

# An expanded role for functional neuroimaging in schizophrenia

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Functional magnetic resonance imaging is a surprisingly versatile tool in the quest for disentangling the complexities of mental illnesses such as schizophrenia. Yet, the identification of pathognomonic physiological features of the illness or even a consensus regarding the interpretation of reported findings remain unfulfilled goals, in spite of the increasing sophistication of this technology. Nonetheless, by providing quantification of brain function during various cognitive challenges, functional MRI has been used to leap ahead of these quandaries to identify relationships between genetic variation and brain function. By examining recent findings and efforts to link these findings to genes, this article will review these exciting developments in schizophrenia research.

## Addresses

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## Abbreviations

<b>COMT</b>	catechol-O-methyl transferase
<b>DLPFC</b>	dorsolateral prefrontal cortex
<b>DZ</b>	dizygotic
<b>fMRI</b>	functional magnetic resonance imaging
<b>met</b>	methionine
<b>MZ</b>	monozygotic
<b>val</b>	valine
<b>VBR</b>	ventricle-to-brain ratio
<b>WM</b>	working memory

## Introduction

Though only ten years old, functional magnetic resonance imaging (fMRI) has had a dramatic impact on the study of mental illness. A complete review of recent developments in the imaging of mental illness is beyond the scope of this article, whereas a review of recent progress in the study of schizophrenia is worthwhile. This is because work with schizophrenia often provides a template upon which researchers base their approach to other mental illnesses. In the past two years, the sequencing of the human genome has raised expectations that the identification of susceptibility genes for the major psychiatric disorders such as schizophrenia should be near

at hand. Perhaps the most promising development in neuroimaging of schizophrenia has been the expansion of functional brain imaging into the characterization of intermediate phenotypes for psychiatric genetics studies. The intermediate phenotype attempts to quantify a physiological aspect of a given illness, analogous to the quantification of blood glucose in diabetes, which impacts on the overall susceptibility to the illness but that carries a simpler physiological basis and, hopefully, genetic architecture. As the heritability of mental illnesses such as schizophrenia is complex this approach is particularly attractive, especially given the frustratingly slow progress of linkage studies that have used the clinical phenotype as a starting point.

Here, I summarize recent findings from the functional neuroimaging literature in schizophrenia as a means of identifying candidate phenotypes. Finally, I discuss recent attempts to define specific genetic abnormalities that are associated with functional intermediate phenotypes. Though issues such as susceptibility to movement artefact and controversial study design remain to be overcome, functional neuroimaging is poised to make revolutionary contributions towards uncovering the etiology of major mental illnesses such as schizophrenia. This progress will be possible largely because of the non-invasive nature of functional neuroimaging and the ease with which large numbers of subjects for this technique can be accumulated.

## Intermediate phenotypes in schizophrenia

The search for brain-imaging phenotypes of schizophrenia has been underway since seminal studies in structural brain imaging were carried out during the late 1970s and early 1980s (for a review see [1]). Early computerized tomography (CT) studies showed that lateral ventricular enlargement, or ventriculomegaly, was a replicable and robust group finding. Johnstone *et al.* [2] examined both 17 elderly institutionalized patients with schizophrenia and matched controls using CT. The patients as a group had larger ventricles and, at the level of the individual patient, ventriculomegaly predicted the extent of cognitive impairment. This study suggested that the phenotype could be defined in a meaningful fashion at the individual level. It only remained to be determined if the lateral ventriculomegaly phenotype was heritable within families afflicted by schizophrenia. Taken together, the results of three seminal studies showed just this. Weinberger *et al.* [3] compared the distribution of lateral ventriculomegaly in seven healthy pairs of siblings, or sibships, with that in nine sibships in which at least one member had schizophrenia. Ventricle-to-brain ratio (VBR) was examined as a

putative heritable phenotype in two ways: first, quantitatively by intra-class correlation of VBR within sibships, and second, qualitatively with scatterplots that compared the VBR of any given individual to an established mean VBR in controls. Both analyses suggested that VBR was heritable. Reveley and co-workers [4] addressed the same questions in monozygotic (MZ) and dizygotic (DZ) twins. Using the VBR, heritability was calculated between 11 pairs of healthy MZ twins, eight pairs of healthy DZ twins, and seven pairs of MZ twins that were discordant for schizophrenia. The VBR was highly heritable in healthy MZ twins ( $h^2 = 0.98$ ), and roughly twice that of healthy DZ twins ( $h^2 = 0.45$ ). The VBR was also highly heritable in schizophrenic DZ twins ( $h^2 = 0.87$ ). A strong family history of psychosis (manifested either by frank schizophrenia or simply by family history) predicts a greater concordance for the phenotype in question within sibships, as found by Weinberger *et al.* [3]. However, echoing this apparent genetic loading effect, the two schizophrenic DZ sibships with a strong family history of psychosis in the study by Reveley *et al.* [4] showed the least within-pair variance. Finally, DeLisi and co-workers [5] demonstrated a significant familial component of lateral ventricular enlargement in 11 sibships (including non-psychotic siblings of schizophrenic patients or so-called unaffected siblings), which was not entirely explained by non-genetic or environmental factors, such as early head injury or obstetrical complications. Taken together, these studies suggested that one could answer both questions using brain imaging — ventriculomegaly was under genetic control and variation was not significantly affected by non-genetic factors. However, following these early studies, the study of intermediate phenotypes languished for nearly two decades.

In principle, a phenotype related to genetic risk should be found in all schizophrenic individuals, and in some 'at risk' individuals who do not manifest the symptoms. Thus, the search for phenotypes at the level of brain imaging begins with patients who manifest schizophrenia. Although functional brain-imaging techniques have been applied to the study of mental illnesses, particularly schizophrenia, for almost 30 years, they have failed to generate diagnostically specific or pathognomonic findings. For instance, 'hypofrontality' remains the most commonly replicated functional brain-imaging finding in patients with schizophrenia. Hypofrontality is widely accepted to mean that patients with schizophrenia have reduced neuronal activity in dorsolateral prefrontal cortex (DLPFC), as assayed by such measures as regional cerebral blood flow (rCBF) or regional cerebral metabolic rate of glucose metabolism (rCMRglu).

#### Global dysfunction?

When reviewing the findings on schizophrenia, it is interesting to ask whether these effects can be localized to certain systems or arise as a reflection of global

dysfunction, and whether functional findings arise as a result of the schizophrenia or as a consequence of poor performance on the cognitive tasks that are used to probe subjects. Several recent fMRI studies raise the question of whether widespread global dysfunction arises in schizophrenics using simple tasks that are designed to probe the response to sensory input. Wible *et al.* [6••] tested an auditory sensory mismatch paradigm in 10 schizophrenic patients and 10 controls. The subjects were required to identify deviant tones that occurred in a string of standard tones. The researchers found that both groups activated auditory processing regions in superior temporal gyrus, but that schizophrenic patients showed a diminished response. Although it is not known to what extent temporal cortex neurons are affected by schizophrenia, these data suggest a fundamental neuronal dysfunction that is likely to be present throughout sensory and association cortices, and thus suggest a global defect. Kiehl and Liddle [7] used a more traditional auditory oddball task in a comparison of 11 schizophrenic patients and 11 controls. Detection of the oddball activated a network including the dorsolateral frontal cortex, the thalamus, the superior temporal gyri, the parietal cortex, and the cingulate gyrus. Once again, schizophrenic patients produced less activation in the superior temporal gyrus but also in the thalamus and the frontal, parietal, and cingulate cortices. These data clearly implicate higher association cortices in addition to sensory cortex dysfunction in schizophrenia. Braus *et al.* [8] examined simple sensory processing in medication-naïve schizophrenic subjects. They used a flashing checkerboard and drumbeats as stimuli and found abnormally reduced activation in the prefrontal cortex, the thalamus, and the parietal lobe, again implicating higher association cortices in schizophrenia. Kodama *et al.* [9] examined brain activation in schizophrenic patients one week after they had undergone motor skills training and found, contrary to the typical pattern of reduced and more-focused brain activation in controls, that schizophrenic patients continued to show increased activation. Kumari *et al.* [10] found that schizophrenic patients failed to activate a network of areas, including the thalamus, the striatum, the precuneus, the cingulate gyrus and the premotor cortex, during a rule-based procedural learning task. The potential significance of abnormalities at entry-level stages of cognitive processing may help to explain some of the symptomatology of schizophrenia. For example, sensory hallucinations could arise as a by-product of extraneous or inappropriate neuronal activity during basic sensory processing, which the individual then misinterprets as real sensory input. Surguladze *et al.* [11] examined schizophrenic patients while they watched a silent lip-reading and tried to perceive something of the meaningless lip movements. They found that patients under-activated their temporal cortex during lip reading but recruited additional frontal, insular, and striatal regions during the perception of meaningless lip movements. However, to

understand some of the most debilitating symptoms of schizophrenia, such as delusions or loss of motivation, it is necessary to look beyond basic processing at more complex cognitive functions.

### Regionally specific dysfunction

A brain region that appears to be a likely candidate for involvement in complex cognitive dysfunction is the DLPFC. The involvement of this region is indicated both by its central role in higher cognition and by similarities between the symptoms of schizophrenia and lesions in the DLPFC, such as lack of motivation and impaired abstract thinking. The most replicated cognitive finding in schizophrenia is the dysfunction attributable to DLPFC. Although numerous reports have documented abnormalities in DLPFC in schizophrenics, there is continuing controversy regarding the specific nature of the prefrontal dysfunction, especially on whether there is increased or decreased DLPFC activity.

The findings of Barch and co-workers [12] are typical of the so-called ‘hypofrontality’ findings. They examined 14 first-episode untreated schizophrenic patients and 12 controls using the AX version of the continuous performance task AX-CPT, which measures context processing because subjects are required to inhibit their responses following certain cues but not others. During the context processing part of the task, patients showed reduced activation in the DLPFC but not in the inferior and posterior prefrontal cortex. Lack of motivation or impairment in executive processes could thus be the result of a reduced capacity to activate needed neuronal subsystems in DLPFC. Using a larger sample of 38 schizophrenic patients and 48 controls who performed both working memory and long-term memory tasks, Barch *et al.* [13\*] found reduced DLPFC activation during both tasks. Similar to Barch *et al.* [13\*], Perlstein *et al.* [14] compared 17 schizophrenic patients to 16 controls during the N-back working memory (WM) task. In these N-back WM tasks, subjects are required to recall a stimulus seen ‘n’ (typically two) times previously in an ongoing string of stimuli. Perlstein *et al.* found reduced activation in the right DLPFC that was associated with reduced WM performance. Furthermore, impairment in the right DLPFC was correlated with symptoms of cognitive disorganization. Perlstein *et al.* [15] reported similarly reduced DLPFC activation using both the N-back task and the AX-CPT. Using the ‘gold standard’ of DLPFC function, the Wisconsin Card Sorting Task (WCST) in which subjects are asked to sort colored shapes based on a changing set of simple rules, Riehemann *et al.* [16] found reduced right DLPFC activation in schizophrenics. This finding is in accordance with a large amount of positron-emission tomography literature that has reported similar results.

DLPFC dysfunction has also been found during tasks that do not require complex processing. For example,

Rubia *et al.* [17] examined six schizophrenic patients and seven controls during the ‘go-no-go’ inhibition task, in which subjects are required to make responses after some stimuli but not after others, and found that patients showed reduced DLPFC activation. Volz and colleagues [18] also found reduced DLPFC function in schizophrenic patients during a time estimation task.

Several fMRI studies on schizophrenia have failed to find hypofrontality. Honey *et al.* [19] used a verbal N-back task in 20 schizophrenic patients and 20 matched controls, and found no difference in DLPFC activation. There was, however, a loss of the normal correlation between reaction time and parietal activation in schizophrenic patients. More strikingly, we [20] found greater activation of the DLPFC in schizophrenics than in controls during the N-back WM test. This level of activation was also correlated with the extent of neuronal pathology, as assessed by proton magnetic resonance spectroscopic imaging. Similarly, Manoach *et al.* [21] found increased DLPFC activation in schizophrenic patients performing both test and retest of the Sternberg Item Recognition Paradigm in which subjects are asked to remember strings of letters or numbers. Quintana *et al.* [22,23] found that patients who were remembering faces over-activated DLPFC, Brodmanns area 44, and the premotor cortex when compared to controls. Finally, Ramsey *et al.* [24\*\*] found increased DLPFC activation during a WCST-like task in medication-naïve schizophrenic subjects.

The relationship of increased DLPFC activation to symptoms in schizophrenia is not straightforward. The data described above suggest that schizophrenics are inefficient in recruiting neuronal resources or, alternatively, in activating appropriate additional DLPFC neurons. The fact that increased DLPFC activation has been directly correlated with the extent of neuronal abnormalities in DLPFC [20] suggests that, even though the interpretation is not straightforward, hyperfrontality has some bearing on schizophrenia. In addition, hyperfrontality is immune from the most common confound that plagues the literature on hypofrontality; that is, the observation that reduced DLPFC activation only occurs in the setting of reduced performance, thus raising the supposition that these findings track poor performance in general and not schizophrenia in particular. For example, healthy subjects can be made hypofrontal during a WM task by exceeding their WM capacity and scanning subjects when WM fails [25].

### Imaging and genetics

Although functional imaging findings have been unable to fully disentangle the pathophysiology of schizophrenia, several studies suggest that greater success has been had in determining the genetic causation of schizophrenia. First, it is important to demonstrate that the functional abnormalities associated with schizophrenia represent

heritable phenomena. We have examined the fMRI response to the N-back task in two cohorts of healthy controls and healthy siblings of patients with schizophrenia [26]. As siblings share on average 50% of their genes, it is likely that schizophrenia-susceptibility genes (and the adverse physiological effects of these genes) will be more frequently transmitted to siblings of schizophrenics relative to the general population. In both cohorts, siblings and controls performed with the same accuracy and reaction time during the task. However, in both cohorts, the siblings of patients with schizophrenia showed increased DLPFC activation (inefficiency) relative to controls. Therefore, these data suggest that hyperfrontality may be heritable.

Three recent papers have directly tied fMRI abnormalities to gene function. Egan *et al.* [27\*\*] examined a well-known functional polymorphism in the enzyme catechol-O-methyl transferase (COMT). A methionine (met) for valine (val) substitution results in a four-fold decrease in the enzymatic breakdown of dopamine. Dopamine levels are therefore lower in subjects with a val COMT allele. In addition to being over-transmitted to patients with schizophrenia, val COMT conferred DLPFC over-activation in healthy subjects, similar to that seen in patients with schizophrenia and their healthy siblings. Although the following studies do not relate directly to schizophrenia, they illustrate the power of functional imaging to document gene effects. Hariri *et al.* [28] examined the response of the amygdala to fearful stimuli, and found that the short allele of the serotonin transporter (5-HTT) was associated with increased amygdala activation. The short 5-HTT allele had previously been linked to pathological anxiety and neuroticism, suggesting that an inappropriately exaggerated amygdala response may explain these earlier findings. Finally, Egan *et al.* [29] examined a functional polymorphism, consisting of a val for met substitution, in the gene encoding the brain-derived neurotrophic factor (BDNF). In addition to reduced secretion of BDNF and impaired memory function, met BDNF was associated in two cohorts of healthy subjects with inappropriate activation of the hippocampus during the N-back WM task.

## Conclusions

Advances in functional brain-imaging coupled with the sequencing of the human genome are promising developments for schizophrenia research. Armed with as little as a broad knowledge of the brain-imaging literature, a standard MRI scanner, and collaborators from several other disciplines (notably psychology, radiology, and genetics), interested investigators from around the world are poised to critically apply functional brain-imaging. Preliminary results suggest that fMRI quantification of brain function is a powerful tool with which to determine the *in vivo* effects of gene variation. Although much of the pathophysiology of schizophrenia remains to be revealed

by brain imaging, we are likely to unravel some of the genetic (and in turn physiological) mysteries that characterize schizophrenia.

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