



Altered resting state functional connectivity in early course schizophrenia

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ABSTRACT

Impaired connectivity is proposed to underlie pathophysiology of schizophrenia. Existing studies on functional connectivity show inconsistent results. We examined functional connectivity in a clinically homogenous sample of 34 early course schizophrenia patients compared with/to 19 healthy controls using resting state functional magnetic resonance imaging (rsfMRI).

Mean duration of illness for schizophrenia patients was 4 ± 1.78 years. Following a comprehensive clinical assessment, rsfMRI data were acquired using a 3.0 T magnetic resonance imaging scanner, and analyzed using FSL version 5.01 software (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Compared to healthy controls, schizophrenia patients had significantly decreased functional connectivity in the left fronto-parietal network, lateral and medial visual network, motor network, default mode network and auditory network. Our data suggests significant functional hypoconnectivity in selected brain networks in early schizophrenia patients compared to controls. It is likely that the observed functional hypoconnectivity may be associated with features of schizophrenia other than those examined in this study. It is possible that hypoconnectivity is necessary but not sufficient to the clinical manifestation of schizophrenia. The examination of functional connectivity as a bio-marker should be extended to a wider array of disease phenotypes to better understand its significance.

1. Introduction

Impaired neural connectivity is implicated in schizophrenia (Friston et al., 1995). Functional imaging has been extensively used to highlight such connectivity deficits. Schizophrenia patients and their relatives show aberrant functional connectivity in default mode networks (Whitfield-Gabrieli et al., 2009), like the medial prefrontal, cingulate and inferior parietal cortices, and regions regulating executive functions such as the dorsolateral prefrontal cortex (DLPFC) (Bhojraj et al., 2010).

Amongst novel functional imaging approaches, resting state functional MRI (rsfMRI) may help unravel some neurobiological abnormalities associated with neuropsychiatric disorders. Resting state fMRI (rsfMRI) is an imaging technique that measures Spontaneous Low-Frequency Fluctuations (SLFFs) in the blood oxygenation level dependent (BOLD) signal during the resting condition (Lee et al., 2013). RsfMRI experiments are less prone to multisite variability and uninfluenced by task performance with low signal-to-noise ratio leading to

higher probability of acquiring more reliable data (Fox and Greicius, 2010). SLFF are postulated to reflect neural synchrony among brain regions. Since reporting of functional significance of SLFFs by Biswal et al. (Biswal et al., 1995), functional connectivity of the brain in the resting state has gained increasing attention. Variations in spontaneous brain activity reflected by these SLFFs can be considered a putative biomarker of schizophrenia (Zhou et al., 2007, 2010).

Impaired connectivity leading to dysfunctional information processing may underlie clinical symptoms of schizophrenia. Deranged communication among critical regions of the brain networks may underlie impairments in multiple cognitive domains, such as executive functions, working memory, language and speed of processing (Whitfield-Gabrieli et al., 2009). RsfMRI data may identify such altered functional connectivity. Although diffusion tensor imaging (DTI) can elegantly show the differences in anatomical connectivity, actual functional significance and flow of neural signals across the regions is difficult to infer. Prior studies showed impaired fronto-temporal and prefrontal commissural anatomical connectivity (Calhoun et al., 2008)

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(Venkataraman et al., 2012). Thus, impaired functional connectivity could illustrate a predictable pattern of synchronous activations that underlie clinical symptoms (Venkataraman et al., 2012).

Inconsistent data from existing rsfMRI studies may be due to the examination of a clinically non-homogenous sample of patients (Guo et al., 2014a, 2015; Ke et al., 2009; Lui et al., 2009; nsisya et al., 2013; Yu et al., 2007; Zhou et al., 2010). Most authors agreed that there was altered functional connectivity in schizophrenia compared to healthy controls in many areas of the brain like default mode network (DMN), medial temporal and prefrontal regions as well as decreased inter-hemispheric connectivity. Examination of patients in the early course of the illness helps avoid some of the confounders such as the duration and course of illness. Our aim in this study was to examine altered functional connectivity in early course schizophrenia compared to healthy control subjects using rsfMRI. We hypothesize that alteration in resting state networks will appear in brain areas that control cognitive and mood functions deficient in schizophrenia.

2. Methods

2.1. Clinical assessments

Persons with early course schizophrenia seeking treatment at the Department of Psychiatry, Dr. Ram Manohar Lohia Hospital, New Delhi, India were enrolled through their treating clinicians. Eligible subjects with early course schizophrenia of both sexes between 18 and 50 years, and controls were explained about all study procedures and written informed consent was obtained. Controls were selected to match age and sex (highlighted in results).

The diagnosis was confirmed by administering a structured interview using the Hindi version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), which has been validated previously (Deshpande et al., 1998). The DIGS includes the Global Assessment Scale (GAS), the Schedule for Assessment of Positive Symptoms (SAPS), and the Schedule for Assessment of Negative Symptoms (SANS). The SANS and SAPS assess the severity of negative and positive symptoms on a six-point scale in the previous month (Andreasen and Olsen, 1982; Andreasen, 1989). Inter-rater reliability of scoring was 0.83–0.92. In addition to structured patient interview, collateral information was obtained through caregivers.

We defined early course schizophrenia as the illness duration of 7 years or less from the onset of first psychotic symptoms. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered to rate the presence and severity of psychotic symptoms. Participants were required to have a score of 4 or more on one or more items of the PANSS, and be on a stable dose of antipsychotics for at least 1 month prior to experimental procedures. For the control group, comparable participants not suffering from any psychiatric illness were enrolled from similar neighborhoods.

Participants with a history of substance dependence in the past 6 months, excluding nicotine dependence, those with a history of or current medical/neurological illnesses, e.g. epilepsy were excluded. Pregnancy, mental retardation (DSM-IV) or any contraindication to MRI procedures, such as having pacemakers or metal fragments/shrapnel were the other exclusion criteria.

2.2. Imaging methods

Brain images were acquired using a 3 T whole-body MRI scanner (Magnetom Skyra, Siemens) while participants lay supine. Foam pads on either side of the head were used to minimize head movement. Participants were instructed not to move, and to lie quietly awake, with closed eyes and not engaged in any specific cognitive activity during the experiment. We collected high-resolution T1-weighted images using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR = 1900 ms; TE = 2.07 ms; inversion time = 900 ms; flip

angle (FA) = 9°; FOV = 256 × 256 mm; slice thickness = 1 mm; number of slices = 160). We acquired T2-weighted images [repetition time (TR) = 10,000 ms; TE = 100 ms; FA = 150°] using a dual-echo turbo spin-echo sequence in the axial plane, with a 256 × 256 matrix size, 220 × 220 mm field of view (FOV), 4.0 mm slice thickness, and 1.2 mm interslice gap to aid in anatomical identification and evaluation for any anatomical defects. We also collected functional brain volumes using an echo-planar T2*-weighted imaging sequence. Each volume consisted of 30 interleaved 5-mm thick slices without interslice gap (TE = 30 ms, TR = 2000 ms, FOV = 240 mm, flip angle = 90°, voxel size = 3.75 × 3.75 × 5 mm³). Total scanning time for fMRI was 6.83 min (205 brain volumes). Images were re-checked for quality at the end of every scan, and if any head movement was noticeable, the scan was repeated.

2.3. Plan of analysis

We used the Statistical Package for Social Sciences (SPSS v21) for assessment of demographic and clinical data. The numerical demographic data and characteristics of schizophrenia and control subjects were compared with independent samples *t*-tests, and categorical characteristics were compared using the Chi-square test. Statistical threshold values of $p < 0.05$ were considered a significant difference.

For resting state fMRI data analysis, we used FSL version 5.01 software (www.fmrib.ox.ac.uk). Firstly, standard preprocessing steps were followed for individual data. This step includes removal of the first 5 brain volumes, high-pass temporal filtering (100 s), motion correction, slice timing, brain-extraction and spatial smoothing (5 mm full width at half-maximum Gaussian kernel). Each fMRI volume was registered on individual structural scans and on the Montreal Regional Institute (MNI152) template (Jenkinson et al., 2002) using the FMRIB Linear Image Registration Tool (FLIRT). Finally, the registered fMRI sequences were temporally concatenated into a single four-dimensional dataset. The data set was decomposed into independent components, with a free estimation for the number of components. We selected components of interest by visual inspection based on previous literature (Beckmann et al., 2005; Damoiseaux et al., 2006) and the frequency spectra of the time courses of the components.

After these preprocessing steps, dual regression analysis was performed for a voxel-wise comparison of the resting functional connectivity for between-group analysis (Filippini et al., 2009). Spatial maps of the group independent component analysis (ICA) were used in general linear model to generate subject-specific versions of the spatial maps, and associated time-series, using dual regression into the subject's 4D dataset. Thereafter, spatial maps of all subjects were collected into single 4-dimensional files for each original independent component.

Then we performed voxel-wise group difference analyses between subjects and controls using nonparametric permutation testing with 10,000 permutations (Nichols and Holmes, 2002). Finally, for multiple comparisons, we conducted a family-wise error (FWE) correction with a significance threshold of $p < 0.05$ (Smith and Nichols, 2009). We used the Harvard–Oxford cortical and subcortical atlases (Harvard Centre for Morphometric Analysis) to identify anatomical representations of clusters of the resulting probabilistic independent component analysis maps, which indicated significant differences between the two groups.

The correlation between clinical symptoms and occupation status with between-network resting state functional connectivity were also assessed using partial correlation. The statistical significance threshold was set at $p < 0.05$, FWE corrected.

3. Results

3.1. Sample characteristics

Demographic and head movement parameters of schizophrenia

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