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Structural connectivity analysis reveals topological aberrations in patients with schizophrenia

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Abstract—**Topological analysis and the associated parameters allow elucidation of brain networks in health and illness. Evidently useful measures for defining network competency such as small-worldness can potentially improve understanding of brain connectivity and their disruptions underlying neuropsychiatric conditions such as schizophrenia. In the current study, we assessed the structural differences of brain networks in schizophrenia patients as compared with healthy controls. As proof of concept investigation, diffusion tensor imaging recordings from 2 schizophrenia patients and 2, gender and age matched, control subjects were subjected to analysis using several graph network distance metrics. Among them, those that appeared to have the ability to encode and highest sensitivity in shedding light about anatomical changes in neuron deficiency were the shortest path length and clustering coefficient parameters. Schizophrenia patients displayed comparatively lower clustering coefficient, longer path lengths and hence reduced small-worldness. These results suggest aberrant topological architecture in the structural brain networks of patients with schizophrenia, which may impact the psychopathological and cognitive manifestations of this potentially crippling illness.**

I. Introduction

The relationship between neurological functions and synchronized activity of specific and functionalized interconnected brain regions has been widely deliberated in neuroscience studies[1]. It is of great value to the biomedical community to investigate how structural connections between brain regions occur and provide a standardized method to measure and assess these interactions. Over the last decade, the development of non-invasive methods based on hemodynamic or electro-magnetic measurements have improved our understanding of the activations of cerebral areas underlying different psychotic spectrum and/or cognitive states. It has been long proven that structurally segregated and functionally specialized cortical regions of the human cerebral cortex are interconnected by a dense network of cortico-cortical axonal pathways [2]. The disruption of such topological architecture is thought to be present in numerous neuropsychiatric disorders, e.g., Alzheimer's disease, Parkinson's disease and depression (for a review, see [3, 4]).

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Diffusion tensor imaging (DTI) is a noninvasive magnetic resonance imaging technique that relies on ascertaining the restricted diffusion of water within tissues to generate images of neural pathways. Hence, it is capable of providing visualization of tissue structures at the microscopic level and revealing the presence or lack of brain white matter pathology. The principal eigenvector of the diffusion tensor can aid in deducing white matter arrangements and thus represents a noteworthy method for the study of white matter tracks (for a review, see [5]).

Earlier studies including gene expression [6], neuropathology [7] and neuroimaging [8] have implicated brain white matter in the pathophysiology of schizophrenia. Existing neuroimaging investigations of white matter deviations in schizophrenia have been concentrated in the study of volumetric (diminished levels in several brain regions) [8] or diffusion anisotropy alterations (reduced fractional anisotropy in other regions) [9], but relatively fewer studies have examined global white matter topology in this potentially disabling and chronic illness.

Graph theory has been reviewed to be useful in perceiving large-scale networks by delineating them with nodes (vertices) and connections (edges) [10]. For example, they enable network structures to be associated with the respective processes, define desirable networks through characteristics such as integration, segregation and efficiency, modeling of development and response to harm. While the small-world concept defined to display 'local clustering' (nodes' connectedness with neighbors) measured by the clustering coefficient (C) and short path lengths (L) (fewer steps between nodes) is evident in healthy humans [11, 12], fewer studies investigate small-world system disturbance and its relationship with psychopathology seen in neuropsychiatric conditions. In light of comparatively increased randomness being reported in schizophrenia patients' brain networks [13-15], it is reasonable to conceive that abnormalities of the small-world networks are found in schizophrenia. In the context of sparse data evaluating small-world network changes in brain white matter microstructures within schizophrenia, we seek to examine and identify large-scale network layout and arrangement deviations in schizophrenia using DTI images and applications of graph theory within this proof of concept study.

II. Methods and Materials

A. Subjects

The study included 2 male patients age 33 years with a DSM-IV diagnosis of first-episode schizophrenia based on

clinical history, mental status examination as well as corroborative history from informants, and administration of the Structured Clinical Interview for DSM-IV disorders I-Patient Version (SCID-I/P) [16]. Two age and gender matched healthy controls were assessed using the non-patient counterpart of the SCID interview schedule. Patients and controls were recruited from the Institute of Mental Health, Singapore, and by advertisements respectively. The study was approved by the Institutional Review Boards of the Institute of Mental Health, Singapore, and the National Neuroscience Institute, Singapore and all subjects had given written informed consent.

B. MRI data acquisition

As described in a previous study [8], structural MR images of the brain corresponding to precise guidelines to ensure consistent high signal-to-noise ratio were recorded (National Neuroscience Institute, Singapore) using a 3-Tesla whole body scanner (Philips Achieva, Philips Medical System, Eindhoven, The Netherlands) with a SENSE head coil. A T1-weighted Turbo Field Echo sequence (inversion time, 860 ms; repetition time, 7.2 s; echo time, 3.3 ms; flip angle, 8°) was utilized to obtain high-resolution T1-weighted MRI volume images (each containing 180, 0.9 mm, gapless axial slices; field of view, 230×230 mm; acquisition matrix 256×256, in-plane resolution, 0.9×0.9 mm) in the direction of the anterior-posterior commissures.

A single-shot echo-planar sequence (repetition time, 3275 ms; echo time, 56 ms; flip angle, 90°; b-factor, 800 s mm^{-2}) from 15 separate directions was utilized to obtain diffusion-encoded images (baseline image without diffusion weighting, b=0; each containing 42, 3.0 mm, gapless axial slices; field of view, 230×230 mm; acquisition matrix, 112×109, reconstructed to 256×256). 3 volumes (3 excitations) were procured to fortify signal-to-noise ratios. The structural and diffusion tensor images were obtained in order within a single scan time without altering position.

C. Network construction

Nodes are the fundamental building blocks constituting brain network construction. The study matched 90 cortical regions to the respective nodes according to the automated anatomical labeling (AAL) [17]. A linear transformation was applied locally within each subject's DTI image correlated with T_1-weighted image to coregister them to the baseline image in the DTI space followed by applying a nonlinear transformation to map to the ICBM152 T_1 template (Montreal Neurological Institute). The subject-specific AAL mask was then weaved from the MNI space to the DTI space with the corresponding inverse transformation such that separate labeling values were maintained via interpolation (nearest neighbor method). The white matter fibers between all cortical region pairs were then estimated from the 3-D curves of maximal diffusion coherence formed by DTI tractography of the diffusion map [18, 19]. All processing and preprocessing, such as eddy current corrections, were implemented with the Pipeline for Analyzing Brain Diffusion Images software accordingly (which is freely available to the research community at the website http://www.nitrc.org/projects/panda/). A flow chart of the brain structural network construction is shown in Fig. 1.

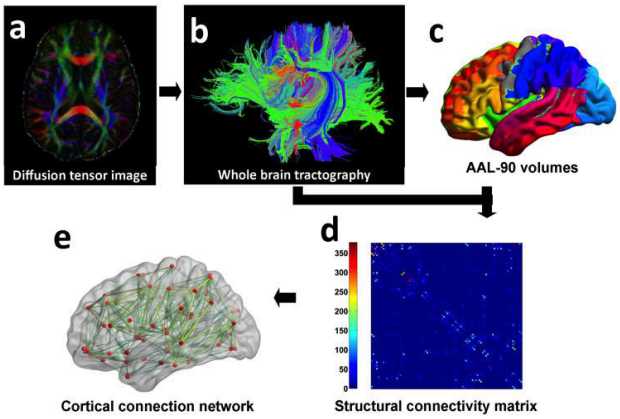

Fig.1. A flow chart of the brain structural connectivity network construction. Fiber pathways estimation was performed using fiber assignment in the (a) diffusion tensor images by continuous tracking (FACT) algorithm to reconstruct a 3-D tractography (b). The structural networks (d) of each subject were then created by computing the fiber numbers that connected each pair of brain regions in the subject-specific AAL mask (c).

D. Network analysis

In this study, the small-world properties of the obtained structural connectivity networks were investigated. The weighted clustering coefficient of a node i is defined as the probability that vertices connected to i are also connected to each other. This understanding can be conceptualized with weighted graphs [10] using

$$C_i^w = \frac{\sum_{l,k}\left(w_{il}w_{lk}w_{ki}\right)^{1/3}}{k_i\left(k_i-1\right)/2} \qquad [1]$$

where w_{ki} is the number of fibers connecting vertex i and k (normalized by the average of all fiber numbers of the network for each subject to reduce inter-participant cost differences). The weighted clustering coefficient of the graph can then be obtained by averaging C_i^w over all nodes.

Path length of an edge conceptualized to weighted graphs is defined as the reciprocal of the edge weight. The sum of all the edge lengths of the path between a vertex pair constitutes the path length. The shortest path L_{ki}^w is intuitively the path with the shortest length linking the respective vertices. The characteristic path length of a graph can be computed as follows:

$$L^w = \frac{1}{N\left(N-1\right)}\sum_{i=1}^{N}\sum_{k\neq i}^{N}\frac{1}{L_{ki}^w} \qquad [2]$$

The small-world concept useful for describing human brain networks is defined as having high clustering coefficient and short characteristic path length. In the present study, the normalized weighted clustering coefficient, $\gamma = C^w / C_{surrogate}^w$, and the normalized weighted characteristic path length, $\lambda = L^w / L_{surrogate}^w$ were further computed, where $C_{surrogate}^w$ and $L_{surrogate}^w$ represent the average weighted clustering coefficient and shortest path length of 100 surrogate random networks with preserved edge weights.

III. Results

A. Global topology of the structural networks

Table I summarizes the global topology analyses of structural networks for schizophrenia patients and controls. We found that both patients and control subjects demonstrated small-world organization of the white matter networks, as exemplified by $\gamma > 1$ and $\lambda \approx 1$. C^w was comparatively lower in schizophrenia patients than controls. In addition, patients displayed significantly larger L^w than that of control subjects, the net result of which being indicative of loss of small-worldness (C/L) in schizophrenia patients. In contrast, we failed to observe consistency of this trend in the normalized C^w and L^w.

TABLE I
COMPARISONS OF THE GLOBAL NETWORK MEASURES BETWEEN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

		C^w	L^w	γ	λ	C/L
Patient	Sub1	0.336	1.652	3.106	1.333	2.331
	Sub2	0.337	1.339	2.972	1.202	2.472
Control	Sub1	0.356	1.318	3.014	1.208	2.495
	Sub2	0.349	1.315	3.049	1.207	2.525

Note: C^w = weighted clustering coefficient, L^w = weighted characteristic shortest path length, γ = normalized clustering coefficient, λ = normalized characteristic shortest path length. 100, degree distribution-preserved surrogate random networks were generated to obtain γ and λ for each subject.

B. Node-based analysis

To determine the nodal characteristics of structural cortical networks, a parameter for examining the regional connections was calculated based on the shortest path length [18]. Briefly, the nodal efficiency for a given node is defined as the inverse of the harmonic mean of the shortest path length between this node and other nodes. Fig. 2 shows the group averaged, normalized nodal efficiency for all 90 cortical regions. Regions with high nodal efficiency imply the importance of their roles in information transfer. In the present study, we determined hubs as cortical regions with nodal efficiencies 1 S.D. greater than the average of the network.

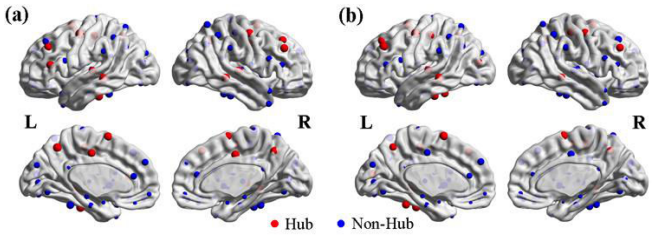

Fig.2. The global network hubs with high nodal efficiency in (a) control subjects and (b) schizophrenia patients. A hub region is defined if its nodal efficiency is larger than the sum of the mean and 1 S.D. of all the nodal efficiencies. Node efficiency values correspond to node sizes. The figures were visualized with the BrainNet Viewer software (http://www.nitrc.org/projects/bnv/).

In the control group, 18 hub regions were identified, while 17 hub regions were identified in schizophrenia patients. Both groups had 13 cortical regions in common (bilateral PreCG, MFG, SMA, PCUN, MTG, left PoCG, left STG, and left ITG) that were identified as hubs. Bilateral PCUN were identified as the most important hubs for both groups. It is worth noting that bilateral PCUN and MFG had previously been proven as the most important regions in white matter networks [14, 19], and our results agree well with previous findings.

C. Edge-based analysis

To investigate how the structural connectivity varies as we increase the distance between neuronal populations, the relationship between the interregional fiber numbers and their corresponding Euclidean distances was analyzed (Fig. 3). Only those Euclidean distances with presence of fiber numbers were obtained for further analysis. The Euclidean distance between two ROIs is determined using the geometrical distance calculated from the mean coordinates of the voxels comprising an ROI in the individual's specific AAL-90 mask (Fig.1(c)). It can be seen in Fig. 3 that most structural connections comprise lower quantity of fibers (the fiber number histogram) for both groups. Also, the distributions of Euclidean distance for structural connectivity reveal a tendency towards short distances. Lognormal fits of the fiber numbers on Euclidean distance show that the *mu* of patients (*mu*=19.23) is smaller compared to control subjects (*mu*=20.60) (Figures not

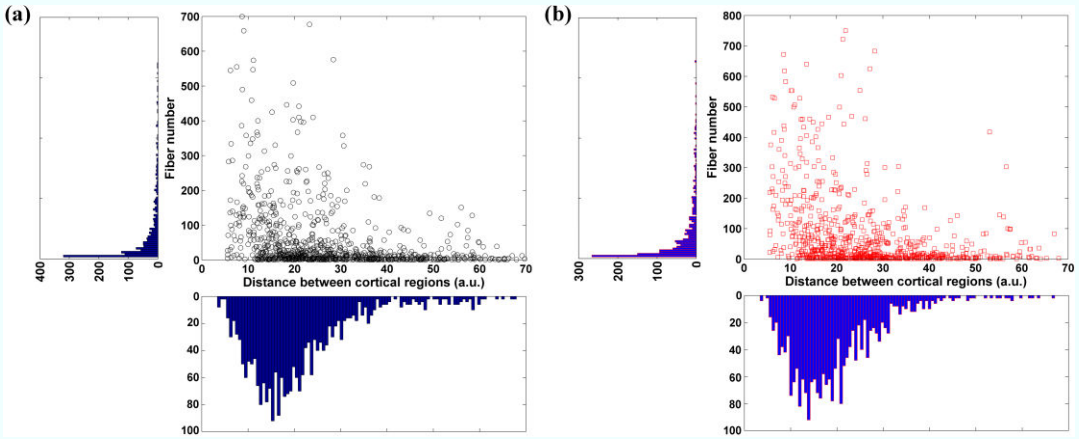

Fig.3. Relations between Fiber numbers and Euclidean distance. Scatter plot of interregional fiber number against the interregional Euclidean distance and the corresponding distributions for (a) control subjects and (b) schizophrenia patients.

shown). Further analysis reveals that fiber numbers are linearly related to the inverse of the geometrical distance between regions (r=0.19 for controls and r=0.17 for patients).

IV. Discussion and Conclusion

By illustrating the diminished capacity for efficient information processing in schizophrenia patients using parameters C^w and L^w, the results of the study further support the notion that the interruption of brain connections forms the basis of how schizophrenia exerts its impact clinically. This concept was corroborated by the graph analysis results unveiling lower C^w and higher L^w in schizophrenia patients, showing reduced small-worldness as an observable trait which may translate to less efficient information processing. These data are consistent with one of the prevailing thoughts that the neural basis of schizophrenia is related to anomalies in brain structural connectivity [20]. Our investigations also suggest that the quantity of hub regions is less likely to account for the pathology. Although the subject number is small in the current proof of concept study, hub regions identified as occurring in both controls and patients are consistent with previously established white matter networks, in particular, bilateral PCUN, bilateral MFG, left STG and left ITG [19]. A notable observation is the recognition of the bilateral PCUN as the most crucial regions of white matter networks in patients and controls, which is in line with earlier reports in healthy subjects [19]. For further analysis, we sought to determine the relationship between interregional fiber numbers and their corresponding Euclidean distance. A novel discovery was that the majority of structural connections exhibited tendency towards being short ranged and limited in numbers. Constructing lognormal fits of the 2 measures revealed lower *mu* in patients than controls, suggesting a potential biomarker for the disease.

A technical comparison with another study revealed a few differences, e.g., in [14], schizophrenia patients displayed increased clustering coefficient as compared to healthy controls. Also, differing regions were identified as hubs. While our study has revealed several differences between patients and healthy controls, further study involving a higher number of subjects is essential to replicate these findings and their relationship with clinical parameters. Continued investigation using these network strategies and their correlations with the clinical characteristics of schizophrenia is important for determining distinctive profiles of networks involved as well as the possibility of their being modulated with treatment. It would also be beneficial to elucidate how various interventions can moderate these structural networks, and how they relate to functional networks as well as clinical measures in schizophrenia.

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