Editorial

Con Brioso E Rigore! – Understanding the Neurobiology of Schizophrenia Spectrum Disorders

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One of the authors (KS) had finished his daily ward round with the multidisciplinary team in an acute inpatient ward a few moments earlier, before mulling over the contents of the present May issue of the AAMS. The care team just had a family session with the parents of Samantha and their string of questions, which concomitantly added to those in the treatment team, still reverberated within his head.

Samantha has 10-year a history of schizophrenia and was recently readmitted for relapse of her symptoms, which included the belief that strangers in her vicinity were controlling her using special waves; auditory hallucinations; and intermittent experiences of tactile hallucinations accompanied by decline in her ability to tutor her students. Within the multidisciplinary team, there were reflections on the frequency and co-existence of non-auditory hallucinations in Samantha, how these symptoms related to her previous and current clinical presentations and treatment outcome, as well as how her relapses may be better prevented and managed. Like all concerned caregivers, her parents had also posed searching questions, such as what caused her illness and attentional and memory lapses, and whether her illness or treatment can affect her brain over time.

Notably over the last two decades, we have seen extensive and intensive research studies of the neural mechanisms underlying psychiatric conditions such as schizophrenia spectrum disorders, in such diverse areas as genetics, molecular biology, neuroimaging, neurocognition, animal models, and more recently, lipidomics, proteomics and metabolomics.[1-4] Whilst these investigations have improved our understanding of the pathophysiology of schizophrenia, precisely those questions posited by the multidisciplinary treatment team and caregivers of Samantha remind us again of the need for a deliberate integration of these research findings and iteration between laboratory study and bedside applications. In this regard, the devotion of the current Annals issue to the theme of 'Neurobiology of Schizophrenia Spectrum Disorders' is especially timely.

The papers appearing in this issue not only seek to consider relevant clinical questions that should continue to be asked, but also strive to ponder the progress made in these neurobiological domains, and their clinical implications. The commentary by Heckers emphasises the importance of neurobiological substrates in validating the different nosological subtypes within the rubric of schizophrenia spectrum disorders. This is pertinent in the context of the current unstinting efforts of the APA DSM-V Task Force[5] to critically evaluate the criteria of these severe psychiatric conditions, which will culminate in a revised and hopefully improved version of the manual soon.

One of the bugbears of research in schizophrenia is the phenotypic heterogeneity, hence the call for use of 'intermediate phenotype' or 'endophenotype' rather than the syndrome as they presumably lie more proximal to the genetic architecture of schizophrenia. Hui et al review the literature with regard to the use of neurological soft signs as specific endophenotypes for research in schizophrenia and question their validity, usefulness and feasibility for such a purpose. Lewandowski et al report the rates of tactile, olfactory and gustatory hallucinations in their study sample within a psychiatric hospital and clinical correlation with other phenomena, highlighting the need to understand the clinical profiles of our patients. Such knowledge can potentially lead to better phenotyping of patients with the benefit of more accurate delineation of underlying genetic relations.

In terms of understanding biological mechanisms in schizophrenia, Ho et al summarise the current progress pertaining to genetic studies including state of the art genome wide association studies (GWAS) and copy number variation (CNV) analyses. A number of GWAS and CNV studies have pointed towards possible susceptibility genes[6-8] although the findings need further replication in different populations. Wood et al review the evidence for oxidative stress in schizophrenia and proposed research into the use

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of agents such as N-acetylcysteine that may enhance the glutathione system, which is the predominant free radical scavenger in the brain.

What are the neuroanatomical changes in the brain in relation to duration of illness and treatment? Chan et al attempt to answer part of the question, and found that grey matter decreased in a distributed network involving both cortical and subcortical regions, prompting more research into the effect of regular treatments on brain structural changes, and their interactions with illness over time. Winton-Brown and Kapur point out the difficulty of extending group results found in most neuroimaging studies to the individual patient. To detect more meaningful differences, there is a need for multicentre collaborations to enlarge the sample size and for developing multivariate approaches to elucidate the relations between the different brain regions. Pantelis and Wood remind us about the most consistent clue in schizophrenia, that is, the heterogeneity of brain imaging findings, and raise the thought provoking idea of mapping developmental trajectories using multimodal imaging approaches as an advance over existing strategies.

In terms of cognition, Keefe and Kraus argue that as the breakdown of the memory prediction system can lead to symptoms such as cognitive deficits seen in schizophrenia, specific tests of memory prediction may be assessed to determine whether they are accurate in predicting the onset of psychosis. Tan ponders the progress made using imaging genetics paradigms to understand the relation between genetic effects and brain function. Dawe et al summarise the animal models available to study the different symptom domains, and the challenges in extrapolating results from animal studies to the clinical manifestations seen in our patients.

A thoughtful integration of the findings from genetic, imaging, neurocognition and animal model research holds the potential for new drug discovery, the development of better interventions, as well as the selection of specific treatments in an era that promises personalised medicine.[9] Even in monozygotic twins, the risk of one twin sibling developing schizophrenia when the other has schizophrenia is only 50%. This outcome shows that non-genetic factors are equally, if not more, important in their interactions with neurobiological factors in the natural history of schizophrenia spectrum disorders. The review by Lim et al underscores the role of psychosocial risk factors, and their interactions with stress induced dysregulation of the hypophyseal-pituitary-adrenal axis, in the pathophysiology of these psychiatric conditions.

In reality, the papers in this issue reflect only a snippet of the tremendous amount of research activity around the world, all aiming to elucidate the neurobiology of schizophrenia and related conditions. Importantly, the papers represent the vigour and rigour of researchers and clinician scientists in trying to better understand the neural basis of schizophrenia spectrum conditions. This indomitable spirit must continue.

Before KS left the ward, Samantha's parents asked the caring team whether Samantha would recover fully from her psychiatric condition. The team was careful in its reply, as it wanted to convey hope and optimism while ensuring that it did not over-promise a positive outcome. There is some way to go in our search for better treatments for this crippling illness. The parents' impassioned plea for the team to consider the best treatments for Samantha reaffirmed our conviction that all the lines of research, which begin with the patient and his or her illness, ultimately have to answer tough questions regarding their real potential to guide the understanding, prevention and management of illness onset, progression, relapse, and treatment resistance of schizophrenia spectrum disorders. On that note, we hope that you will enjoy reading the papers in this issue just as much as we have enjoyed editing them.

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