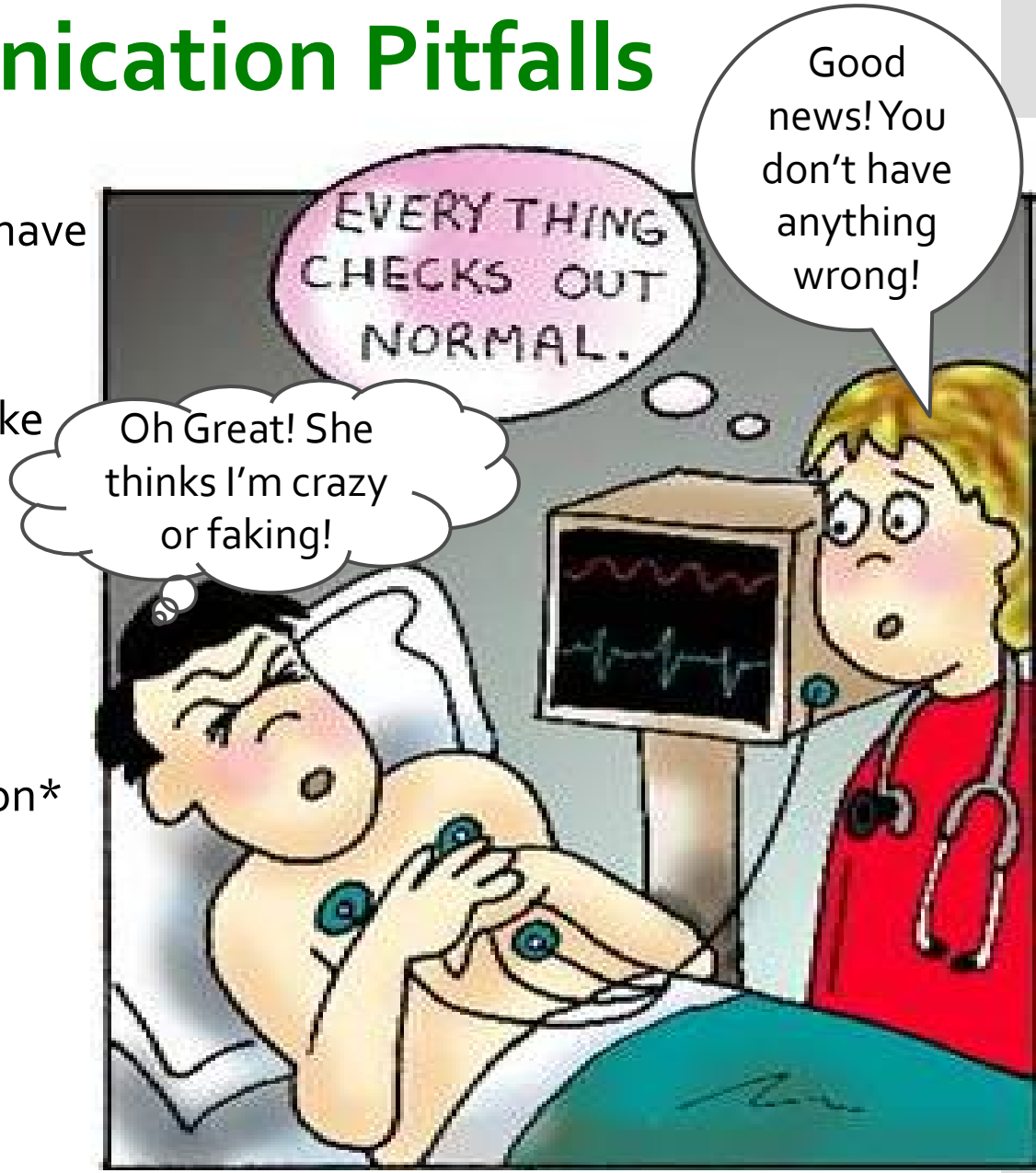
Let's look at us in the ED…

Video is courtesy of Bernd Pohlmann

Video demonstrating what we regularly have been doing in the ED with patients with FND

Communication Pitfalls

Only explaining what they don't have
Attributing symptoms to stress/ psych
Implying it is 'all in their head', fake ("not real")
Reporting normal test results as evidence of the diagnosis
Blaming the patient
Not believing symptoms*
Not inviting 2-way communication*
Not developing rapport*
Not allowing follow-up



***Trauma-Informed-Care (TIC)** : Safety, choice, collaboration, trustworthiness, empowerment

Curriculae have been lacking…

International Parkinson and Movement Disorder Society

United Council for Neurologic Subspecialties — Training Quality Patient Care

American Academy of Neurology

American Psychiatric Association

American Board of Psychiatry and Neurology, Inc.
A Member Board of the American Board of Medical Specialties (ABMS)

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

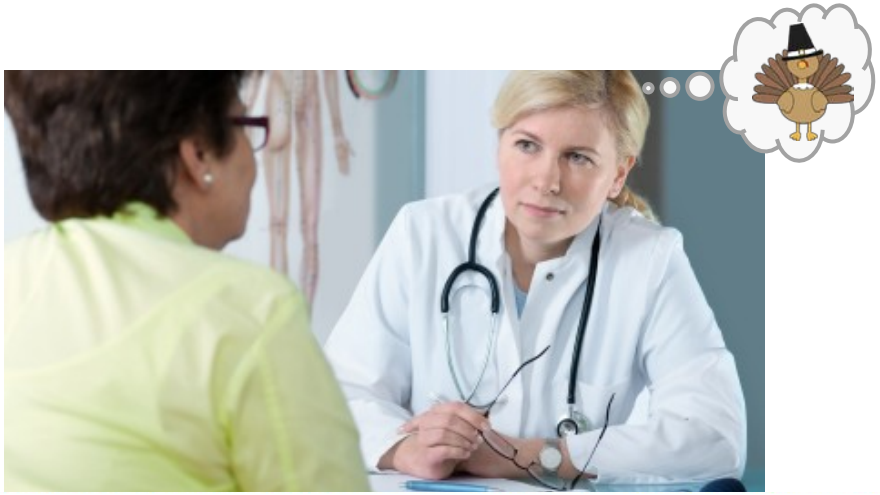
American Epilepsy Society

ACGME Accreditation Council for Graduate Medical Education

American Neuropsychiatric Association (ANPA)

AMERICAN NEUROPSYCHIATRIC ASSOCIATION

except as a neurological differential diagnosis…



Neurol Clin ■ (2023) ■–■
https://doi.org/10.1016/j.ncl.2023.02.007
0733-8619/23/© 2023 Elsevier Inc. All rights reserved.
neurologic.theclinics.com

Functional Neurological Disorder

Definition from *Hallett et al, Lancet, 2022:*

Clinical syndrome consisting of symptoms and signs of **genuinely experienced** alterations in motor, sensory, or cognitive performance which are **distressing or impairing**, and manifest as one or more patterns of deficits that are consistent predominantly with **dysfunction of the nervous system** and show **variability in performance** within the same task or between different tasks.

nature reviews neurology

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Perspective | Published: 16 February 2023

Why functional neurological disorder is not feigning or malingering

Mark J. Edwards, Mahinda Yogarajah & Jon Stone

Nature Reviews Neurology **19**, 246–256 (2023) | Cite this article

***FND is stigmatized** because it is commonly **confused with feigning**. The problem lies in the voluntary motor system where performance may change with attention. It is **not fake**, and **we do great harm** to patients with implicit or explicit bias revealing beliefs which are incorrect and not based on the most up to date evidence.*

Objectives

1. Know how to diagnose FND using positive signs
2. Be aware of the pitfalls of FND in the ED
3. Discuss initial management of FND in the ED

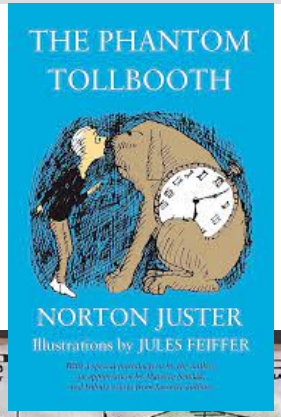
Acute Neuro Symptoms to the ED

Merkler et al, JNNP 2016; Moeller et al, 2008; Walzl, Carson, Stone J Neurol 2019; Lange et al, 2011; Williams et al, To the emergency room and back again: circular healthcare pathways for acute FND, J Neurolog Sci, 2022. Mastrangelo, Baglioni 2021

- ~15% of Adult ED visits are neurological, ~ 30% pediatric visits
- Most common: **HA**, **Stroke/ TIA, Syncope/Seizure/SE, FND, decompensation of neuro disorder, dizziness, weakness, sensory loss, ΔMS**
- **FND** often presents **acutely, for the first time,** to the ED;
- But not infrequently has **repeat presentations** to ED <u>including</u> for other functional symptoms making it <u>quite challenging</u> and it is **often misdiagnosed as another neurological disorder**

- ***Nontraumatic HA common comorbidity in FND****: worst HA of life, LOC or AMS, seizure, lost vision, vomiting, prolonged, sudden/severe at onset, infection,pregnant, immune suppressed, age>50, AC, substance use, papilledema, meningismus, fever*

Pitfalls: our biases



- Prediction based on RF (premature closure**, confirmation bias
- Short circuit of history and rapport
- Believing a test will help with diagnosis
- Test and treat to avoid medicolegal consequences

Our brain can anchor on wrong diagnosis framed by risk factors and can mislead us (not suspecting correct diagnosis)

"It's really quite simple: every time you decide something without having a good reason, you jump to Conclusions whether you like it or not. It's such an easy trip to make that I've been here hundreds of times."

Be nonjudgmental, open minded

Kahnmann, Thinking Fast and Slow 2011; Groopman How Doctors Think 2008

Risk of Misdiagnosis in ED

FND presenting to the ED

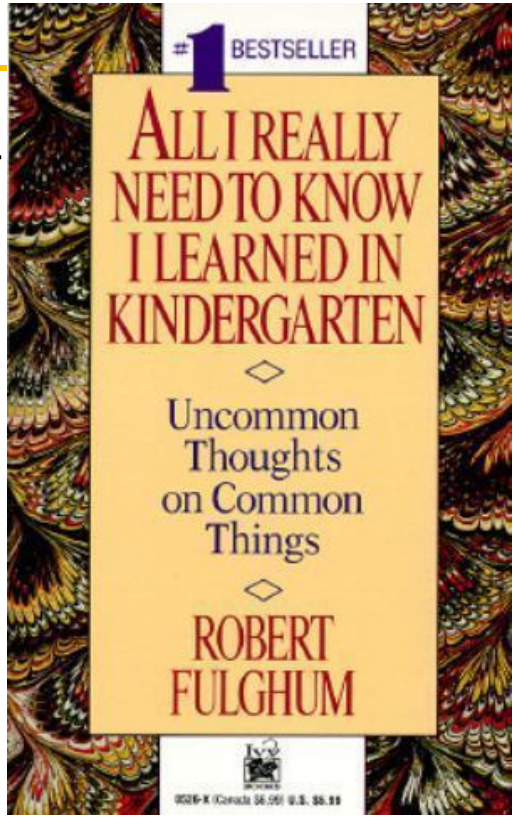
- Prevalence 0.4 – 4% (likely an **underestimate**)[1],high return rate[2]
- 9% acute neuro admits;[3] 13% ED neuro consults[4]
- 12% of "strokes" to ED are FND[5]
- 15% of FND sz 1st present to ED[1] and ~11% sz in ED=FND[6]
- 25% "SE" in ED is FND[7]
- 1.4% Functional movement disorder[8]

1. Stephen et al, JAMA Neurol 2021; 2. Merkler et al, JNNP, 2016; 3.Beharry et al, Eur J. Neuro, 2021; 4. Moeller et al; Can J Neurol Sci, 2008; 5. Neves Briard et al, 2018; 6.Dickson et al, BMJ Open, 2017; 7. Reuber et al, J. Neurology 2003; 8.Dallochio et al, Neurolog Sci, 2019.

History suggestive of FND

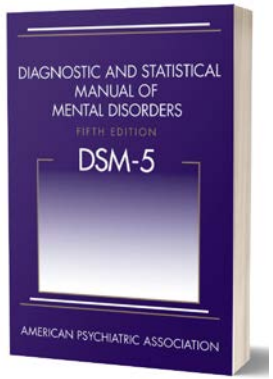
"Listen to your patient; he/she is telling you the diagnosis." Sir William Osler

- Sudden, maximal at onset, rapid progression, trigger
- Prior similar episodes; resolve, recur
- Variability, fluctuations in sx in one day
- "Panic w/o the panic" (autonomic symptoms)
- Dissociation: derealization, depersonalization
- Medical comorb. (ie, FBM, IBS,CFS, chronic pain/HA)
- Neuro. comorbid.* (ID, migraine, epilepsy, mild TBI)
- Psych. comorbid.* (depression, anxiety, PTSD)



*also common in many neurological disorders

Diagnosis requires positive signs



- FND is a neuropsychiatric disorder in which neurological symptoms are caused by a problem in brain networks
- Diagnosis is based on **POSITIVE ("RULE IN")** signs or semiological features **typical of FND**:

showing **INCONGRUENCE / INCONSISTENCY / REVERSIBILITY** of symptoms

- *No longer a diagnosis of exclusion*

- *No longer need psychological or other stressor preceding to make diagnosis*

CONTEMPORARY ISSUES IN NEUROLOGIC PRACTICE

Trick or treat?

Showing patients with functional (psychogenic) motor symptoms their physical signs

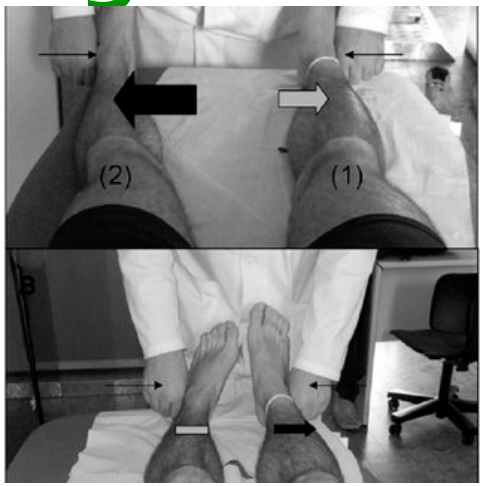
Dragging leg gait

Drift w/o pronation

Spasms of face muscles

Neurological Exam

Hoover sign



Abductor sign

Adapted from: Stone and Edwards, Neurology 2012

Seizure/Attack

<u>Seizure ED visits</u>:
~ 1% adult
~ 2% pediatric

Pallin et al, J Int Med Emerg 2008

Most common causes for TLOC* (>90%)

Epilepsy (ES)
Functional Seizure (aka PNES)
Vasovagal syncope (VVS)

***<u>transient</u> loss of consciousness**

Children
Breath-holding spells
Vasovagal syncope
Migraine
Benign paroxysmal vertigo
Staring spells
Tic disorders and stereotypies
Rhythmic movement disorder
Parasomnias
Adolescents and young adults
Vasovagal syncope
Narcolepsy
Periodic limb movements of sleep
Sleep starts
Paroxysmal dyskinesia
Tic disorders
Hemifacial spasm
Stiff-person syndrome
Migraine
Psychogenic nonepileptic seizures
Hallucinations
Older adults
Cardiogenic syncope
Transient ischemic attack
Drop attacks
Transient global amnesia
Delirium or toxic-metabolic encephalopathy
Rapid eye movement sleep behavior disorder

*

Reliability of Positive Signs for diagnosis

Adapted from Popkirov et al, Stroke, 2020; Syed et al, Ann Neurol, 2011; Avbersek and Sisodiya, JNNP 2010;

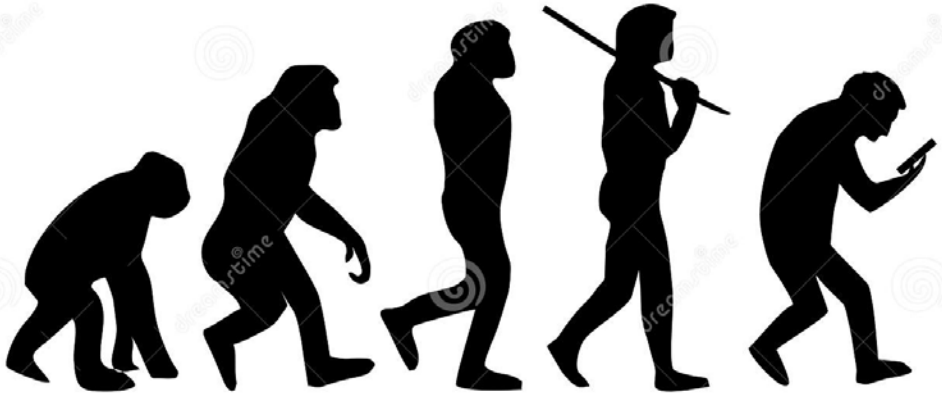
Clinical Sign	Sensitivity %	Specificity %	Comments
Hoover's	60-100	86-100	In unilateral leg weakness; not SMA, parietal
Hip adductor sign	-	100	Unilateral leg weakness
"Give way" weakness	20-90	95-100	Absence of joint pain
Dragging leg gait	20-100	100	
Drift w/o pronation	47-93	100	Palms up, wait 10 seconds; mild-mod UE weakness
Ictal eye closure	**34-88**	**74-100**	**Geotropic gaze w/ forced eye opening; blinking after rubbing eyelashes**
Ictal weeping	**3.7-37**	**100**	**Not postictal**
Pelvic thrusting	**1-44**	**92-100**	**Exclude FLS**
Side to side head/body	**25-63**	**96-100**	**Convulsive events only**
Asynchronous movements	**44-96**	**93-96**	**Exclude FLS**
Fluctuating course/long duration	**47-88**	**96-100**	
Sensory loss- midline split			Not reliable, seen with thalamic stroke

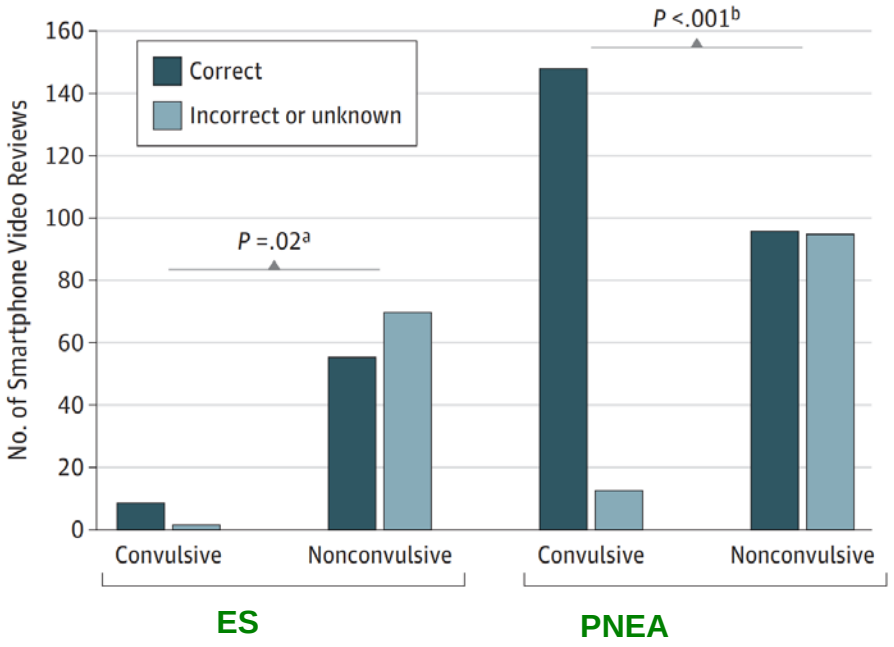
Video EEG: gold standard for diagnosis

Video of a functional/dissociative/nonepileptic /psychogenic seizure

Confirm no ictal correlate on EEG
Confirm video is c/w seizure type

High specificity/sensitivity positive signs:
Long duration, Fluctuating course, asynchronous movements, side-to-side head/body movements, closed eyes, recall/responsiveness





Adapted from Fig. 2, Tatum et al , JAMA Neurology 2020

Number Of Smartphone & Mobile Phone Users Worldwide (Billions)

	Number of smartphones	Number of mobile phones
2025*	7.33	7.49
2024*	7.13	7.41
2023*	6.92	7.33
2022*	6.64	7.26
2021	6.37	7.10
2020	6.05	6.95

*Forcast figures by Ericsson & The Radicati Group

If motors signs: ↑ accuracy of smartphone videos and combined with HX/PE → O.R. 5.45

Status Epilepticus (SE)

- *A life threatening emergency, if not stopped within one hour can cause lasting brain damage*
- Usual GTCS duration --1-2 min
- Prolonged -- >5 min.
- Official -- >30 min.
- Transitional state: seizure clusters

Functional SE (aka nonepileptic status): duration not tracked for FS[1]; ~78% pts w/FS report >30 min event and ~39% have "recurrent SE"[2]

Generally, not "life threatening" **however**: risk of iatrogenic harm (intub., procedures)[3,4] and higher rates of mortality[2,5,6]

1. Dworetzky et al, 2010 2. Reuber et al, 2003; 3. Howell et al, 1989; 4. Reuber et al, 2004; 5. Nightscales et al, Neurology 2020; 6. LeZhang et al, JNNP, 2022;

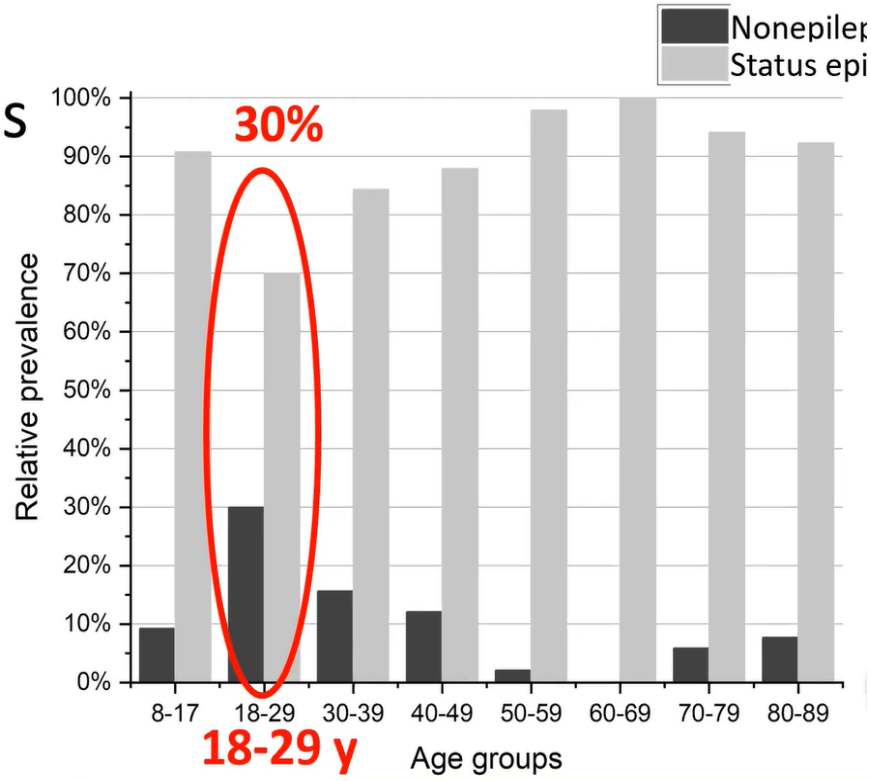
Kapur et al, Established status epilepticus treatment trial(ESETT), *NEJM 2019;Chamberlain et al, Lancet 2020*

ESETT trial: 313 cases (≥ 8 y)
33 (**10.5%**) with final diagnosis 'nonepileptic event'

48% adverse event
30% admitted to ICU
12% intubated!

Other trials

Navarro et al, Lancet, 2016	4.4%	(6/136)
Aldredge et al, NEJM 2001	5%	(10/205)
Silbergleit et al, NEJM 2012	7%	(63/893)
Chamberlain et al, JAMA 2014	10%	(31/310)



Adapted from Popkirov, FNDS educational webinar

Distinguishing ES v. FS in the ED

Adapted from Lehn et al, PNES treated as ES in the ED, Epilepsia 2021

	Epileptic seizure	Functional seizure (PNES)	Significance, p=
Seizure duration	*	*	0.751, NS
Postictal duration	***	*	<0.001
Lactate level	**		.0026
Previous FND dx	*	***	<0.001
Anxiety	*	**	0.005
Brain surgery or hem.	***	*	<0.001
Intracranial Neoplasm	***	*	.002
Multiple event types	*	***	<0.001

55.6% szs to ED→ ES, 26.5% functional sz; 92% sz to ED received rx for epilepsy

Given timing of blood draw v. baseline, inability to distinguish VVS, focal epilepsy,PNES →prolactin, CPK not very useful (maybe useful in low resource settings)

Fisher, Neurology Clin Pract 2016; Chen et al, Neurology 2005

Diagnostic Pitfalls

Examining a patient with suspected functional seizure and ongoing unresponsiveness

- Do NOT attempt or threaten exam maneuvers designed to 'trick' the patient, such as dropping arm over face
- Unresponsiveness to noxious stimuli is possible in a deep dissociative state
- Appropriate to use typical methods to assess responsiveness (verbal, nail bed compression)
- Stereotyped episodes <2 min should be evaluated for epilepsy, even if dissociation or emotional features are prominent

Adapted w/ permission from a slide by Sarah Finklestein MD; Finklestein, Popkirov, Neurology Clinics, 2023

Risks of missing diagnosis of FS

- Risk of ASMs* and delay to dx/rx[1]
- Risk of rescue procedures (ie, TPA, ICU/intub, catheters/IVs)[2]
- Risk of treating as SE in RCTs, 8% tot, 20% young, 3x>benzos[3]
- Trust eroded in healthcare system and us
- Delay to treatment>30d linked to worse outcomes[4]
- ~4% misdiagnosis rate of other neuro disorder as FND[5]
- **positive signs of FND does not rule out comorbid neuro. disorder** (~ overlap 20%)
  - **anti-seizure medications*

Video of same patient have an epileptic convulsion demonstrating comorbid epilepsy in a patient with frequent functional (nonepilepic) seizures

1.Kerr et al, Seizure 2016; 2.Reuber et al, Neurology, 2004; 3.Jungilligen et al, JNNP, 2021 (ESETT, RAMPART); 4. Fredwall et al, Epilepsia 2021; 5. Stone et al, BMJ, 2005;

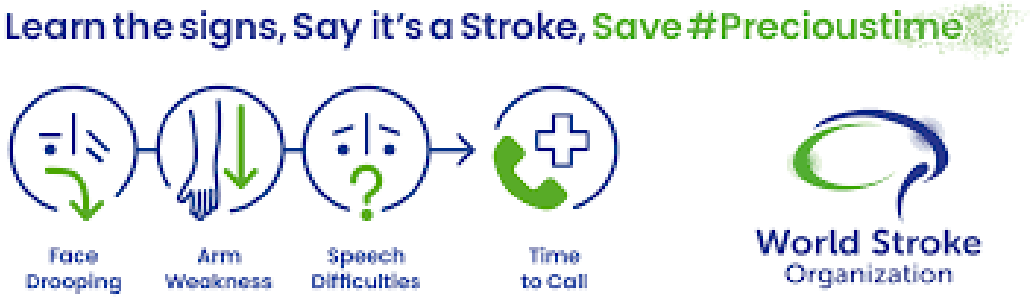
Take Homes: Functional Seizures:

1) Look for presence of multiple typical semiological features

2) Avoid unnecessary escalation of care

3) Connect patient to Follow up

TIME IS BRAIN



Symptoms/signs of Acute Stroke

- Sudden arm/ leg /face weakness } ~70%
- Sudden sensory disturbance
- Sudden speech disturbance ~17%
- Sudden vision disturbance- double vision or field cut
- Sudden difficulty walking or with balance
- Sudden HA, dizziness, vomiting

Gargalas et al, JNNP 2017; Wilkins et al, Psychosom Med, 2018; Keselman et al, Eur J Neuro, 2019; Jones et al, Eur J Neurol 2019

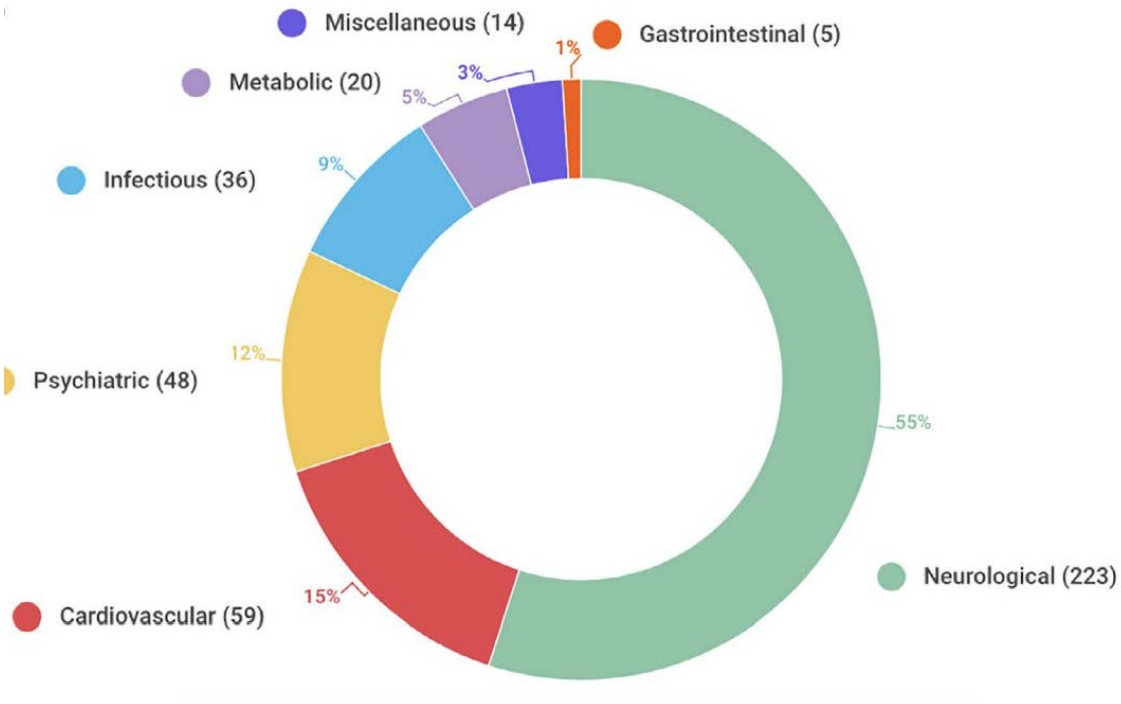
Reliability of Positive Signs for diagnosis

Adapted from Popkirov et al, Stroke, 2020; Syed et al, Ann Neurol, 2011; Avbersek and Sisodiya, JNNP 2010;

Clinical Sign	Sensitivity %	Specificity %	Comments
Hoover's	**60-100**	**86-100**	**In unilateral leg weakness; not SMA, parietal**
Hip adductor sign	**-**	**100**	**Unilateral leg weakness**
"Give way" weakness	**20-90**	**95-100**	**Absence of joint pain**
Dragging leg gait	**20-100**	**100**	
Drift w/o pronation	**47-93**	**100**	**Palms up, wait 10 seconds; mild-mod UE weakness**
Ictal eye closure	34-88	74-100	Geotropic gaze w/ forced eye opening; blinking after rubbing eyelashes
Ictal weeping	3.7-37	100	Not postictal
Pelvic thrusting	1-44	92-100	Exclude FLS
Side to side head/body	25-63	96-100	Convulsive events only
Asynchronous movements	44-96	93-96	Exclude FLS
Fluctuating course/long dur.	47-88	96-100	
Sensory loss- midline split			**Not reliable, seen with thalamic stroke**

Stroke Mimics

- Common stroke mimics include **migraine, seizure, FND** (~10%) *Jones 2020*
- Across studies, pts w/ FND tend to be younger (**age < 40 may be a predictor of a stroke mimic)** *Sivakuraman 2016; Chernyshev 2010; Kostulas 2017;*



Neves Briard et al, J Stroke Cerebrovasc Disorders, 2018

Consider pre-test probability of stroke vs other condition (age >50, other RF)

Use of tPA in Stroke and Mimics

72582 pts in 485 U.S. Hospitals over 7 yrs using data from "Get with the Guidelines"- Stroke Registry

Year	Stroke rx w/TPA	Stroke mimic	%
2012	6775	134	1.9
2013	8335	195	2.3
2014	9262	268	2.8
2015	10515	373	3.4
2016	12002	695	5.5
2017	12801	740	5.5

Adapted from Ali-Ahmed et al. 2019 Circ Cardiovasc Qual Outcomes

tPA complications in stroke v. mimics

	Stroke Mimics (N=2517)	Ischemic Stroke (N=70,065)	Adjusted OR (95% CI)	*P* value
Symptomatic ICH	11 (0.4)	2451 (3.5)	0.29 (0.17-0.50)	< 0.001
Serious systemic hemorrhage	1 (0)	516 (0.7)	0.15 (0.03-0.84)	0.03
Other serious complication	26 (1.0)	1938 (2.8)	0.73 (0.51-1.03)	0.08
Any tPA complication	38 (1.5)	4803 (6.9)	0.48 (0.36-0.64)	< 0.001

Adapted from Ali-Ahmed et al *Circulation* 2019

NOTE: Safety data for TNK in stroke mimics is not well-established

Other potential harms: Cost, adverse psychological impact

→Probably safe to use tPA in FND if unsure

Diagnostic Pitfalls

- Over-reliance on mildly positive or single rule-in sign
- Overlooking minor concomitant symptoms that are not functional
- Allowing demographic or psychological factors to bias diagnosis

Borrowed from Sara Finklestein w/permission

Take homes: Stroke mimics

- 1) Stroke work-up is appropriate for sudden onset neurological symptoms of unknown etiology
  2) If diagnosis is unclear better to err on side of OVER-treating in patients with disabling symptoms
  3) If FND is high in differential, inform pt that stroke was not found

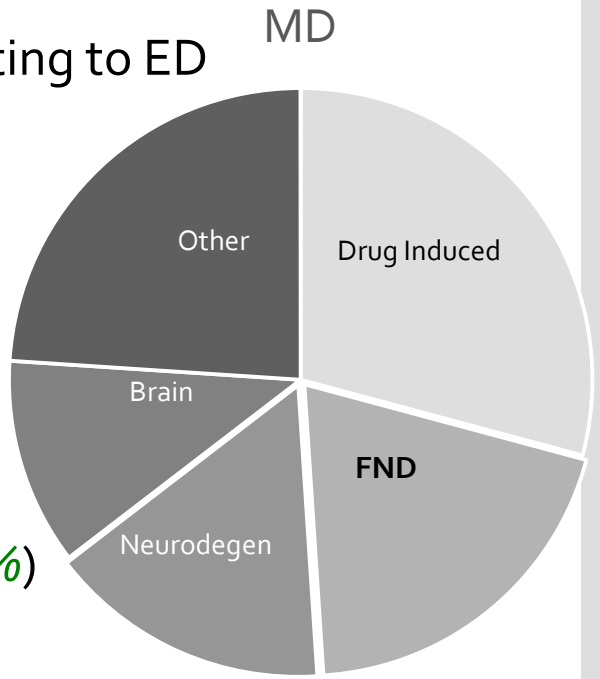
Adapted w/ permission from slide by Sarah Finklestein

Movement Disorders in ED

Dallochio et al, Neurologic Sciences, 2019

- 96 consecutive pts w/ **acute** movement d/o presenting to ED
- 46% male *(other studies show 70% female)*
- **74% hyperkinetic**, 26% hypokinetic, 20% mixed

- **Etiology**
- 29% Drug induced
- **20% FND** (↓ w/distraction, entrainment) (*other 10%*)
- 15.6% Neurodegenerative
- 11.5% Structural brain lesion
- 24% other (metab., infect., inflam., etc)



Functional Movement Disorder in ED

- FMD is the **second most common cause** of movement disorder in the ED
- Prevalence ~2-4% adults and children
- 35% unfavorable outcome *Dallochio, et al, 2019*
- Positive features for diagnosis= entrainment (tremor), distractibility, variability

Positive features of functional movement disorders

Video of functional gait removed

Video of functional tremor removed

Tremor entrainment

Excessively slow, “walking on ice” with knee buckling

Diagnostic Pitfalls

Bizarre movements do not=FMD

FMD often overlap with other FNS or movement disorder (ie,tremor, gait, tics, myoclonus, parkinsonism)

Caution not to miss: NMS*, Parkinson's Disease, startle myoclonus in need of urgent work up

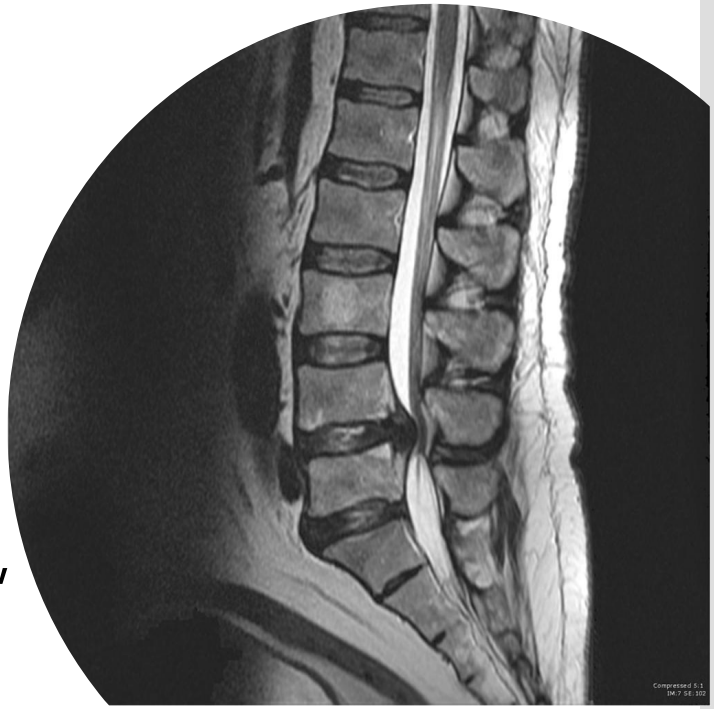
Adapted from slide from Sara Finklestein, w/permission

Cauda Equina Syndrome (CES)

- Rare condition in 7/100,000 adults
- Age onset ~ 40 yr , 70% F
- 2/3 normal scans
- **Symptoms**: Pain (back/post. legs), weakness, numbness (inner thighs, buttocks, heels; bowel/bladder/sexual dysfunction

Scan Negative "Cauda Equina Syndrome (CES)" v. FND *Hoeritzauer et al, Neurology 2021*

- Few robust findings on exam; Best may be absent ankle jerks *Hoeritzauer 2021*
- High frequency of positive Hoover sign (associated FND) in CES *Hoeritzauer 2018*
- Over 50% of patients with "CES presentation" have normal scans *Rooney 2009; Bell 2007*
- Post-void residual and anal sphincter tone are NOT good differentiators *Hoeritzauer 2021*
- May be due to a combination of pain, panic/anxiety, medication side effects, ***and features of FND***



Adapted from Slide courtesy of Sara Finklestein, MGH, Boston

Pitfall: No historical/exam features eliminate the need for urgent neuro-imaging with suspected CES

Management of FND in the ED

If episode is over

- Documented FND+ typical presentation→ connect to follow up, avoid iatrogenic harm, no testing, DC home
- Documented FND, new symptoms, remain unbiased and weigh risk/benefit of testing/treatment
- First presentation, test, treatment likely indicated

If episode is ongoing

- Documented FND + typical presentation→ likely need to admit to neurology. Use positive signs to test for FND, avoiding harm (pt may hear you)
- Documented FND, new symptoms, do not assume FND, likely need for testing/treatment
- First presentation, test, treat likely indicated

Take homes:

If patient has a neurologist or other clinician who knows them, contact them while pt still in ED. Use transparent two-way discussion about possible/likely diagnosis of FND (use protocol) and provide written material or website AND provide appropriate follow up care referral.

Challenges: Barriers to Care

Patient	Lack acceptance of diagnosis (stigma) Non-adherence to treatment External locus of control Symptom migration: heterogeneous presentations Disability benefits Social isolation
Clinician	Lack of knowledge and understanding of what to do Lack of empathy and negative attitudes Lack of collaboration/ownership for management Concern for malingering or misdiagnosis (liability) No follow up provided
Healthcare System	Lack of access to care (e.g., mental health services) Lack care co-ordination Lack communication among healthcare systems and providers

Adapted from Sawchuk, Austin, Terry, 2017 in Dworetzky & Baslet: PNES: Toward the Integration of Care; Kanemoto et al, Epilepsia, 2017

Treatment considerations in ED

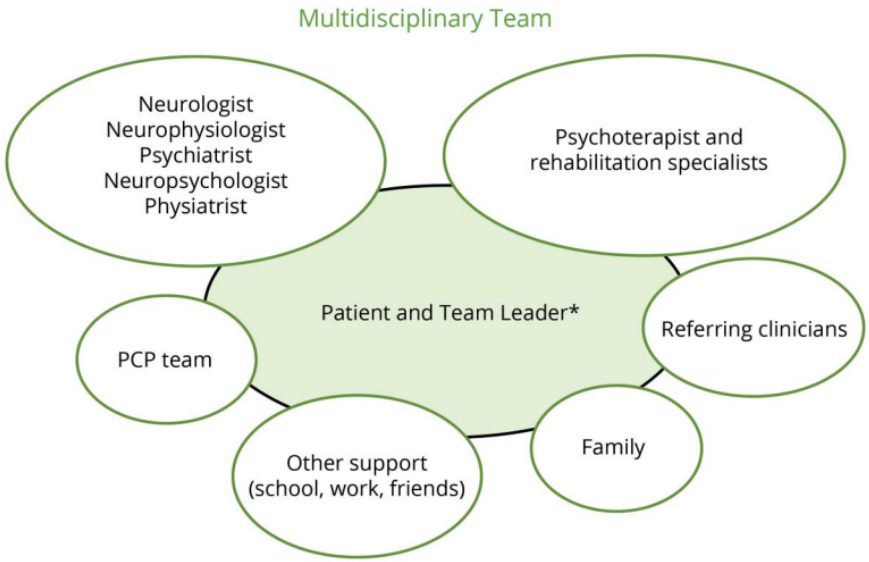
- Avoid iatrogenic harm (ie, invasive procedures, sedation, or **just in case** meds)
- Slow down, **communicate possible or likely FND empathically/effectively**
- **Set expectations about normal or nonspecific findings** if FND high in ddx and why you will be ordering tests in the ED
- Anchor in the here and now with gentle communication (esp. helpful for active "dissociative" seizures: "*we are taking care of you in the ED, the beeping you hear means your VS are ok. It's a bit cold here, we can get you a blanket. The shaking seems to be easing off and should stop any moment now…*")

Silverman et al, FND in the ED, Acad Emerg Med, 2021;
Anderson et al, Assessment and Acute Management in the ED, Semin Neurol 2019

Pts subjective experience in ED/ICU: physical restraints, clothing cut off/removed; repeated painful stimuli to test consciousness, insertion of catheters, ICU associated PTSD Reuber et al, J Neurol 2003; Seneveratne et al Epilepsia, 2018

Multidisciplinary team

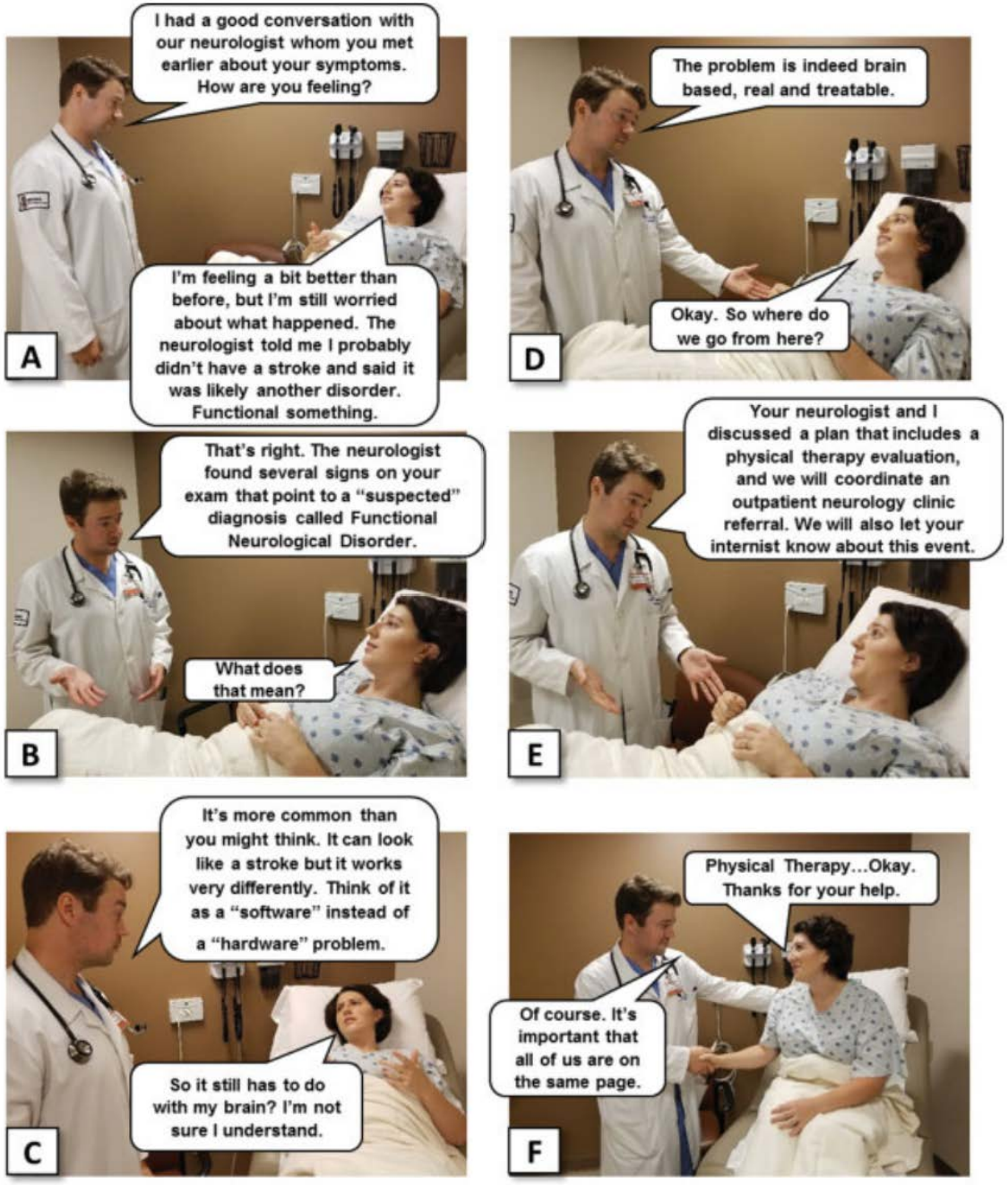
Figure The Ideal Multidisciplinary Care Team for a Patient With FND



Members of the team interact in a fluid nature as determined by the patient's needs. A neurologist may be the referring clinician or part of the multidisciplinary team.

*The Team Leader is the individual most engaged with the patient. This could be the PCP, neurologist, or one of the mental health providers.

Adapted from O'Neal, Baslet, Polich, Raynor, Dworetzky, Functional Neurological Disorder: The Need for a Model of Care, Neurology Clin Practice, April 2021

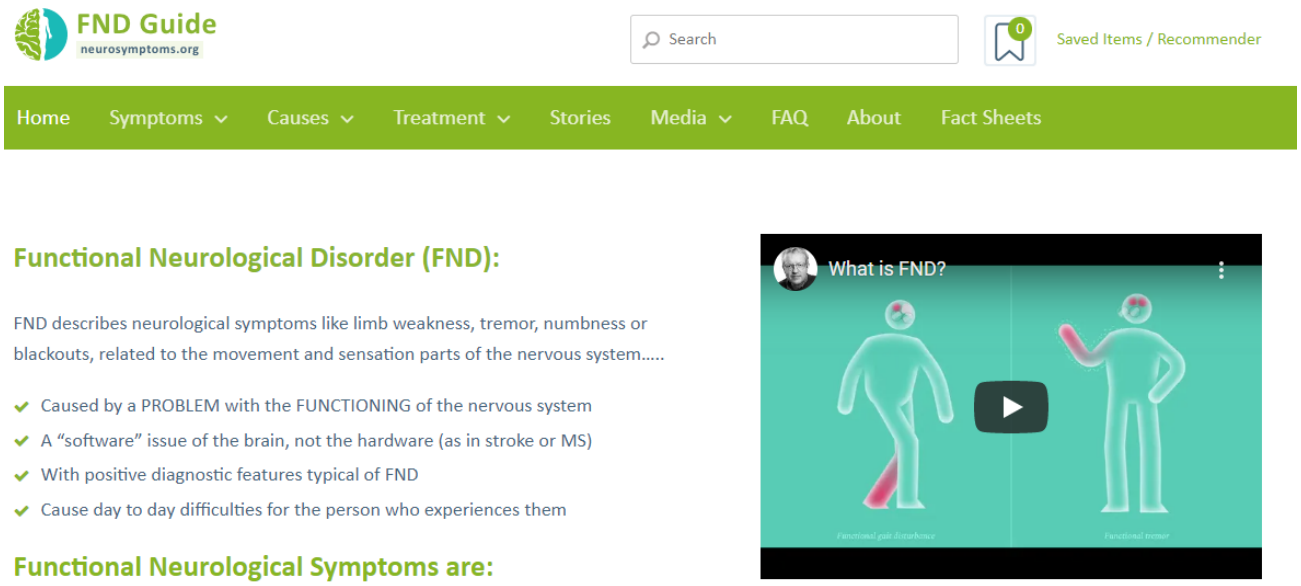


Communicating the possibility or likelihood of FND if it is strongly suspected

Anderson et al, Semin Neurology 2019

Education is critical for everyone

- **www.neurosymptoms.org** (UK) (FND); www.fndsociety.org/fnd-education
- **www.fndhope.org** (US, UK, Australia)(patient support groups)
- **www.nonepilepticseizures.com** (US – includes info in Spanish)
- www.nonepilepticattacks.info (UK)



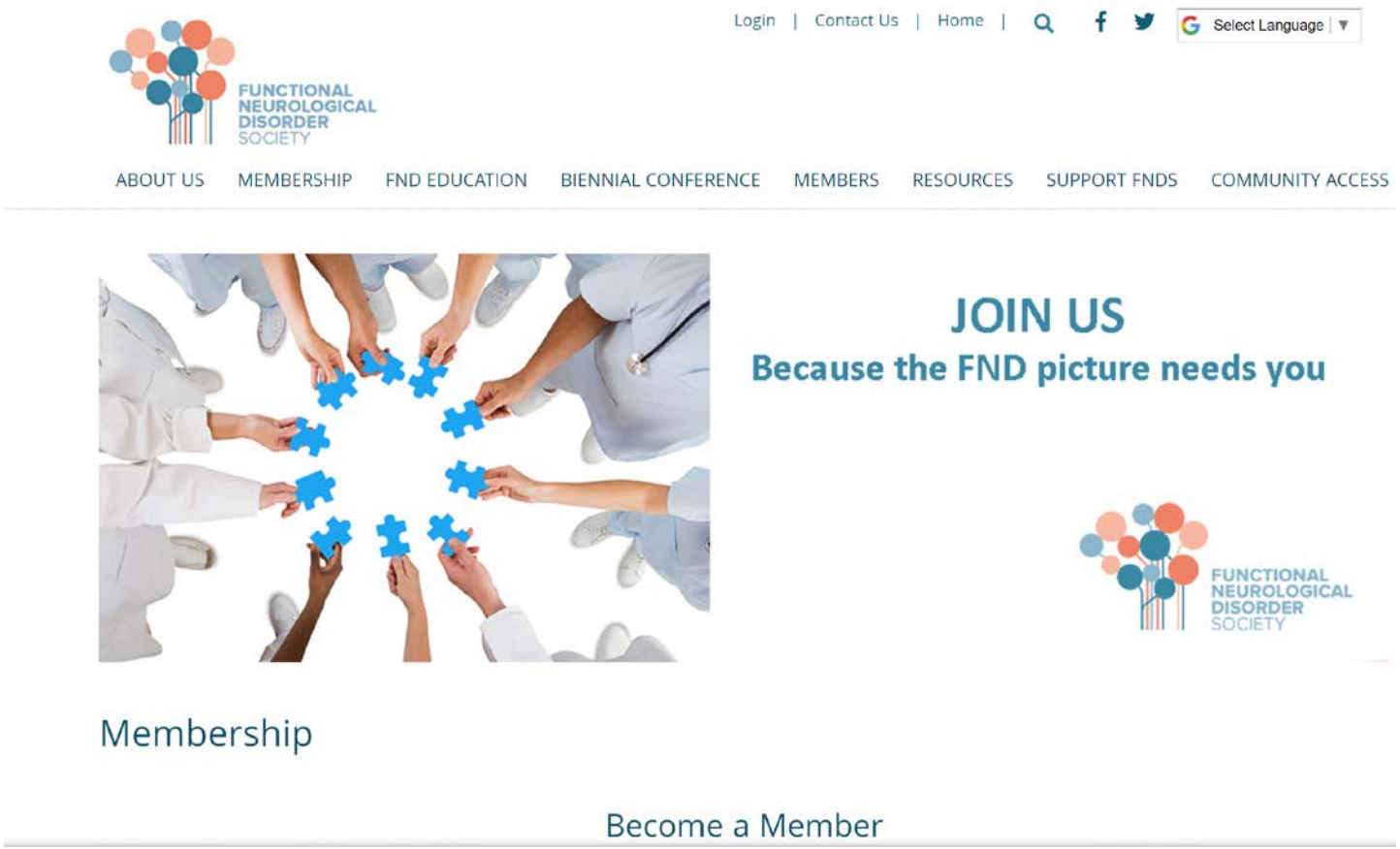
- More public awareness needed[2]

1. Popkirov et al, Hiding in Plain Sight: FND in the News, J Neuropsych Clin Neurosci 2019

Take-Homes: FND in ED

- FND is quite common in the ED
- Diagnose by "positive" features but know the pitfalls*
- More uncertainty in ED but mention possibility of FND
- Acute Rx, testing: often unavoidable (especially 1st time)
- Set expectations of incidental findings
- Nonjudgmental language(TIC)→*avoid stigma ("software")*
- If FND strongly suspected, communicate, provide written resources, and indicate that "stroke" was not found
- Refer for follow up, connect with outpt clinician

*ie, can have comorbid other neurological disorder



https://www.fndsociety.org/membership

First year free for trainees

Education/webinars available to members

Verona, Italy June 8-11, 2024 Next International FNDS Meeting