Published in final edited form as:
Int Rev Psychiatry. 2007 August ; 19(4): 417–427. doi:10.1080/09540260701486365.

Neuroimaging of cognitive disability in schizophrenia: Search for a pathophysiological mechanism

J. D. RAGLAND, **J. YOON**, **M. J. MINZENBERG**, and **C. S. CARTER**
Department of Psychiatry and Behavioral Sciences, Imaging Research Center, University of California at Davis, Sacramento, CA, USA

Abstract

This article reviews how functional neuroimaging research of cognitive dysfunction in schizophrenia has resulted in a progression of influential pathophysiological models of the disorder. The review begins with discussion of the 'hypofrontality' model, moving from resting studies examining anterior to posterior gradients of cerebral blood flow (CBF), to cognitive activation studies employing the Wisconsin Card Sorting Test, and current functional magnetic resonance imaging (fMRI) studies of working memory and cognitive control utilizing parametric task designs and event-related procedures. A similar progression is described for development of the temporal lobe model of schizophrenia, moving from research on the temporal cortex and language processing to the hippocampal formation and long-term memory (LTM). These LTM studies found that hippocampal dysfunction was often accompanied by disrupted prefrontal function, supporting a hybrid model of impaired fronto-temporal connectivity. Developments in image analysis procedures are described that allow assessment of these distributed network models. However, given limitations in temporal and spatial resolution, current methods do not provide 'real-time' imaging of network activity, making arrival at a definitive pathophysiologic mechanism difficult. Dorsolateral prefrontal cortex (DLPFC) dysfunction and disrupted fronto-temporal integration appear to be equally viable current models. The article concludes with a discussion of how fMRI can help facilitate development of novel psychosocial and pharmacological interventions designed to improve cognition and functional outcome in patients with schizophrenia.

Keywords

Functional brain imaging; human brain mapping; schizophrenia; cognition

Introduction

Since the earliest descriptions of schizophrenia, impaired cognition has been noted as a fundamental feature of the illness (Bleuler, 1911; Kraepelin, 1919). For example Kraepelin, being both a psychiatric clinician and a student of the original cognitive psychologist,

Correspondence: J. Daniel Ragland, Department of Psychiatry and Behavioral Sciences, University of California at Davis, 4701 X Street, Sacramento, CA 95817, USA. jdragland@ucdavis.edu.

Wundt, suggested that schizophrenia is associated with impairments in coordinating cognitive processing, describing patients as 'like an orchestra without a conductor'. However, with the serendipitous discovery in the 1950s that chlorpromazine could be used to treat positive symptoms, research moved to clinical features in an attempt to identify biological mechanisms and improve patient outcome. Despite success in treating psychotic features of the illness (e.g., hallucinations, delusions), neither first nor second generation neuroleptic medications have been fully successful in improving patients' daily function. For example a prospective study that followed 73 patients with schizophrenia over the past 20 years found that although 40% of the sample showed periods of recovery, the majority of patients continued to fluctuate between moderate and severe disability and 12% committed suicide over the 20 year period (Harrow & Jobe, 2005).

The realization that continued disability can be attributed to cognitive dysfunction has led to a renewed interest in cognitive features of schizophrenia over the past several decades. Unlike psychotic features, cognitive dysfunction shows, at best, a modest improvement with currently available therapies for schizophrenia (Green, 1998; Goldberg et al., 1993; Harvey & Keefe, 2001), and the vast majority of patients treated with our very best second generation antipsychotic drugs remain significantly cognitively disabled. Moreover, this continued cognitive disability strongly predicts poor functional outcomes (Green, 1996, 1998; Weinberger & Gallhofer, 1997). Continued deficits in attention, memory, language and executive control interfere with patients' ability to complete school, get and hold a job, and maintain social relationships, leading to a downward drift in life skills. These cognitive deficits have, therefore, become important targets for development of new psychosocial and pharmacological treatments.

A second factor that contributed to renewed interest in the cognitive features of schizophrenia was the advent of functional neuroimaging, which promised to identify neural mechanisms for this continued dysfunction. Prior to functional imaging, localization of cognitive abilities depended upon naturally occurring focal lesions in humans, and surgically or chemically induced lesions in epilepsy patients and animal models. These focal lesion studies led to seminal discoveries such as the role of Brocas' and Wernickes' areas in language processing, and the role of the hippocampal formation in memory consolidation, but were not adequate models of neurodevelopmental impairments such as schizophrenia. However, with the advent of 133Xenon clearance and 15-Oxygen positron emission tomography (PET) methods it became possible to use change in regional cerebral blood flow (CBF) to localize discrete cognitive abilities to specific networks in the brains of awake, behaving individuals. Utilization of functional neuroimaging exploded in the 1990s with the introduction of more widely available, less invasive and less expensive blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI).

The current paper will review how these functional neuroimaging methods have been used to improve our understanding of cognitive disability in schizophrenia and map these cognitive impairments to specific brain regions. We will begin with a discussion of the initial studies implicating the prefrontal cortex as the site of neurophysiologic dysfunction in schizophrenia. These studies of resting metabolism and CBF change during performance of the Wisconsin Card Sorting Task (WCST) instigated functional neuroimaging research of

schizophrenia, and remain influential today. We will describe how this research evolved from using complex tasks such as the WCST to more discrete working memory and response inhibition paradigms that allowed for a parametric manipulation of task demands and the isolation of specific aspects of prefrontal cognitive control functions associated with discrete subregions within the prefrontal cortex.

A second prominent model implicated the left hemisphere temporal cortex and underlying hippocampal formation as the site of brain dysfunction and memory impairment in schizophrenia. We will explain how these memory studies began to reveal a dynamic interplay between the prefrontal cortex and temporal-limbic regions, leading to a currently prominent model of disrupted fronto-temporal integration. This model relies on the concept of disrupted functional connectivity, and new analytic methods will be described that are being used to test this model. However, it will also be acknowledged that much of the current functional neuroimaging literature in schizophrenia can be explained equally well by a return to the dorsolateral prefrontal cortex (DLPFC) as the site of primary pathophysiology, employing the concept of impaired cognitive control. The chapter will close with discussion of how these functional imaging methods can be used to facilitate development of new psychosocial and pharmacological interventions that can augment current treatments to more fully restore the daily functioning of patients with schizophrenia.

Frontal lobe model

The advent of functional neuroimaging studies of schizophrenia began with resting CBF studies using the 133Xenon clearance method. Ingvar and Franzen (1974) were the first to do this research, which compared the gradient of frontal to posterior CBF in healthy volunteers and patients with schizophrenia. Although there was no group difference in whole brain blood flow, patients had a reduced gradient of frontal to posterior blood flow, leading to the conclusion that schizophrenia is characterized by ‘hypofrontality’. A second study observed that hypofrontality was greatest in patients with restricted affect who were withdrawn and mute (Franzen & Ingvar, 1975). Several subsequent resting studies using both 133Xenon (Berman, Zec, & Weinberger, 1986; Mathew, Wilson, Tant, Robinson, & Prakash, 1988), and positron emission tomography (PET; Buchsbaum et al., 1982; Volkow et al., 1987) replicated this pattern of a reduced gradient of frontal to posterior blood flow. However, not all resting studies found evidence of hypofrontality (Catafau et al., 1994; Ebmeier, Lawrie, Blackwood, Johnstone, & Goodwin, 1995; Gur et al., 1987a,b), and an increasingly critical view developed of the resting hypofrontality model (Gur & Gur, 1995).

A limitation of these initial resting studies was lack of behavioral control over subjects’ mental activity. This led to a transition to ‘cognitive activation’ paradigms in which changes in CBF were examined in relation to specific task demands. The most popular task in these initial studies was the Wisconsin Card Sorting Test (WCST; Berg, 1948; Grant & Berg, 1948). The WCST is a measure of concept formation, cognitive flexibility, feedback processing and working memory that is quite sensitive to frontal lobe lesions. It requires subjects to sort a deck of cards to one of 4 key cards that match the response cards on several dimensions. The subject must use experimenter feedback (‘correct’ or ‘incorrect’) to

develop a successful sorting principle, and switch to a new sorting principle when the rule changes.

In a series of studies Weinberger and colleagues (Berman et al., 1986; Berman, Illowsky, & Weinberger, 1988; Weinberger, Berman, & Zec, 1986; Weinberger, Berman, & Illowsky, 1988) measured CBF change between the WCST and a psycho-motor control task. These studies revealed that patients failed to show a normal increase in blood flow in the DLPFC during WCST performance. These results were specific to the WCST task, were replicated when patients were both on and off medication, and did not appear due to global cortical dysfunction. The reliability of activation results and inconsistency of resting baseline studies led to a re-formulation of the hypofrontality hypothesis, stressing the importance of activation paradigms and clarifying that, 'hypofrontality appears to be dependent on the behavioral state of the patients during the brain imaging experiment' (Weinberger, Berman, & Daniel, 1991, p. 276). Andreasen and colleagues (1992, p. 955) further clarified that hypofrontality may best be defined as, 'an inability for an individual to raise significantly his or her cerebral perfusion to the prefrontal region when given an experimental prefrontal cognitive challenge.'

A limitation of these initial studies is that they averaged activity across multiple trials within a block and were, therefore, unable to control for lower levels of WCST performance in the patient group, raising the possibility that hypofrontality might be secondary to patient's inability to perform the task rather than due to actual physiological differences between the brains of patients and controls (Ebmeier et al., 1995). Efforts to address this criticism included studies of other patient samples that were also impaired but did not have reduced DLPFC activation, studies of tasks on which patients were impaired but showed normal prefrontal response, and examination of low-performing controls and high performing patients (Weinberger & Berman, 1996). A second concern raised with these initial studies is that the WCST is a complex task, making it difficult to link CBF change to specific cognitive components. During the WCST subjects must maintain the correct sorting principle in working memory when they are within a given category, and use feedback to inhibit the use of that principle when the rules change and a new strategy must be generated. The multi-factorial nature of the WCST led investigators to utilize experimental cognitive neuroscience tasks that could parametrically adjust working memory load, manipulation demand, and response inhibition components. This parsing of distinct cognitive components was also facilitated by development of event-related fMRI (Zarahn, Aguirre, & D'Esposito, 1997).

In contrast to previous block design studies that averaged brain activity over multiple trials, event-related procedures allowed the investigator to measure fMRI activation to specific trials and thereby differentiate cognitive components and account for individual and group differences in task performance (i.e., correct versus incorrect trials). Together with working memory tasks such as the N-Back and Sternberg paradigm, and response inhibition tasks such as the Stroop and AX-CPT, a more refined understanding developed on how schizophrenia could disrupt function in specific subregions within the frontal cortex and thereby lead to deficits in different aspects of working memory and response control.

Of the many prefrontally dependent cognitive processes affected by schizophrenia, working memory (WM), the ability to temporarily hold 'on line' and manipulate information for later use (Baddeley, 1986), has been a particularly rich area of study. Many of the prominent cognitive and behavioral deficits of schizophrenia can be conceptualized as a product of WM abnormalities. For example, disorganized speech and thought process could be a manifestation of the inability to maintain a linguistic schema in mind. Additionally, WM deficits may form the basis of other cognitive abnormalities, such as planning and multi-tasking. This has led some investigators to conclude that WM impairments represent a core deficit in schizophrenia (Cohen, Braver, & O'Reilly, 1996; Goldman-Rakic, 1994; Silver, Feldman, Bilker, & Gur, 2003). A large number of studies have documented abnormalities in WM in schizophrenia using a variety of different paradigms over multiple domains, including verbal (Kim, Glahn, Nuechterlein, & Cannon, 2004), spatial (Carter et al., 1996; Park & Holzman, 1992), and visual objects (Park, Püschel, Sauter, Rentsch, & Hell et al., 2002). WM deficits have also been observed in unaffected relatives (Park, Holzman, & Goldman-Rakic, 1995), medication-naïve individuals (Barch et al., 2001), as well as in acute and non-acute phases of the illness (Park, Puschel, Sauter, Rentsch, & Hell, 1999).

The vast majority of fMRI WM studies have been consistent in their conclusion of DLPFC dysfunction in schizophrenia. Most fMRI studies have demonstrated DLPFC hypoactivity in subjects with schizophrenia during WM conditions requiring manipulation of information across working memory delays (Barch et al., 2001; Callicott et al., 1998; Perlstein, Carter, Noll, & Cohen, 2001). However, task-related DLPFC hypoactivity is not a universal finding with some studies revealing no difference between control and schizophrenia groups (Honey et al., 2002), and others showing hyperactivity in the DLPFC (Callicott et al., 2000; Manoach et al., 2000). Recent studies have provided evidence supporting both hypo- and hyperactivity of the DLPFC during WM in schizophrenia, supporting the notion of an inverse U-shaped function relating WM load to DLPFC activation (Callicott et al., 2003; Manoach, 2003). There is also growing evidence that schizophrenia-related abnormalities during WM are not restricted to the DLPFC. In a recent quantitative meta-analysis Glahn and colleagues (Glahn et al., 2005) reviewed 12 imaging studies where patients with schizophrenia were contrasted with healthy comparison subjects while performing the N-Back WM paradigm. In addition to confirming expected DLPFC reductions in patients, the analysis also revealed normal ventrolateral prefrontal cortex (VLPFC) activation, and abnormally increased activation in anterior cingulate and left frontal pole regions. It is important to note that this meta-analysis includes a number of studies that reported hyperfrontality as their primary finding. Its results suggest that careful attention must be paid to the location of activation differences in schizophrenia, since the prefrontal cortex has a number of important subdivisions that appear to make unique contributions to WM and cognitive control. The Glahn et al. study suggests that while DLPFC activity appears to be generally reduced, across these studies other more anterior, ventral and medial regions may be recruited in an effort by schizophrenia patients to compensate for their difficulties performing the N-Back task. This insight also recommends a network level analysis that is informed by what is known within basic cognitive neuroscience about how circuits and their individual elements support cognition. This basic cognitive neuroscience perspective has

begun to guide the design and analysis of fMRI studies of cognitive impairment in schizophrenia.

Studies investigating cognitive control have revealed that the anterior cingulate gyrus (ACC) is also a key region of disrupted frontal lobe function in schizophrenia. Recent studies using fMRI with a wide variety of paradigms have shown reduced ACC activity in schizophrenia. These findings have been reported in a variety of different patient populations, and during a wide range of tasks that engage ACC in healthy subjects, including conflict verbal fluency (Boksman et al., 2005), oddball detection (Laurens, Kiehl, Ngan, & Liddle, 2005), tone discrimination (Holcomb et al., 2000) 'inhibition' tasks (Rubia et al., 2001), and conflict tasks (Dehaene et al., 2003; Heckers et al., 2004; Kerns et al., 2005). In an event-related fMRI study of error-related activity in the ACC, Carter and colleagues reported that people with schizophrenia exhibited less activation of the ACC after errors than did controls (Carter, MacDonald, Ross, & Stenger, 2001), a finding recently replicated and extended to show reductions in both conflict and error-related activity in the ACC (Kerns et al., 2005). In both studies individuals with schizophrenia exhibited less slowing of reaction times after error trials than did control participants. In the Kerns et al. study reduced conflict related adjustments were also found, suggesting impaired performance monitoring in people with schizophrenia.

Not all neuroimaging studies of ACC activity have reported decreases in patients. For example the Glahn et al. (2005) meta-analysis showed abnormally increased fMRI response in the caudal ACC/ pre-SMA area in patients with schizophrenia. The N-Back task produces variable amounts of ACC activation in healthy subjects, presumably because successfully performing subjects experience little conflict when responding during this task. Patients might be experiencing more conflict than controls and, to the degree that their ACC can respond to conflict, are activating this region accordingly. In contrast, during incorrect responding and during tasks such as the Stroop, Go-No-Go, and Verbal Fluency, which reliably activate the ACC in healthy subjects, reduced activation in schizophrenia appears to be a very consistent finding.

Temporal lobe model

The left hemisphere temporal lobe model was the other prominent theory of schizophrenia pathophysiology beginning in the 1980s. As with the frontal lobe model, research began by examining gradients of resting CBF - in this case left versus right hemisphere function. The left hemisphere is responsible for verbal, linguistic and analytic functions, whereas the right hemisphere appears to be specialized for visuospatial and synthetic processes in healthy right-handed individuals. Features of thought disorder including analytic and language processing deficits were suggestive of greater left hemispheric dysfunction in schizophrenia and motivated a search for laterality differences between affected and unaffected groups.

The first experiments were performed with the 133Xenon clearance method, and studied patients and controls when they were at rest and during performance of verbal analogy and spatial line orientation tasks. The initial study (Gur et al., 1983) failed to find any group differences in anterior-posterior or left-right gradients of CBF when patients and controls

were at rest. However, when engaged in task performance patients failed to show normal left hemispheric activation for the verbal task and right hemispheric activation for the spatial task. Patients did not produce any laterality effects for the verbal task, and showed greater left hemispheric activation during the spatial task, suggesting a left hemispheric overactivation model of the disorder. A subsequent study examined un-medicated patients with the same task paradigm (Gur et al., 1985). This untreated patient sample showed left hemispheric overactivation both at rest and during task performance, leading to the conclusion that medication may serve to restore normal resting asymmetries in cerebral blood flow. A series of resting PET metabolism studies also found evidence of left hemispheric overactivation in patients with severe versus mild clinical symptoms (Gur et al., 1987a), and showed that higher right versus left hemispheric metabolism was correlated with clinical improvement (Gur et al., 1987b). These studies also found evidence of a steeper subcortical to cortical gradient in schizophrenia, motivating a search for abnormalities in temporal and limbic brain regions during long-term memory (LTM) tasks.

Initial PET and 133Xenon CBF studies of LTM in schizophrenia found evidence of reduced CBF and atypical asymmetries in frontal and temporal cortex during memory retrieval (Ganguli et al., 1997; Gur, Ragland, Resnick, Jaggi, Skolnick, & Gur, 1994; Ragland et al., 1998; Wood & Flowers, 1990). In a series of PET studies of prose recall Andreasen and colleagues (Andreasen et al., 1996, 1997; Crespo-Facorro et al., 1999) extended these findings to the thalamus and cerebellum and supported a distributed dysfunction (‘cognitive dysmetria’) model. Relatively few initial studies examined LTM encoding. However, both SPECT (Nohara et al., 2001) and PET (Hazlet et al., 2000) found that impaired semantic organization during encoding was associated with reduced activation in frontal and temporal lobe regions. In the first PET study to directly contrast word encoding and retrieval, Ragland and colleagues (2001) found evidence of left frontal and temporal lobe dysfunction during both stages of LTM processing. Whereas retrieval success was associated with focal left DLPFC activation in controls, patients relied on a more diffuse ‘compensatory’ network of motor and posterior association regions to support retrieval success.

As this LTM research moved from PET to fMRI, evidence increased for hippocampal as well as frontal lobe abnormalities. Heckers and colleagues (1998) were the first to find evidence of abnormal hippocampal recruitment during word retrieval. Unlike healthy participants who activated a right frontal-temporal network during word retrieval, patients had reduced hippocampal and abnormally increased frontal activation. Reductions in hippocampal volume and memory-related activation have been well documented in the schizophrenia literature (see Preston, Shohamy, Tamminga, & Wagner, 2005; for a review). However, these hippocampal abnormalities are invariably accompanied by abnormal modulation of prefrontal cortex (Ragland et al., 2004), and even strong proponents of the hippocampal model have concluded that the pathophysiology of memory impairment may best be characterized as a disruption of prefrontal integration with the hippocampus and other brain regions rather than an isolated deficit in either frontal or mesial temporal cortex (Weiss & Heckers, 2001).

Disrupted connectivity or loss of prefrontal control

Friston, Liddle, Frith, Hirsch and Frackowiak (1992) were among the first to suggest that frontal and temporal lobe deficits may be related to an underlying fronto-temporal network dysfunction in schizophrenia. Growing awareness of the reciprocal inter-connectivity of prefrontal regions with the hippocampus (Goldman-Rakic, Selemon, & Schwartz, 1984) and the rest of the brain (Fuster, 1980; Nauta, 1971) made it increasingly difficult to view frontal and temporal lobe systems in isolation. Evidence that impairment on frontal-lobe tasks such as the WCST can result from temporal lobe pathology (Weinberger, Berman, Suddath, & Torrey, 1992) provided further support for the theory that schizophrenia is best conceptualized as a disruption in the integration of widely distributed brain networks rather than as a disorder of a single brain region (Andreasen et al., 1996).

Early support for this disrupted connectivity model came from verbal fluency tasks in which individuals must rapidly generate words belonging to a specific phonemic (e.g. the letter ‘s’) or semantic category (e.g., ‘animals’). In healthy subjects speeded word generation increases prefrontal and decreases superior temporal lobe activity (Frith, Friston, Liddle, & Frackowiak, 1991; Friston, Frith, Liddle, & Frackowiak, 1991). With one exception (Spence et al., 2000), investigators found that patients fail to modulate the superior temporal gyrus (STG) during word generation, leading to abnormally increased STG activity in schizophrenia (Frith et al., 1995; Liddle, 1997; Yurgelun-Todd et al., 1996). Verbal fluency results for the prefrontal cortex (PFC) were less consistent, with evidence of PFC reductions (Curtis et al., 1998; Yurgelun-Todd et al., 1996), unimpaired PFC function (Frith et al., 1995; Liddle, 1997), and reduced PFC lateralization in schizophrenia (Weiss et al., 2004). Similar reversals (i.e., increased prefrontal and decreased temporal-limbic, or decreased prefrontal and increased temporal-limbic activity) have also been documented in a series of fMRI studies of verbal learning and memory (Heckers et al., 1998; Ragland et al., 2001, 2004, 2005; Weiss et al., 2003).

Although these activation studies can generate results consistent with a disrupted connectivity model, they cannot provide a direct test of this model because they do not examine functional relationships between brain regions. Functional connectivity (Friston, 1994) analyses examine temporal correlations in neural activity between brain regions and provide a methodological framework for testing theories of disrupted network dysfunction. There are several approaches to functional connectivity analysis (Horwitz, 2003), and their relative merits have not been established. The most widely utilized approach has been the timeseries correlation method (Biswal, Yetkin, Haughton, & Hyde, 1995; Lowe et al., 1998), which examines interregional correlations within individual subjects over the timecourse of an experiment. This approach has been effectively applied to measure functional connectivity across a wide range of cognitive and physiological states (e.g., Anand et al., 2005; Honey et al., 2003; Koshino et al., 2005; Lowe et al., 2002; Menon & Levitin, 2005).

Most studies explicitly measuring fronto-temporal correlations have confirmed the presence of abnormalities in schizophrenia. In a PET study of verbal fluency, Friston, Frith, Fletcher, Liddle and Frackowiak (1996) found an abnormal positive correlation between left STG and left DLPFC in schizophrenia. Fletcher, McKenna, Friston, Frith and Dolan (1999) also

found an abnormal positive correlation between left STG and left DLPFC in patients using a verbal memory task. Jennings McIntosh, Kapur, Zipursky, & Houle (1998) used structural equation modelling in a PET study of semantic categorization and found that the influence of left VLPFC on left STG activity was positive in controls but negative in patients, despite equal levels of performance and PFC activation between groups. Boksman et al. (2005) used a timeseries covariation approach to examine ACC connectivity in an fMRI study of word fluency and observed significant ACC connectivity with the left STG in patients, but not in controls. In a canonical variates analysis of group PET data during an N-Back working memory task, Meyer-Lindenberg et al. (2001) found high intra-temporal and low intra-frontal functional correlations in patients, with the reverse finding in controls. In a more recent PET N-Back study, Meyer-Lindenberg and colleagues (2005) used a within-subject timeseries covariation approach to explore fronto-temporal connectivity, and found negative correlations of the left hippocampal formation with right DLPFC that were task-dependent in controls, but did not vary between task conditions in the patient sample.

In contrast to these significant findings of disrupted connectivity, several PET studies of word fluency did not find evidence of left fronto-temporal abnormalities in minimally-symptomatic schizophrenia patients (Dye et al., 1999; Spence et al., 2000). Taken together with the results of other studies that have directly assessed the relationship of fronto-temporal dysfunction to illness severity (Andreasen et al., 1997; Fu et al., 2005; Lawrie et al., 2002), these negative results suggested that the degree of left STG overactivation and abnormally positive STG-prefrontal interactions might be state-dependent, correlating with the severity of active illness, and tending to normalize during remission. However, in a recent functional connectivity analysis of fMRI data acquired during word encoding, Ragland and colleagues found evidence of disrupted frontal-temporal connectivity even though patients were clinically stable with mild to moderate symptoms, supporting the notion that this disruption may be a trait-like variable (Wolf et al., 2007). The lack of correlation between fronto-temporal connectivity and measures of positive symptoms (SAPS), negative symptoms (SANS), and duration of illness was also consistent with a trait model of disrupted fronto-temporal connectivity. The study found that patients with schizophrenia had reduced DLPFC and increased VLPFC connectivity with temporal lobe areas. In contrast, patients showed increased connectivity between the VLPFC and these same temporal lobe regions. Connectivity between temporal lobe regions and DLPFC during encoding was correlated with subsequent recognition accuracy in controls, but not in patients. It was concluded that reduced temporal-DLPFC connectivity could underlie LTM encoding deficits in schizophrenia, and increased temporal-VLPFC connectivity might represent a compensatory effort. Interestingly, reduced DLPFC and unimpaired or increased VLPFC activity has also been noted in a number of other studies (Barch et al., 2001; MacDonald et al., 2005; Perlstein et al., 2001), suggesting regional specificity in the effects of schizophrenia on lateral prefrontal function.

Although there is growing support for disrupted fronto-temporal connectivity in schizophrenia, current imaging and analytic methods cannot resolve real-time network activity with a high degree of spatial accuracy. Given limitations in temporal resolution and statistical modelling, it is equally plausible that distributed dysfunction in temporal/ limbic and more posterior brain regions is the downstream result of a more focal deficit in the

DLPFC. As suggested by Kraepelin a century ago, it remains plausible that impaired ability of the DLPFC to control cognitive processing leads to dysfunction in disparate brain regions. Cognitive control is a construct from contemporary cognitive neuroscience that refers to processes that allow information processing and behaviour to vary adaptively from moment to moment depending on current goals (Posner & DiGirolamo, 1998; Shallice, 1988). Cognitive control processes include a broad class of mental operations, for example, goal or context representation and maintenance, strategic processes such as attention allocation and stimulus response mapping and performance monitoring (Cohen, Dunbar, & McClelland, 1990; Miyake & Shah, 1999; Shallice, 1988). Cognitive control is associated with a wide range of cognitive processes (Posner & Abdullaev, 1996) and is not restricted to a particular cognitive domain (Banich, 1997; Smith & Jonides, 1999). Thus, given that cognitive control processes are mediated by the DLPFC and are involved in many of the cognitive domains previously discussed, impaired cognitive control could account for DLPFC dysfunction and many of the widespread cognitive impairments exhibited by people with schizophrenia. Deficits in cognitive control have served as the basis of a number of general theories of cognitive dysfunction in schizophrenia (Braff, 1993; Callaway & Naghdi, 1982; Cohen & Servan-Schreiber, 1992; Liddle, 1993). However, the specific abnormality or abnormalities underlying disturbed cognitive control and the way in which this may lead to impairments across a broad range of higher cognitive functions and brain regions in schizophrenia have yet to be delineated.

Concluding remarks

This chapter has provided a review of how the two most prominent theories of brain dysfunction in schizophrenia developed and evolved into current models that focus on the integration of pre-frontal and temporal-limbic activity. This development has been facilitated by improvements in task paradigms that allow for parametric manipulation of specific cognitive components, event-related fMRI methods that provide control over individual and group performance differences, and analytic techniques that are beginning to provide methods for testing functional network models of the disorder. With these technical and conceptual developments investigators have also begun to attempt to translate their functional neuroimaging research to development of new pharmacological and behavioural interventions to improve cognition and functional outcome in patients with schizophrenia.

Pharmaco-fMRI is a rapidly-expanding area of research that capitalizes on numerous advantages of fMRI (Honey and Bullmore, 2004; Stein, 2001). These include high levels of temporal and spatial resolution that permit a more precise delineation of drug action on information processing sequence and brain topography. fMRI’s capacity for easy and reliable repeat scanning (without exposure to ionizing radiation) is also a significant advantage, as it allows for full washout of drugs with a long elimination half-life (which is a desirable feature of agents for clinical use). The capacity for repeat scanning also permits evaluation of drug effects that may be region- and time-sensitive, such as delayed treatment response, tolerance, sensitization and withdrawal effects (Stein, 2001). Repeat studies also allow for within-subject study designs, conferring greater statistical power in testing dose-response relationships and the comparative efficacy of different agents, by varying doses or agents within subjects across sessions (Honey et al., 1999). Since schizophrenia, like

psychiatric illness in general, lacks fully adequate animal models, fMRI presents the opportunity to enhance translational research by circumventing animal models to derive a spatio-temporal neural activity profile of cognitive enhancing agents, which can then be established as a standard for comparison of future agents. To date, pharmaco-fMRI studies of schizophrenia patients have offered preliminary insights into the effects of second generation antipsychotic medications on PFC-based cognitive dysfunction (Bertolino et al., 2004; Snitz et al., 2005).

While the neural effects of psychosocial interventions have not been tested to date in schizophrenia patients, there is evidence from studies of mood and anxiety disorder patients that the neural basis of these treatment modalities can also be characterized by fMRI (Linden, 2006; Roffman, Marci, Glick, Dougherty, & Rauch et al., 2005; Siegle, Carter, & Thase, 2006). Combining fMRI with behavioural interventions designed to compensate, and hopefully remediate, patients' cognitive deficits is a promising area for future research. For example, Ragland and colleagues demonstrated that when patients were provided with a semantic organizational strategy during initial word encoding they showed the same performance benefit as healthy comparison subjects and restored activation within the VLPFC (Ragland et al., 2005). These initial pharmacological and behavioural intervention studies hold the promise that, in addition to improving understanding of pathophysiology, fMRI will facilitate development of truly novel therapies aimed at improving cognition and lessening the functional impact of schizophrenia on affected individuals, their families and society.

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