Editorial

Thinking and Schizophrenia: Challenges and Opportunities

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World Schizophrenia Day falls on 24 May. Schizophrenia is a devastating brain disorder affecting about 1% of the population worldwide. With typical onset in late adolescence and early adulthood, it is for most patients a chronic relapsing psychotic illness, with persisting cognitive deficits that impair return to premorbid social and occupational function. Medications effectively reduce psychotic symptoms like hallucinations and delusions. However, they do not impact cognitive deficits and negative symptoms. So, antipsychotic medications have not led to further improvements in functional outcomes. The antipsychotic pharmacopoeia has increased the choices from which doctors and patients can collaborate on individual medication tolerability and treatment compliance, but each drug has largely similar efficacy (with the exception of Clozapine). With most spheres of cognitive and social functioning impaired in schizophrenia, young lives are often derailed and return to full employment difficult. In some cases, there are complications of alcohol or drug problems, even violence and suicide. Patients also have poorer physical health and reduced life expectancy. The unvarnished reality of this brain disease fuels, rightly or wrongly, the stigma attached to it.

There is, nevertheless, legitimate prospect for optimism. Healthcare professionals and researchers have a choice where they devote their life's work. Thankfully, increasing numbers have dedicated it to caring for these patients and discovering new knowledge about this illness. Important efforts have been made in improving the mental healthcare system to enable (and encourage) patients to seek treatment early, whether in the first illness presentation,[1] or in relapse.[2] These efforts have real impact in reducing social and family disruptions from active psychosis. At the least, they reduce the damage to the already limited social networks patients ultimately end up with.

Research to understand enough of schizophrenia to alter its course is proceeding with several important paradigm shifts that could accelerate progress. These have been well articulated recently elsewhere.[3] In what follows, I highlight several research perspectives I think might be particularly relevant to the Asia Pacific region that Singapore is part of.

Schizophrenia as a Complex but Solvable Genetic Disease

We are probably near the end of the beginning of the genetic revolution.[4] Genome-wide association studies have yielded important new genetic mechanisms for a host of eye, metabolic and inflammatory bowel diseases. It has been more challenging for neuropsychiatric genetics. Until several years ago, there had been few replicated genome-wide signals associated with schizophrenia. In part, this could have been because our broad multi-symptom definition of disease would map more imprecisely onto specific genetic brain mechanisms of dysfunctional information processing, than would for example the pathological tissue definitions of Crohn's disease map onto the genetic mechanisms of inflammatory bowel disease. Hence, the power of the statistical association in neuropsychiatric genetics is diminished. Nevertheless, with pooled patient sample sizes now into the tens of thousands, genome-wide studies of schizophrenia have begun to yield replicated new targets,[5] with promise of more to come soon as more data sets are combined. These discoveries will begin the longer road to tease out their precise roles in the developmental pathogenesis of disease and cognitive dysfunction, and from there perhaps some rational basis for improved treatments.

The genome-wide association studies of schizophrenia also show that the risk effects at the level of each common genetic variant is small (odds ratio ~1.10).[5] However, this might be expected since genes do not directly code for, say, hearing of voices. Instead, genetic variants code for subtle changes in how proteins are expressed or regulated in brain cells, which then alter the response of neural circuits to environmental perturbations during childhood and adolescent development.[6] Twin studies have implicated higher cognitive function—critical for processing abstract information and complex social cues that are dysfunctional in schizophrenia—as being particularly heritable characteristics related to schizophrenia.[7] These brain functions are impaired relatively early in disease.[8] Functional neuroimaging of the genetic influence on these very brain circuit functions evidence much larger effects

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than the association with schizophrenia.[9] Thus, more direct measurements of human brain function using imaging technologies would be important in the efforts to elucidate the genetic brain mechanisms of schizophrenia.

It may also be worth noting that genes do not necessarily respect disciplinary boundaries, and much can be learnt from the genetics of diverse disease systems. The same genetic variation implicated in cellular expression relevant to cancer biology may play a role in the development of brain systems. For example, the same oncogene AKT1 genetic variation that influences expression in lymphoblasts[10] and response to gefitinib in non-small cell lung cancer[11] also alters its protein expression in prefrontal brain tissue.[12] Because AKT1 couples dopamine D2 receptor function in neurons, this same variant influences a host of prefrontal and hippocampal functions implicated in schizophrenia, as well as brain responses to antipsychotics.[13,14] But the specific allele implicated in schizophrenia is opposite to that implicated in cancer metastasis. This observation appears consistent with a host of epidemiological observations of opposing risks for neuropsychiatric disease and cancer.[14,15] It also highlights opportunities for synergy across these apparently diverse disciplines. With appropriate caveats, the wealth of data emerging from cancer genomics may soon be harnessed to improve our understanding of the brain. Physician-scientists in psychiatry in the coming years should be conversant not only in cognitive neuroscience, but with much interdisciplinary science and medicine.

Gene-Environment Interactions

Genes are expressed within brain cells, one of whose key function is to enable the organism to interact with and process information from the environment. As we endeavor to understand how the brain breaks down in schizophrenia, it would be critical to understand this in the context of the early childhood environment during brain development. Ultimately, modifications to the environment may be more efficient than changing one's genes. In-utero infections, starvation and obstetric complications have been implicated in risk for schizophrenia; there are also now more than 10 epidemiological studies showing that urbanicity carries higher risk for schizophrenia compared to growing up in a rural environment.[16] Vulnerabilities in genes and the urban environment conspire in an interaction to result in further increased risk.[17] A landmark study showed the brain's information processing systems under social stress becomes more dysregulated in those who have had urban versus rural childhoods, suggesting that this may be a candidate mechanism translating the gene-environment interaction to disease risk.[18] Urban centres are dramatically enlarging in China, India and many places in Asia (even Singapore), making this research even more important for the region.

Therefore, moving forward, cross-disciplinary and cross-national research partnerships will be increasingly critical. Large European and US consortia have resulted in sufficient statistical power to discover new genome-wide signals in schizophrenia.[5,19] Major efforts in genetics and genomics are underway in Singapore and the region, which has promised results of great interest.[20] The Lieber Institute for Brain Development will be working with Peking University in a programme to understand gene and childhood environment interactions in brain systems implicated in schizophrenia. But there remains much to be done to tap the potential in the Asia Pacific region, given their diverse genetic and environmental variance that pose substantial scientific opportunities. Geographic differences in genetic allele frequencies and unique environmental exposures may aid in defining disease processes hidden to Western populations. As an indication of promise, the region has contributed recent findings of impact in the genetics of schizophrenia.[21,22] Much like its economic growth potential, the region's scientific output should accelerate in the years ahead. It has by far not seen its best days yet for schizophrenia research.

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