Editorial

Thinking in schizophrenia: perspectives from community clinic to neural circuitry

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Since 1992, World Mental Health Day has been commemorated every October 10th. It aims to promote mental health advocacy and education, which are certainly important quests, given the high morbidity, disability and stigma associated with psychiatric problems. In Singapore, the point prevalence of mental health problems is suggested to be about 16.6%[1]. Schizophrenia, a more serious disorder and a focus in this editorial, affects about 1% of the population worldwide. However, it appears that only some 10% of those with mental health problems here seek professional help[2]. Cultural attitudes and stigma remain as barriers to care, often delaying treatment[3,4]. Major challenges therefore remain on the road for psychiatry, in terms of meeting the clinical needs of patients, and better understanding the biological, social and cultural underpinnings of mental illness to meet these needs. In this perspective on the cognitive deficits of schizophrenia, recent epidemiological, functional neuroimaging and genetics studies of local interest are highlighted and framed in the context of advances in the world literature. There is cause for optimism that enhanced efforts to bridge the clinic and scientific enterprise could one day lead to improved treatment strategies. Concurrently, efforts need to be advanced in the psychosocial domain, particularly with families, the workplace and in destigmatisation.

Schizophrenia, like many psychiatric disorders, is often misunderstood as having little known pathophysiological basis. It is, in fact, a complex disorder, with a myriad of clinical symptoms, and demonstrable involvement of numerous cognitive processes, neural circuits, neurotransmitter systems, and genes. This is often overshadowed by its psychosocial ramifications as it characteristically strikes at a critical period in one's life, in early adulthood, when foundations are being laid for independence, intimate relationships and careers. In its chronic course, some 10% of sufferers end their lives by suicide; and it is estimated that only 30% to 40% of patients are eventually able to lead relatively normal lives, whereby persons are able to live independently and maintain a job[5,6]. Heavy loads rest on patients, families and society, making schizophrenia one of the leading sources of economic burden and suffering[7].

A study on the quality of life (QOL) of local patients found that even those with relatively good outcomes, who were living with their family without need for hospitalisation for more than ten years, had poorer QOL than general practice outpatients living in the same area[8]. Dissatisfaction with and poorer participation in family relationships, and dissatisfaction with emotional well-being were key factors predicting poorer QOL in patients. Factors associated with cognitive impairment, such as fewer years of education, and poorer reading abilities, were significantly over-represented in patients. This emphasises a linchpin of its pathophysiology, that of cognitive deficits, which strongly influence functional and occupational outcome, even after acute psychotic episodes have abated[9]. Conceivably, cognitive deficits also lead to difficulties processing and responding to nuanced stimuli relevant for effective social or family interactions[10], and result in social disabilities and poorer QOL.

Cognitive deficits and other symptoms develop early in the course of schizophrenia, even before the first psychotic episode. In detailed studies of first-onset psychosis patients, it was found that many had already manifested mood and anxiety symptoms, social withdrawal, odd mannerisms, deterioration in school results and perceived disturbances in attention, concentration and memory, which occurred years before the onset of psychosis[11]. Compared to unaffected children with nearly identical primary school leaving examination (PSLE) results at the age of 12 years, individuals who subsequently developed schizophrenia at the ages of 18 to 24 years had greater deterioration in general certificate of education (GCE) "O" level results by the age of 16 years[12]. Another local

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study described similar comorbidity with mood and anxiety disorders at the first psychotic break[13]. These findings, consistent with that reported elsewhere[14-16], suggest that the trajectory of illness development involved a relatively greater deterioration in cognitive functioning several years before psychosis onset, possibly interacting with brain systems implicated in adolescence, mood regulation, anxiety and stress.

Complementing worldwide efforts to investigate the neurophysiological basis of this cognitive deterioration, we studied working memory as well as its subprocesses of maintenance and manipulation in first-episode schizophrenia patients using functional magnetic resonance imaging (fMRI)[17]. Working memory enables information to be kept online and manipulated in the brain, which is crucial for our ability to have coherent thoughts, speech and goal-directed behaviour. It is impaired in chronic schizophrenia and could be a critical factor explaining many cognitive deficits[18]. Our results showed that early in the illness, patients evidenced patterns of subtle prefrontal cortical dysfunction on fMRI, although overt measures of working memory performance accuracy did not reveal deficits. Higher level manipulation taxing the dorsolateral prefrontal cortex appeared particularly vulnerable. It resulted in a relative failure of neural activation in patients, who, presumably because they were at an early stage of the illness, were able to compensate for this via increased neural activation from another region, the ventrolateral prefrontal cortex. Somewhat similar vulnerability to more complex tasks occurred when normal individuals were administered low doses of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine and scanned with fMRI[19]. Thus, working memory deficits in early illness seemed to critically involve this NMDA-related circuitry. These results extend work on the NMDA receptor in schizophrenia[20], working memory[21], adolescence[22], and its interaction with other neurotransmitters in schizophrenia[23,24]. It is also consistent with recent findings of promising schizophrenia candidate genes[25]. For example, GRM3 on chromosome 7q, which codes for a metabotropic glutamate receptor that is related to the NMDA receptor, gives rise to similar changes in working memory prefrontal activation measured with fMRI[26].

Complex pathways linking susceptibility genes, associated proteins, neural circuitry, cognition and behaviour undoubtedly occur in schizophrenia. These will be elaborated with increasingly fine detail in the near future. Ultimately, the translation of these discoveries to diagnostic, early intervention and medication strategies based on an individual's genotype, neuroimaging and clinical characteristics might be possible. In steps towards such a goal of personalised medicine, the efficacy of antipsychotics on patients' working memory and prefrontal physiology have already been shown to interact predictably with dopamine genotypes[27]. Local researchers have also identified dopamine receptor polymorphisms that increased risk for tardive dyskinesia, a disabling side-effect of antipsychotic medications, in Chinese patients[28].

With the convergence of genomic, imaging and clinical technologies, the outlook for improved treatments of schizophrenia appear optimistic, although the human brain certainly does not yield its secrets easily and the work ahead should not be underestimated. This brief overview is necessarily limited in outlining the vast scope of advances in the field of cognitive research in schizophrenia, but hopes to give the reader a sense that the pathophysiological bases of mental illness is being defined with increasing detail. However, while keeping apace with the glitter of molecular and imaging advances, we also need to be reminded that strategies in the psychosocial realm can play important, possibly immediate roles. Research shows that family relationships, for instance, present foci for intervention which could improve QOL[8]. Stigma places the patient at considerable disadvantage socially and occupationally, delays treatment, and leads to shame, unemployment or termination of employment. Jobs confer some degree of self-esteem, indirectly related to QOL, whereas low educational attainment and poor cognitive abilities make it less likely that the sufferer will get a job in view of the emphasis on paper qualifications. Sympathetic employers need recognition, support and respect.

Understanding that subtle biological changes in the brain account for some of the social and cognitive deficits of the illness could go some way towards alleviating the "blame" levied on patients and family. Traditionally an under-serviced field, there is today a global resurgence of translational research in psychiatry and the neurosciences. Its mission, therefore, lie not only in generating clinically relevant knowledge about molecules and neural circuits, but also in linking with community healthcare, demystifying mental illness, instilling hope, and training and supporting generations of clinician-researchers crucial in the continuation of this meaningful work.

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