Review Article

Cognitive Dysfunction in Schizophrenia: A Perspective from the Clinic to Genetic Brain Mechanisms

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Abstract

Schizophrenia is a brain disease with differing symptomatic presentations, outcomes, and complex genetic mechanisms. A selection of recent work integrating clinical observations, human brain imaging and genetics will be reviewed. While the mechanics of brain dysfunction in schizophrenia remains to be well understood, the emerging evidence suggests that a number of interacting genetic mechanisms in dopaminergic and glutamatergic systems affect fundamental disease-related cognitive brain processes and may do so early in disease neurodevelopment. The availability of new imaging and genetic technologies, and institutional support for research in the translational neurosciences, extends the hope that increased understanding of these brain processes could yield meaningful clinical applications.

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Introduction

In Singapore, the prevalence of mental health problems is suggested to be about 16.6%.[1] Schizophrenia, the focus in this review, 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] Thus, outcomes may be improved, at least in the short term, with earlier treatment of diagnosable mental disorders. However, in addition to these major challenges, there are real biological limitations to treatment efficacies in terms of psychotic symptom management and patient acceptability in the long term, a clear message out of the recent large real-world clinical antipsychotic trials in schizophrenia.[4,5]

Unfortunately, even less is known about treatments that can improve the cognitive deficits associated with schizophrenia. Arguably, cognitive deficits accounts for the lion's share of the morbidity and cost of schizophrenia.[6] In its chronic course, some 10% of sufferers end their lives by suicide; and it is estimated 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.[7,8] Heavy loads rest on patients, families and society, making schizophrenia one of the leading sources of economic burden and suffering.[9] A study on the quality of life (QOL) of Singaporean patients found that even those with relatively good outcomes, who were living with their family without need for hospitalisation for more than 10 years, had poorer QOL than general practice outpatients living in the same area.[10] 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.[6] Conceivably, cognitive deficits also lead to difficulties processing and responding to nuanced stimuli relevant for effective social or family interactions,[11] 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-episode psychosis patients in Singapore, we 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

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memory, which occurred years before the onset of psychosis.[12] Compared to unaffected children with nearly identical Primary School Leaving Examination results at age 12, individuals who subsequently developed schizophrenia at ages 18 to 24 had greater deterioration in GCE 'O' Level results by age 16.[13] These findings, consistent with that reported elsewhere,[14,15] 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.

Cognitive deficits are the likely manifestations of underlying changes in brain function and structure. Genes (and the environment) could play important roles. Classical twin and adoption studies from the late Seymour S Kety and others have established that schizophrenia has a strong genetic diathesis.[16,17] More recent brain imaging studies have also found that cognitive and functional brain imaging changes occur not only in patients with schizophrenia, but also occur more frequently in the unaffected siblings of patients, including in unaffected monozygotic cotwins, than in control subjects.[18-23] These various brain changes therefore appear to represent biologic expressions of increased genetic risk, intermediate between the cellular effects of susceptibility genes and the manifest psychopathology.[24-26] These genetic links with brain-based changes should, given advances in brain imaging and genetic research outlined below, facilitate the elucidation of the underlying genetic brain mechanisms of cognitive dysfunction, and potentially advance ideas about new treatment development.

Working Memory Dysfunction in Schizophrenia

Working memory is a cognitive process that underlies much of higher-order thinking, language and planned behaviour. It is what enables us to temporarily hold, update and work with relevant information.[27] Working memory, which engages prefrontal brain systems, is an example of a number of cognitive functions that has been repeatedly shown to underlie cognitive deficits observed in schizophrenia.[28-30] An extensive body of functional imaging experiments reflect prefrontal cortical physiological dysfunction in schizophrenia, although the precise nature of these functional changes are complex and non-linear (e.g. see Reviews by Callicott[31]; Tan[32]). It has been suggested in recent conceptualisations that an interplay of dysfunctional and compensatory cortical regions or networks occur in schizophrenia. For example, we observed that in response to dysfunctional dorsolateral prefrontal cortical activation during an executive component of working memory taxing this very brain region in healthy individuals, first-episode schizophrenia patients engaged additional ventrolateral prefrontal regions in negotiating this task.[33] An elaboration of this work suggests that a larger, putatively inefficient and compensated network of brain regions are engaged in order for patients to perform a complex working task with similar accuracy as healthy individuals.[34] These data are consistent with hypotheses that neural information processing in schizophrenia could be interfered with by noise components arising from aberrations in dopaminergic and glutamatergic signalling,[35] with resultant increased computational load and brain plasticity changes to adapt to these functional deficits.

Yet, how are elements of these brain changes related to the genetic mechanisms of schizophrenia? Indeed, functional neuroimaging of prefrontal cortical changes during working memory and cognitive control also have been observed to be familial and heritable.[19,21,36] Specifically, networks of inefficient prefrontal activity occur in healthy siblings and twins of patients with schizophrenia. Thus, it might follow that the genetic mechanisms of these intermediate cognitive brain processes may be tractable using these neuroimaging paradigms and genetic approaches targeted at these prefrontal brain systems.

Imaging Genetics of Human Working Memory and Prefrontal Brain Systems

Neural mechanisms of working memory have been shown in animal and computational models to be critically dependent on dopaminergic modulation of glutamatergic and GABAergic brain systems during the processing of maintenance and manipulation of information. For example, dopamine D1 receptors in brain may allow a focused augmentation of the task-relevant signal processing in cortical neuronal networks[37,38] by enhancing NMDA-receptor mediated post-synaptic currents in prefrontal pyramidal neurons, which are also active during the delay period.[39-41] Concurrently, D1-receptors also trigger a tonic increase in the firing of GABAergic inhibitory interneurons acting further afield, reducing irrelevant firing activity while allowing the focused increase in task-relevant activity, thus optimising neural signal-to-noise.[38]

At the human systems level, initial experiments on the impact of dopaminergic gene variation on cortical function examined catechol-o-methyltransferase (COMT). This is a major enzyme in prefrontal synaptic dopamine catabolism which impacts prefrontal cortical dopamine signaling because of the relative lack of dopamine transporters within synapses in this region.[42,43] A common polymorphism in the COMT gene resulting from a valine-to-methionine Val(108/158)Met substitution gives rise to a significant reduction in its enzymatic activity.[42,44,45] This was found to correspond to reduced prefrontal dopamine in proportion to the Val-allele load. Located on chromosome 22q11, COMT is also deleted in velocardiofacial syndrome, a

condition that has 20 times increased risk for psychosis.[46] However, although this susceptibility locus has been implicated in some meta-analyses of linkage to schizophrenia,[47,48] the overall effect on risk for schizophrenia of the specific COMT Val(108/158)Met polymorphism is small and inconsistent.[49-51] This is not surprising given the manifold factors associated with schizophrenia pathogenesis, such as the involvement of combinations of single nucleotide polymorphisms or haplotypes in the gene,[52,53] interactions across different susceptibility genes,[54] and interactions between genes and environment.[55]

In contrast, the effect of the COMT Val(108/158)Met polymorphism on more specific intermediate measures of human brain function has reflected predictions from the basic cellular models of prefrontal dopamine described earlier. Reduced prefrontal dopamine in COMT Val-carriers should lead to decreased tonic D1-receptor activation. This might result firstly, in reduced cortical signal-to-noise; and secondly, in a relatively inefficient prefrontal cortical activation pattern if performance accuracy is still maintained. Using fMRI to study cortical activity, healthy COMT Val-allele carriers engaged relatively greater prefrontal cortical activation to perform the working memory task at the same speed and accuracy as those with the Met allele; this finding is consistent with the interpretation that Val carriers are relatively less efficient without advantages in performance accuracy or reaction time.[56-59] Beyond just the prefrontal cortex, it has been observed using genetic imaging of COMT that dopaminergic modulation integral to differing components of working memory sub-processes occurred with a degree of spatial and process specificity within the human prefrontal-parietal-striatal network.[59]

Interacting Gene Mechanisms on Human Prefrontal Cortical Function

Glutamatergic abnormalities, in addition to dopamine, are relevant in schizophrenia and working memory deficits. The NMDA receptor system is a critical partner in working memory processes,[40,60,61] and disease-related changes in glutamate signaling impairs working memory. For example, the metabotropic glutamate receptor, GRM3 on chromosome 7q21-22, modulates NMDA receptor transmission.[62-64] GRM3 regulates synaptic glutamate via a presynaptic mechanism and by regulating the expression of the glial glutamate transporter, which inactivates synaptic glutamate. A polymorphism in intron 2 and related haplotypes were significantly associated with schizophrenia in several samples,[62,65-67] though negative studies also have been reported.[68] Risk variants in GRM3 may also influence alternative splicing of GRM3 mRNA and its products.[69] In postmortem brain, the risk allele is associated with reduced prefrontal glial glutamate transporter EAAT2, a protein modulating synaptic glutamate.[62] Consistent with the role of the glutamatergic system in schizophrenia and working memory, the risk allele was associated with inefficient prefrontal cortical fMRI activation and reduced working memory performance even in normal subjects.[62]

Importantly, given the tight relationships governing dopaminergic and glutamatergic (and GABAergic) dynamics in the biology of working memory,[61] and their putatively greater involvement in executive aspects of working memory at the dorsolateral prefrontal cortex,[57,59,70] we would expect that higher-order working memory processes taxing dorsolateral prefrontal cortex might be more vulnerable to the combined effect of suboptimal dopaminergic and glutamatergic influence. Consistent with the interplay of cortical macrocircuits suggested by these possibilities, a recent fMRI study revealed that the integrity of higher executive areas in the dorsolateral prefrontal cortex could be disproportionately compromised and inefficient in the presence of combined deleterious COMT and GRM3 genotypes in normal subjects.[71] These subjects also engaged a larger inefficient and compensated network of brain regions to negotiate the working memory task, mirroring patterns observed in patients. Thus, genetic variation impacting important nodes in the dopamine and glutamatergic systems at a molecular level, when combined, had disproportionate or non-additive influence on executive cognitive brain function at the human systems level that could be relevant to disease-related mechanisms.

Conclusion

A selection of recent work that integrates clinical observations of cognitive deficits in schizophrenia with putative dopaminergic and glutamatergic genetic mechanisms of prefrontal cortical function was briefly reviewed. The study of heritable human neuroimaging intermediate phenotypes provides an opportunity to examine component genetic pathophysiology in this uniquely human brain disease. It is suggested that the complexity of this disease could be systematically de-constructed with combinations of multiple neuroimaging paradigms and genetic markers. Ultimately, the goal is to discover new treatments that could improve cognitive function in this disease. Encouraging recent data has suggested that targeting metabotropic glutamate receptors (including GRM3) were potentially effective in treating symptoms of schizophrenia.[72] Speculatively, some of the genetic imaging work[71]could suggest that these treatments might be combined with dopaminergic ones to improve working memory, and monitored by studying the interactions of dopaminergic and glutamatergic systems in functional imaging. In the near future, we might well expect acceleration in work to detail the critical molecular nodes impacting human cognitive processes, and an exponential

yield of biomarkers and potential targets for intervention in the eventual march towards new treatments to improve the lives of patients and their families.

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