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Risk and resilience brain networks in treatment-resistant schizophrenia

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ABSTRACT

Background: Genes, molecules and neural circuits that are associated with, or confer risk to developing schizophrenia have been studied and mapped. It is hypothesized that certain neural systems may counterbalance familial risk of schizophrenia, and thus confer resilience to developing the disorder. This study sought to identify resting-state functional brain connectivity (rs-FC) representing putative risk or resilience endophenotypes in schizophrenia.

Methods: Resting-state functional magnetic resonance imaging (rs-fMRI) was performed in 42 individuals with treatment resistant schizophrenia (TRS), 16 unaffected first-degree family members (UFM) and 42 healthy controls. Whole-brain rs-FC networks were mapped for each individual and analysed graph theoretically to identify network markers associated with schizophrenia risk or resilience.

Results: The ~900 functional connections showing between-group differences were operationalized as conferring: i) resilience, ii) risk, or iii) precipitating risk and/or illness effects. Approximately 95% of connections belonged to the latter two categories, with substantially fewer connections associated with resilience. Schizophrenia risk primarily involved reduced frontal and occipital rs-FC, with patients showing additional reduced frontal and temporal rs-FC. Functional brain networks were characterized by greater local efficiency in UFM, compared to TRS and controls.

Conclusions: TRS and UFM share frontal and occipital rs-FC deficits, representing a 'risk' endophenotype. Additional reductions in frontal and temporal rs-FC appear to be associated with risk that precipitates psychosis in vulnerable individuals, or may be due to other illness-related effects, such as medication. Functional brain networks are more topologically resilient in UFM compared to TRS, which may protect UFM from psychosis onset despite familial liability.

1. Introduction

Schizophrenia has a strong genetic component, with the most prominent risk factor for developing the disorder being family history (Gottesman and Gould, 2003; Kendler and Neale, 2010). Studying unaffected relatives of individuals with schizophrenia can therefore offer insight into the heritable pathophysiology of the disorder, independent of factors that often confound studies in patients, such as illness progression and chronic antipsychotic use (Braff et al., 2007). A number of structural brain alterations are shared between schizophrenia patients and their unaffected family members (UFM) representing candidate endophenotypes (Moran et al., 2013; Turetsky et al., 2007), such as cortical thinning (Goghari et al., 2007; Gogtay et al., 2007; Yang et al., 2010), reduced morphological covariance (Zalesky et al., 2015), whole brain (McIntosh et al., 2011; Thermenos et al., 2013) and subcortical

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volume reductions (Peper et al., 2007; Thermenos et al., 2013). Less understood, however, is the nature of structural and functional brain connectivity abnormalities in UFM. Decreased resting-state functional connectivity (rs-FC) is commonly reported in schizophrenia patients, although increased rs-FC is also described (for review, see Fitzsimmons et al., 2013). Similarly, studies in UFM have generated mixed results, with some findings showing increased rs-FC relative to controls (Jang et al., 2011; Jukuri et al., 2013; van Buuren et al., 2012; Whitfield-Gabrieli et al., 2009), while others report reduced rs-FC (A. Fornito et al., 2013; Jang et al., 2011; Jukuri et al., 2015; Khadka et al., 2013; Liu et al., 2012; Meda et al., 2012; Sole-Padulles et al., 2016). On the whole, rs-FC is predominantly reduced in schizophrenia patients (Fornito et al., 2012), and the functional brain networks most affected often show milder rs-FC reductions in UFM (Wang et al., 2015). Aberrant rs-FC networks shared between patients and UFM may therefore represent a marker of genetic vulnerability to schizophrenia, rather than solely the result of illness duration, medication and/or other secondary environmental factors (Repovs et al., 2011).

Alternatively, rs-FC alterations that are unique to UFM *and* absent or moderated in affected relatives and the general population might be hypothesized to represent putative markers of resilience to schizophrenia, and counterbalance familial liability. Resilience biomarkers have not been extensively studied in schizophrenia, with resilience in psychiatry traditionally broached in terms of psychological response to stress and trauma (Feder et al., 2009; Russo et al., 2012). Recent evidence suggests that functional brain networks in UFM show increased resilience to pathological disruptions, compared to schizophrenia patients and controls (Lo et al., 2015). Similarly, UFM show resilience in that they recover from developmental delays in structural connectivity (Chakravarty et al., 2015; Zalesky et al., 2015). Resilience endophenotypes inferred from rs-FC have also been reported in depression (Peterson et al., 2014). These previous studies motivate investigation of functional brain networks associated with resilience in schizophrenia.

Here, we perform resting-state functional magnetic resonance imaging (fMRI) in individuals with treatment-resistant schizophrenia (TRS), UFM and healthy controls, with the aim of identifying functional brain networks associated with schizophrenia risk or resilience. We operationalize resilience as functional connections or functional network properties that are uniquely present (or absent) in UFM individuals, whereas network properties that are shared between TRS and UFM (but not evident in the general population) are considered risk markers. We consider TRS patients in this study to ensure a homogeneous clinical phenotype (Jablensky, 2006), and thereby maximize the reproducibility of our findings. We and others have found that TRS is associated with widespread abnormal rs-FC (Ganella et al., 2016; Vercammen et al., 2010; White et al., 2016; Wolf et al., 2011) and we hypothesize that investigating UFM of TRS patients will provide insight into functional networks associated with schizophrenia risk and resilience. Specifically, we hypothesize both the TRS and UFM groups to show reduced rs-FC and network efficiency relative to controls, albeit to a lesser extent in UFM.

2. Methods

2.1. Participants

Forty-two TRS individuals (mean age 41.3 ± 10.0, 30 males) were recruited from inpatient and outpatient clinics located in Melbourne, Australia, as previously described (Ganella et al., 2016). TRS was defined as at least two unsuccessful trials (4–10 weeks) of two or more different antipsychotic types (dosage equivalent to 1000 mg/d chlorpromazine) within the last 5 years, with a Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score ≥ 90 and currently taking clozapine (Kane et al., 1988; Suzuki et al., 2012). The study consisted of 16 UFM first-degree relatives of TRS patients (mean age 57.5.4 ± 11.7, 2 males) and 42 (unrelated) healthy controls (mean age 38.4 ± 10.4, 24 males) who were recruited from the general community. Ten UFM had a biological first-degree relative with TRS included in this study, the remaining 6 UFM had a biological first-degree relative with TRS who either did not participate in the MRI component (n = 5), or participated but was excluded due to excessive movement at the time of scanning (n = 1).

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 psychiatric illness in healthy controls. Clinical symptoms were assessed using the PANSS, 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 mm^2, 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 mm^3. 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 × 3.5; matrix size = 64 × 64). Data was acquired for 8 min, resulting in 200 volumes.

2.3. fMRI data preprocessing

Data preprocessing was performed 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, coregistered to the structural T1-weighted scan via rigid-body registration and then spatially normalized by non-linear registration to the Montreal Neurological Institute (MNI) 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. The global signal was not regressed due to ongoing controversy surrounding whether this step is warranted when mapping rs-FC in schizophrenia probands (Yang et al., 2014). Given that measures of rs-FC may be influenced by head motion (Power et al., 2012), each individual's movement during scanning was quantified using 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. Functional network mapping and operationalization of risk and resilience

For each individual, a whole-brain resting-state functional network was mapped using established methods (Fornito et al., 2016). In brief, regionally-averaged fMRI signals were determined for the $N = 116$ region automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), and the $N = 360$ region Glasser atlas (Glasser et al., 2016) (see Supplementary material). For each individual, regionally-

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