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Disruption of brain anatomical networks in schizophrenia: A longitudinal, diffusion tensor imaging based study

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ABSTRACT

Despite convergent neuroimaging evidence indicating a wide range of brain abnormalities in schizophrenia, our understanding of alterations in the topological architecture of brain anatomical networks and how they are modulated over time, is still rudimentary. Here, we employed graph theoretical analysis of longitudinal diffusion tensor imaging data (DTI) over a 5-year period to investigate brain network topology in schizophrenia and its relationship with clinical manifestations of the illness. Using deterministic tractography, weighted brain anatomical networks were constructed from 31 patients experiencing schizophrenia and 28 age- and gender-matched healthy control subjects. Although the overall small-world characteristics were observed at both baseline and follow-up, a scan-point independent significant deficit of global integration was found in patients compared to controls, suggesting dysfunctional integration of the brain and supporting the notion of schizophrenia as a disconnection syndrome. Specifically, several brain regions (e.g., the inferior frontal gyrus and the bilateral insula) that are crucial for cognitive and emotional integration were aberrant. Furthermore, a significant group-by-longitudinal scan interaction was revealed in the characteristic path length and global efficiency, attributing to a progressive aberration of global integration in patients compared to healthy controls. Moreover, the progressive disruptions of the brain anatomical network topology were associated with the clinical symptoms of the patients. Together, our findings provide insights into the substrates of anatomical dysconnectivity patterns for schizophrenia and highlight the potential for connectome-based metrics as neural markers of illness progression and clinical change with treatment.

1. Introduction

Schizophrenia is a complex neuropsychiatric disorder with a myriad of clinical manifestations (Howes and Murray, 2014). Whilst the precise neural substrates underpinning the clinical manifestations of schizophrenia are far from understood, the disorder is thought to stem from neurodevelopmental abnormalities of brain structure and function. Using neuroimaging techniques, convergent evidence has revealed a wide range of brain abnormalities, including a general reduction of whole brain volume, increases in ventricular volume (McDonald et al., 2006), and volume reductions in frontal, temporal, limbic, parietal, thalamic gray matter (GM) (Douaud et al., 2007; Ellison-Wright and Bullmore, 2010). More recently, aberrations of white matter (WM) involving frontal and temporal cortices (Kuswanto et al., 2012; Kyriakopoulos and Frangou, 2009; Szeszko et al., 2005), corpus callosum (Collinson et al., 2014), and cingulum (Abdul-Rahman et al., 2011) have been observed.

A recent conceptualization suggests that the human brain forms a large-scale network of interconnected regions within the human connectome that provides the anatomical substrate for neural communication. Accumulated studies have shown that healthy brain networks have special topological organizations, including small-worldness (high local clustering and short paths between nodes), as well as highly connected network regions (hubs), and modular structure (for reviews, see (Boccaletti et al., 2006; Bullmore and Sporns, 2009)). Changes in topology have been related to normal cognitive development and to a wide range of brain diseases, including schizophrenia. The current pathophysiological theories of schizophrenia suggests that the clinical emergence of the disorder represents a failure of integration of functional and anatomical brain connectivity because the heterogeneous presentation of schizophrenia (i.e., disorganized, positive, and negative symptoms) may arise from variability in abnormalities of interregional interactions rather than from abnormality in a specific regions (Fitzsimmons et al., 2013; Friston, 1998; Konrad and Winterer, 2008;

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Pettersson-Yeo et al., 2011; Uhlhaas, 2013; van den Heuvel and Fornito, 2014). Recent advances in non-invasive neuroimaging techniques such as diffusion tensor imaging (DTI) and graph theoretical analysis have enabled quantitative mapping of brain anatomical networks in unprecedented detail. Studies of structural brain networks in schizophrenia have found the presence of small-world properties in these individuals albeit that there is reduction of local network connectivity (Zalesky et al., 2011), increases of minimum path length and network robustness (Zhang et al., 2012), loss of hubs in frontal regions (Bassett et al., 2008; van den Heuvel et al., 2010), abnormal rich club organization (highly interconnected hubs) (van den Heuvel et al., 2013). Notwithstanding the significance of these findings, evidence pertaining to the intactness of overall brain anatomical connectivity has not been entirely consistent (for reviews, see (Fornito et al., 2012; Griffa et al., 2013)). It is also worth noting that reported aberrations in structural brain networks are found exclusively in cross sectional studies. As structural changes can manifest and alter at various stages throughout life, longitudinal studies are crucial if a more comprehensive understanding of brain architecture differences and their implications is to be achieved (Pfefferbaum et al., 2013). Although several longitudinal volumetric studies have been successful in shedding light on important focal changes in GM and WM of patients with schizophrenia (Andreasen et al., 2011; Asami et al., 2012; Whitford et al., 2007), the question of how network properties in schizophrenia are conserved or affected over time is still largely unexplored.

To the best of our knowledge, this is the first study employing graph theory analysis for investigating longitudinal effects of schizophrenia on structural brain networks. By applying a longitudinal design over 5 years, we recorded repeated DTI images in 31 patients with schizophrenia and 28 age- and gender-matched healthy individuals. Whole-brain anatomical networks were constructed using the commonly used deterministic tractography approach. We calculated several network measures to assess small-world properties (e.g., clustering coefficient, path length, and small-worldness), global and local efficiencies, and relative nodal characteristics. In the context of significance of investigation structural brain network topological changes in schizophrenia and paucity of longitudinal data, we set out to assess: 1) how network architecture is aberrant in schizophrenia, 2) how these disruptions change over time, and 3) whether there is any longitudinal association between the disrupted network topology and clinical variables.

2. Methods and materials

2.1. Participants

In this study, thirty-one patients experiencing schizophrenia and twenty-eight matched healthy comparison subjects were recruited at baseline from the Institute of Mental Health (IMH), Singapore, and the local community by advertisements respectively. All the subjects participated in the follow up study with a mean gap of around 5 years. Scan intervals of each participant were shown in Fig. 1. Diagnostic evaluation was performed by a board-certificated psychiatrist (K. S.). The inclusion and exclusion criterial are detailed in the Supplementary materials. This study was approved by the Institutional Review Boards of the IMH, Singapore, as well as the National Neuroscience Institute (NNI), Singapore, and informed consent was obtained from each participant. Antipsychotic medication dosage was recorded at baseline and mean dose at follow-up was calculated by averaging the cumulative received antipsychotic dose over the period of treatment. The socio-demographic and clinical features of the subjects are shown in Table 1.

2.2. Data acquisition

Structural magnetic resonance images with consistent high signal-to-noise ratio were recorded using a 3-Tesla whole body scanner (Philips Achieva, Philips, Medical System, Eindhoven, The Netherlands) using an eight-element SENSE receiver head-coil at the National Neuroscience Institute, Singapore. A T1-weighted Magnetization Prepared Rapid Gradient Recalled Echo sequence (repetition time [TR] = 7.2 ms; echo time [TE] = 3.3 ms; flip angle = 8°) was utilized to obtain high-resolution T1-weighted MRI volume images (each volume contains 180 gapless axial slices of 0.9 mm thickness, field of view [FOV] = 230 × 230 mm^2; acquisition matrix = 256 × 256; in-plane resolution: 0.9 × 0.9 mm^2) in the direction of the anterior–posterior commissures (AC–PC). A single-shot echo-planar sequence (TR = 3275 ms; TE = 56 ms; flip angle = 90°; b-factor = 800 s/mm^2; 1 baseline image with b = 0 s/mm^2) from 15 separate non-parallel directions was utilized to obtain diffusion encoded images (each volume containing 42 slices, 3.0 mm with no gap; FOV = 230 × 230 mm^2; acquisition matrix = 112 × 109, reconstructed to 256 × 256). For each participant, the diffusion sequences were scanned three times to improve the signal-to-noise ratios. During the scanning, head motion was minimized using restraining foam pads provided by the manufacturer. The same scanner was used for both the baseline (software version R2.6) and follow-up scans (software version R3.2). The scanning settings were maintained for both baseline and follow-up studies.

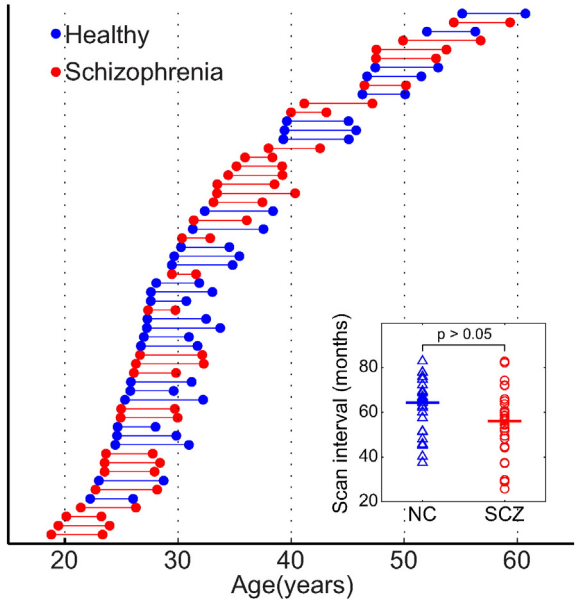

Fig. 1. Age at scan for longitudinal study. Each subject is shown in a different row, with their scans connected by a straight line. Healthy participants (blue) and patients with schizophrenia (red) are marked separately. Most subjects received two scans approximately 5 years apart. There was no statistical ($p > 0.05$) difference in scan intervals between both groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.3. Data preprocessing and structural brain network construction

Data preprocessing and structural brain network construction were conducted using FSL (Smith et al., 2004), diffusion toolkit (Wang et al., 2007), and PANDA (Cui et al., 2013), and had been described in detail previously (Sun et al., 2015). In short, preprocessing approaches included correction for head motion and eddy current distortions through registering the DW images to the b0 image with an affine transformation. The gradient direction of each DWI volume was rotated according to the resultant affine transformations to further reduce the influence of motion artifacts (Leemans and Jones, 2009). Six elements of the diffusion tensor were then estimated from which fractional anisotropy (FA) was calculated. Whole-brain fiber tractography was subsequently performed using fiber assignment by continuous tracking (FACT) algorithm (Mori et al., 1999). This algorithm computes fiber trajectories starting from the deep WM regions and terminating at a voxel with a

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