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Altered intrinsic and extrinsic connectivity in schizophrenia

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ABSTRACT

Schizophrenia is a disorder characterized by functional dysconnectivity among distributed brain regions. However, it is unclear how causal influences among large-scale brain networks are disrupted in schizophrenia. In this study, we used dynamic causal modeling (DCM) to assess the hypothesis that there is aberrant directed (effective) connectivity within and between three key large-scale brain networks (the dorsal attention network, the salience network and the default mode network) in schizophrenia during a working memory task. Functional MRI data during an n-back task from 40 patients with schizophrenia and 62 healthy controls were analyzed. Using hierarchical modeling of between-subject effects in DCM with Parametric Empirical Bayes, we found that intrinsic (within-region) and extrinsic (between-region) effective connectivity involving prefrontal regions were abnormal in schizophrenia. Specifically, in patients (i) inhibitory self-connections in prefrontal regions of the dorsal attention network were decreased across task conditions; (ii) extrinsic connectivity between regions of the default mode network was increased; specifically, from posterior cingulate cortex to the medial prefrontal cortex; (iii) between-network extrinsic connections involving the prefrontal cortex were altered; (iv) connections within networks and between networks were correlated with the severity of clinical symptoms and impaired cognition beyond working memory. In short, this study revealed the predominance of reduced synaptic efficacy of prefrontal efferents and afferents in the pathophysiology of schizophrenia.

1. Introduction

Schizophrenia is a severe mental illness, with a variety of positive and negative clinical symptoms and cognitive impairments. The dysconnection hypothesis frames schizophrenia as a brain disorder, characterized by abnormal functional integration among brain regions (Andreasen et al., 1998; Bullmore et al., 1997; Friston et al., 2016; Friston and Frith, 1995; Stephan et al., 2006; Weinberger, 1993). Increasing evidence from functional connectivity studies, which examine correlations between fMRI timeseries across the brain, suggests that this dysconnection involves changes in coupling between large-scale brain networks (Fornito and Bullmore, 2015; Jiang et al., 2013; Pettersson-Yeo et al., 2011). However, functional connectivity methods do not reveal the causal influence of one neural system on another (Friston, 2011) and it remains unclear how the causal influences within and between large-scale brain networks are disturbed in schizophrenia.

Several studies have performed effective connectivity analyses to address this question (Crossley et al., 2009; Deserno et al., 2012; Nielsen et al., 2017; Schmidt et al., 2013; Schmidt et al., 2014; Zhang et al., 2013). Effective connectivity is the directed (causal) influence of one neural system over another, which is inferred by modeling the neuronal interactions that give rise to fMRI time series (Breakspear, 2004; Friston et al., 1993). Dynamic causal modeling (DCM) (Friston et al., 2003) is a widely adopted framework for effective connectivity analysis. Traditionally, DCM has been used to test competing hypotheses about brain networks comprising only a few regions (usually < 6) and directed connections. These hypotheses are specified in the form of subgraphs or models, which are subsequently

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compared using Bayesian model selection and averaging. Following this approach, several studies have found abnormalities in effective connectivity in the fronto-temporal network (Crossley et al., 2009), the fronto-parietal network (Deserno et al., 2012; Nielsen et al., 2017; Schmidt et al., 2013; Schmidt et al., 2014) and the default mode network (Zhang et al., 2013) during working memory tasks in schizophrenia or psychosis. However, each of these studies focused on examining connectivity between regions *within* a single brain network and did not examine the connectivity *between* large-scale networks that contextualize functional integration in the brain.

In this study we investigated the effective connectivity within and between three key large-scale networks during a working memory task in schizophrenia. Working memory impairment is a common cognitive deficit in schizophrenia (Forbes et al., 2009; Lee and Park, 2005; Piskulic et al., 2007) and is considered to be a fundamental impairment that underwrites schizophrenic thought disorder (Goldman-Rakic, 1994). Multiple brain regions including lateral prefrontal cortices, posterior parietal cortices, insula and supplementary motor cortex extending to the anterior cingulate cortex (SMA/ACC) show co-activation during working memory tasks (Chu et al., 2015; Owen et al., 2005; Rottschy et al., 2012). These are commonly segregated into two key large-scale networks: the frontoparietal dorsal attention network (DAN) (Corbetta and Shulman, 2002; Fox et al., 2006) and the cingulate-opercular salience network (SN) (Dosenbach et al., 2007; Menon and Uddin, 2010; Seeley et al., 2007). Meanwhile, medial prefrontal and medial parietal regions often show deactivation during working memory tasks – these are part of the default-mode network (DMN) (Andrews-Hanna et al., 2010; Buckner et al., 2008; Raichle, 2015). In patients with schizophrenia, regions in the DAN and SN often show decreased activation (Anticevic et al., 2013; Kim et al., 2010; Kyriakopoulos et al., 2012), while the regions within the DMN often fail to deactivate during working memory tasks (Anticevic et al., 2013; Haatveit et al., 2016; Whitfield-Gabrieli et al., 2009). By including regions of the DAN, SN and DMN in a single connectivity model, we set out to investigate how the coupling between these networks is disturbed in schizophrenia.

A further novel feature of this study is that we apply recent developments in hierarchical Bayesian modeling, to make inferences based on a relatively large dataset (n = 102). In the Parametric Empirical Bayes (PEB) framework for DCM (Friston et al., 2016), an individual subject's connections are modeled as being sampled from a group mean, with additive random effects and systematic intersubject variability modeled by between-subject covariates. This hierarchical modeling of random parametric effects offers several advantages over previous methods. In particular, the uncertainty (variance) of estimated connection strengths at the single-subject level is properly accommodated when making inferences at the group level. This increases the sensitivity of the approach and renders it robust to outlier subjects with noisy data (Friston et al., 2016).

In this study, we used DCM – in conjunction with hierarchical modeling – to ask whether patients with schizophrenia show abnormalities in intrinsic (within-region) connectivity and extrinsic (between-region) connectivity in three large-scale brain networks (DAN, SM, DCM) while performing a working memory task. We further asked whether working memory load modulates this connectivity. Finally, we asked whether any abnormal directed connections are related to symptom severity and wider cognitive function to establish the functional validity of the effective connectivity estimates – that might be used a biomarker or endophenotype in subsequent studies.

2. Materials and methods

2.1. Participants

Patients with schizophrenia were recruited from the Department of Psychiatry, Renmin Hospital of Wuhan University (Wuhan, China). The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM-IV) (SCID) was administered, to confirm diagnosis. The patients also met the following inclusion criteria: (1) the total score of Positive and Negative Syndrome Scale (PANSS) was over 60, (2) duration of illness was < 5 years, (3) 18–45 years of age, (4) at least 9 years of education, (5) right-handed, and (6) Han Chinese. Patients were excluded if they met the diagnosis criteria of any other DSM Axis-I disorders, had severe physical illness including cardiovascular disease, had received electroconvulsive therapy six months prior to recruitment, or had structural changes in the brain (such as a white matter lesion) diagnosed by a radiologist. Healthy controls were recruited by word of mouth and bulletin board postings both in the hospital and nearby communities. The healthy controls, who matched the patients on age, gender and educational level, had the same inclusion and exclusion criteria; except that healthy controls were excluded if they or their first-relatives met any diagnosis of a psychiatric disorder according to the DSM-IV criteria.

Fifty-one patients and 66 healthy controls were recruited. All the patients were receiving antipsychotic medications, which were converted to their chlorpromazine equivalents. Six patients and 4 healthy controls were excluded from the data analyses due to severe head motion during scanning (x,y,z translation > 3 mm or x,y,z rotation > 3°), 3 patients were excluded due to extremely high values in the mean frame displacement (FD) value and 2 patients were excluded due to extreme low scores in the 0-back performance (see details in Methodology). Finally, 40 patients and 62 normal controls were included in the following data analyses.

Each participant or at least one first-degree relative for each patient provided informed consent before participation. The Ethics Committee of Renmin Hospital of Wuhan University and the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences approved the study.

2.2. Experimental design and task

The WM paradigm used a blocked design, numeric n-back task, with numbers 0–9 as stimuli, which has been used in previous studies (Deserno et al., 2012; Salomon et al., 2011; Wu et al., 2017). The paradigm alternated between rest and task. Rest periods, in which subjects were instructed to fixate on a cross at the centre of the screen, lasted for 5 scans (i.e. 10 s). The task consisted of two conditions, 0-back (baseline) and 2-back (WM load condition), arranged as 0-2-0-0-2-2-2-0-0-2-2-0, each with duration of 12 scans (i.e. 24 s). Before each block a visual cue of one scan (i.e. 2 s) was presented, indicating the condition of the subsequent block. Each block comprised 12 stimuli, three of which were targets, each presented for 1000 ms with a 1000 ms interstimulus interval. Subjects were instructed to match the current number to a target, either the number 9 (0-back) or the number presented two trials earlier (2-back).

In order to ensure compliance during the subsequent acquisition, a training session was conducted prior to scanning. The training procedure was the same as that used in our previous study (Wu et al., 2017). In brief, the training task was similar to the formal task, though only one 0-back and one 2-back trial were included. Accuracy was displayed on the monitor at the end of the practice task, and patients were provided with further practice opportunities, until they clearly understood the task.

2.3. Cognition assessments

Several cognitive assessments were conducted outside of scanning. These included the Digit Symbol Coding task, Digit Span (forward and backward) and Category Fluency test. The Digit Symbol Coding task assesses information processing speed and is known to detect impairments in schizophrenia reliably (Bora et al., 2010). The Category Fluency test is the cognitive assessment with the second largest effect size,