이학석사 학위논문

Aberrant structural network in children with attention-deficit/hyperactivity disorder (ADHD) using network filtration analysis

주의력결핍 과잉행동장애 아동의

구조적 뇌 연결성 변화

2014 년 2 월

서울대학교 대학원

협동과정 인지과학 전공

허 영 민

Aberrant structural network in children with attention-deficit/hyperactivity disorder (ADHD) using network filtration analysis

지도 교수 이 동 수

이 논문을 이학석사 학위논문으로 제출함

2014 년 2 월

서울대학교 대학원

인지과학 협동과정

허영민

허영민의 이학석사 학위논문을 인준함

2014 년 2 월

위 원 장 ______ 최진영 ______ (인)

부위원장 ______ 이동수 ______ (인)

위　　원 ______ 이인아 ______ (인)

Abstract

Aberrant structural network in children with attention-deficit/hyperactivity disorder (ADHD) using network filtration analysis

Youngmin Huh

Interdisciplinary Program in Cognitive Science

The Graduate School

Seoul National University

In attention-deficit/hyperactivity disorder (ADHD), previous functional and structural studies which investigated regional abnormalities have been reported several brain regions as a key neuroanatomy of ADHD: prefrontal, striatal, parietal, cerebellum regions, and fiber tracts including superior longitudinal fasciculus (SLF). In this study, beyond regional abnormality, I investigated whole brain network abnormality using structural diffusion tensor image (DTI) in children with ADHD, and examined connectivity patterns for every threshold levels to find characteristics of ADHD's structural

network topology. Whole brain network was constructed with tractography method, and examined by graph theoretical analysis and network filtration of persistent homological framework. Persistent homology allows understanding the topological feature, connected component of brain network, in this study.

Diffusion tensor images of 19 ADHD children (15 male, 4 female; mean age 8.1±1.5; mean IQ 105.1±14.5) and age-matched 9 psychiatric control children (6 male, 3 female; mean age 9.5±2.8; mean IQ 106.1±8.3) were obtained. For structural network construction, network node was defined by 116 AAL (Automated Anatomical Labeling) regions of interest in individual space. We constructed connectivity matrix based on the number of tract which connects pair of regions extracted by deterministic tractography using TRACKVIS. To examine the network characteristics, graph theoretical measures such as clustering coeffcient, nodal efficiency, betweenness centrality, and single linkage distance as a network filtration approach were compared between ADHD and psychiatric control group.

In graph network analysis, node distribution of clustering coefficient was significantly different between two groups. The ADHD group showed more nodes with small network values, and disrupted local information processing was found, but no nodal difference in clustering coefficient was found. Right parahippocampal

gyrus was the only node that showed significant nodal difference, and it showed reduced betweenness centrality in ADHD. Both global and local differences in network theoretical measures merely showed evidence for network abnormality. In contrast, network filtration found locally changed connections in connectivity patterns in ADHD. Tighter connections between right supramarginal gyrus and bilateral dorsal frontal regions, and looser connections between left angular and left temporal regions were found in ADHD compared to psychiatric control group which imply disrupted balance in attention systems.

In summary, structural network was constructed using tractography, and network filtration method found altered structural connectivity in ADHD. Unlike the psychiatric control subjects, abnormal connections of fronto-pareital, temporo-parietal regions, which belong to SLF and MdLF, might be associated with deficit in attention systems in children with ADHD. The network filtration revealed abnormality of whole brain network in ADHD.

Keywords: Network, graph theory, ADHD (attention-deficit/hyperactivity disorder), DTI (Diffusion Tensor Image), tractography, Network filtration
Student Number : 2011-23120

Contents

Tables

Figures

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders. Children with ADHD cannot filter undesirable stimulus, selectively pay attention, and stay focused for a period of time. Also they tend to act without considering consequences, and to be more active than a usual condition. Symptoms can persist into adulthood (Cubillo et al., 2012b) , and ADHD is related to many undesirable conditions including academic underachievement (Barry et al., 2002) and psychiatric disease such as anxiety, mood, behavioral disorders (Biederman et al., 1996).

Many studies proposed neuropsychological models of ADHD. The particular cognitive dysfunction models suggest deficit on executive functions such as working memory, attention, inhibition, and distribution of cognitive energetic resources (Schachar et al., 1995, Pennington and Ozonoff, 1996, Barkley, 1997, Sergeant, 2000). Most of these models indicate prefrontal-related circuits as underpinning brain regions(Aron et al., 2004a, Aron et al., 2004b). Alternative models assume disruptions on motivation system. Sagvolden suggested that children with ADHD have problem to assess relation between present action and future reward, and disruption in fronto-striatal circuit as a candidate (Alexander et al., 1991, Sagvolden et al., 1998). Another model insists that ADHD is related with delay aversion (Sonuga-Barke, 1994). Children with ADHD made faster decisions with more mistakes on tasks in spite of fixed trial time length (Sonuga-Barke et al., 1994). This model denotes that disrupted fronto-striatal circuits and meso-limbic branches underpin symptoms of ADHD (Sonuga-Barke, 2003). Although many models were proposed, none of them clearly figured out the cause of ADHD, and its neuroanatomy. Hence, finding biomarker using neuroimaging method for deeper understanding of ADHD is required, and it will enable us proper clinical intervention and prognosis for ADHD.

In previous studies, prefrontal subregions, cingulate gyrus, basal ganglia, inferior parietal regions and cerebellum have been considered as key regions underlying neural mechanism. In studies using diffusion tensor imaging (DTI) studies, abnormal white matter integration and altered connectivity on fiber bundles connecting key regions was reported. One of key fiber tract is Superior longitudinal fasciculus (SLF) connecting parietal, occipital and frontal lobes, and related to cognitive functions such as attention and spatial working memory (Shinoura et al., 2009, Frye et al., 2010, Vestergaard et al., 2011). It showed abnormal fractional anisotrophy (FA) in ADHD which suggests disruption of attention (Hamilton et al., 2008, Makris et al., 2008, Pavuluri et al., 2009). Tractography method was used to reconstruct major white matter tracts, and significantly high mean diffusivity (MD) of the fiber tracts including SLF was found in ADHD (Lawrence et al., 2013). The fibers connecting inferior parietal lobule and inferior frontal lobe, identified as SLF, showed weaker structural connectivity in ADHD implying a deficit on executive network (Supekar and Menon, 2012). Another candidate tract is corticospinal tract, originated from motor cortex and projected to cerebellum, plays a crucial role for motor function (Schmahmann and Pandya, 2009). Reduced FA of corticospinal tract in ADHD implies disruption of motor inhibition (Hamilton et al., 2008, Makris et al., 2008). Cingulum, which connects cingulate gyrus and temporal area, has been consistently discussed for abnormal white matter integrity in ADHD (Makris et al., 2008, Pavuluri et al., 2009). A study about whole brain structural connectivity, as well as ones about specific white matter tracts, was conducted using probabilistic tractography and network analysis (Cao et al., 2013). It revealed decreased connectivity in prefontral related circuitry, increased connectivity in orbitofrontal-striatal circuitry, and their correlations with inattention/hyperactivity scores.

Most of previous studies investigated abnormalities in regional white matter integrity or targeted fiber tracts, but not connectivity of whole brain. Only one study tried to examine whole brain connectivity of ADHD using network theory, but the study excluded cerebellum in analysis, which is one of key regions of ADHD. Volume changes in vermis, altered resting state baseline activity in cerebellum suggests dysfunctions in cerebellar regions may underlie main symptoms of ADHD (Berquin et al., 1998, Mostofsky et al., 1998, Yu-Feng et al., 2007). Furthermore, they applied thresholds to remove spurious connections of whole brain connectivity, which could influence results in group difference (Rubinov and Sporns, 2010). The study recruited only boys, so it has limitation to generalize the results.

In this study, we investigated network characteristics of male/female subjects with ADHD using tractography method, network theory, and network filtration. Whole brain fiber tracking using DTI data was implemented to generate connectivity of entire brain including cerebellar regions. Graph theoretical analysis examined group differences in segregation and integration of the network with graph measures: clustering coefficient, nodal efficiency, and betweenness centrality. In addition, graph filtration originated from persistent homology frame was also applied to investigate network with filtration (Lee et al., 2011, Lee et al., 2012). A distance matrix was calculated, and transformed into a single linkage matrix. A threshold varied with distance and gradually applied to a distance matrix, and a single linkage matrix, which represents connected components according to filtration values, was generated. Graph filtration enables investigation of coupling patterns without loss of information caused by arbitrary thresholding.

The aim of this study is to find out characteristics of ADHD's brain connectivity compared with healthy controls using white matter tractography method in a data-driven way. Anatomical brain connectivity on ADHD and healthy control will be compared using graph theoretical measures, and graph filtration which could examine coupling patterns without applying a threshold to data.

2. Methods

2.1. Subjects

We recruited 19 children with ADHD (15 male, 4 female; mean age = 8.1±1.5; mean IQ = 105.1±14.5) and 9 controls (6 male, 3 female; mean age = 9.5±2.8; mean IQ = 106.1±8.3). Since PET images were also obtained from all subjects, relatively few control subjects participated in the study. The recruited children with ADHD were diagnosed by psychiatrists using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Korean versions of the ADHD rating scale IV (ARS), Schizophrenia for School-Age Children-Present and Lifetime version and had psychological test. They were also evaluated by Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC). Every child met criteria for ADHD, and no other developmental disorder or abnormal condition were observed except transient tic disorder, oppositional defiant disorder, mild anxiety disorder, and enuresis. Patient group comprised of 8 combined sub-type, seven inattentive sub-type, and 4 hyperactivity/ impulsive subtype. None of them was medicated, and no other abnormal condition except ADHD was observed. All subjects were assessed with Continuous Performance Test which in Korean version of

ADHD diagnosis system (ADS). It evaluated commission errors, omission errors, and response time for performance tasks. Demographic characteristic of ADHD patient and control group are depicted on Table 1.

Control group consist of children who visited clinic for diagnosis, but didn't met criteria, and children who visited to assess IQ. Every control subjects had interview with board-certified child psychiatrists using Child Behavior Checklist, Diagnostic Interview Schedule for Children, and ADI-R. Only remitted transient tic symptom, mild anxious symptom, and depressive symptom were found in four control subject, but any condition which causes abnormal brain function was found .The parent of all participants gave informed consent, which was approved by Institutional Review Board (IRB) of Seoul National University Hospital.

2.2. Image acquisition

DTI data were obtained on 3T scanner (GE Signa EXCITE 3.0T) in the Seoul National University Hospital. We used single shot echoplanar imaging sequence to get diffusion weighted images (TE=88.3 ms; TR=10000.0 ms; FOV=240 $\times$ 240mm^2; 25 diffusion directions with one b=0). T1 structural image was acquired for each subject by identical scanner using 3D spoiled gradient-echo (SPGR) sequence (TE=4.0 ms; TR=22.0 ms; FOV=240×240mm^2).

2.3. Image preprocessing

All diffusion images of DICOM (Digital Imaging and Communications in Medicine) format were converted to NIFTI (Neuroimaging Informatics Technology Initiative) image format using MRIConvert software (http://lcni.uoregon.edu/~jolinda/MRIConvert/). Before tractography, preprocessing was performed using FMRIB's Diffusion Toolbox implemented FSL 5.0.1 (http://www.fmrib.ox.ac.uk/fsl). All images were resampled to isotropic dataset (2×2×2mm voxels) using FMRIB's Linear Image Registration Tool (FLIRT) since diffusion weighted images were highly anisotropic (0.94×0.94×3.5). Then eddy current correction and non-brain masking using binary brain mask were performed.

2.4. Voxel based analysis: TBSS

Diffusion tensor model was fitted to each voxel of data and determine the values such as Fractional anisotropy (FA). To compare FA image for voxel-wise analysis, we used Track-Based Spatial

Statistics (TBSS) (Smith et al., 2006).All individual's FA image was transformed into standard space, and mean FA skeleton which represents center of white matter tract commonly found across the subjects was generated and thresholded (FA > 0.2). Voxel-wise statistics were performed using subject-specific projected skeletonized FA data. A Randomize permutation testing tool was used to examine regional white matter difference. T-tests were used to assess FA difference using Threshold-Free Cluster Enhancement (TFCE) option, which is more robust than cluster based thresholding.

2.5. Network analysis

Tractography

Preprocessed diffusion weighted images were exported to Diffusion Toolkit (http://tracvis.org) , and whole brain fiber tracking was performed using a FACT (fiber assignment by continuous tracking) algorithm(Mori et al., 1999). FACT algorithm starts tracking from seed locations and propagates a streamline along each voxel's principal diffusion direction until terminate criteria is met. Tractography was terminated when trajectory curvature was greater than 35°. Whole brain tracking was carried out on every voxels in whole brain; one seed point per each voxel was used.

Node definition for network analysis

We used automated anatomical labeling (AAL) template to parcellate brain. It contains 116 brain areas including cerebral cortex, subcortical structures, and cerebellum (Table 2). Tractography is performed in diffusion space, so subject-specific AAL templates were generated as below.

Anatomical T1 images were coregistered to b=0 images, and transformed T1 images were nonlinearly warped to ICBM152 T1 template in MNI space using a segment function in Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Transformation matrix for diffusion space to standard space is obtained by segmentation, and its inverse matrix was applied to warp AAL template from standard space to the diffusion space. Every subject has 116 AAL templates in own diffusion space, and they were defined nodes consisting whole brain network.

Generate connectivity matrix

A fiber was counted as connecting two specified ROI regions if a fiber passes through them. There is no optimal way to normalize connectivity matrix. Normalize scheme which corrects ROI size and length difference is been widely used (Hagmann et al., 2007, Hagmann et al., 2008) , but It overestimates ROI and length effects. White matter tract intersects with gray matter region in relatively small area. In this study, ROI and length factor will not be considered, and purely topological normalization will be used (Duarte-Carvajalino et al., 2012). Connectivity strength between ROI i and j was identified as weight, w_{ij}. Fiber tract count connecting two regions were divided by each subject's mean fiber tract count, and further scaled with each subjects maximum w_{ij} to make every values 0 to 1.

2.5.1 Graph theoretical analysis

Graph measures

Structural connectivity topology was analyzed by graph network measures (Rubinov and Sporns, 2010) . Following measures of a weighted network G with N nodes and N edges were quantified: clustering coefficient (C_w), betweenness centrality (B_w), Nodal efficiency (E_{nodal}).

Degree of i, K_i is the number of every connection that linking the node i:

$$k_i = \sum_{j \in N} a_{ij}$$

where a_{ij} is the edge between node i and j. Clustering coefficient of a node is the ratio A/B, where A is the number of connections of a node with neighbors, and B is the maximum possible connections with neighbors. It measures a tendency of a node to cluster with neighbors. C_i, a clustering coefficient of node *i* is computed as following:

$$C_i = \frac{2}{K_i(K_i - 1)} \sum_{j,k} (\widetilde{w_{ij}} \widetilde{w_{jk}} \widetilde{w_{ki}})^{1/3}$$

where K_i denotes a degree of a node *i*, and $\widetilde{w}$ is the weight which is scaled by mean weight of the network to normalize multiple networks' cost.

Nodal efficiency also measures efficiency of parallel information transfer across whole network in a node as following equation on a node(Achard and Bullmore, 2007):

$$E_{\text{nodal}}(i) = \frac{1}{N-1} \sum_{i \neq j \in G} \frac{1}{L_{ij}}$$

L_{ij} denotes the shortest path length between node *i* and j, which represents interconnection of a node with any node in network. The betweenness centrality (B_i) indicates the number of shortest paths from *i* to all other nodes which pass through *i* within the network G(Freeman, 1977). B_i is calculated as below.

$$B_i = \sum_{j \neq i \neq k \in G} \frac{\sigma_{jk}(i)}{\sigma_{jk}}$$

σ_{jk} is the number of shortest path length between *j* and *k*, that passes through *i*. L_p quantifies a network's capacity for information processing across whole brain(Latora and Marchiori, 2001). A path length is the lengths of an edge connecting pair of nodes *i* and *j*. Shortest path length, $L_{ij,}$ is the edge which transverses *i* to *j* with minimum length while L_i is the average shortest path length of node *i* with every other nodes. The L_p of a network is the mean of every node, and calculated as:

$$L_p(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} L_{ij}$$

We investigated small worldness of networks by examining L_p, and C_w (Watts and Strogatz, 1998). A random network which has same degree distribution with each subject's network was generated, and $L_p{}^{rand}$ and $C_w{}^{rand}$, graph measures for random networks, were calculated. γ, normalized C_w calculated with mean C_w of real networks and random networks, and λ, normalized L_p calculated with L_p of real networks and random networks, were used to investigate small worldness property. A real network was considered to be a small world, if it meets following criteria:

$$= C_w{}^{real}/C_w{}^{rand} \gg 1 \text{ and } \lambda = L_p{}^{real}/L_p{}^{rand} \approx 1.$$

2.5.2. Network filtration

SLM was generated by calculating single linkage distance (SLD) of w_{ij}. Distance between two nodes was calculated (1- w_{ij}), and SLD was estimated. This enables comparing patterns of connecting component pattern in two groups by thresholding distance matrix. Distance for threshold was gradually increased, and iteratively applied to distance matrix. Nodes which have shorter distance than a threshold were identified as connected component, and shorter distance of nodes reflects closer coupling between nodes (figure 2).

2.6. Statistical analysis

Structural connectivity topology was analyzed by graph network measures (Rubinov and Sporns, 2010) . Network theoretical measurers (C_w, B_w, E_{nodal}) were quantified to estimate integration and segregation of brain network. Nonparametric permutation tests (5,000 times) were performed to investigate between group differences on graph topologies. Subjects were randomly assigned into two groups, and nonparametric Wilcoxon test was executed for network measures of two groups. It was iteratively performed 5,000 times to make null distribution. z value obtained from Wilcoxon test for ADHD and Control group was compared with ones from null distribution ($p < 0.005$). IQ and age was regressed out as covariates before statistical tests. Kolmogorov–Smirnov test (KS test) compared distributions of two group's network measures ($p < 0.005$, uncorrected).

Single linkage matrix was also generated for each subject, and local differences between two groups were examined with nonparametric permutation test (5,000 times, $p < 0.01$). Gromov-Hausdorff (GH) distances between SLMs of subjects were also calculated to investigate global differences. Differences in GH distances of within group and between groups were examined by Wilcoxon test ($p < 0.005$). Results were visualized using BrainNet Viewer (Xia et al., 2013).

3. Results

3.1. Voxel-wise FA analysis using TBSS

Clusters that contained more than 20 voxels were found as follows. FA increased in Vermis VIIIa, Right VIIIa, and Right crus VIIIa in ADHD children (p < 0005, uncorrected) (Figure 3). There were no significantly altered clusters, but cerebellar regions showed tendency for increased FA in ADHD.

3.2. Abnormal network characteristics in children with ADHD

Graph network measures were used to find group differences in networks of two groups. Fist, small world property was examined to find if every subject's networks are organize with certain rules, rather than randomly organized. Networks of every subject showed small-worldness properties, and no group difference was found ($p < 0.005$, permutation). To investigate global differences in network measures, distributions of network measures were compared. Distribution of betweenness centrality (B_w), clustering coefficient (C_w) and nodal efficiency (E_{nodal}) between two groups were significantly different ($p < 0.005$, permutation). ADHD had narrower distribution, and had more nodes with small betweenness centrality (B_w) and Clustering coefficient (C_w) (Figure 4). Also, ADHD had wider distribution and larger nodal efficiency (E_{nodal}) compared with Disease control group (Figure 4). As for nodal differences, betweenness centrality (B_w) only showed significantly decreased value in right parahippocampal gyrus ($p < 0.005$, permutation) (Figure 5). No other nodes showed significant differences in nodal network measures.

3.3. Abnormal connected component of structural network in children with ADHD using network filtration

No significant global group difference was found in filtration analysis ($p < 0.05$, permutation). As for local difference, ADHD showed more closely coupled connected components on right supramarginal gyrus, bilateral middle frontal gyri, left superior frontal gyrus, bilateral medial superior frontal gyrus, right dorsolateral frontal gyrus, and bilateral supplementary motor area. Connected components which have looser coupling in ADHD was found on left angular gyrus, right middle cingulate, right medial frontal gyrus, left paracentral lobule, left superior parietal gyrus, right cuneus, left opercular inferior frontal gyrus, right precuneus, left inferior temporal gyrus, left middle temporal gyrus, left superior temporal gyrus, left thalamus, right supplementary motor area, left postcentral gyrus, and left precentral gyrus ($p < 0.005$, permutation) (Table 3, Figure 6).

4. Discussion

Network analysis was used to investigate white matter alterations in ADHD. Graph theoretical analysis found decreased centrality in ADHD on parahippocampal gyrus. Network filtration disclosed abnormally connected components between frontal regions, parietal regions, occipital regions, and temporal regions. Especially, left angular gyrus and right supramargunal gyrus had most atypically connected components.

As for graph network measures, global alteration of network measures in ADHD was found in distribution of nodes, but not in individual nodes. Right parahippocampal gyrus was the only node that showed nodal difference between two groups, and decreased betweenness centrality was found. Only small group differences were found in network theoretical measures.

Although there was no global difference in connection patterns between two groups, connected components showing significant differences were found. Nodes in parietal region showed abnormally connected components with temporal regions and frontal regions in network filtration results. Especially, Right supramarginal gyrus and left angular gyrus located parietal region showed abnormal connection patterns with frontal regions. Left angular gyus showed abnormally connected patterns with temporal regions and other parietal regions. Parietal regions are related to attention, especially shifting attention and attention orientation (Tamm et al., 2006). ADHD children showed significantly lower performance in oddball task, and significantly reduced activation in bilateral parietal regions were found while oddball task (Tamm et al., 2006).

Right supramarignal gyrus and connected frontal regions share key regions with fronto-parietal attention network (Castellanos and Proal, 2012, Cubillo et al., 2012a), which is associated to self-regulation, reward processing, and sustained attention. There are two attention systems in fronto-parietal attention network; a dorsal attention system involving intra parietal sulcus and superior frontal gyrus, and a ventral attention system involving temporoparietal junction (TPJ) and ventral frontal cortex (Majerus et al., 2012). Two networks are segregated, since they are comprises of different anatomical components and show different functional specializations. The dorsal attention system is related to feature-based attention, and the ventral attention system is associated with salient and unexpected stimulus-related response. Key regions of ventral attention system was activated by an oddball stimulus (Marois et al., 2000). It has been discussed that the dorsal system is associated to top-down system, and the ventral system to bottom up system (Corbetta and Shulman, 2002, Vossel et al., 2013). Supramargunal gyrus, including TPJ, comprises inferior parietal lobe which is crucial structure of ventral attention system. Connected components consist of supramarginal gyrus and frontal regions including superior dorsolaterl frontal gyrus showed abnormal coupling pattern in ADHD. These results may reflect disrupted ventral attention network in ADHD.

A white matter tract which traverses the supramargunal gyrus and angular gyrus is the superior longitudinal gyrus (SLF). Subcomponents of SLF extend to angular gyrus from insula, and another subcomponent transverse to the supramarginal gyrus from prefrontal regions and premotor regions (Makris et al., 2005, Schmahmann and Pandya, 2009). SLF is known to be related with spatial working memory, attention and impulsivity (Takahashi et al., 2010, Vestergaard et al., 2011). The results of this study are consistent with previous studies which reported decreased white matter integrity in SLF (Figure 7) (Pavuluri et al., 2009, Davenport et al., 2010) .

Recently, middle longitudinal fasciculus (MdLF) has been discovered (Maldonado et al., 2013). It is a major fiber tract which connects temporal lobe and parietal lobe. It is believed that MdLF is related to language and attention, since parietal and temporal regions are involved in spatial attention and visuospatial information processing (Makris et al., 2013). Besides, angular gyrus, the region that ADHD showed looser connectivity with temporal regions in network filtration analysis, is the key brain region for MdLF (figure 7). This implies ADHD has abnormal white matter connection in MdLF, and attention problem might be related to the abnormality.

Results discussed above indicate aberrant connection components mainly located in parietal and frontal regions related to the attention system. Altered connections in parietal regions, frontal regions and temporal regions also imply abnormal microstructural integrity in SLF. Inattention is major symptom of ADHD, and the above mentioned regions could induce the symptoms. Particularly, detection of salient stimulus would be impaired, and bottom up system in information process may be disrupted. Previous studies discussed about hypertrophy (Madras et al., 2002), and delayed brain development (Durston et al., 2003) in ADHD, which might cause problems in white matter microstructural integrity.

We investigated structural topology and white matter intigration in ADHD, but several issues should be discussed. First, tractography was implemented using deterministic algorithm. It is not robust method to noise, since it terminiates tracking when FA is greater than 0.2. Tracking could me terminiated by some noise or crossing fibers. Second, children in ADHD group had heterogenous subtypes.

Subjects with hyperactivity or inattentive subtypes suffer from different main symptoms.It is possible that there exists between subtype differences. It was impossible to investigate between subtype differecnes, since the group size was small. Third, few control subjects showed abnoraml conditions, and visited clinic for diagnosis. Although any problems which could affect structural and functional connectivity was not found, but control group for studies should have been recruited with more conservative criteron. However, this is the first study that investigated whole brain connectivity including the cerebellum although there were only few abnormal cerebellar regions found. Also, graph filtration, which enables examination between two groups' difference whitout applying arbitrary threshold, was performed. An arbitrary threshold could discard important information, and affect results. Multiscale filtration method utilize every information of network, and presents every connected components according to filtration values.

In future researches, multimodal network study is required since only strutural or functional studies could not fully examine neural network characteristics in ADHD. Many functional studies reported abnormal metabolism and activities in ADHD. Some studies tried multimodal analysis using more than two modalities. But most of them investigated only regional abnormalities, not whole brain network.

Method and conceptual insight for combinig strucutral and functional brain networks should be found. Also, It is desirable to combine brain imaging with other various research methods such as neuropsychological tests, genes, and molecular biological perspectives to examine cause and prognosis clearly. Genetic factor is considered as major factor for developing ADHD, and parenting is also importatntly discussed for managing symptoms of ADHD. Logitudinal studies combining brain imaing, genetic investigation, and envioronmental factors might give us deeper understanding on ADHD.

In summary, abnormalities in fronto-parietal connection and temporo-parietal connection imply imbalance in attention system which could induce attention deficit. SLF and MdLF are the major white matter tracts which connect fronto-parietal regions and temporo-parietal regions, and both tract is realted to attention system. This results suggestes that attention system is altered in ADHD, and It might be related to abnormal white matter connectivity of fiber tracts such as SLF and MdLF. Also, we prosposed network filtration method which shows connectivity patterens applying every thresholds, and also greater statistical power than usual network analysis.

References

Achard S, Bullmore E (2007) Efficiency and cost of economical brain functional networks. PLoS computational biology 3:e17.

Alexander GE, Crutcher MD, DeLong MR (1991) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor,“prefrontal” and “limbic” functions. Progress in brain research 85:119-146.

Aron AR, Monsell S, Sahakian BJ, Robbins TW (2004a) A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. Brain : a journal of neurology 127:1561-1573.

Aron AR, Robbins TW, Poldrack RA (2004b) Inhibition and the right inferior frontal cortex. Trends in cognitive sciences 8:170-177.

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychological bulletin 121:65.

Barry TD, Lyman RD, Klinger LG (2002) Academic underachievement and attention-deficit/hyperactivity disorder: The negative impact of symptom severity on school performance. Journal of School Psychology 40:259-283.

Berquin P, Giedd J, Jacobsen L, Hamburger S, Krain A, Rapoport J, Castellanos F (1998) Cerebellum in attention-deficit hyperactivity disorder A morphometric MRI study. Neurology 50:1087-1093.

Biederman J, Faraone S, Milberger S, Guite J, Mick E, Chen L, Mennin D, Marrs A, Ouellette C, Moore P (1996) A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. Archives of general psychiatry 53:437.

Cao Q, Shu N, An L, Wang P, Sun L, Xia MR, Wang JH, Gong GL, Zang YF, Wang YF, He Y (2013) Probabilistic diffusion tractography and graph theory analysis reveal abnormal white matter structural connectivity networks in drug-naive boys with attention deficit/hyperactivity disorder. The Journal of neuroscience : the official journal of the Society for Neuroscience 33:10676-10687.

Castellanos FX, Proal E (2012) Large-scale brain systems in ADHD: Beyond the prefrontal–striatal model. Trends in cognitive sciences 16:17-26.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience 3:201-215.

Cubillo A, Halari R, Smith A, Giampietro V, Taylor E, Rubia K (2012a) Fronto-cortical and fronto-subcortical brain abnormalities in children and adults with ADHD: a review and evidence for fronto-striatal dysfunctions in adults with ADHD followed up from childhood during motivation and attention. Cortex; a journal devoted to the study of the nervous system and behavior 48:194-215.

Cubillo A, Halari R, Smith A, Taylor E, Rubia K (2012b) A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex; a journal devoted to the study of the nervous system and behavior 48:194-215.

Davenport ND, Karatekin C, White T, Lim KO (2010) Differential fractional anisotropy abnormalities in adolescents with ADHD or schizophrenia. Psychiatry Research: Neuroimaging 181:193-198.

Duarte-Carvajalino JM, Jahanshad N, Lenglet C, McMahon KL, de Zubicaray GI, Martin NG, Wright MJ, Thompson PM, Sapiro G (2012) Hierarchical topological network analysis of anatomical human brain connectivity and differences related to sex and kinship. NeuroImage 59:3784-3804.

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti I-M, Yang Y, Ulug AM, Casey B (2003) Differential patterns of striatal activation in young children with and without ADHD. Biological Psychiatry 53:871-878.

Freeman LC (1977) A set of measures of centrality based on betweenness. Sociometry 35-41.

Frye RE, Hasan K, Malmberg B, Desouza L, Swank P, Smith K, Landry S (2010) Superior longitudinal fasciculus and cognitive dysfunction in adolescents born preterm and at term. Developmental Medicine & Child Neurology 52:760-766.

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS biology 6:e159.

Hagmann P, Kurant M, Gigandet X, Thiran P, Wedeen VJ, Meuli R, Thiran J-P (2007) Mapping human whole-brain structural networks with diffusion MRI. PloS one 2:e597.

Hamilton LS, Levitt JG, O'Neill J, Alger JR, Luders E, Phillips OR, Caplan R, Toga AW, McCracken J, Narr KL (2008) Reduced white matter integrity in attention-deficit hyperactivity disorder. Neuroreport 19:1705.

Latora V, Marchiori M (2001) Efficient behavior of small-world networks. Physical review letters 87:198701.

Lawrence KE, Levitt JG, Loo SK, Ly R, Yee V, O'Neill J, Alger J, Narr

KL (2013) White matter microstructure in subjects with attention-deficit/hyperactivity disorder and their siblings. Journal of the American Academy of Child and Adolescent Psychiatry 52:431-440 e434.

Lee H, Chung MK, Kang H, Kim B-N, Lee DS (2011) Computing the shape of brain networks using graph filtration and Gromov-Hausdorff metric. In: Medical Image Computing and Computer-Assisted Intervention–MICCAI 2011, pp 302-309: Springer.

Lee H, Kang H, Chung M, Kim B, Lee D (2012) Persistent brain network homology from the perspective of dendrogram.

Madras BK, Miller GM, Fischman AJ (2002) The dopamine transporter: relevance to attention deficit hyperactivity disorder (ADHD). Behavioural brain research 130:57-63.

Majerus S, Attout L, D'Argembeau A, Degueldre C, Fias W, Maquet P, Perez TM, Stawarczyk D, Salmon E, Van der Linden M (2012) Attention supports verbal short-term memory via competition between dorsal and ventral attention networks. Cerebral Cortex 22:1086-1097.

Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, Brown AB, Bush G, Monuteaux MC, Caviness VS (2008) Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections.

Cerebral Cortex 18:1210-1220.

Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS, Pandya DN (2005) Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cerebral Cortex 15:854-869.

Makris N, Preti M, Wassermann D, Rathi Y, Papadimitriou G, Yergatian C, Dickerson B, Shenton M, Kubicki M (2013) Human middle longitudinal fascicle: segregation and behavioral-clinical implications of two distinct fiber connections linking temporal pole and superior temporal gyrus with the angular gyrus or superior parietal lobule using multi-tensor tractography. Brain imaging and behavior 1-18.

Maldonado IL, Champfleur NM, Velut S, Destrieux C, Zemmoura I, Duffau H (2013) Evidence of a middle longitudinal fasciculus in the human brain from fiber dissection. Journal of anatomy.

Marois R, Leung H-C, Gore JC (2000) A stimulus-driven approach to object identity and location processing in the human brain. Neuron 25:717-728.

Mori S, Crain BJ, Chacko V, Van Zijl P (1999) Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Annals of neurology 45:265-269.

Mostofsky SH, Reiss AL, Lockhart P, Denckla MB (1998) Evaluation of cerebellar size in attention-deficit hyperactivity disorder. Journal of child neurology 13:434-439.

Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, Sweeney JA, Zhou XJ (2009) Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Biological Psychiatry 65:586-593.

Pennington BF, Ozonoff S (1996) Executive functions and developmental psychopathology. Journal of child psychology and psychiatry 37:51-87.

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. NeuroImage 52:1059-1069.

Sagvolden T, Aase H, Zeiner P, Berger D (1998) Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder. Behavioural brain research 94:61-71.

Schachar R, Tannock R, Marriott M, Logan G (1995) Deficient inhibitory control in attention deficit hyperactivity disorder. Journal of abnormal child psychology 23:411-437.

Schmahmann JD, Pandya D (2009) Fiber pathways of the brain: Oxford University Press.

Sergeant J (2000) The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. Neuroscience & Biobehavioral Reviews 24:7-12.

Shinoura N, Suzuki Y, Yamada R, Tabei Y, Saito K, Yagi K (2009) Damage to the right superior longitudinal fasciculus in the inferior parietal lobe plays a role in spatial neglect. Neuropsychologia 47:2600-2603.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31:1487-1505.

Sonuga-Barke EJ (2003) The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. Neuroscience & Biobehavioral Reviews 27:593-604.

Sonuga-Barke E, Houlberg K, Hall M (1994) When is “impulsiveness” not impulsive? The case of hyperactive children's cognitive style. Journal of child psychology and psychiatry 35:1247-1253.

Sonuga-Barke EJ (1994) Annotation: On dysfunction and function in psychological theories of childhood disorder. Journal of child psychology and psychiatry 35:801-815.

Supekar K, Menon V (2012) Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. PLoS computational biology

8:e1002374.

Takahashi M, Iwamoto K, Fukatsu H, Naganawa S, Iidaka T, Ozaki N (2010) White matter microstructure of the cingulum and cerebellar peduncle is related to sustained attention and working memory: a diffusion tensor imaging study. Neuroscience letters 477:72-76.

Tamm L, Menon V, Reiss A (2006) Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder: event-related fMRI evidence. American Journal of Psychiatry 163:1033-1043.

Vestergaard M, Madsen KS, Baaré WF, Skimminge A, Ejersbo LR, Ramsøy TZ, Gerlach C, Åkeson P, Paulson OB, Jernigan TL (2011) White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. Journal of Cognitive Neuroscience 23:2135-2146.

Vossel S, Geng JJ, Fink GR (2013) Dorsal and Ventral Attention Systems Distinct Neural Circuits but Collaborative Roles. The Neuroscientist.

Watts DJ, Strogatz SH (1998) Collective dynamics of ‘small-world’networks. nature 393:440-442.

Xia M, Wang J, He Y (2013) BrainNet Viewer: a network visualization tool for human brain connectomics. PloS one 8:e68910

Yu-Feng Z, Yong H, Chao-Zhe Z, Qing-Jiu C, Man-Qiu S, Meng L, Li-Xia T, Tian-Zi J, Yu-Feng W (2007) Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain and Development 29:83-91.

Table 1. Demographic information of ADHD and disease control group.

Demographic characteristics		Mean ± SD	
		ADHD (n=19)	DC (n=9)
Age		8.1 ± 1.5	9.5 ± 2.8
Gender (M : F)		15:4	6:3
IQ		105.1 ± 14.5	109.0 ± 16.9
Subtypes	combined	8	
	Inattentive	6	
	hyperactive/impulsive	4	
	Not Otherwise Specified	1	

ADHD: subjects with attention-deficit/hyperactivity disorder, DC: Disease controls.

Table 2. 116 AAL templates were used for region of interests including cortical regions, subcortical regions, and cerebellum.

index	Anatomical description	Label
1, 116	Olfactory cortex	OLF
2, 115	Gyrus rectus	REC
3, 114	Inferior frontal gyrus, orbital part	ORBinf
4, 113	Inferior frontal gyrus, opercular part	IFGoperc
5, 112	Inferior frontal gyrus, triangular part	IFGtriang
6, 111	Middle frontal gyrus, orbital part	ORBmid
7, 110	Middle frontal gyrus	MFG
8, 109	Superior frontal gyrus, orbital part	ORBsup
9, 108	Superior frontal gyrus, medial orbital	ORBsupmed
10, 107	Superior frontal gyrus, medial	SFGmed
11, 106	Superior frontal gyrus, dorsolateral	SFGdor
12, 105	Paracentral lobule	PCL
13, 104	Supplementary motor area	SMA
14, 103	Precentral gyrus	PreCG
15, 102	Rolandic operculum	ROL
16, 101	Anterior cingulate and paracingulate gyri	ACG
17, 100	Median cingulate and paracingulate gyri	DCG
18, 99	Postcentral gyrus	PoCG
19, 98	Superior parietal gyrus	SPG
20, 97	Precuneus	PCUN
21, 96	Inferior parietal, but supramarginal and angular gyri	IPL
22, 95	Supramarginal gyrus	SMG
23, 94	Angular gyrus	ANG
24, 93	Superior temporal gyrus	STG
25, 92	Heschl gyrus	HES
26, 91	Middle temporal gyrus	MTG
27, 90	Inferior temporal gyrus	ITG
28, 89	Temporal pole: superior temporal gyrus	TPOsup
29, 88	Temporal pole: middle temporal gyrus	TPOmid
30, 87	Insula	INS
31, 86	Caudate nucleus	CAU
32, 85	Lenticular nucleus, putamen	PUT
33, 84	Lenticular nucleus, pallidum	PAL

34, 83	Thalamus	THA
35, 82	Amygdala	AMYG
36, 81	Hippocampus	HIP
37, 80	Parahippocampal gyrus	PHG
38, 79	Posterior cingulate gyrus	PCG
39, 78	Fusiform gyrus	FFG
40, 77	Inferior occipital gyrus	IOG
41, 76	Middle occipital gyrus	MOG
42, 75	Superior occipital gyrus	SOG
43, 74	Calcarine fissure and surrounding cortex	CAL
44, 73	Cuneus	CUN
45, 72	Lingual gyrus	LING
46, 71	Cerebellum 03	CRBL3
47, 70	Cerebellum 04 05	CRBL45
48, 69	Cerebellum 06	CRBL6
49, 68	Cerebellum Crus1	CRBLCrus1
50, 67	Cerebellum Crus2	CRBLCrus1
51, 66	Cerebellum 07b	CRBL7b
52, 65	Cerebellum 08	CRBL8
53, 64	Cerebellum 09	CRBL9
54, 63	Cerebellum 10	CRBL10
55	Vermis 01 02	Vermis12
56	Vermis 03	Vermis3
57	Vermis 04 05	Vermis45
58	Vermis 06	Vermis6
59	Vermis 07	Vermis7
60	Vermis 08	Vermis8
61	Vermis 09	Vermis9
62	Vermis 10	Vermis10

Table 3. Edges which showed abnormal coupling in ADHD comparing control group in SLM.

Node 1	Node 2
Middle frontal gyrus, left	Supramarginal gyrus, right
Middle frontal gyrus, right	Supramarginal gyrus, right
Superior frontal gyrus, dorsolateral, left	Supramarginal gyrus, right
Superior frontal gyrus, medial, left	Supramarginal gyrus, right
Superior frontal gyrus, medial, right	Supramarginal gyrus, right
Superior frontal gyrus, dorsolateral, right	Supramarginal gyrus, right
Supplementary motor area, left	Supramarginal gyrus, right
Supplementary motor area, right	Supramarginal gyrus, right
Angular gyrus, left	Cuneus, right
Angular gyrus, left	Inferior frontal gyrus, opercular part, left
Angular gyrus, left	Precuneus, right
Angular gyrus, left	Inferior temporal gyrus, left
Angular gyrus, left	Middle temporal gyrus, left
Angular gyrus, left	Superior temporal gyrus, left
Median cingulate, paracingulate gyri, right	Thalamus, left
Superior frontal gyrus, medial, right	Supplementary motor area, right
Paracentral lobule, left	Postcentral gyrus, left
Paracentral lobule, left	Precentral gyrus, left
Superior parietal gyrus, left	Superior temporal gyrus, left

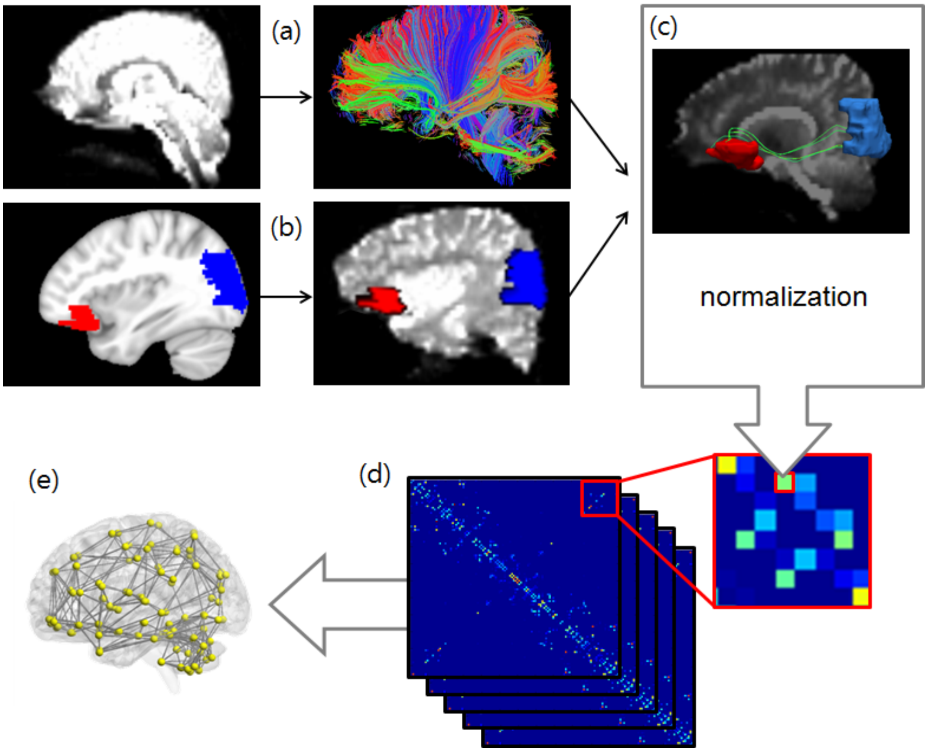

Figure 1. Workflow to generate whole brain connecectivity matrix. (a) eddy current correction and skull strip was performed to DTI data, and principal direction for each voxel was calculated. Whole brain tractography using FACT algorithm was carried out. (b) ROI using AAL templates were transformed into subject native diffusion space to examine ROI to ROI connection. (c) fiber tracts connecting pair of ROIs were counted and normalized by mean of each subject's connectivity matrix to generate weight matrix. Each weight matrix was further scaled by each subject's maximum weight value to make every element 0 to 1. (d) A scaled weight matrix was generated for each subject. (e) Network analysis was conducted.

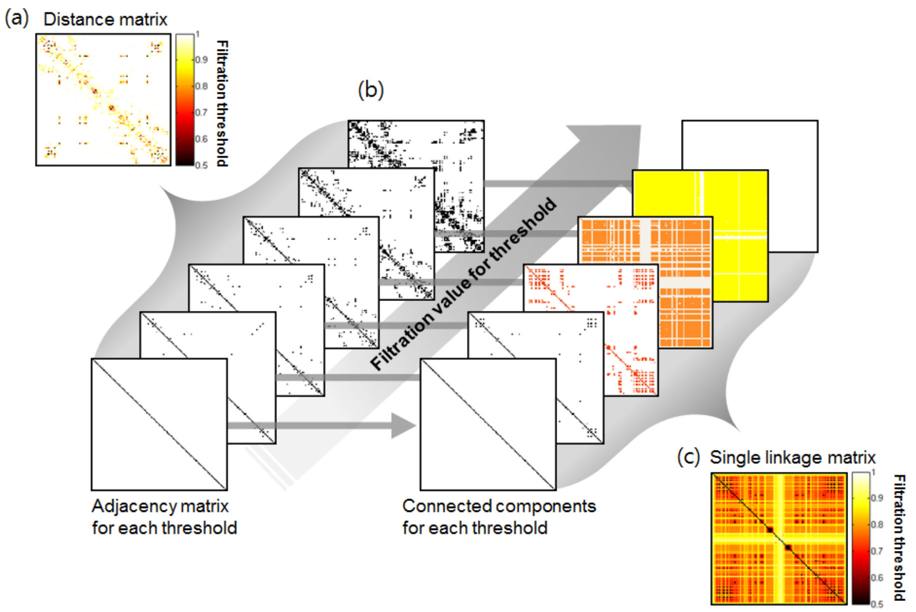

Figure 2. Workflow of multiscale filtration. (a) distance matrix was calculated with (1- w_{ij}). (b) filtration values for thresholding was applied to distance matrix, and connected components were found for each threshold level. (c) single linkage matrix was generated by merging every connected component.

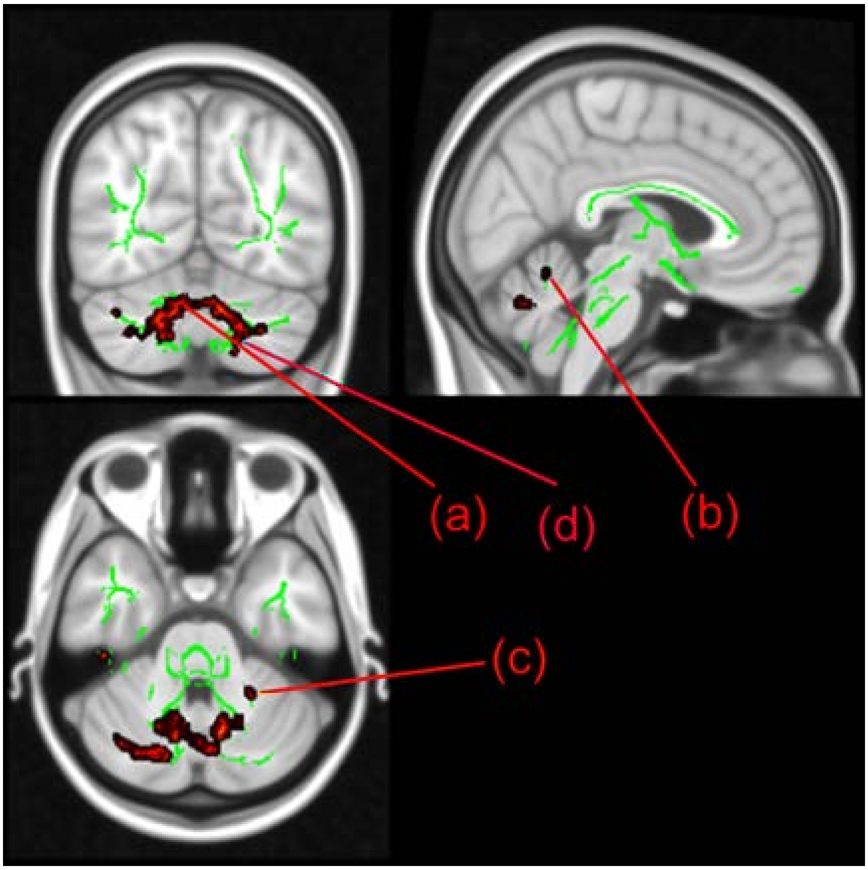

Figure 3. Regions with increased FA in ADHD. (a) vermis VIIIa, (b) right VI, (c) right crus I, (d) left VI ($p < 0.005$, uncorrected).

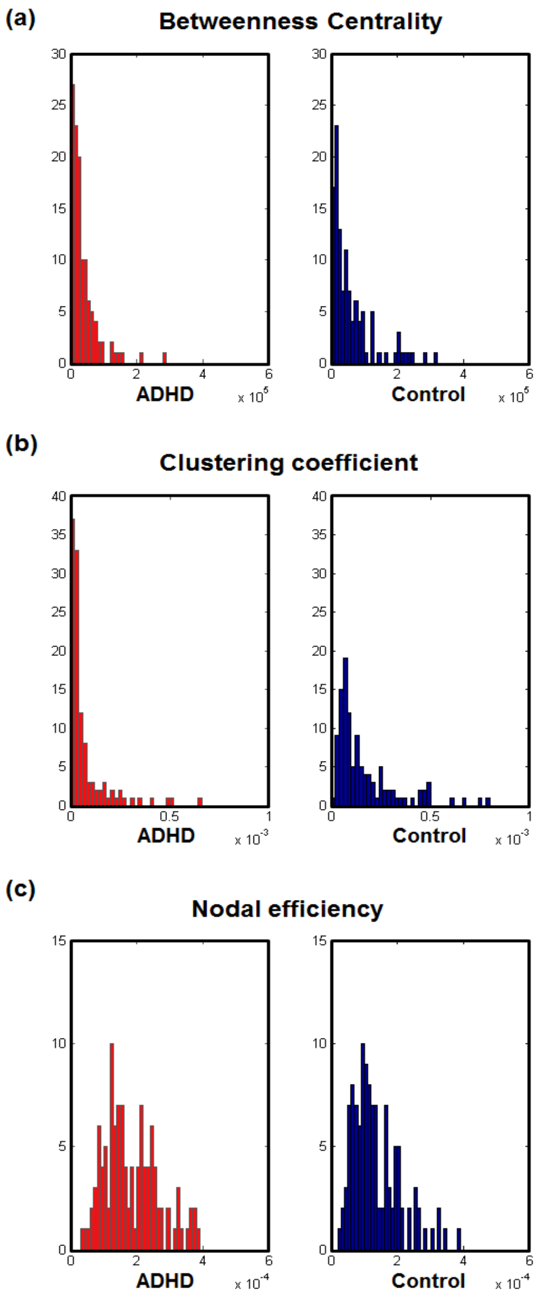

Figure 4. Distriburion of 116 nodes for (a) betweenness centarlity, (b) clustering cefficient, and (c) nodal efficiency in both groups. ADHD showed significantly altered distribution patterns in betweenness centrality, clustering coefficienct, and nodal efficiency ($p < 0.005$).

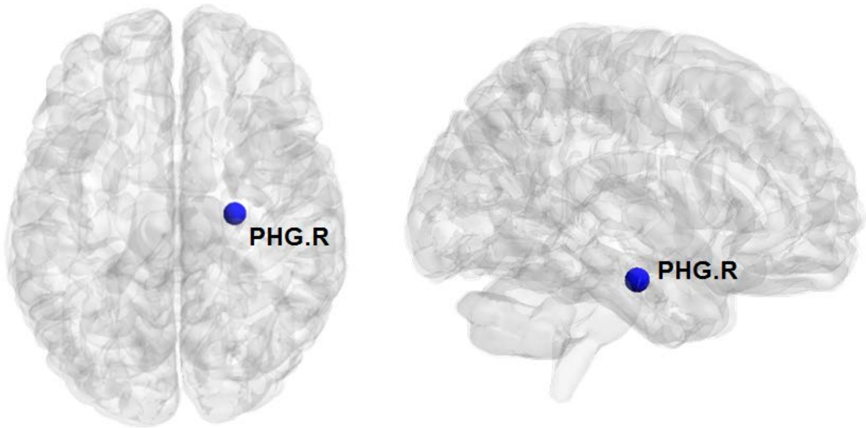

Figure 5. Nodes showing alteration in network theoretical measures. ADHD showed significantly decreased betweenness centrality in right parahippocampal gyrus (p < 0.005, permutation). No other measures showed significant group difference.

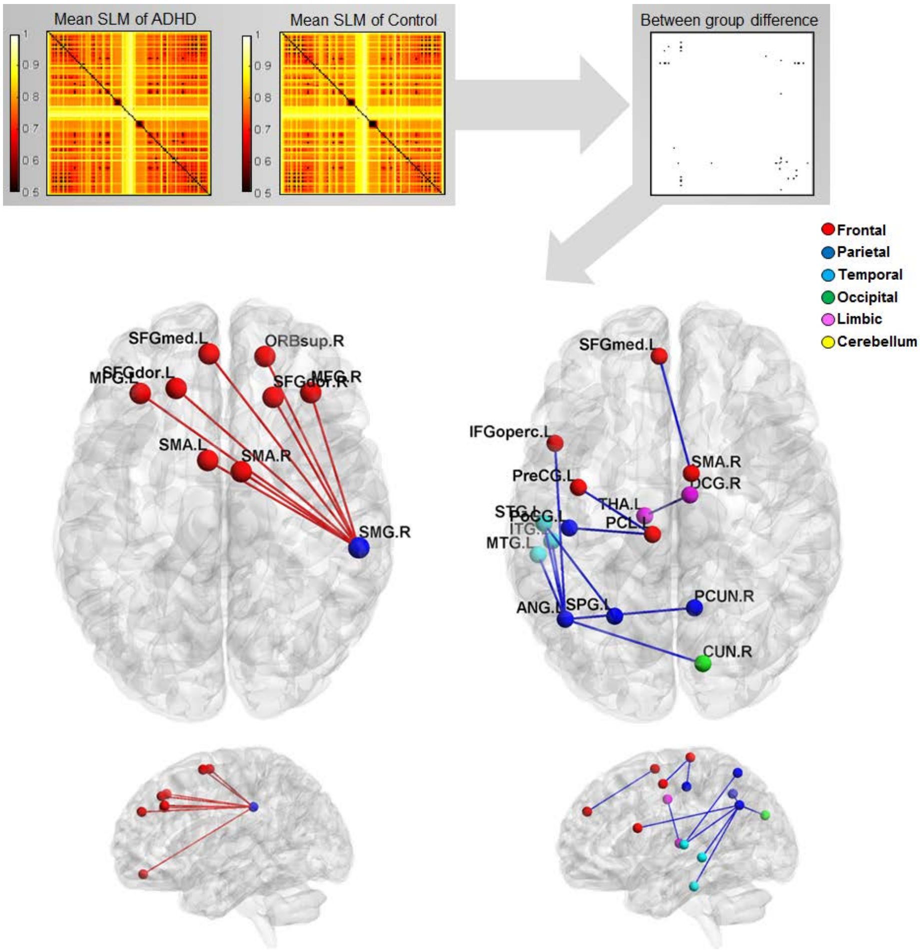

Figure 6. Group difference on single linkage matrix. Single linkage matrix for each subjects were generated, and tested for between group difference. Nonparametric permutation method was used (5,000 times). ADHD showed abnormally closer connected component on right supramarginal gyrus and frontal regions, and looser one in left angular gyrus and temporal and frontal regions. Except two largest components, right middle cingulate, left superior parietal gyrus, right cunes, right precuneus, left inferior temporal gyrus, left middle temporal gyrus, left superior temporal gyrus, left thalamus, left postcentral gyrus, and left

precentral gyrus was found for abnormal connected components in ADHD ($p < 0.005$, permutation).

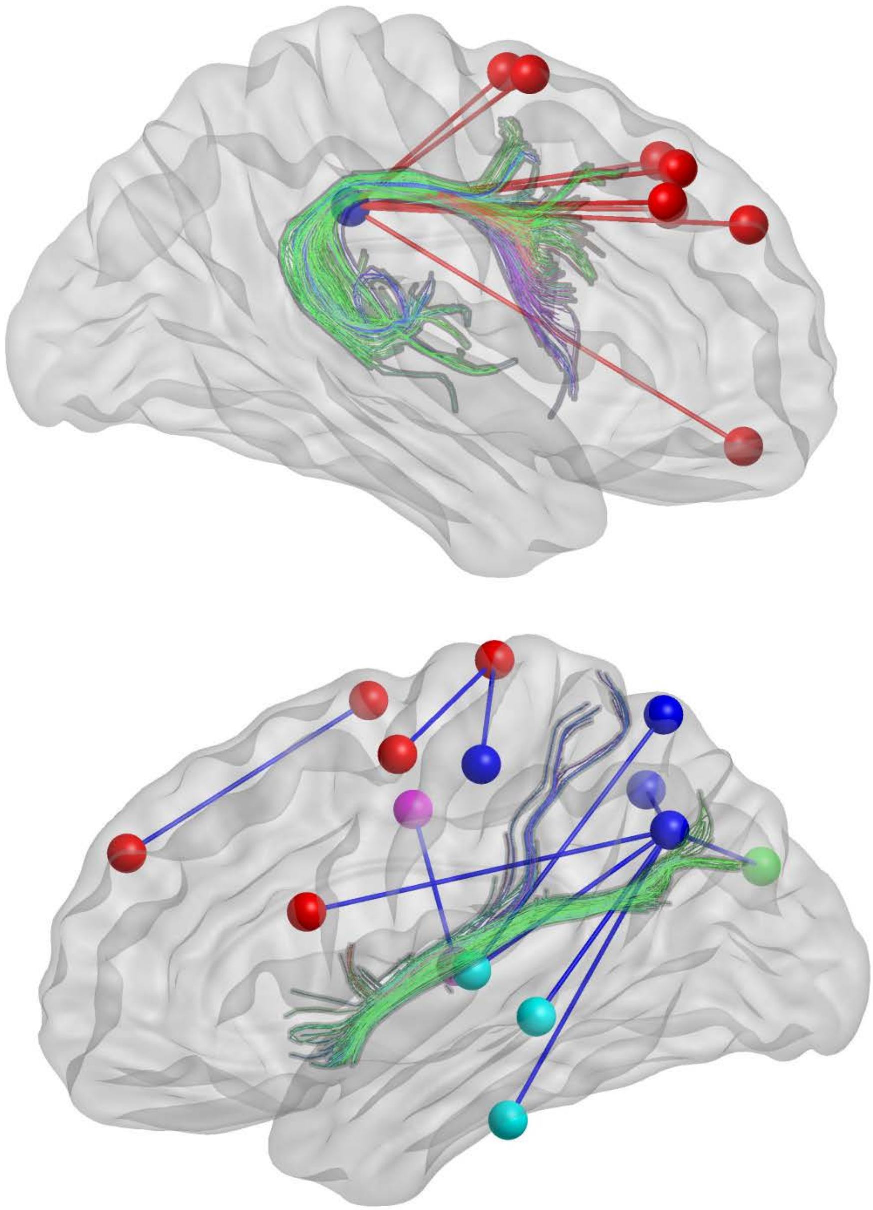

Figure 7. Altered connected components in ADHD and related fiber tracts. Top: closely connected components in ADHD and SLF, Bottom: loosely connected components in ADHD and MdLF.

국문 초록

주의력결핍 과잉행동장애 아동의 구조적 뇌 연결성 변화

허영민
협동과정 인지과학 전공
서울대학교 대학원

주의력결핍 과잉행동장애 (attention-deficit/hyperactivity disorder, ADHD)는 아동기에 흔하게 나타나는 발달장애이며, 주로 주의력 저하나 충동적인 행동 양상을 보인다. 적절한 임상적 개입이 이루어지지 않으면 성인기까지 증상이 지속되며, 우울이나 불안 등의 증상을 동반하기도 하므로 원인 규명을 통해 신속한 진단과 개입이 필요하다. ADHD의 원인을 밝히기 위해 많은 뇌 영상 연구들이 이루어졌으나, 대부분의 연구들이 국소적 뇌 영역에 한정되어 있다. 본 연구에서는 ADHD 증상을 보이는 아동들의 구조적인 뇌 연결성 (whole brain structural network) 이 대조군에 비교해 어떠한 연결성 차이를 보이는가를 알아보았다.

연구에는 총 19명의 ADHD 아동들 (15 남, 4 여; 평균 연령 = 8.1±1.5; 평균 IQ = 105.1±14.5)과 9명의 대조군 아동들 (6 남, 3 여; 평균 연령 = 9.5±2.8; 평균 IQ = 106.1±8.3)이 참여하였다. 아동들의 구조적 네트워크를 구성

하기 위해 위해 확산 텐서 영상 (Diffusion Tensor Imaging, DTI)과 트랙토그래피 (Tractogrpahy) 방법을 사용하였으며, 트랙 기반 통계 (Track-based statistics, TBSS), 그래프 이론 (Graph theory), 그리고 네트워크 필트레이션 (Network filtration)이라는 세 가지 분석 방법을 사용하여 두 그룹 간 구조적 뇌 연결성을 비교하였다. 네트워크 필트래이션은 임의의 역치값 (threshold) 을 적용해 정보값의 손실을 야기하는 기존 네트워크 분석 방법의 한계점을 보완한 방법으로서, 모든 역치값에 따른 네트워크의 연결성 패턴을 구성하여 분석한다.

트랙 기반 통계 방법과 그래프 이론을 이용한 분석에서는 두 그룹 간의 차이가 뚜렷하게 나타나지는 않았다. 특히 그래프 이론의 경우, 오른 쪽 해마방회 (hippocampal gyrus) 가 ADHD에서 사이 중앙성 (Betweenness centrality) 이 감소하는 양상을 보였는데, 이를 제외학고는 세 가지 측정값 모두에서 전반적인 차이만을 보일 뿐, 특정 노드 (node)에서의 유의한 연결성 차이를 보이지는 않았다. 그에 반해 네트워크 필트레이션의 경우에는 각회 (Angular gyrus) 와 연상회 (Supamarginal gyrus)를 포함하는 전두-두정 (fronto-parietal) 및 측두-두정 (temporo-parietal) 영역의 변화된 연결성이 ADHD 아동들에게서 관찰되었다.

전두-두정 영역은 주의력에 있어 주요한 영역이며, 해당 영역들을 연결하는 백질 경로는 상세로다발 (Superior longitudinal fasciculus, SLF) 로서 역시 주의력과 연관되어 있고, 선행연구들에 의해 ADHD 아동들에게서 백질 밀도 변화가 관찰된 바 있다. 또한 최근 새롭게 발견된 중측 종속 (Middle longitudinal fasciculus, MdLF)은 측두-두정 영역을

연결하는 백질 경로이며, 공간 주의력과 관련이 있다고 알려져 있다. 이러한 결과들은 ADHD 아동들의 주요 증상인 주의력 결핍이 전두-두정 및 측두-두정 영역의 연결성 변화와 밀접한 관련이 있음을 시사한다.

주요어 : 네트워크, 그래프 이론, 주의력결핍, 확산 텐서 영상, 트랙토그래피, 네트워크 필트레이션
학 번 : 2011-23120