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Further evidence of alerted default network connectivity and association with theory of mind ability in schizophrenia

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ABSTRACT

Background: Resting-state functional magnetic resonance imaging (rs-fMRI) has repeatedly shown evidence of altered functional connectivity of large-scale networks in schizophrenia. The relationship between these connectivity changes and behaviour (e.g. symptoms, neuropsychological performance) remains unclear.
Methods: Functional connectivity in 27 patients with schizophrenia or schizoaffective disorder, and 25 age and gender matched healthy controls was examined using rs-fMRI. Based on seed regions from previous studies, we examined functional connectivity of the default, cognitive control, affective and attention networks. Effects of symptom severity and theory of mind performance on functional connectivity were also examined.
Results: Patients showed increased connectivity between key nodes of the default network including the precuneus and medial prefrontal cortex compared to controls ($p < 0.01$, FWE-corrected). Increasing positive symptoms and increasing theory of mind performance were both associated with altered connectivity of default regions within the patient group ($p < 0.01$, FWE-corrected).
Discussion: This study confirms previous findings of default hyper-connectivity in schizophrenia spectrum patients and reveals an association between altered default connectivity and positive symptom severity. As a novel find, this study also shows that default connectivity is correlated to and predictive of theory of mind performance. Extending these findings by examining the effects of emerging social cognition treatments on both default connectivity and theory of mind performance is now an important goal for research.

1. Introduction

Schizophrenia is characterised by deficits in cognitive processes such as working memory and attention (Nuechterlein et al., 2004). These deficits are among the strongest predictors of functional outcome, making better understanding of cognitive deficits an important priority (McGurk et al., 2007; Lewandowski et al., 2011). Theory of mind (TOM) is the ability to attribute thoughts, beliefs and intentions to other people (Van Overwalle, 2009). Schizophrenia patients also show large deficits in TOM (Bora et al., 2009), which predicts 15–50% of variation in social functioning (Roncone et al., 2002; Brüne et al., 2007), suggesting TOM is a particularly important target for new treatments in order to improve social function and rehabilitation.

To examine cognitive deficits at the level of the brain, functional magnetic resonance imaging (fMRI) has been used to identify differences in brain activity in schizophrenia patients compared to healthy controls during performance of cognitive tests (Glahn et al., 2005). Interest in using fMRI data acquired during rest has also grown, in part because data can be obtained in as little as 5 min and does not carry any behavioural demands, which can be stressful for some patients (Whitfield-Gabrieli and Nieto-Castanon, 2012). Neural networks show low-frequency synchronous fluctuations of the blood oxygen-level dependent (BOLD) signal during rest, allowing researchers to examine functional connectivity between different areas of the brain (Whitfield-Gabrieli and Nieto-Castanon, 2012). Several resting-state networks have now been identified, including networks that play an important role in TOM, working memory and attention (Fox et al., 2006; Sheline et al., 2010).

Altered functional connectivity has been consistently observed in schizophrenia patients suggesting it may be a primary factor contributing to illness (Stephan et al., 2009). Functional connectivity has also been shown to explain more variance in behaviour than either brain activity or brain structure, suggesting that connectivity changes may have a particularly strong impact upon behavioural outcomes (Pezawas et al., 2005; Meyer-Lindenberg, 2009). Patients with schizophrenia show altered functional connectivity across several resting-state networks

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Table 1
Five networks examined in this study, prominent brain regions, proposed cognitive functions and relevance to schizophrenia.

Resting-state network	Prominent brain regions	Proposed cognitive functions	Relevance to schizophrenia
Default mode	Precuneus/posterior cingulate, medial prefrontal cortex, and temporo-parietal junction	Theory of mind; internally focussed tasks such as autobiographical memory	Theory of mind impairment is a core feature (Bora et al., 2009).
Cognitive control	Lateral prefrontal cortex, posterior parietal cortex	Executive function, including working memory	Working memory impairment is a core feature (Lee and Park, 2005).
Affective	Anterior cingulate cortex, amygdala	Emotion processing and regulation	Emotion processing deficits are a core feature (Aleman and Kahn, 2005)
Dorsal attention	Frontal eye field and intraparietal sulcus	Control of attention based on internal goals	Attentional deficits are a core feature (Keefe and Harvey, 2012; Nuechterlein et al., 2015)
Ventral attention	Temporo-parietal junction and ventral frontal cortex	Reorienting of attention to salient stimuli	Attentional deficits are a core feature (Keefe and Harvey, 2012; Nuechterlein et al., 2015)

with increased connectivity and spatial extent of the default network the most consistent finding (Whitfield-Gabrieli et al., 2009; Garrity et al., 2007; Zhou et al., 2007).

In order to better understand resting-state connectivity changes in schizophrenia and the relation of these changes to clinical measures of symptom severity, the present study examined each of five networks involved in cognitive functions disrupted in schizophrenia in a sample of 27 patients and 25 healthy controls and effects of positive and negative symptoms, following resting-state fMRI (rs-fMRI) methods previously employed in our group (McCarthy et al., 2013) (see Table 1). To investigate the relationship between connectivity changes and cognitive function, we also performed a post-hoc analysis examining effects of TOM test scores on connectivity of all networks showing initial differences between patients and controls.

2. Materials and methods

2.1. Participants

28 patients with a DSM-IV diagnosis of schizophrenia/schizoaffective disorder were recruited for this study. Participants were right-handed, aged 18–65, had no history of substance abuse in the preceding six months, no previous head injury associated with a loss of consciousness of more than a few minutes and provided written consent in accordance with local ethics committee guidelines. One patient was excluded from the study due to excess movement in the MRI scanner (Section 2.3), leaving a total of 27 patients. 25 healthy participants that matched the patient group in age and gender were selected from a larger sample of healthy volunteers that were recruited as part of an imaging and cognitive genetics study on psychosis (Mothersill et al., 2014a, 2014b).

2.2. Instruments

Positive and negative symptoms were measured using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), where separate symptoms are rated between 0 (absent) and 5 (severe) based on interview with patients. We used SAPS/SANS as they are among the most common symptom rating scales used and have been used in previous rs-fMRI studies on schizophrenia (Whitfield-Gabrieli et al., 2009).

Patients and controls showed significant differences in connectivity between brain regions that play an important role in TOM (Section 3.2). In a post-hoc analysis, we therefore examined the relationship between TOM and functional connectivity of these regions to better understand effects of these connectivity changes on TOM. To do this, we examined effects of Reading the Mind in the Eyes test score (Baron-Cohen et al., 2001) on connectivity of all seed regions showing patient-control differences. Participants had to verbally identify the correct mental state of individuals from four possible answers from visual inspection of 36 black and white photographs of the eye region of the face. We used the Eyes test because it is a sensitive measure of TOM, schizophrenia patients consistently show large deficits in Eyes performance (Bora et al., 2009) and it has previously been associated with increased precuneus and TPJ activity under fMRI (Baron-Cohen et al., 1999; Schurz et al., 2014).

For this analysis we focussed on patients, given that we were primarily interested in examining effects of dysconnectivity on behavioural performance in schizophrenia. In addition, only a small number of healthy controls had data available for this test ($N = 11 / 25$) compared to the patient group ($N = 20 / 25$).

Table 2
Resting-state networks and associated seed coordinates in MNI space.

Network	Seed coordinates (x y z)
Default mode network (precuneus)	±9 −60 25
Cognitive control network (DLPFC)	±40 33 24
Affective network (ACC)	±12 39 −11
Dorsal attention network 1 (FEF)	±28 −7 53
Dorsal attention network 2 (IPS)	±31 −55 55
Ventral attention network 1 (TPJ)	±59 −47 22
Ventral attention network 2 (VFC)	±41 21−6

DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; FEF = frontal eye fields; IPS = intraparietal sulcus; TPJ = temporo-parietal junction; VFC = ventral frontal cortex.

2.3. Procedures

First, SAPS and SANS were administered to patients as part of our larger study on psychosis prior to recruitment for MRI scanning and were assessed by clinical researchers. A printed version of the Eyes test was also administered to patients by a member of the research team separately to the MRI scan. Finally, the MRI scans were performed as part of a longer MRI assessment in the Trinity College Institute of Neuroscience for our larger study on psychosis.

2.4. MRI acquisition parameters

Participants were scanned using a Philips Intera Achieva 3-T MRI scanner with a SENSE 8-channel head coil. We acquired whole-brain BOLD EPI with 35 3.5 mm slices, TR = 2000 ms, TE = 30 ms, field of view = 224 × 224 mm, flip angle = 90°. Before functional MRI scanning, participants were asked to close their eyes and relax for approximately 6 min.

Structural images consisted of a T1-weighted image (180 slices; duration: 6 min) acquired using a TFE gradient echo pulse sequence, with slice thickness of 0.9 mm, a 230 × 230 mm field of view and a spatial resolution of 0.9 × 0.9 × 0.9 mm^3.

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