1. Introduction

Schizophrenia is a severe and chronically debilitating psychiatric disorder, with a two to three-fold increase in early mortality compared with the general population (Saha et al., 2007). Although use of first and second generation antipsychotics has significantly improved treatment response and quality of life for many individuals with schizophrenia, symptoms persist for up to one third of affected individuals, despite trialing various types of antipsychotic medications. This population has been termed “treatment resistant” (i.e., TRS). Currently clozapine is the only evidence-based atypical antipsychotic that has been found effective in ameliorating psychotic symptoms in TRS (Asenjo Lobos et al., 2010). However, clozapine is effective in only a fraction of patients, as up to 70% of TRS individuals do not respond (Papetti et al., 2007). Consequently, TRS is one of the greatest therapeutic challenges, with patients often suffering a more severe and chronic form of the disorder than those who respond to antipsychotic treatment (Bolonna and Kerwin, 2005). Many clinicians have posited that TRS may in fact be more accurately understood as a distinct subtype of schizophrenia, as opposed to being a chronic illness phase (Farooq et al., 2013; Lee et al., 2015). This notion has been supported by recent findings of differences in dopamine concentrations in the limbic and associative striatal subdivisions and glutamate levels in the anterior cingulate cortex between treatment-responsive schizophrenia and TRS groups (Demjaha et al., 2014; Demjaha et al., 2012). The relation between striatal dopamine and disrupted functional connectivity remains unclear in schizophrenia,
however elevated dopamine levels may worsen the signal-to-noise ratio of spontaneous brain activity in the striatum, leading to a reduction in functional connectivity between striatum and frontal regions (Sorg et al., 2013). Despite the clinical relevance of TRS, few neuroimaging studies have focused on this population.

The theory of ‘dysconnectivity’ between spatially separated brain systems is one of the most prominent and widely researched hypotheses in schizophrenia (Friston and Frith, 1995; Zalesky et al., 2011; Zalesky et al., 2015). Findings however are inconsistent, with reports of both increased resting-state functional connectivity (rs-FC) (Jafri et al., 2008; Lui et al., 2010; Sorg et al., 2013; Whitfield-Gabrieli et al., 2009) and decreased rs-FC (Bluhm et al., 2007; Bluhm et al., 2009; Camchong et al., 2011; Gavrilcusc et al., 2010; Hopman et al., 2010; Liang et al., 2006; Meda et al., 2012; Ongur et al., 2010; Rotarska-Jagiela et al., 2010; Vercammen et al., 2010; Zhou et al., 2007; Zhou et al., 2008). Few studies have used functional imaging to investigate rs-FC in individuals with TRS. Using independent component analysis, one study found that TRS individuals with auditory-verbal hallucinations (AVH) showed reduced rs-FC between the left tempo-parietal junction and right Broca’s area and anterior cingulate cortex (Vercammen et al., 2010). A later study also investigated AVH in TRS and found an increase in connectivity between bilateral temporal regions and a decrease in connectivity within the cingulate cortex (Wolf et al., 2011). These studies however, had relatively small samples (n = 27, n = 10) and explored connectivity predominantly in the context of AVH (Vercammen et al., 2010; Wolf et al., 2011). The most recent study by White et al. (2016) found reduced FC between the ventral striatum and substantia nigra in TRS compared with non-TRS patients, indicating there may be fundamental differences in network properties (reduced FC) between treatment-responsive and TRS patients.

More recently, in conjunction with measures of FC strength, graph theoretical methods have been applied to functional magnetic resonance imaging (fMRI) data in an attempt to understand the topology of brain networks. Two such measures that address the question of functional network organization are global and local efficiency. The efficiency of a brain network is inversely related to the number of intermediate regions that must be traversed for a pair of brain regions to communicate with each other. A directly connected pair of regions can communicate most efficiently since they do not utilize any intermediate regions. However, many pairs of brain regions are not directly connected, and thus communication between such regions is via a path that traverses one or more intermediate regions. The greater the number of intermediate regions traversed, the less efficient communication becomes, due to increasing energy requirements and potential signal dispersion (Bullmore and Sporns, 2012; Fornito et al., 2016). A reduction in brain network efficiency in patients may indicate a bias in the trade-off between metabolic costs and topology (Rubinov and Sporns, 2010; Wang et al., 2010).

Here, we characterized the connectivity and efficiency of whole-brain functional networks inferred from rs-fMRI in a group of individuals with TRS, compared to healthy controls. We also investigated whether a relationship between network connectivity and topology and symptomatology/functioning is evident. In light of previous research and the chronicity of the present sample, we hypothesize that the TRS group will show widespread reduced rs-FC, predominantly between frontal-temporal regions and topological abnormalities in the form of reduced global efficiency compared with controls. We also hypothesize that these abnormalities will correlate with symptom severity and functioning in the TRS group.

2. Methods

2.1. Participants

Forty-two treatment resistant schizophrenia (TRS) individuals (mean age 41.3 ± 10.0, 30 males) were recruited from inpatient and outpatient clinics in Melbourne, Australia. TRS was defined as at least two unsuccessful trials of two or more different antipsychotic types and currently taking clozapine (Kane et al., 1988; Suzuki et al., 2012).

Inclusion criteria for the TRS group were a diagnosis of schizophrenia, currently prescribed and taking clozapine and aged 18–65 years. Forty-two healthy control participants (mean age 38.4 ± 10.4, 24 males) with similar socio-economic backgrounds were recruited from the general community. All participants were administered the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to confirm diagnosis of schizophrenia and to rule out current or past psychopathology in healthy controls. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and all participants were evaluated using the Global Assessment of Functioning (GAF) (Hall and Parks, 1995) and the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992).

The study was approved by the Melbourne Health Human Research Ethics Committee (MHREC ID 2012.069); and all participants provided written informed consent prior to participation.

2.2. Imaging data acquisition

Magnetic resonance images were acquired on a Siemens Avanto 3T Magnetom TIM Trio scanner. T1-weighted images were acquired using an optimized Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. The sequence parameters were: 176 sagittal slices of 1 mm thickness without gap, field of view (FOV) = 250 × 250 mm², repetition time (TR) = 1980 ms, echo time (TE) = 4.3 ms, flip angle = 15°, using an acquisition matrix of 256 × 256 resulting in a final reconstructed voxel resolution of 0.98 × 0.98 × 1.0 mm³. Resting-state fMRI was acquired using a T2*-weighted echo-planar imaging sequence (TE = 40 ms; TR = 2.4 s; voxel dimensions = 3.3 × 3.3 × 3; matrix size = 64 × 64). Data was acquired for 8 min, resulting in 200 volumes.

2.3. fMRI data preprocessing

Data was preprocessed using FSL (FMRIB Software Library, www.fmrib.ox.ac.uk) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm). For each subject, echo-planar images were slice-time corrected, realigned to the mean functional image to correct for motion, and co-registered to the structural T1-weighted scan via rigid-body registration then spatially normalized by non-linear registration to the Montreal Neurological Institute (MINI) 152 template with 2 mm resolution. Data was spatially smoothed using a Gaussian kernel of full width at half maximum 4 mm, and bandpass filtered (0.01–0.1 Hz).

Head motion was controlled with the Friston 24-parameter model (Friston et al., 1996) and signals from white matter and the ventricles were regressed to account for physiological noise. Given measures of FC may be influenced by head motion (Power et al., 2012), each participant’s movement during scanning was quantified by framewise displacement (FD) (Power et al., 2013). FD is a compressed single index calculated from derivatives of the six rigid-body realignment parameters. Volumes exceeding a FD of >0.5 mm, a commonly used threshold (Power et al., 2012) were eliminated, otherwise known as “scrubbing”.

2.4. Whole-brain connectivity analysis

An overview of the methodology is shown in Fig. 1. A FC matrix was generated for each subject by anatomically parcellating the registered fMRI volumes into 116 nodes using the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). For each of the 116 regions, the mean time-series was calculated by averaging the fMRI time series across all voxels. The Pearson correlation coefficient was then calculated between each of the distinct regional pairs to determine a measure of FC. The network-based statistic (NBS) (Zalesky et al., 2010) was used
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