Disrupted topological organization of white matter structural networks in bipolar disorder

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Introduction Bipolar disorder is a common psychiatric illness affecting approximately 1.5-3% of the general population. It is associated with considerable morbidity and mortality, and represents a significant public health problem [1]. Although the specific neurobiological basis underlying this disorder is unclear, increasing evidence suggests that abnormalities in white matter integrity may play an important role in the psychopathology of bipolar disorder [2, 3]. Despite these advances, little is known about alterations of the topological organization of whole-brain white matter structural networks in bipolar patients. Here, we used diffusion tensor imaging (DTI) and graph-theory methods to investigate the architecture of the white matter structural networks in bipolar disorder. We hypothesized that patients with bipolar disorder would show disrupted topological organization of white matter structural networks.

Materials and Methods *Subjects:* Eighteen patients with bipolar disorder (six males; mean age 28.5±11.1 years) and sixteen healthy controls (four males; mean age 29.9±9.2 years) participated in this study. *Image acquisition:* DTI scans were performed by a GE Signa 1.5T scanner with the following parameters: TR/TE: 12,000/96 ms; NEX: 5; matrix: 128×128 zero-filled to 256×256; FOV: 24 cm×24 cm; slice thickness: 4 mm without gap; 13 non-collinear gradient encoding directions with b=1000 s/mm^2. *Network node:* Ninety node regions were defined in DTI native space using by the anatomical automatic labeling template, for details see [4]. *DTI tractography and Network edge:* Deterministic tractography was performed in each subject to reconstruct whole-brain neural fiber tract connectivity. Two regions were considered structurally connected if at last three fibers with two endpoints were located in these two regions. We defined the fiber number (FN) of the connected fibers between two regions as the weights of the network edges. As a result, a symmetric 90×90 FN-weighted white matter structural network was constructed for each participant. *Network analysis:* We calculated the following network measures [5]: network strength (Sp), global efficiency (Eglob), local efficiency (Eloc), absolute (Cp) and normalized clustering coefficient (γ), absolute (Lp) and normalized shortest path length (λ) and small-worldness (σ). For regional nodal characteristics, we used the nodal efficiency. To localize specific pairs of brain regions in which structural connectivity were disrupted in bipolar patients, we employed network-based statistic (NBS) approach [6]. *Statistical analysis:* Two-sample t-test was performed to evaluate the topological differences between the two groups.

Results Both of the bipolar patients and control subjects showed a small-world organization of white matter structural networks, as expressed by γ>1 (4.64±0.30 for controls and 4.69±0.29 for patients) and $\lambda\approx$1 (1.23±0.05 for controls and 1.27±0.05 for patients) (i.e., σ>1; 3.77±0.25 for controls and 3.71±0.25 for patients). However, bipolar patients have significantly decreased Sp (p=0.038), decreased Eglob (p=0.013) and increased Lp (p=0.006) as compared to controls. Both groups shared similar hub distributions, mainly located in the medial fronto-parietal cortex (Fig 1). However, bipolar patients had reduced efficiencies in several parietal (right inferior parietal lobe and angular gyrus), temporal (left inferior, middle, and superior temporal gyrus and temporal lobe), frontal (left orbital part of middle frontal gyrus), occipital (left middle and inferior occipital gyrus) and limbic (right median and posterior cingulated gyrus) regions (all p<0.05, uncorrected; Fig 2). NBS found that a sub-network was significantly impaired in bipolar patients (p<0.05, corrected; Fig 3). As shown in Fig 3, the connections in this sub-network are primarily involved in the prefrontal cortex, temporal cortex and limbic system.

Discussion In this study, we used network analysis methods to investigate the architecture of the white matter networks in the patients with bipolar disorder. We found disrupted topological organization of the white matter structural networks in bipolar patients. These findings may improve our understanding of the potential mechanisms of the underlying neurobiological basis of bipolar disorder.

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References [1] Angst J, J Affect Disord, 50: 143-151, 1998. [2] Mahon K et al., Neurosci Biobehav Rev, 34: 533-554, 2010. [3] Lin F et al., Affect Disord, 131: 299-306, 2011. [4] Gong G et al., Cereb Cortex, 19: 524-536, 2009. [5] Rubinov M et al., Neuroimage, 52: 1059-1069, 2009. [6] Zalesky A et al., Neuroimage, 53: 1197-1207, 2010.

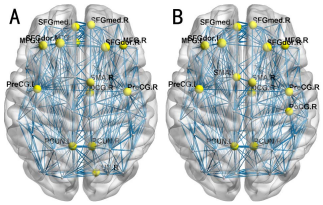

Fig 1. Distribution of hub regions in each group. (A, healthy controls; B, bipolar patients)

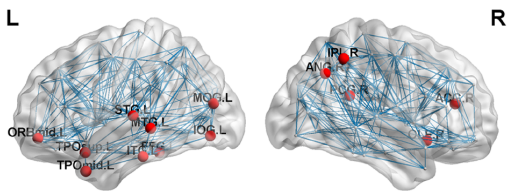

Fig 2. Distribution of nodes with decreased efficiencies in bipolar patients. (L, left; R, right)

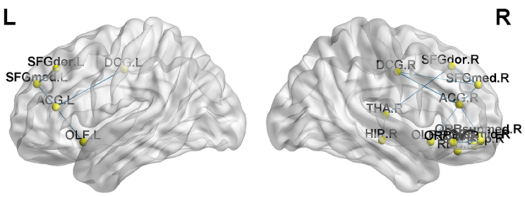

Fig 3. A sub-network with decreased connections was identified in bipolar patients. (L, left; R, right)