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Task-related fronto-striatal functional connectivity during working memory performance in schizophrenia

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ABSTRACT

Working memory (WM) deficits and associated brain dysfunction are among the most well replicated candidate endophenotypic processes in schizophrenia. However, previous studies demonstrate inconsistent over- and under-activation of dorsolateral and ventrolateral prefrontal cortices (DLPFC; VLPFC), inferior parietal lobule (IPL) during WM performance, as well as subcortical structures including the striatum, and dysfunctional connectivity among fronto-striatal regions in schizophrenia. However, no previous study has investigated task-related functional connectivity (FC) of DLPFC and striatal regions using a seed-based method; here we employed this method to assess patterns of cortical and subcortical functional connectivity among WM structures during a standard 2-back WM task performed by 28 schizophrenia (SZ) and 28 healthy controls (HC). Initial group comparisons of blood oxygenation level dependent (BOLD) responses during the WM task revealed significantly greater bilateral activity in the striatum in SZ relative to HC, but there was no significant group difference in WM cortical activity (right DLPFC, VLPFC or IPL). Analyses of FC within the cortico-subcortical WM network in the HC group revealed positive performance-related FC between the right DLPFC and the right caudate, and between the right VLPFC and the right IPL; this pattern was absent in SZ. In contrast, SZ patients showed negative performance-related functional connectivity between the left putamen and the right VLPFC. Direct group comparisons in functional connectivity showed significantly greater performance-related FC between the VLPFC and bilateral putamen, as well as unilaterally between the VLPFC and the right IPL, in HC. Results suggest a critical dysfunction of cortico-striatal connectivity underpinning information retrieval for SZ patients during WM performance.

1. Introduction

Aberrant functional and structural connectivity between cortico-striatal structures are increasingly implicated in psychiatric phenomena (Quan et al., 2013; Shepherd, 2013), and have recently been associated with executive dysfunctions in working memory (WM; Fornito et al., 2012). Impaired WM is a promising endophenotypic candidate for schizophrenia, having filled a number of requirements for endophenotypic status (Gottesman and Gould, 2003): that is, the WM deficit is associated with illness, evident in unaffected relatives (Snitz et al., 2006; Gur et al., 2007), associated with an identifiable brain network (Bertolino et al., 2006; Ceaser et al., 2012), and there have been many replications of genetic association of the catechol-O-methyltransferase (COMT) Val158Met polymorphism with WM performance (Alfimova et al., 2007; Lopez-Garcia et al., 2012). However, there remains ambiguity with respect to the precise neurophysiological substrate of WM dysfunction, partly owing to mixed findings of hypo- and hyper-activation of frontal brain networks during WM performance in schizophrenia that have now accumulated in the literature (Eisenberg and Berman, 2010), and partly owing to the emergence of recent studies highlighting the importance of cortico-striatal connectivity for WM dysfunction (Meda et al., 2009; Satterthwaite et al., 2012). Accurate characterisation of the neurophysiological substrate of WM dysfunction is important for future imaging genetic investigations that may be relevant to disorders beyond schizophrenia, in accord with the Research Domain Criteria (RDoC) endorsed by the NIMH (Cuthbert and Insel, 2010; Insel et al., 2010). In this context, the present study sought to determine *task-related* patterns of functional connectivity among the cortical and sub-cortical structures of the WM network, in relation to individual WM performance in schizophrenia.

Substantial neuroimaging literature has accumulated to implicate inefficient activity of the DLPFC in association with WM deficits in schizophrenia, but the neurophysiological response of this structure does not appear to be linearly related to behavioural task performance: instead mixed findings from the many studies of brain activity during

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WM performance in schizophrenia indicate increased DLPFC activation (Manoach et al., 1999; Callicott et al., 2000; Manoach et al., 2000; Callicott et al., 2003b; Thermenos et al., 2005; Potkin et al., 2009) or decreased DLPFC activation (Barch et al., 2001; Perlstein et al., 2001; Barch et al., 2003; Perlstein et al., 2003) of this prefrontal region. An inverted U-shape model of the relationship between WM performance and prefrontal brain function has been offered to reconcile these contradictory findings, such that both over- and under-activation activation of the DLPFC during WM performance is posited to represent 'inefficiency' in relation to achieving optimal performance (Callicott et al., 2003b; Manoach, 2003; Deserno et al., 2012). However, an obvious factor relevant to the ambiguity of DLPFC activity during WM is that prefrontal activity reflects only part of a neural network supporting WM processes; other relevant cortical structures include the inferior parietal lobule (IPL) and ventrolateral prefrontal cortex (VLPFC) (Callicott et al., 2003b; Thermenos et al., 2005; Barch and Csernansky, 2007; Schneider et al., 2007; Schlagenhauf et al., 2008; Broome et al., 2009; Thormodsen et al., 2011), as well as subcortical structures such as the basal ganglia (Manoach et al., 2000; Lewis et al., 2004; Landau et al., 2009; Simpson et al., 2010; Voytek and Knight, 2010). These structures have been particularly implicated in WM performance in young healthy (Satterthwaite et al., 2012) and young schizophrenia patients (Diwadkar et al., 2012), and have shown aberrant functional activation in schizophrenia during WM performance (Manoach et al., 2000). While several previous studies have examined functional and effective connectivity among the WM cortical network (Meyer-Lindenberg et al., 2001; Anticevic et al., 2012; Deserno et al., 2012), studies of cortical and subcortical structures are also now emerging in relation to WM pathology (Schlosser et al., 2003; Marenco et al., 2012; Yoon et al., 2013), and large-scale brain circuitry such as the default-mode network (Pettersson-Yeo et al., 2011; Whitfield-Gabrieli and Ford, 2012).

However, the contribution of aberrant cortico-striatal connectivity to the WM impairments seen in schizophrenia remains unclear. Previous neuroimaging studies have reported altered function of these brain regions in schizophrenia patients and their siblings (Callicott et al., 2000, 2003a; Manoach, 2003; Jansma et al., 2004; Whitfield-Gabrieli et al., 2009), but not all studies have used methodology that enables individual WM task performance to inform the measurement of functional connectivity among cortico-striatal regions; this is important to elucidate the specific neurophysiological substrate of WM impairments in schizophrenia, as a future genetic and pharmacological target. One recent study moving toward this goal used independent components analysis (ICA) of fMRI data from schizophrenia patients and healthy controls during the Sternberg WM task (Meda et al., 2009). The unique advantage of ICA is in detecting any intrinsic or task-related synchronous signals [representing networks], across the whole-brain, and thus provides one means of examining whole-brain functional connectivity during WM in schizophrenia (Meda et al., 2009). Meda et al.'s study revealed three components (neural networks) associated with "normal" WM performance, that were less engaged in schizophrenia. One of these components included a network comprising the left posterior parietal, left dorsal/ventrolateral prefrontal cortex, anterior cingulate, and basal ganglia, that was reduced in strength (of connectivity among all regions) in schizophrenia, relative to controls. However, ICA analyses as performed by Meda et al. cannot determine group differences in functional connectivity among *specific regions* within this network. This can be achieved using a seed-based functional connectivity approach to the analysis within a task-specific paradigm that restricts itself to the time-course of the seed regions (single metric of functional connectivity) (Joel et al., 2011). We adopted this method here, with the aim to characterise more directly the strength of functional connectivity between seed regions implicated in the WM network (as indicated in many previous studies), in association with WM performance in schizophrenia.

The present study thus set out to determine whether schizophrenia patients demonstrate differential cortico-striatal functional connectivity among a defined WM network, in association with WM performance, compared to healthy controls. We administered a well-established visuospatial n-back task (Callicott et al., 1998) to schizophrenia and healthy participants during functional neuroimaging, and performed a seed-based connectivity analysis between the frontal (DLPFC and VLPFC) and parietal (IPL) cortices, as well as with subcortical basal ganglia structures (caudate and putamen). We included task accuracy as a covariate of interest to provide greater task specificity: that is, to detect functional connectivity effects that are related to individual WM performance. Finally, we tested the hypothesis that reduced functional connectivity among the striatal and frontal cortical regions would be associated with poor WM performance in schizophrenia.

2. Methods and materials

All volunteers provided written informed consent to participate in the study according to procedures approved by the UNSW Human Research Ethics committees (HC12384), the South East Sydney and Illawarra Area Health Service (HREC 09/081) and St Vincent's Hospital (HREC/10/SVH/9).

2.1. Participants

Participants were 28 patients with a diagnosis of schizophrenia ($n = 20$) or schizoaffective disorder ($n = 8$) and 28 healthy adults (HC) with no personal history of a DSM-IV Axis 1 disorder, and no history of psychosis in their first-degree biological relatives. All patients fulfilled relevant DSM-IV criteria (APA, 2000). Patients with schizophrenia/schizoaffective disorder (SZ) were recruited from outpatient services of South Eastern Sydney and St Vincent's Hospital health services, as well as the Australian Schizophrenia Research Bank (ASRB; Loughland et al., 2010). Healthy participants were recruited from the ASRB and via advertisements placed in local community publications and on noticeboards. Exclusion criteria included inability to communicate sufficiently in English, current neurological disorder, head injuries with loss of consciousness, a diagnosis of substance abuse or dependence in the past six months, and/or having been treated with electro convulsive therapy in the previous six months.

2.2. Neuropsychological and clinical assessments

All participants were assessed using the Depression, Anxiety and Stress Scale (DASS; Lovibond and Lovibond, 1995), the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999); and the Edinburgh Handedness Inventory (Oldfield, 1971). Psychotic symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989).

2.3. Functional magnetic resonance imaging

2.3.1. Imaging acquisition

We acquired 128 whole brain T2* weighted echo-planar images (EPI) using a Philips Achieva 3T scanner: 4 mm slices, 0.3 mm gap, 32 ascending axial slices, repetition time (TR) 2000 ms, echo time (TE) 30 ms, flip angle 80°, matrix 96×96, field of view: 240 mm. A T1-weighted high-resolution anatomical scan (MPRAGE) was also obtained for each participant for registration and screening: TR 8.9 ms, TE 4.1 ms, field of view 240 mm, matrix: 268×268, sagittal plan, 0.9 mm slices with no gap, 200 slices.

2.3.2. N-back working memory task

The n-back task consisted of well-validated task comprising a 2-back and a 0-back condition (Callicott et al., 1998). The task was presented as a continual run in which four alternating 30-s epochs of each condition occurred. All participants underwent "offline" n-back training before the fMRI data acquisition, for as long as required to achieve at least