DISRUPTED WHITE-MATTER STRUCTURAL NETWORKS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Ni Shu[1], Qingjiu Cao[2], Li Sun[2], Li An[2], Peng Wang[2], Jinhui Wang[1], Mingrui Xia[1], Yufeng Wang[2], and Yong He[1]

[1]*State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, Beijing, China, People's Republic of,* [2]*Institute of Mental Health, Peking University, Beijing, China, People's Republic of*

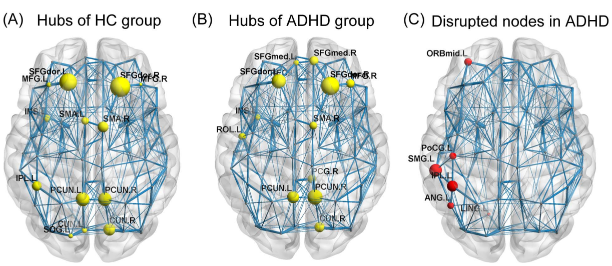
Introduction

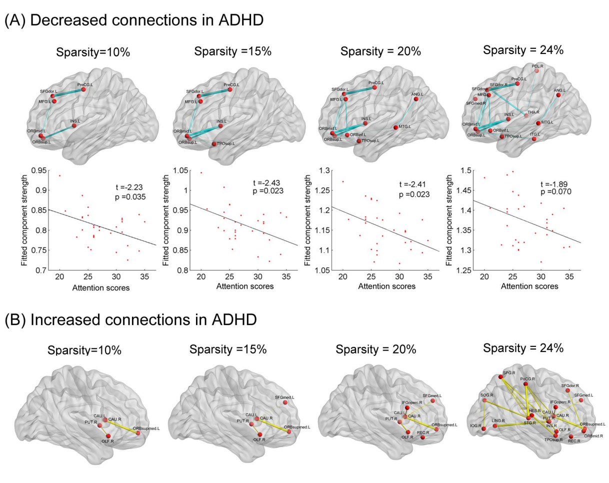
Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood neuropsychiatric disorders persisting into adolescence, even into adulthood. It is characterized by symptoms of inattention, hyperactivity and impulsivity that cause significant functional impairments across multiple academic and social domains [1]. Although the neurobiological basis underlying this disorder is unclear, increasing evidence suggested that the functional and structural abnormalities in the fronto-striatal circuit may play an important role in the psychopathology of ADHD [2, 3]. Despite these advances, little is known about alterations of the topological organization of whole-brain structural networks in ADHD patients. In this study, we used diffusion tensor imaging (DTI) and graph theoretical approaches to investigate the whole-brain white matter connectional architecture in ADHD patients. We hypothesized that the topological organization of white-matter networks would be disrupted in patients and this disruption would be associated with the clinical characteristics of the ADHD, such as the symptoms of inattention and hyperactivity/impulsivity.

Methods

Data acquisition: The present study included 60 participants [30 ADHD patients (age: 10.3±1.9) and 30 healthy controls (age: 10.3±1.6), all males]. MRI data were acquired using a SIEMENS TRIO 3T scanner. DTI data were acquired with following parameters: resolution=1.8x1.8x2.5mm^3, 64 directions, b=1000s/mm^2, repetition=1. T1 weighted images (MPRAGE) were scanned with 1x1x1.3mm^3 resolution. *Network node definition:* Ninety regions defined by automated anatomical labeling in DTI space were obtained for each subject, for details see [4]. *DTI tractography and network edge definition:* For each node region, probabilistic tractography was performed to estimate the connectivity probability from each voxel by FSL package. Then the connectivity probability P_{ij} between each pairs of nodes i and j was calculated and defined as the edge weight between nodes i and j [5]. To remove spurious connections, we applied a thresholding range between 0.01 and 0.1 at intervals of 0.0025, corresponding network sparsity range from 24% to 6%. Finally, for each subject, a 90×90 symmetric weighted network was constructed. *Network analysis:* For brain networks at each threshold, we calculated the following measures: network strength (S_p), global efficiency (E_{glob}), local efficiency (E_{loc}), absolute (L_p) and normalized shortest path length (λ), absolute (C_p) and normalized clustering coefficient (γ) and small-worldness [6]. For regional nodal characteristics, we considered the nodal efficiency. To localize specific pairs of brain regions in which structural connectivity were altered in patients, we used a recently developed network-based-statistic (NBS) approach [7]. *Statistical analysis:* For group effects in network properties, statistical comparisons were performed using permutation tests. Linear regression analyses were performed to identify the correlations between neuropsychological test scores (attention and impulsion scores) and altered network properties in ADHD patients. Of note, all of the statistical analyses were performed with age, IQ and brain size as confounding covariates.

Results





ADHD-related alterations in global network properties: First, both controls and ADHD patients showed a small-world organization of white-matter networks expressed by a $\lambda \approx 1$ and $\gamma > 1$. However, ADHD patients have significantly decreased E_{glob} (p=0.038), increased L_p (p=0.029) and increased λ (p=0.046) as compared to controls. *ADHD-related alterations in regional nodal characteristics:* Both groups shared similar hub distributions, mainly located in the medial fronto-parietal cortex. However, ADHD patients had reduced efficiencies in several parietal (left supramarginal gyrus, inferior parietal lobe, postcentral gyrus and angular gyrus), frontal (left orbital part of middle frontal gyrus) and occipital (left lingual gyrus) regions (all $p<0.05$) (Fig 1). *ADHD-related alterations in structural connectivity:* A component of network was found to be significantly impaired in patients ($p<0.05$, corrected). As shown in Fig 2, the connections in the component are primarily involved in the left prefrontal cortex and insula. A tendency of a component with increased connections in patients was also found ($p<0.1$, corrected), which mainly includes the striatum structures and orbital frontal cortex (medial part). The results remained robust across a range of network sparsity (10~24%). *Relationship between network measures and neuropsychological scores:* The mean connectivity strength of impaired fronto-insula component was negatively correlated with the attention scores in ADHD patients but not in controls (Fig 2). No other correlations between network measures and neuropsychological scores were found.

Fig 1. Distribution of hub regions in each group and the nodes with decreased efficiencies in ADHD patients.

Fig 2. Components with decreased and increased connections were identified in ADHD patients. The mean strength of decreased component was associated with the attention scores in patients.

Conclusion

This study revealed disrupted topological organization of the white-matter structural networks in ADHD patients. Both decreased and increased connections in the patients were mainly located in the frontal regions, insula and striatum structures, thus providing evidence for the hypothesis of abnormal fronto-striatal-insular circuitry in ADHD. Specifically, the disrupted connections in the fronto-insular component were associated with the inattention performances in patients, improving our understanding of the potential mechanisms underlying the behavior deficits in patients with ADHD.

References

[1] Biederman J et al. *Am J Psychiatry* 2000; 157: 816-818. [2] Konrad K et al. *Hum Brain Mapp* 2010; 31: 904-916. [3] Wang L et al. *Hum Brain Mapp* 2009; 30: 638-649. [4] Shu N et al. *Cereb Cortex* 2011; 21: 2565-2577. [5] Gong G et al. *J Neurosci* 2009; 29: 15684-15693. [6] Rubinov M et al. *Neuroimage* 2010; 52: 1059-1069. [7] Zalesky A et al. *Neuroimage* 2010; 53: 1197-1207.