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REVIEW

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Neuroimaging and molecular genetics of schizophrenia: pathophysiological advances and therapeutic potential

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There is impressive evidence for the involvement of several genetic risk factors in the aetiopathogenesis of schizophrenia. Most of these genes impact on neuropharmacological systems. Examining their relationship with brain imaging indices is arguably the best currently available method of examining these effects *in vivo*. In a sample of young, initially healthy people at high genetic risk of schizophrenia brain structure was measured with structural magnetic resonance imaging (sMRI) and brain function was indexed with neuropsychological tests and functional MRI. Regular detailed clinical assessments established whether subjects had developed psychotic symptoms and/or schizophrenia itself. The Catechol-*O*-Methyl Transferase (COMT) Val allele increased the risk of schizophrenia in this cohort in a dose-dependent manner. Subjects with this allele had reduced grey matter density in anterior cingulate cortex and increased fMRI activation in lateral prefrontal cortex and anterior and posterior cingulate. The risk allele in the Neuregulin 1 (NRG1) promoter region, on the other hand, was associated with the development of psychotic symptoms, decreased premorbid IQ and decreased activation of pre-frontal and temporal lobe regions. The NRG1 gene appears to be a risk factor for an extended or intermediate phenotype, while the COMT Val allele, which decreases the rate at which cortical dopamine is degraded compared to the Met allele, is associated with an increased risk of schizophrenia in subjects at increased familial risk. We provide examples of how these advances in our knowledge could lead to the development of new treatments for psychosis.
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Abbreviations: EHRS, Edinburgh High-Risk Study; MRI, magnetic resonance imaging; PFC, prefrontal cortex

Introduction

In this brief article, we will seek to relate two of the best replicated genetic risk factors for schizophrenia with the abnormalities known to occur in the disease on structural and functional magnetic resonance imaging (MRI), both in patients with schizophrenia and in subjects at high risk of developing schizophrenia because they come from multiply affected families. We do so in the light of the prevailing dopamine and glutamate hypotheses of schizophrenia, and consider how these pathophysiological insights could help in the development of new drugs for schizophrenia.

Structural imaging phenotype

Numerous controlled studies of patients with schizophrenia and healthy controls, and meta-analyses of them, have conclusively demonstrated volumetric reductions in the whole brain, parts of the prefrontal cortex (PFC) and various parts of the temporal lobes—particularly the medial temporal lobes and superior temporal gyrus (Lawrie and Abukmeil, 1998; Wright *et al*., 2000; Lawrie *et al*., 2004; Gur *et al*., 2007). These *in vivo* findings, from semi-automated tracings of region of interest, are supported by various automated approaches to 'computational morphometry' (Honea *et al*., 2005) and by post-mortem studies (Harrison, 1999; Harrison *et al*., 2003). The key question is what causes them.

The vast majority of structural MRI studies of the relatives of patients with schizophrenia have demonstrated reduced volumes of the medial temporal lobes on region-of-interest tracing that are midway between the volumes found in healthy people and those found in patients with schizophrenia (Lawrie *et al*., 1999; Boos *et al*., 2007). Computational morphometry studies of relatives have replicated these results but more consistently found PFC abnormalities, particularly reductions in medial PFC and anterior cingulate grey matter density (Job *et al*., 2003; Gur *et al*., 2007).

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Schizophrenia is known to be a highly genetic disorder (Gottesman, 1991; Craddock *et al*., 2005), and the volumes of these brain regions are known to be under at least partial genetic control (Thompson *et al*., 2001; Wright *et al*., 2002; Glahn *et al*., 2007). Further, we and others have shown that some of these regional volume decrements can be related to genetic measures of liability to psychosis (Lawrie *et al*., 2001; Steel *et al*., 2002; McIntosh *et al*., 2006; Glahn *et al*., 2007). It therefore seems likely that some of this (intermediate) phenotype is genetically mediated. Further, there are few other plausible explanations, apart from a likely interaction between genetic liability to schizophrenia and hypoxic obstetric complications being associated with further reduced volumes of the medial temporal lobes in patients (van Erp *et al*., 2002). Moreover, twin studies, which can specifically model genetic and environmental contributions, point to both factors being relevant in the abnormalities in PFC and medial temporal lobes (Cannon *et al*., 2002; Narr *et al*., 2002; Wright *et al*., 2002; van Erp *et al*., 2004; van haren *et al*., 2004).

Functional imaging phenotype

The functional imaging phenotype of schizophrenia is a slightly more complex issue, as the results one can obtain in studies of patients and controls depend on the scanning technology being used, the task being done in the scanner, if there is one, and whether or not patients are doing this task to a similar level as controls. Nonetheless, it cannot be disputed that patients with schizophrenia tend to show a generalized hypofrontality in functional brain imaging studies, particularly in dorsal and lateral PFC (Achim and Lepage, 2005; Glahn *et al*., 2005). There are, however, a number of studies and reviews that suggest that there might be a more general medial hyperfrontality in anterior cingulate (Lawrie *et al*., 2004; Glahn *et al*., 2005). It is likely that at least some of the apparently deficient activation of PFC is attributable to a relatively overactive baseline.

There are as yet comparatively few functional imaging studies of relatives, and most of these have been performed in recent years with functional MRI. The majority of these studies report a lateralized hyperfrontality in the relatives of patients with schizophrenia (Seidman *et al*., 2006) on a variety of tasks.

A brief account of the Edinburgh High-Risk Study

In Edinburgh over the past 10 years or so, we have been involved in a prospective cohort study of young (aged 16–25 years initially) healthy subjects at genetic high risk of schizophrenia because they had one or more close affected relatives with the disorder. One hundred and sixty-three of them provided clinical, behavioural and/or neuroimaging data, and 21 of them developed schizophrenia, on average, 3.5 years after enrolment into the study. One unexpected and intriguing observation was that about half of the remaining sample ($N = 66$) had one or more transient or partial psychotic symptoms at one or more points during follow-up, but have not developed a formal psychotic illness and remain with high functioning, suggesting that psychotic symptoms in minor degree themselves may also be part of the intermediate phenotype of schizophrenia (Johnstone *et al*., 2005).

As already stated, we found reduced medial temporal lobe volumes and anterior cingulate grey matter density in subjects at high risk compared to healthy controls at baseline (Lawrie *et al*., 1999; Job *et al*., 2003). We also found temporal lobe volume reductions in those who acquired schizophrenia (Job *et al*., 2005). On functional magnetic resonance imaging, we found reduced activation of anterior cingulate, thalamus and cerebellum in all our high-risk subjects, with over activation of the parietal cortex in those with psychotic symptoms (Whalley *et al*., 2004). Underactivations of the medial temporal lobe, in particular, predicted subsequent schizophrenia (Whalley *et al*., 2006). These findings are in themselves of great interest but are of unclear aetiology. We therefore sought to relate them to some of the best replicated genetic risk factors for schizophrenia, that is, to identify genetically mediated intermediate phenotypes as a means of increasing our understanding of the pathophysiology of schizophrenia.

Genetic risk factors for schizophrenia

Several genetic risk factors for schizophrenia have been identified in recent years, based on replicated linkage analyses (Lewis *et al*., 2003) and replicated association studies (Craddock *et al*., 2005; Harrison and Weinberger, 2005). Two of the best, which we shall consider here, are the catechol-*O*-methyl transferase (COMT) gene and the neuregulin 1 (NRG1) gene.

COMT is a comparatively weak risk factor for schizophrenia but may have particularly strong effects in those from multiply affected families (Glatt *et al*., 2003). The COMT gene is located at 22q11.23, a region implicated in schizophrenia by linkage. A common substitution of valine by methionine in exon 4 (at amino acid 158 of the membrane-bound form of the protein found in the brain) affects the thermal stability of COMT, leading to conformational changes and a subsequent significant decrease in enzyme activity in the brain (and in lymphocytes). The Met substitution preferentially increases prefrontal extrasynaptic dopamine because COMT provides the major clearing step for dopamine released from the synapse in PFC. As dopamine affects PFC neuronal activity, this leads to changes in activation observed during functional neuroimaging using paradigms that challenge the PFC. Moreover, COMT genotype places people at predictable points along the putative inverted U-shaped curve when PFC dopamine stimulation is graphed against neuronal activities/performance. Homozygotes for the Val-encoding allele—with less synaptic dopamine due to more COMT activity—are positioned to the left of Met allele carriers, who seem to be located near the optimum of that curve (Meyer-Lindenberg and Weinberger, 2006). COMT genotype also has an impact on the prefrontal regulation of midbrain dopamine synthesis in a genotype-dependent direction consistent with the inverted

U-shaped model (Meyer-Lindenberg *et al*., 2005). This suggests that the risk for schizophrenia associated with this common variant is due to reduced signal-to-noise in the PFC, an idea supported by the finding that PFC activity levels on various tasks are inversely coupled to midbrain dopamine synthesis and directionally dependent on COMT genotype (Meyer-Lindenberg and Weinberger, 2006). This neuroimaging and some emerging neurochemical evidence indicate that COMT could contribute, along with other mechanisms, to both cortical dopamine deficiency and mesolimbic hyperdopaminergia in schizophrenia (Harrison and Weinberger, 2005).

NRG1 is a large, multi-exon gene on chromosome 8p with several transcripts, grouped into types I–VI according to their 5′ exon. NRG1 has multiple roles in the CNS, in neuronal migration, myelination and in the regulation of receptor expression and plasticity. Stefansson *et al*. (2002) identified a 5′ haplotype (HapICE) in the NRG1 gene associated with an increased risk of schizophrenia, and this was rapidly replicated in the Scottish population. Association of NRG1 with schizophrenia has been found in most subsequent studies, and a meta-analysis has confirmed association of the original risk haplotype (HapICE) with schizophrenia (Li *et al*., 2006). The risk-associated variants in the NRG1 gene are primarily in non-coding intronic and promoter regions, leading to the suggestion that the causative variants may operate by altering gene expression or splicing, rather than by changing protein structure. In support of this hypothesis, Law *et al*. (2006) demonstrated that genetic variation at a single-nucleotide polymorphism (SNP) from the schizophrenia-associated HapICE haplotype is associated with altered NRG1 expression. The risk allele of SNP8NRG243177, which lies within the NRG1 type IV promoter region, was found to be associated with altered expression of NRG1 type IV in post-mortem human hippocampal tissue. Furthermore, this risk allele alters putative binding sites for three transcription factors in the NRG1 type IV promoter. These results are consistent with SNP8NRG243177 being a functional variant in NRG1 that contributes to risk for schizophrenia by altering gene expression.

The large number of NRG1 signalling mechanisms and isoforms parallel the range of its effects on neural development and plasticity, many of which could be involved in schizophrenia. However, all NRG1 isoforms contain an epidermal growth factor-like motif that is critical for cell–cell signalling. In the best-described mode of NRG1 signalling, proteolytic cleavage of NRG1 releases the N-terminal part, including the epidermal growth factor domain, which interacts with a membrane-associated human epidermal growth factor receptor B4 (ErbB4)-type tyrosine kinase receptor. This interaction can lead to receptor dimerization, tyrosine phosphorylation and activation of downstream signalling pathways (Harrison and Weinberger, 2005). For example, NRG1 transgenic mice have been shown to have reduced numbers of *N*-methyl-D-aspartic acid receptors (Roy *et al*., 2007) and increased levels of dopamine receptors (Stefansson *et al*., 2002) in the PFC, as well as behavioural abnormalities consistent with schizophrenia.

Genetic imaging in schizophrenia

Egan *et al*. (2001) were the first to relate a genetic risk factor for schizophrenia to its imaging phenotype. They showed that controls, sibs and patients all had greater activation of dorso-lateral pre-frontal cortex (DLPFC) if they were Val/Val homozygotes. This result has been extensively replicated (for example, see Ho *et al*., 2005). Several groups have also related COMT Val status to reduced volumes of the PFC and temporal lobes (see especially Ohnishi *et al*., 2006). Intriguingly, Ho *et al*. (2005) found a tendency to a gene by group interaction in prefrontal lobe CSF volumes, and Ohnishi *et al*. (2006) found a significant group by gene interaction in that those with the Val/Val SNP status have greater reductions in PFC and medial temporal lobe volumes if they were patients than if they were controls. These again may point to particularly strong effects in particular genetic and/or environmental backgrounds.

Genetic imaging in the Edinburgh High-Risk Study

In contrast with this body of consistent evidence for COMT, our study of the Edinburgh High-Risk Study (EHRS) was the first to relate brain imaging measures to NRG1 status (Hall *et al*., 2006). None of the subjects were receiving treatment at the time of the study. Genotype information was available for 79 high-risk subjects. There was a highly significant effect of SNP8NRG243177 genotype on the development of psychotic symptoms in this cohort with 100% of individuals homozygous for the risk allele (T/T) developing psychotic symptoms (auditory hallucinations or persecutory ideas) across the course of the study. This effect was selective to SNP8NRG243177 and was not seen for other markers from the deCODE haplotype; nor was there an association with symptoms such as visual hallucinations (which are not typical of schizophrenia). During functional magnetic resonance imaging, subjects performed the Hayling sentence completion task, a task known to activate frontal and temporal brain regions. Subjects with the risk (T/T) genotype showed significantly decreased activation of right medial PFC (and right posterior medial temporal gyrus, as a failure of deactivation) relative to those without the risk allele in the contrast of sentence completion versus rest, even though there was no difference between groups in behavioural measures on this task. Finally, using the National Adult Reading Test (NART), a measure of pre-morbid intelligence quotient (IQ), we found a significant effect of the same genotype on IQ, with the T/T group having a significantly decreased IQ compared to the C/T and C/C groups. A similar pattern of IQ deficits was seen using the Wechsler Adult Intelligence Scale (WAIS), a measure of current IQ, although this effect failed to reach statistical significance. This study therefore demonstrated that a specific genetic variant in the NRG1 gene was associated with the development of psychotic symptoms and abnormalities in cortical function and cognition. That the association was with psychotic symptoms whether or not subjects developed syndromal schizophrenia suggested that variation in NRG1 contributes risk for an intermediate or extended

phenotype—a liability to psychotic symptoms, which only in some individuals translates into schizophrenia.

Our COMT results deliver a complimentary picture (McIntosh *et al*., 2007). This study sought to clarify the effects of the COMT Val158Met polymorphism on structure and function of brain and risk of developing schizophrenia in the 78 people at high genetic risk of schizophrenia who provided all the necessary data. Intriguingly, the COMT Val allele increased the risk of schizophrenia in this cohort in a dose-dependent manner. Subjects with the COMT Val allele had reduced grey matter density in anterior cingulate cortex on structural MRI. In addition, there was evidence of increased activation on functional magnetic resonance imaging in lateral PFC and anterior and posterior cingulate, with increasing sentence difficulty on the Hayling task, in those with the COMT Val allele despite a similar level of performance. At least in the EHRS, therefore, the COMT Val allele is associated with an increased risk of schizophrenia in subjects at increased familial risk, in whom it has demonstrable effects on prefrontal brain structure and function.

Therapeutic potential

These imaging indices and gene variants could be used as 'biomarkers' to identify individuals at particularly high risk for schizophrenia. These people could be targeted for close monitoring and early intervention with existing pharmacological and psychosocial therapies as they wished.

The insights these novel techniques have provided could also aid in the development of new treatments. NRG1 potential targets include the downstream signalling pathways. It may be possible, for example, to develop molecules to sequester the ligand NRG1, or compounds that inhibit binding to the ErbB3/ErbB4 receptor, or that inhibit the ErbB3/ErbB4 receptor dimerization or tyrosine kinase activity (Philibert and Gershenfeld, 2007).

There are also a number of approaches to pharmacological intervention based on the COMT enzyme. CNS-penetrant COMT inhibitors such as tolcapone are, however, not generally suitable for long-term use. An alternative strategy would be to seek to increase extracellular dopamine concentrations in the PFC by blocking the noradrenaline reuptake system, a secondary mechanism responsible for the disposal of dopamine from synaptic clefts in the PFC. As Apud and Weinberger (2007) have observed 'drugs to improve executive cognitive function by selectively increasing dopamine load in the frontal cortex but not in subcortical territories, and the possibility that response to them may be modified by a COMT polymorphism, provide a novel genotype-based targeted pharmacological approach without abuse potential for the treatment of cognitive disorder in schizophrenia and in other conditions involving prefrontal cortex dysfunction'.

Conclusion

In conclusion, we know that schizophrenia is highly genetic and associated with reduced volumes and disturbed function of PFC and medial temporal lobe in particular. These alterations in structure and function, which are otherwise difficult to explain, can be related to genetic risk factors for schizophrenia. In our study, in particular, we found evidence that an NRG1 risk genotype may be associated with an extended phenotype of schizophrenia that increases risk rather than being linked to the disease *per se*, whereas COMT was associated with characteristic features of the disorder and the development of schizophrenia itself. A number of interacting pharmacological factors are likely to provide a link between these genetic and brain imaging abnormalities, and could also provide new therapeutic interventions. We did not have enough power in our study to specifically examine interactions between different genes, but it is likely that these occur in complex multi-factorial pathways to the disease. These interactions will require large multi-centre collaborative studies to have sufficient power to identify them. As these pathways and interactions are elucidated, we should be in a better position to rationally diagnose our patients and perhaps predict treatment response, and in time perhaps move towards early detection and more effective intervention.

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Conflict of interest

The authors state no conflict of interest.

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