Neurobiology of mental illness: from reductionism to integration

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From its inception until now, psychiatry has continually searched for knowledge of brain-behavior relationships and the neurobiological underpinnings of psychopathology. The tendency to view mental illnesses as brain diseases is not new and goes back to Hippocrates, being dominant in the nineteenth century. This theoretical tradition was interrupted during the first decades of the twentieth century by a predominant psychological vision, embodied in different theories such as psychoanalysis, and a range of behavioural, humanistic and cognitive perspectives. However, in the last forty years the tendency to view psychiatric patients as individuals who have some kind of brain disorder has grown to the point of being an almost indisputable truth. In the second edition of Biological Psychiatry, Michael Trimble [1] said that biological psychiatry has a long past—which establishes its respectability—but a short history—which establishes its scientificity. Indeed, this part of the story is relatively short and researchers all over the world continue to struggle for discovering the...
neuronal and neurochemical bases of psychiatric symptoms. The corollary of this brain-centered vision, which is now firmly rooted in the mind of most psychiatrists, and is at the core of the contemporary neuroscience thinking, is that the mind is simply what the brain does. Consequently, mental pathology is merely the behavioral consequence of identifiable neuromolecular abnormalities. However, we must dispute this kind of simplistic brain-centered reductivism, emphasizing that this view must be tempered with the notion that mental illness is multidetermined. This awareness should remind us the great density of causal factors involved in mental illness and prevent us from falling into a simplistic and linear causal thinking. The explanation of this complex causality, including inside and outside-the skin factors is now well addressed within disciplines such as critical neuroscience and social neuroscience.

The contemporary biological way of thinking mental illness is also favored by technological advances that permit us to see and compare the brain in action, in healthy individuals and psychiatric patients. This kind of epistemological stance, allows us to molecularize behavior to its lower determinants - genetic variants. However, the progress of genomic analysis did not respond to the expectation that psychiatric classification would become more etiologically-based, particularly in biological terms, and specifically on genetic grounds. In a way, it even had an almost opposite effect, showing that psychiatric diseases are complex phenotypes that are genetically influenced, but in which environmental influences also play a necessary role. Additionally, it was found that this genetic susceptibility result from a multiplicity of genetic variants of minor effect and some of larger magnitude of effect. Many of these variations are neither necessary nor sufficient to determine the disease and require an additional interaction with environmental factors to produce the manifestations that we call symptoms [2]. This is what we can observe, even in disorders with heritabilities over 70-80%, such as bipolar disorder [3] or schizophrenia [4, 5]. Thus, the post-genomic era brought with it a greater blurring of the boundaries between normality and disease. Peter McGuffin and colleagues [6] defined it as “a postgenomic era of polygenetic susceptibilities”. In this context, as Nikolas Rose pertinently stated, at the genomic level the traditional notion of normality has disappeared [7]. None of us is “normal” in the sense that we all carry genomic vulnerabilities to different conditions – “we are all asymptotically presymptomatically ill” [8]. Thus, behavioural phenotypes can be seen as quantitative traits that have a continuous distribution, at the extreme of which are the common psychiatric disorders [9].

However, we are still far from having a full knowledge of the biological mechanisms underlying the psychiatric disorders. Thus, we wanted to dedicate this supplement of the International Journal of Clinical Neurosciences and Mental Health to a wide range of topics related with the neurobiology of mental illness, some of which review the cutting edge of the technologic advances and others address areas that somehow have been neglected.

One of the major obstacles to progress in understanding the biological underpinnings of mental illness lies in the imprecision of its phenotypic definitions and lack of validity of the diagnostic categories currently used. This obstacle has fueled a vicious circle: the diagnostic categories do not have a direct correspondence with a specific biological substrate and consequently the research of their biological correlates is hampered, and has not been able to produce outputs with sufficient discriminative power to define biologically-based diagnostic categories. Thus, the need for biological markers which may have diagnostic, prognostic or treatment prediction value is pressing.

In this context, the paper of Bruno Manadas and co-workers Circulating biomarkers in schizophrenia – a proteomics perspective present a review on proteomics studies performed in body fluids of schizophrenic patients, using mass spectrometry to search for protein markers. The authors stress that emerging proteomic platforms have facilitated the identification of several biomarker candidates by the simultaneous measurement of thousands of proteins. However, the authors warn that due to the complex and multidetermined nature of schizophrenia it will be necessary to move towards integrative models that simultaneously combine the information from multiple omics-markers (genomics, proteomics, metabolomics) and a combination of imagining techniques, neuropsychology, and electrophysiological data to identify a specific signature of the disease.

Genetics/genomics is one of the oldest and most promising source of biological markers capable of helping to clarify the etiology and pathophysiology of psychiatric diseases showing high heritability. In this context, the paper of Manuela Grazina and coworkers Association of p.Val158Met COMT polymorphism with paranoid ideation in drug addicts report differences in genotype and allele frequencies of COMT variants between controls and drug abusers, with the later having a higher frequency of the Val allele. Additionally, the authors also sought to establish correlations between phenotypic data and genetic variations reporting an association between Met/Met genotype and a higher risk of developing paranoid ideation in drug abusers. The authors speculate this is “probably due to the lower enzyme activity that leads to higher synaptic dopamine levels”.

Another promising source of biomarkers is neuroimaging. Two papers in this issue review this topic. The first is the paper of Miguel Bajouco and colleagues The quest for biomarkers in Schizophrenia - from neuroimaging to machine learning reviewing different modalities of neuroimaging studies, which may be able to provide relevant biomarkers in schizophrenia, and describing the current application of novel machine learning methods to the analyses of imaging data. As the authors underline, this new approach may allow the translation of neuroimaging findings into...
potential biomarkers enabling the prediction of clinical outcomes at the individual level, and the development of personalised treatment strategies. The second paper in the area of imaging related biomarkers is “Neural connectivity in youth at-risk for Bipolar Disorder: a review of functional magnetic resonance imaging studies” from Vitor Santos and colleagues. The authors review the literature on fMRI studies that employed measures of functional or effective connectivity or network based statistics in individuals at-risk for bipolar disorder. Ten studies focusing on 4 functional imaging domains were identified, namely emotion processing, affective cognition, reward processing and resting-state. The authors concluded that three frontolimbic dysconnectivity patterns emerged as putative risk biomarkers: altered functional connectivity between amygdala and ventrolateral prefrontal cortex (PFC); amygdala and anterior cingulate cortex, and between anterior cingulate cortex, ventrolateral PFC and dorsolateral PFC.

In their paper “Facial emotion processing in schizophrenia: a review of behavioural and neural correlates” Joana Grave and co-workers carried out a review of the behavioural and neural correlates of one of the most important components of social cognition in schizophrenia: emotion perception. The authors emphasize that, in this clinical condition, the deficits in the interpretation of the emotional expression of others, and of social cognition globally, contribute more to the social impairment of these patients, than neurocognitive deficits. Thus, in addition to the existing neurocognitive rehabilitation techniques, the development of psychosocial interventions specifically aimed at improving deficits in social cognition can contribute decisively to the recovery of these patients.

Sarrana Belgrave and co-workers in their paper “Estrogen and schizophrenia in women: animal models lend a hand in understanding cognition” focus on the effect of estrogen on symptom onset, illness course, and possibly on cognitive deficits in women with schizophrenia. Research on the role of estrogen in schizophrenia reveals many inconsistencies. However, as the authors point out, it is worth to further investigate this topic, particularly with animal models, in order to better understand the neuromodulatory effects of this hormone, and its role as modifier of the clinical characteristics of the disease. Also relevant are the therapeutic implications that this hormone may have, namely indirectly by the knowledge of the mechanisms it exerts on the various neurotransmitter systems.

Claudia Pereira and co-workers present a paper “The ups and downs of cellular stress: the "MAM hypothesis" for Bipolar disorder pathophysiology” which is a detailed and updated review of the molecular mechanisms of cellular resilience to stress that may be involved in the pathophysiology of bipolar disorder (BD). These mechanisms underline the role of stress-response mediators such as Mitochondria-Associated Membranes (MAMs). The authors present the evidences supporting the “MAM hypothesis” for BD pathophysiology which involves Ca2+ dyshomeostasis and cytoskeleton abnormalities, changes in the ER stress responses, mitochondrial dysfunction and oxidative stress, proteostasis (autophagy) impairment and inflammasome activation, as significant events leading to diminished cellular resilience to stressful conditions. This hypothesis may open an innovative avenue for new drugs design, and at the same time constitutes a new field of possibilities to develop biomarkers for a more accurate and earlier diagnosis and/or evaluation of therapeutics response.

The intricate web of causality in mental illness includes necessarily the complex bi-directional interactions that the person maintains with its environment. In this context, the paper of Jorge Valderrama and co-workers. A relationship between early life stress and depression: the role of the serotonin transporter gene polymorphism (5-HTTLPR) pertinently addresses the relationship between early life stress and depression. The authors review the evidence on the factors that might explain how certain 5-HTTLPR genotypes interact with early life stress to produce sensitivity to stress and adulthood depression, acknowledging that results from the literature are contrasting. However, it is relevant to maintain this line of research, because examining the role of 5-HTTLPR and its relationship to depression may greatly increase our understanding of how the environment and genes might interact to produce altered biological and cognitive processes in an individual.

The complex nature of the causality of psychiatric disorders is also well illustrated in the case of eating disorders (ED) which are the result of the interaction of cultural factors related to body image and patterns of eating with neurobiological mechanisms. The paper of Cristiana Marques and co-workers “Psychological risk factors, cognitive-contextual approaches and neural correlates in eating disorders: An integrative review” highlight that ED are influenced by a large set of environmental and social factors, also acknowledging that ED have important biological and psychological determinants. The authors review the literature on ED concerning key components for the development and maintenance of ED, i.e. psychological processes such as rumination, experimental avoidance, cognitive fusion, self-criticism, shame and their neuroimaging/electrophysiological studies correlates. A growing body of research has shown abnormalities in neural systems underlying decision-making and reward, emotional and body image processing, involving structures such as the dACC, insula, precuneus/parietal and cerebellum, as well as frontal regions such as the medial, dorsolateral and ventromedial PFC. The authors also emphasized that contextual cognitive-behavioural approaches can interrupt the effects of maladaptive processes and consequently diminish eating disordered symptoms, improving psychological flexibility, well-being and quality of life.

Another area of interaction between the environment and the individual that may have psychiatric implications is through the impact of infectious and parasitic agents. The interesting paper by Penelope Georgakopoulos and co-workers “Toxoplasmosis and Psychosis: Environment makes
a difference reminds us of a relatively overlooked topic - toxoplasmosis and psychosis. The authors review the role of *Toxoplasma gondii* infection in association with psychiatric illnesses, stressing that toxoplasmosis could be related to developing a psychotic disorder. The study of the mechanisms by which infectious and parasitic agents act may shed some light to the clarification of the pathophysiology of diseases such as schizophrenia and other psychotic disorders.

Taking into account that the etiology of psychiatric illness is extremely complex and largely unknown, effective therapeutic strategies have been difficult to find. Thus, the emergence of new therapeutic options is always viewed with great expectation. The paper by Joana Andrade and co-workers *Neuromodulation in Psychiatric disorders: recent findings and clinical implications* reviews the evidence for the therapeutic efficacy, in several psychiatric disorders, of promising techniques that use neuromodulation, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS).

Discovering the etiology of mental illness has proved to be a long and arduous task that is far from over. It is clear that its multifactorial nature makes the path winding and fraught with difficulties. However, it is also true that in the neurobiological field, research strategies that have been advantageous in the past may not be contributing to the solution in the present. Excessive reductionism may have been useful at a particular point in time, but it is also responsible for an excessive dispersion of research, both at the interdisciplinary and intradisciplinary levels, scattering the findings in multiple pieces and bits, not allowing a comprehensive and inclusive view. Now, the motto must be integration, allowing the combination of multiple areas into integrative projects and the exploration of multiple data sources. Only then will we be able to proceed towards the unravelling of the neurobiological basis of mental illness.

**Competing interests**

The authors declare no conflict of interest.

**References**