

## **Comorbidity influences in neuropsychiatry: Symptom plasticity constraints on etiology and treatment**

Under the benign influence of the warm and gentle ambience in the south-western corner of Andalucia, at the *Parador de Mazagón* (Huelva) venue, an inspiring presentation of scientific papers concerning “Implications of Comorbidity for Etiology and Treatment of Neuropsychiatric Disorders” was unravelled. Despite the Herculean burdens originating from complications arising from venue, travel and logistics, Tomas Palomo and the Fundacion Cerebro y Mente succeeded brilliantly in assembling an uniquely -renown group of leading clinicians and neuroscientists to present and discuss topics from the ‘Genetic variation underlying comorbidity’ and “Neuronal substrates of comorbidity”, through “Movement disorders in psychotic states”, “Cognition learning and comorbidity” and “Comorbidity in addiction with other psychiatric illness”, to the “Implications of comorbidity for etiology and treatment of neuropsychiatric disorders”. As one may suspect, both the order and content of these different sections were indeed beneficially chosen, unfolding a wealth of neuroscientific finesse to bolster the clinical realities and multitude of comorbidities.

German Berrios of the Dept. Psychiatry, Univ. Cambridge, Addenbrooke’s Hospital, Cambridge, UK provided a comprehensive discourse on the implications of comorbidity from a perspective of definition, epistemology and history, but also questioned both the tautology and quasi-synonymy of terms and applications. Several issues concerning comorbidity were confronted: (i) its nature, meaning and typology, (ii) challenges to neuropsychiatric nosology, (iii) relevance to disorder diagnosis, (iv) the extent to which it applies to symptom profiles and syndromes, and (v) its existence between psychological and physical expressions. In proposing a classification of comorbidity originating from etiological, interactional and coincidental types, it is to be borne in mind that current notions involve a ‘shift-of-focus’ from disease diagnosis to the symptom- profiles and their presumed genetic ordering. This approach, that utilised allelic association and linkage analysis methodologies, was presented by Janet Hoenicka of the Unit of Addictive Behaviours, Service of Psychiatry, Univ. Hospital 12<sup>th</sup> October, Madrid, Spain *et al.*, and her co-workers, using single nucleotide polymorphisms (SNPs). They have developed new technologies for studying dopaminergic and cannabinoid pathways involved in neuropathology, including alcoholism, schizophrenia and antisocial personality disorder. It appears there are about 20,000 different genes of which about 10,000 are expressed in the brain with candidate genes for schizophrenia at 1q [Disrupted in Schizophrenia 1 (DISC1)], 6q (RGS4), 7q (DTNBP1), 8p [(Neureglin, (NRG1)], 13q, 22g, and GRIK4 – kainate-type glutamate-R – directly disrupted on chromosome 14q. Douglas Blackwood of the Dept. Psychiatry, School of Molecular and Clinical Medicine, Univ. Edinburgh, UK confronted the issue of whether there

were genetic risk factors common to schizophrenia and depression. From family linkage studies, it was indicated that certain genes, DISC1 (Disrupted in Schizophrenia 1) and NRG1 (Neureglin 1), contributed to affective and non-affective psychoses. Other candidate genes in the disorders included GRIK4, a kainate glutamate receptor mapped to chromosome 11q23, and NPAS3 (Neuronal PAS domain protein 3), a transcription factor mapped to chromosome 14q. Isidro Ferrer of the Institute of Neuropathology, Pathological Anatomy Service, *Hospital de Bellvitge, Univ. Barcelona, Hospitalet de Llobregat*, Spain outlined the principles of quantitative monitoring of gene expression patterns with cDNA microarrays based on the notion of hybridisation between two complementary strands of nucleic acids, one fixed to a solid substrate and the other for analysis (cf. Schena *et al.* 1995), as a platform for studying differential gene expression between samples. Thus, several properties of nervous tissue, developmental and age-dependent variations, and functional and pathological status were considered. He analysed the application of DNA microarray technology to current practice using brain-banked tissues to recognise and minimise sub-optimal processing of brain samples and to correct pitfalls due to inadequate procedures. RNA preservation and RNA degradation effects on expression patterns were critical, since minimizing RNA degradation and improving detection of resistant RNA in postmortem brain is central to the efficiency and reliability of DNA microtechnology in the understanding of brain pathology (e.g. Buesa *et al.* 2004). Together these papers provided many clues to the genetic contributions to symptom profiles in comorbid disorders.

In his treatise of Reward Deficiency Syndrome (RDS), Ken Blum of the Dept. Physiology and Pharmacology, Wake Forest Univ., Winston-Salem NC, USA explored and unravelled the hypothesis that dysregulation of prefrontal glutamate outputs to the ventral tegmental area and nucleus accumbens underly progressive sensitisation and relapse in addiction and schizophrenia. Susan Totterdell of the Dept. Pharmacology, Univ. Oxford, Oxford, UK outlined the intricate synaptic interactions of aminergic terminals with cortical and subcortical neurons providing the anatomical basis of disorder comorbidity. Thus, the convergence of dopamine and cortical inputs onto single medium spiny neurons in the ventral striatum, and between differential cortical inputs to individual neurons, set the provides the basis for mechanisms underlying the interactive gating. She described both the for local and extrinsic connections in the prefrontal cortex and serotonin regulation of cortical neurons and midbrain dopamine neurons from the raphe nuclei. The concept of 'convergence' received further impetus with relation to circuits involving dopaminergic projections from the ventral tegmentum to prefrontal cortex and nucleus accumbens, and (ii) glutamatergic projections from the prefrontal cortex to the nucleus accumbens and back to the ventral tegmentum (see above), in schizophrenia and addiction, as related by Peter Kalivas of the Dept. Neurosciences, Medical Univ South Carolina, Charleston SC, USA. Central to these notions, was the often-repeated observation of poly-applications of an often-used model of schizophrenia- and drug addiction-like symptoms is sensitization to repeated administrations of amphetamine and related psychostimulants leading to a 'schizophrenia-like' psychosis. Thus, 'neuroplasticity' in the tegmental – prefrontal cortical – accumbens dopamine and glutamate circuitry is induced by repeated psychostimulant administration, a progressive neurodevelopment of sensitisation, underlying the dysregulation of the prefrontal glutamatergic output to the accumbens and tegmentum. The relevance of dendritic spines – stubby, mushroom and thin – their loss in schizophrenia and in the HPC-neonatal ven-

tral hippocampal lesion model of the disorder, with and the concurrent role of F-actin in all the post-synaptic density of dendritic spine changes ought to be was emphasised. Unsurprisingly, it should not be noted that the theme of a neuropathological “progressive sensitisation” of behavioural expression was remarkably recurring. These papers provide clues to the anatomical and neurochemical substrates and associated neuroplastic changes that may occur in comorbid brain disorders including substance abuse and schizophrenia.

In exemplifying neuropsychiatric comorbidity, it seems inevitable that the basic and clinical manifestations of schizophrenia and drug addiction, particularly in the context of behavioural neuroplasticity, assumed a singularly major influence upon the paths of investigation. Bita Moghaddam from the Dept. Neuroscience, Univ. Pittsburgh, Pittsburgh PA, USA maintained the notion of repeated amphetamine –focus on psychostimulant sensitization as a model of psychosis but shifted the ‘axis-of-regional-coercion’ locus of neuroplastic change to medial prefrontal cortex – orbitofrontal cortex neurons. This also shifted the focus to incorporate neurocognition ve propensities, by bringing about confrontations with consideration of competition between advantageous decision-making and short-term impulsive behaviours. Her notion of the “dDouble whammy” relies on prefrontal cortex (PFC) executive functioning, illustrated by reasoning and decision-making (Palomo *et al.* 2004), in opposition with the encoding of the salient value of internal and external stimuli by the orbitofrontal cortex. The electrophysiological basis of potent PFC regulatory influences upon limbic regions, particularly the amygdala, in affective and psychotic conditions, under the physiopathological duress of dopaminergic interference was and the effects of stress were described by Anthony Grace of the Dept. Neuroscience, Univ. Pittsburgh, Pittsburgh PA, USA. Besides a functioning PFC-amygdala circuit in affective states, hippocampus-PFC interactions within the nucleus accumbens are critical such that induction of long-term potentiation (LTP) interferes with the afferent drive to the accumbens from the other pathway (i.e. PFC or HPChippocampus) with DA dopamine exerting modulatory control. For example, in cocaine-sensitized animals, LTP is induced in the HPC-accumbens pathway with consequent disruption of the PFC-accumbens pathway control over goal-directed behaviour. Therese Jay of INSERM Unit E0117, Physiopathology of Psychiatric Diseases, St. Anne’s Hospital, Paris, France related how exposure to long-term stress induced a remarkable and long-lasting inhibition of LTP that could be prevented by the glucocorticoid receptor antagonist, mifepristone, thereby demonstrating the essential role of not only the HPC hippocampus (according to as described by Sapolsky, 2005 kian notions) but also the frontal cortex in the stress response cascade. Both antidepressant compounds, e.g., fluoxetine and tianeptine, and clozapine, but not haloperidol, restored stress-disrupted LTP, suggesting that the effective compounds share the PFC as their common target by restoring the functional balance at HPC hippocampus/PFC synapses, presumably impaired in depression and/or schizophrenia. The contributions of antidepressant agents to addiction and depression was maintained elaborated by Athina Markou of the Molecular and Integrative Neuroscience Dept., Scripps Research Institute, La Jolla CA, USA in studies examining the reversal of the anhedonia observed in laboratory rats under the influence of spontaneous nicotine/amphetamine withdrawal. Co-administration of SSRIs the serotonin-selective uptake inhibitors (SSRIs), fluoxetine or paroxetine, or the 5-HT-1A receptor antagonist, p-MPPI, reversed the threshold elevations of brain stimulation reward observed in nicotine-/amphetamine-withdrawing rats; under both acute and chronic conditions of administration, the DA dopamine transporter inhibitor,

bupropion, the metabotropic glutamate-2/3 receptor antagonist, LY341495, and clozapine, all reversed the threshold elevations observed in nicotine-withdrawal, suggesting commonality of substrates mediating depressive symptomatology under drug withdrawal relevant to psychiatric conditions. The overall picture created by these papers is one of complex cortical-subcortical interactions both influencing and influenced by monoaminergic systems as a basis for comorbid brain disorders.

In certain respects the presentation of an unusual, 'anti-intuitive' perhaps counter-intuitive, demonstration of drug-induced behavioural sensitisation, namely haloperidol-induced DAdopamine-activity reduction leading to behavioural inhibition (not activation as in conventional sensitisation and yet fulfilling all the criterion involving classification of the sensitisation process), by Werner Schmidt of the Dept. Neuropharmacology, Zoological Institute, Univ. Tuebingen, Tuebingen, Germany, provided the most astonishing display manifestation of neuroplasticity to be seen currently at the meeting. Remarkably, neither a low dose of haloperidol nor partial DA dopamine-depletion (50%) with 6-OHDA failed to abolish the phenomenon, but rather led to the gradual development of catalepsy with repeated testing. Further testing without drug in the case of haloperidol induced an extinction-like stepwise reduction. This highly persistent sensitisation response was shown to be susceptible only to contextual conditions; it was markedly context-dependent. These results would appear to open new horizons implicating neurodegenerative disorders, e.g. Parkinson's disease (PD), in the neuroplasticity normally associated with neuropsychiatric conditions and symptomatology in neurodegenerative disorders such as Parkinson's disease.

The dysfunctional influences of neurocognitive disruptions that contribute both etiological complexity and treatment inadequacy in neuropsychiatric comorbidities (e.g. Harvey *et al.* 2003) were addressed in several treatises that covered psychosis, depression, anxiety states and the far-flung distributions of multiple memory systems. Rick Beninger of the Depts. Psychiatry and Psychology, Queen's Univ., Kingston ON, Canada tested the cognitive abilities of schizophrenic patients treated with either typical neuroleptic compounds or atypical compounds, like clozapine or olanzapine or risperidone (cf. Beninger *et al.* 2003). The cognitive tests included: probabilistic classification learning or the Iowa gambling task, a tests of implicit memory respectively requiring intact striatal functioning (Knowton *et al.* 1996) and ventromedial PFC functioning (Bechara *et al.* 1997), and the Iowa Gambling Task or tests of Theory of mind, testing more explicit memory and requiring intact medial PFC functioning. Patients treated with typical or atypical neuroleptics were impaired on the probabilistic classification learning where the group treated with typical neuroleptics performed more like controls on the Iowa Gambling Task. On the Theory of mind task, schizophrenic patients treated with clozapine and/or olanzapine-treated patients performed as controls whereas those treated with typical neuroleptics or risperidone were impaired, implying a complex interaction between individual-cognitive abilities and the long-term effects of treatment. Klaus Ebmeier of the Division of Psychiatry, Univ. Edinburgh, Edinburgh, UK applied fMRI to investigate brain activity in patients with depressive episodes; depressed patients displayed an increased error signal in the rostral anterior cingulate cortex and parahippocampal cortex during a gambling task (cf. Ebert and Ebmeier 1996; Steele *et al.* 2004). In a visual working memory task, significant group differences were obtained in the medial orbitofrontal cortex/ rostral anterior cingulate cortex. Both

regions seem implicated in the cognitive deficits associated with clinical depression. These studies suggested that different aspects of cognitive functioning are affected in different brain disorders and by the medications used to treat them.

Jose María Delgado-Garcia of the Division of Neurosciences, *Univ. Pablo de Olavide*, Seville, Spain applied electrophysiological recording techniques during acquisition and retrieval of cognitive tasks to study associative learning in mice. Applications of NMDA antagonists were critical in preventing LTP induction, acquisition of learned eyelid responding and synaptic changes at CA3-CA1 synapses across conditioning. Mark Geyer of the Dept. Psychiatry, Univ. California San Diego, La Jolla CA, USA reported that deficits in Prepulse Inhibition (PPI), assessing the pre-attentive process of sensorimotor gating, deficits are associated with cognitive disorganization in schizophrenic patients and in laboratory animals with 'psychotic inductions' animal models of schizophrenia symptoms, e.g., neurodevelopmental interventions, acute NMDA antagonists, mutant animals with glutamatergic or other abnormalities, CRF corticotriphin releasing factor administration, etc. Nevertheless, these PPI deficits have been observed in a plethora of neuropsychiatric disorders: Obsessive-Compulsive disorder, Tourette's syndrome, Huntington's disease, Schizotypy, Bipolar mania, Panic disorder, Asperger's syndrome, 22q deletion syndrome, Lewy body dementia, Fragile X syndrome and under some conditions ADHD (attention deficit hyperactivity disorder and PTSD; post-traumatic stress disorder). Martin Cammarota of the Memory Centre, Institute of Biomedical Research, Pontifical Catholic Univ of the *Rio Grande Do Sul*, Porto Alegre, Brazil described the cascade of molecular events underlying retrieval of a simple step-down conditioning task and the memory for resistance to extinction involving functional NMDA receptors in addition to activation of several signalling pathways in the hippocampus, including those mediated by PKA, ERK1/2, p38MAPK and Src. On a similar note, Ivan Izquierdo of the Memory Centre, Dept. Biochemistry, Institute of Basic Health Science, Federal Univ. of the *Rio Grande Do Sul*, Porto Alegre, Brazil compared problems of memory arising from temporo-limbic and striatal malfunctioning by regarding instances of declarative or procedural memory tasks. His two major investigative thrusts involved: (i) reversal learning in the circular water maze task whereby the declarative component is altered but the procedural one maintained (but see also reference versus working memory), and (ii) inhibitory avoidance conditioning studies suggesting the 'shift of memories' over distributed systems due to tasks initiating further learning. Collectively, these studies revealed how different brain structures and signalling pathways contributed to multiple cognitive functions.

The etiological and interventional factors underlying the comorbidity of schizophrenia with substance abuse and addiction not only received a major focus but brought into consideration further aspects on the enigmatic nature of neuroplasticity. In tackling the prevalence of alcohol, nicotine and other substance abuse in schizophrenic patients, John Krystal of the Dept. Psychiatry, Yale Univ, New Haven CT, USA examined two hypotheses directed at this enhanced risk for substance abuse: (i) vulnerability for substance abuse reflects an independent risk process, i.e. a primary comorbid substance abuse disorder, and (ii) the risk of substance abuse may reflect patients' attempts to ameliorate subjective distress associated with the disorder, although genetic evidence indicates that substance abuse vulnerability is distinct from schizophrenia vulnerability. He reviewed and discussed notions concerning the 'self-medication model' of

substance abuse among patients and the significance of self-medicating positive and negative symptoms pertaining to subjective distress and cognitive dysfunction. Abuse potential in schizophrenia was a recurring theme, not least in the particular vulnerability for smoking and nicotine addiction where the genetic component poses much consideration (cf. Dalack and Meador-Woodruff 1996; Sacco *et al.* 2005; Smith *et al.* 2002 and 2005). The magnitude of substance abuse in schizophrenics would appear to be of the order: nicotine > heroin > cocaine > cannabis (the prevalence of nicotine abuse > 85% is remarkable), with patients possessing a 4.6-fold greater risk of any substance, and 3.3-fold greater risk of alcohol, abuse compared to controls. Thus, in the light of some of these statistics, the pharmacological management/intervention in schizophrenia and substance abuse examined by Alan Green of the Dartmouth Medical School, Lebanon NH, USA, offered intriguing new horizons. It appears that the substance abuse disorders occur commonly in schizophrenic patients with a comorbidity associated with increases in violence, hospitalisation, treatment non-compliance and overall deterioration in prognosis. He showed that typical antipsychotic agents showed a bad prognosis for substance abuse whereas clozapine reduced smoking. The percent remission attainment on alcohol abuse was markedly higher for clozapine (79%) than for typical neuroleptics (33%). It seems that clozapine influences the limbic loop system together with the striatal loop – basal ganglia system, thereby modulating the mesolimbic-mesocortical loop system to affect an anti-impulsivity, gratification intervention. Abuse control was shown to be of the order: clozapine > olanzapine > risperidone > typical neuroleptics. Joe Coyle of the Dept. Psychiatry, Harvard Medical School, McLean Hospital, Belmont MA, USA presented a remarkable treatise on the notion that the endophenotype of schizophrenia involves the hypofunctioning of a subpopulation of cortico-limbic NMDA receptors. It is well documented that low doses of NMDA receptor (NMDA-R) antagonists, e.g. ketamine, produce the positive, negative and cognitive symptoms of schizophrenia in normal healthy volunteers, as well as associated neurophysiological alterations, such as abnormal eye-tracking movements and abnormal event-related evoked potentials. Glutamate functioning is reduced in schizophrenic patients and this may be reflected in the low concentrations of glutamate in the csf cerebrospinal fluid of patients, as well as the reduced levels of D-serine. An alteration in metabolism appears to be associated with tryptophan conversion to kynurenine acid, the only endogenous NMDA-R antagonist. Putative risk genes, directly or indirectly, affect NMDA-R, and clinical trials indicate that compounds enhancing NMDA-R functioning at its glycine modulatory site reduce negative symptoms, and in the case of D-serine and sarcosine, improve cognition and reduce positive symptoms in patients receiving concurrent antipsychotic medications (cf. Krystal and D'Souza 1998). Pierre Sokoloff of the Pierre Fabre Research Institute, Castres, France discussed association studies implying a modest contribution of the brain-derived neurotrophic factor (BDNF) gene to schizophrenia susceptibility due to abnormal expressions of BDNF and its receptor TrkB in postmortem cortical tissue of patients. Consistent down-regulation of TrkB was accompanied by both up- and down-regulations of BDNF. Single infusions of BDNF increase responsiveness to cocaine cues and potentiate cocaine-seeking behaviour. BDNF-mediated effects, modulated through BDNF-controlled genes, such as the DA D3 receptor, sustain the long-lasting, neuroplastic changes that facilitate a variety of drug-oriented behaviours, including cue-signalled seeking and craving. Taken together with all the above implications of the deranged glutamate plasticity in substance abuse disorder, these illustrations of NMDA-R dysfunction provide a plausibility for shared comorbid neuropathological processes.



Abraham Weizman of the Research Unit, Geha Mental Health Center, Tel Aviv Univ., Tel Aviv, Israel examined the comorbid facets of schizophrenia and obsessive-compulsive disorder, reminding the heterogeneity of the former and the co-occurrence of the latter (estimated 7.8 to 25% of schizophrenic patients) in the context of clinical aspects, neurobiology and treatment. Several studies described a five to six stepped continuum ranging from obsessive-compulsive disorder through schizophrenia alone to the disorder combinations and their shared features, and along the path of drug abuse disorders-affective disorders to suicidal behaviour. Ongoing studies on the role of structure and function of the PFC are directed the clinical characteristics, brain abnormalities and dopamine/serotonin activity relationships. Obsessive-compulsive disorder precedes the diagnosis of schizophrenia with a predisposing incidence of Tourette's disorder, implying the same gene responsible for tics and obsessive-compulsive disorder; these various threads must reinforce implications of the relations to obsessional repetitive (dare one say, 'stereotypical' behaviours). Neuropathophysiological convergence was suggested by the therapeutic efficacy of antipsychotic agents and SSRIs in both disorders, and yet, the distinctiveness of each as clinical entities, both in the "pure" and "overlapping" gestalt, urges the phenomenological consideration of schizo-obsessive condition. Henry Szechtman of the Dept. Psychiatry and Behavioural Neuroscience, McMaster Univ., Hamilton ON, Canada reiterated the comorbid aspect of obsessive-compulsive disorder with a remarkably high incidence with other neuropsychiatric pathologies. He outlined a 'security motivation system' representing a biologically-primitive special motivation, activated by potential (rather than imminent) danger signals to 'self' or 'intimate-others', that engages a set of specialized species-typical behaviours that are meant to handle the threat. To attain a "switching-off" of the security motivation system, a self-generated affective state of knowledge or particular insight must occur, a satiety signal termed "Yedasentience". Obsessive-compulsive disorder develops from failure to generate or respond to the yedasentience signal: thus, patients persist in the prolonged repetitive sequences of security-related behaviours (checking, washing, locking, unlocking, counting) reflecting the strong motivational state characteristic of the disorder. The extreme affective nature of a high prevalence negative outcome of untreated depressive comorbidity in a hospitalised patient follow-up was described by Antonio Lobo of the Psychosomatic and CL-Psychiatric Service, *Hospital Clínico, Universitario*, Zaragoza, Spain from a Zaragoza sample. Of the 498 (70.2% of the original hospitalised sample) patients fulfilling inclusion and exclusion criteria, most presented "complex", severe physical conditions and several medical diagnoses. In the follow-up investigations (completed in two thirds of the sample), 35.2% of the index group and only 13.6% of the controls were rated as depressed ( $p < 0.001$ ); additionally, 74.1% of the depression group but only 40.9% of the control group presented a "poor outcome" [depression or mortality] ( $p < 0.001$ ). The study confirmed that the prevalence of depressive comorbidity in hospitalised medical patients is considerable and with a negative outcome: depression increases the use of medical services and decreases quality of life (Lobo *et al.* 2005). The purpose of these and other multicentre studies was to design intervention treatment strategies to improve negative outcome (Lobo *et al. in press*). These papers focused on the comorbidity of obsessive-compulsive disorder and schizophrenia, the mechanisms of obsessive-compulsive disorder and the comorbidity of psychiatric and somatic disorders.

Since i) there exists elements of controversy between epileptic and psychotic disorders, ii) electroconvulsive therapy (ECT) (therapeutic generalized seizures) is regularly applied in depression and mania and iii) several anticonvulsive agents are effective in bipolar disorder, the presentation of Tom Bolwig from the Dept. Psychiatry, Neuroscience Center, Copenhagen Univ. Hospital, Copenhagen, Denmark was provided an important perspective on the comorbidity between of epilepsy and several affective/non-affective disease states. He expressed the notion that temporal lobe epilepsy may initiate several psychopathological phenomena that may provide putative mechanisms of action in each case, i.e. temporal lobe epilepsy elements of bipolar symptomatology and ECT. Thus, the notion of "Forced normalization" implies that with the disappearance of EEG-configurations psychosis may develop. The "kindling" model of epilepsy, developed used in the his laboratory, shows that seizures may be blocked by a variety of anticonvulsant drugs and electroconvulsive seizures. A "kindling model of depression" was considered in the light of temporal lobe imbalance thereby enhancing/inhibiting impulse traffic in epilepsy and affective disorder. Thus, discrete HPChippocampus-hyperactivity in epilepsy patients free of EEG -abnormalities may be manifested as affective disorder and psychosis whereas whereas massive hyperactivity with induction of generalized seizures (essentially ECT) in non-epileptic patients with depression or mania is therapeutic. Norbert Müller's Müller of the Hospital for Psychiatry and Psychotherapy, Ludwig-Maximilians Univ, Munich, Germany presented an overview that provided a necessary bridge between the far-reaching psychoneuroimmunological discoveries and current findings from pharmacological, neurochemical and genetic studies in schizophrenia. One aspect concerned the role of glutamatergic hypo-functioning, as mediated by NMDA-R antagonism. Another concerns perinatal infection in the pathogenesis of schizophrenia, as expressed by an imbalance between Type I and Type II immune responses: the former partially inhibited and the latter over-activated. Inhibition of indoleamine dioxygenase, an enzyme located in astrocytes and microglia, is inhibited by Type II cytokinases so that tryptophan is predominantly metabolised by tryptophan 2,3-dioxygenase in the astrocytes that lack the neurochemical agents for normal tryptophan metabolism. Lack of kynurate-OHase in astrocytes allows build-up of kynurenate acid (see above, endogenous CNS NMDA-R antagonist) which is found together with an increase in tryptophan 2,3-dioxygenase activity in the CNS of schizophrenics. It would appear then that the immune-mediated glutamatergic-dopaminergic imbalance may be circumvented through selective intervention by anti-inflammatory cyclo-oxygenase-2 inhibitors that provide direct reduction of kynurenate acid to ameliorate the disease process.

Vicente Molina of the Dept. Psychiatry, *Hospital Clínico Universitario*, Salamanca, Spain and co-workers in Salamanca and the schizophrenia group of Tomas Palomo at the 12<sup>th</sup> October Hospital, Department of Psychiatry, Madrid have carried out longlasting longitudinal brain imaging studies on structural and functional aspects of schizophrenic brain imaging. Applying PET positron emission tomography and MRI magnetic resonance imaging techniques in 1<sup>st</sup> first episode and chronic schizophrenic patients at baseline and six-month follow-up, his group they have shown, in a series of studies, that risperidone induces an increase in visual area activity at resting, and a significant increase in grey matter volume in the occipital and parietal areas after two years. Clozapine induced a symptom-improvement associated increase in occipital activity accompanied by a decrease in basal ganglia and frontal activity, and, after two years, significant increases in grey matter volume in the frontal, occipital and parietal regions. Olanzapine induced



a substantial positive symptom improvement associated with increased occipital metabolism. Several others structural and functional changes due to long-term applications of atypical neuroleptics were described that prompt the interesting insight that even structural abnormalities in the disorder may, to some extent, be reversible. These studies, carried out over decades, represent a truly yeoman-like persistence that has only recently started to provide the group with the remarkable findings pertaining to the fate of atypical neuroleptics in the schizophrenic brain, and it is expected that a plethora of both interesting and important results are under examination.

Christine Barrowclough, Dept. Clinical Psychology, Univ. Manchester, Manchester, UK addressed the issue of alcohol and drug use by psychotic individuals, a prevalence estimated to be as high as 60%, and a formula for disastrous outcome, with symptom exacerbations, relapse, violence and suicide. She described the “Manchester Pilot Study” demonstrating that psychotic patients with substance abuse benefited from a sustained psychological approach, combining family motivational interviewing and cognitive behaviour therapy, to the ‘dual diagnosis problem-profile’. Similarly, Miguel Casas of the Dept. Psychiatry, *Vall d’Hebron* Univ. Hospital, Barcelona, Spain and co-workers set out to evaluate whether or not there are differences between patients with “dual diagnosis”, an intermediate category between mental illness and addictive disorder, and patients with a mental disorder or an addiction. The most prevalent pathology in “dual diagnosis” patients (one out of five inpatients) are alcoholism and affective disorders which account for 38.9% of the comorbidity, with alcohol abuse as the predominant problem, accounting for 79.6% of the “dual diagnosis” patients’ abuse. A high frequency of psychiatric disorder with substance abuse, presented by Marta Torrens from the Drug Abuse Unit, *Institute D’Atencio* Psychiatry, *Hospital del Mar*, Univ. *Autonoma de Barcelona*, Barcelona, Spain, was associated with high psychopathological severity, increased rates of risk behaviours with related infections, high psychosocial impairment (unemployment and homelessness) and an exaggerated number of violent and/or criminal behaviours. She reviewed the advantages and disadvantages, pros and cons of the available diagnostic manuals and tools, outlining a cornerstone of three categories: “primary psychiatric disorders”, “substance-induced disorders” and “expected effects” of the substances, implying expected intoxication and/or withdrawal symptoms not diagnosed as symptoms of a psychiatric disorder. The use of PRISM (Psychiatric research Interview for Substance and Mental disorders), a structured interview, has provided a suitable tool for assessment of comorbidity.

Four presentations dealt with aspects of neurodegenerative diseases of either idiopathic or drug-induced origin: Peter Reiderer from the Clinic and Polyclinic of Psychiatry and Psychotherapy, Dept. Clinical Neurochemistry, Univ. Wuerzburg, Wuerzburg, Germany, Moussa Youdim from the Dept. Pharmacology, Univ. Haifa, Haifa, Israel, Richard Kostrzewa from the Dept. Pharmacology, Quillen College of Medicine, East Tennessee State Univ., Johnson City TN, USA and our own presentation (i.e. Archer and Fredriksson). These papers lay outside the scope of neuropsychiatric comorbidity, as approached above, and will be dealt with elsewhere at greater length in a special issue of Neurotoxicity Research that will publish full-length papers from the meeting participants. Nevertheless perhaps a critical insight pertaining to the comorbid, neurodegenerative aspect of Parkinson’s disease (PD) and parkinsonism was provided by discussions of the Braaks’ theory (cf. Braak *et al.* 2003a and b) theory whereby PD-like brain disorders develop progressively over years and the loss of neurons encompasses both pre-sympto-

matic and post-symptomatic phases. Multiple neuronal systems are involved in sporadic PD with a putative etiology stemming from developmental progressive changes in a few susceptible types of neurons with essential synuclein-immunopositive Lewy neurites and Lewy bodies components. According to this notion, lesions occur initially in the motor nuclei of the glossopharyngeal and vagus nerves as well as anterior olfactory nervenucleus, from which nuclear greys and cortical areas become affected gradually, the disease process arising advancing in an ascending fashion. The anteromedial temporal mesocortex first afflicted, after which the neocortex, then the high order sensory association and PFC areas followed by first order sensory association/premotor areas and primary sensory/motor fields, each step tracing the course of brain pathology. From a perspective of neurologic-psychiatric comorbidity, Przuntek *et al.* (2004) have proposed that the motor symptoms in PD patients are preceded by the insidious onset of mild, unspecific, sensitive, vegetative, psychopathological, i.e. cognitive and perceptual, disturbances expressed by olfactory and visual dysfunction, with the consequent alteration of personal behaviour, e.g. reduced stress tolerance. They have described an initial premotor phase, originating in non-dopaminergic areas, a conflagration of onset of gastrointestinal-brain stem-associated and sensory deficits leading to motor symptom expressions and further pathological development. Taken together, these two notions present a concept incorporating diseases of the gastrointestinal tract and psychosomatic, implicating an unknown pathogen, whether viral or nutritional, in a genetically predisposed individual with a long-term disturbed enteric system, thereby encapsulating comorbidity of polypathogenic proportions.

Everyone (Speakers, participants, organisers, etc.) agreed that the seventh Biennial Meeting on Strategies for Studying Brain Disorders held by the *Fundación Cerebro y Mente* was a resounding success. The meeting met with and exceeded the Foundation's mandate of fostering a fertile exchange of ideas and experiences between experts in clinical and basic neuroscience with a goal of improving the understanding and treatment of brain disorders. The latest Meeting on the Implications of Comorbidity for Etiology and Treatment of Neuropsychiatric Disorders both integrated current understanding and pointed to new directions that challenge clinician and basic researcher alike. It was agreed that understanding neuroplasticity is central to eventually conquering comorbidity and that a future emphasis on symptoms rather than disorders may lead to new strategies for understanding the etiology and treatment of brain disease states.

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