Aberrant Functional Connectivity in Resting State Networks of ADHD Patients Revealed by Independent Component Analysis (ICA)

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Abstract
Background ADHD is one of the most common psychiatric disorders in children and adolescents. Altered functional connectivity has been associated with ADHD symptoms. This study aimed to investigate abnormal changes in the functional connectivity of resting-state brain networks (RSNs) among adolescent patients with different subtypes of ADHD. Methods: The data were obtained from the ADHD-200 Global Competition, including fMRI data from 88 ADHD patients (56 patients of ADHD-Combined and 32 patients of ADHD-Inattentive, ADHD-I) and 67 Typically-Developing Controls (TD-C). Group ICA was utilized to research aberrant brain functional connectivity within different subtypes of ADHD. Results: Compared with TD-C group, the clusters of decreased functional connectivity were located in the left inferior occipital gyrus (p=0.0041) and right superior occipital gyrus (p=0.0011) of DAN, supplementary motor area (p=0.0036) of ECN, left supramarginal gyrus (p=0.0081) of SN, middle temporal gyrus (p=0.0041) and superior medial frontal gyrus (p=0.0055) of DMN in ADHD-C group. In the ADHD-I group, decreased functional connectivity was found in the right superior parietal gyrus (p=0.0017) of DAN and left middle temporal gyrus (p=0.0105) of DMN. The decreased functional connectivity of ADHD-C group was found in superior temporal gyrus (p=0.0062) of AN, inferior temporal gyrus (p=0.0016) of DAN, dorsolateral superior frontal gyrus (p=0.0082) of DMN compared to ADHD-I group. All the clusters surviving at p<0.05 (AlphaSim correction). Conclusion: The results suggested that decreased functional connectivity within the DMN and DAN was responsible, at least in part, for the symptom of inattention in ADHD-I patients. Similarly, we believed that the impaired functional connectivity within networks may contribute to the manifestations of ADHD-C patients, including inattention, hyperactivity/impulsivity, and unconscious movements.

Background
Attention-deficit/ hyperactivity disorder (ADHD) emerges as a common contributor to neurodevelopmental disorders, as well as frequent psychological and behavioral problems among children (1). The global prevalence of ADHD is about 5.29%. According to the previous studies, any variation in prevalence estimates was caused by the methodological characteristics of different
researches, instead of the discrepancies in the actual distribution of ADHD (2). There are a great number of adolescent ADHD patients in the world, thus it is very important for the management and treatment of ADHD patients. ADHD is mainly characterized by symptoms of inattention, impulsivity, and hyperactivity. The current practice in the diagnosis of ADHD is mainly according to the levels of symptoms listed in DSM-IV (3) and is usually conducted by the parents or teachers, which is subjective. Typically, ADHD can be categorized into three subtypes: hyperactive-impulsivity (ADHD-HI), persistent inattention (ADHD-I), and a combination of both (ADHD-C) (4, 5). This disorder is often accompanied by learning difficulties or conduct disorders (6, 7), which can greatly affect the interpersonal skills and academic performance of patients who suffer from it. Many studies have pointed out that the subjective diagnosis is difficult to draw a line between normal level and the level of ADHD symptoms that need treatment (8). Thus, the researches of the objective diagnosis of ADHD are of great significance. And the researches of ADHD have become a hot topic in medicine and psychology in recent years.

In previous studies, resting-state functional MRI (rs-fMRI) has been widely used to examine the brain of ADHD patients (9, 10). In studies of brain function using rs-fMRI, abnormalities were found in the prefrontal cortex, anterior cingulated cortex, putamen, temporal cortex, and cerebellum (11, 12). The rs-fMRI has become a research hotspot among more and more scientists, it has achieved obvious results in many fields, such as neuroscience, spiritual science, biological science, and statistics, and it is helpful for the diagnosis and treatment of ADHD (13, 14). A growing literature shows that communication abnormalities among and within neural networks may underlie ADHD (15). Rs-fMRI can effectively identify such network abnormalities, and it's unconstrained yet reliable. In rs-fMRI experiments, subjects are awake and are asked to simply rest while lying in the MRI scanner, so brain activity can be considered ‘spontaneous’ rather than stimulus- or task-driven. As previously mentioned, most researchers focused on DMN, while less attention was paid to other brain networks or differences between two types of ADHD. So, we speculated that auditory network (AN), dorsal attention network (DAN), executive control network (ECN), salience network (SN), and sensorimotor network (SMN) are also related to ADHD, and we compared the differences in the functional
connectivity (FC) of six resting-state brain networks (RSNs) between two ADHD subtypes.

In the present study, the Group ICA, a data-driven approach, was adopted to extract the components (16). Independent component analysis (ICA) is a widely used method for the statistical analysis of fMRI data (17, 18). Without any prior information, this method can effectively determine the functional characteristics of mutually correlated brain components (19). We hope to find out the differences in these RSNs among patients with different subtypes of ADHD by comparing the FC of the six RSNs between the three groups. We speculate that the symptoms of ADHD patients are associated with abnormal FC of these RSNs.

Methods

2.1 Subjects

Public fMRI data were downloaded from the ADHD-200 Global Competition (http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html) and selected exclusively from the New York University (NYU) Child Study Center. In accordance with HIPAA guidelines and 1000 Functional Connectomes Project protocols, all datasets are anonymous, with no protected health information included. For both ADHD and TD subjects, the inclusion criteria included: an age of 7–17 years, no history of neurological disease, and no diagnosis of either schizophrenia or affective disorder, an image covering at least 95% of the brain, and an IQ score > 80, and head movement is less than 2.0. Subjects were enrolled if they were right-handed and the information was complete (e.g., age, Verbal IQ, or Performance IQ). Finally, fMRI data from a total of 155 volunteers aged between 7 and 17 were collected, including 67 Typically-Developing Controls (TD-C), 56 ADHD-C patients and 32 ADHD-I patients (the number of ADHD-HI group was too small to be studied). IBM SPSS software (Armonk, NY, v. 22.0) was used for statistical analysis. One-way analysis of variance was performed on age, ADHD index, verbal IQ, performance IQ, and Full IQ, and chi-square test was used to evaluate the difference of gender among 3 groups, a p-value of <0.05 was considered statistically significant, as shown in Table 1. The symptoms of ADHD were assessed using the Conners Parent Rating Scale-Revised, Long version (CPRS-LV).

The fMRI data were acquired using a single-shot echo-planar imaging (GRE-EPI) sequence with the
following imaging parameters: repetition time (TR)=2000 ms; echo time (TE)=15 ms; flip angle (FA)=90°; FOV read=240 mm; slice thickness=4 mm; number of slices=33; and voxelsize = 3×3×4 mm³, time points = 176, acquisition matrix=80×80.

2.2 Data preprocessing

The original data of fMRI were preprocessed by using a public toolbox named DPABI (for Data Processing & Analysis of Brain Imaging, http://rfmri.org/dpabi). The preprocessing steps were as follows: 1) Remove the first 10 volumes to ensure that the BOLD signal was stable; 2) Slice Timing, correct the difference due to the acquisition time between slices in the volume; 3) head motion correction; 4) Normalization, the data were registered to the EPI standard template and resampled to 3.0*3.0*3.0mm³, 5) spatial smoothing with a 6 mm full width at half maximum (FWHM) Gaussian kernel (20). Subjects whose head movement exceeded 2.0mm were excluded.

2.3 ICA and Determine RSNs

We conducted group independent component analysis (ICA) using Group ICA/IVA of fMRI Toolbox (GIFT, http://mialab.mrn.org/software/). We chose ICA because of its effectiveness at separating signal from noise (21). Six independent components (ICs) were selected as corresponding to major RSNs.

The used group ICA approach and tests with simulation data are described in detail in publications by the research group of Dr. Calhoun (22, 23, 24). This toolbox implements a group approach comprising estimation of the independent components (ICs) on concatenated data and followed by a computation of the subject-specific spatial maps and time courses (25). Usually, there are three main steps: (a) compression of the data; (b) estimation of the ICs in an aggregate dataset; (c) back reconstruction of the ICs.

Regarding the data reduction, the dimensionality of the data was reduced using principal components analysis (PCA). The number of independent hemodynamic sources was estimated using the minimal length description criterion (MLD), indicating 20 ICs for our functional dataset, which is sufficient to capture the most frequently observed large-scale resting-state networks (26). Then, using the Infomax algorithm, which was repeated 20 times in the ICASSO to obtain a more reliable estimation
result, maximally independent components were estimated, and the data were transformed into a linear mixing matrix and 20 ICs. The individual ICs were back reconstructed by multiplying the section of data corresponding to each subject by that mixing matrix. The ICs were then transformed to z score values, which provide an index of the degree of synchronization of the BOLD signal in that voxel with the time course of the relevant component.

The RSNs components were subsequently selected via an automated process that defines the components that most closely matched the RSNs for each individual subject, based on spatial correlation analyses with the RSNs templates. All templates represent regions that have repeatedly been implicated in the RSNs.

There were six RSNs of our interest, including auditory network (AN), dorsal attention network (DAN), default mode network (DMN), executive control network (ECN), salience network (SN), and sensorimotor network (SMN). All RSN templates were created by virtue of WFU_PickAtlas (https://www.nitrc.org/projects/wfu_pickatlas/) in the SPM toolbox based on centroid coordinates and radii. The component with the largest correlation coefficient was selected as the RSN we interested in. Totally, six components were identified. In order to verify whether the 6 ICs of each group were zero, a one-sample t-test was performed and according to the settings in the previous study (27), we set a threshold of p<0.05. As shown in Figure 1.

2.4 Statistical Analysis

According to the number of the original subjects, the selected ICs (z-score value) were reclassified into three groups. The Resting-State fMRI Data Analysis Toolkit plus V1.2 (RESTplus V1.2, http://restfmri.net/forum/RESTplusV1.2) was the toolbox of our choice for statistical analysis. In order to verify whether the six ICs differed between the three groups, Analysis of Variance (ANOVA) on ICs (AlphaSim correction, P<0.05) was performed with the result of one-sample t-test as an explicit mask, where age and gender were controlled as covariates. The differences between the groups of ICs were obtained by two-sample t-test (AlphaSim correction, P<0.05, Cluster>10) with the result of ANOVA as an explicit mask. Similarly, age and gender were eliminated as covariates. Finally, a Spearman correlation analysis was performed between the ADHD index and mean signals of ICs that we
delineated as ROIs.

Results

3.1 ANOVA showed differences between the three groups

The ANOVA results for all ICs were shown in Figure 2 and Table 2, it shows the brain regions where there may be differences between the six ICs in the three groups of subjects. The regions depicted in red-yellow showed in Fig 2 indicated that there were differences in RSNs between the three groups. The F values and p values of the most significant difference in each RSN were shown in Table 2. As shown in Fig 2, brain regions with significant differences appeared in superior temporal gyrus of AN, superior parietal gyrus and occipital lobe of DAN, middle temporal gyrus and superior medial frontal gyrus of DMN, supplementary motor area of ECN, precentral gyrus of SMN, as well as supramarginal gyrus of SN.

3.2 Comparison between groups

The results of two-sample t-test were shown in Table 3, which shows the differences between the groups of 6 ICs.

3.2.1 The differences between ADHD-C and TD-C

Compared with the TD-C group, decreased FC was found in DAN, ECN, SN, and DMN of the ADHD-C group (shown in Figure 3). The clusters of weaker connectivity were located in the left inferior occipital gyrus (p=0.0041) and right superior occipital gyrus (p=0.0011) of DAN, supplementary motor area (p=0.0036) of ECN, left supramarginal gyrus (p=0.0081) of SN, middle temporal gyrus (p=0.0041) and superior medial frontal gyrus (p=0.0055) of DMN, with all areas surviving at p<0.05 (AlphaSim correction). However, the RSNs with considerably enhanced FC in ADHD-C were not observed.

3.2.2 The differences between ADHD-I and TD-C

According to the areas shown in Figure 4, decreased FC was found in the ADHD-I patients in comparison to TD-C group, including the right superior parietal gyrus (p=0.0017) of DAN and the left middle temporal gyrus (p=0.0105) of DMN. In contrast, stronger FC was observed within three RSNs, including the supramarginal gyrus (p=0.0027) of AN, the precentral gyrus (p=0.0024) of SMN and the
medial frontal gyrus (p=0.0265) of DMN.

3.2.3 The differences between ADHD-C and ADHD-I

Compared to ADHD-I group, the weaker FC was mainly distributed in the superior temporal gyrus (0.0062) of AN, inferior temporal gyrus (p=0.0016) of DAN, as well as dorsolateral superior frontal gyrus (p=0.0082) of DMN. However, an increase in the FC was found in middle temporal gyrus (p=0.0051) of DMN, as illustrated in Figure 5.

3.3 Correlation Analysis

The above results have demonstrated a significant area of FC abnormalities in RSNs in ADHD patients. A Spearman correlation analysis was performed between ADHD index and mean signals of ICs that we delineated as ROIs, in order to verify whether the ADHD index of the two groups of ADHD patients was associated with FC abnormalities. All the correlation analysis was performed in the ADHD-C and ADHD-I group. Opposite relationship with ADHD index was only found in the left supplementary motor area of ECN in the ADHD-C group (r = -0.267, p = 0.047). And there was no significant difference in this result (p > 0.05) after a multiple comparison correction.

Discussion

In this research, the Group ICA was performed and both subtypes of ADHD patients showed impaired FC in major RSNs compared with TD-C. We found that the FC of the DAN, ECN, SN, and DMN was significantly reduced in ADHD-C patients, including the right inferior occipital gyrus and the superior occipital gyrus of DAN, supplementary motor area of ECN, left supramarginal gyrus of SN, middle temporal gyrus and superior medial frontal gyrus of DMN.

Many previous studies have demonstrated that there were abnormal functional connections within the DMN of ADHD patients, especially the temporal lobe (28, 29, 25). DMN is a commonly used brain network in fMRI studies and is considered to be associated with a wide range of neuropsychiatric diseases (30). In our study, compared with TD-C group, both subtypes of ADHD patients showed reduced FC in the occipital lobe of DAN and the middle temporal gyrus of DMN. However, in the superior medial frontal gyrus of DMN, the two groups performed inversely. Although people believed the opposite trend in DMN and DAN activity (31, 32), Matthew L. Dixon proved that there is no
anticorrelation between some subsystems and DMN (33). These could explain our findings that reduced FC occurred simultaneously in DAN and DMN. There were also differences in FC between the two groups of ADHD subtypes. Patients with ADHD-C showed more reduced FC, such as inferior temporal gyrus of DAN and superior frontal gyrus of DMN. Only a portion of the middle temporal gyrus of DMN has shown an enhanced FC. The one explanation of the difference may be the diverse clinical symptoms between the two subtypes of ADHD patients. DMN activates more when people remain silent or rest state (30). While DAN is routinely activated when people perform attention-demanding cognitive tasks (34). Thus, we speculated that abnormal changes in FC exhibited by DMN and DAN may be related to attention deficit in ADHD patients, which has been proven by some previous research (35, 36).

When comparing the ADHD-I to the TD-C group, we found that there were a few regions showing enhanced FC, such as supramarginal gyrus of AN and precentral gyrus of SMN. Previous studies have found that patients with ADHD were more sensitive to sound, which may be related to the enhanced FC in AN (5). Jean-Arthur has reported that ADHD patients had perceptual inundation (37). To our best knowledge, there are few studies focused on the changes of AN and SMN. And few voxels in these regions were found in our study, which may be due to differences in sample size. Thus, we have not made more discussions about these regions.

Daniel von Rhein proved that SN plays a role in supervision and decision when the brain processes external stimulus (27). The main functions of the SN are to integrate information from different modalities such as sensory information and bodily states in order to establish goal-directed behavior and to process emotion-related information. Combined with our findings, the reduced FC of the SN in ADHD-C patients just confirmed the conclusion of Daniel von Rhein (27). In addition, it has been demonstrated that the ECN participated in multiple advanced cognitive tasks and played an important role in adaptive cognitive control (38). The decreased FC in ECN may explain why ADHD-C patients fail to control their emotions and exhibit impulsive aggression or other conduct disorders (39, 40). Two subtypes of ADHD patients also differ in FC of ECN. In the ADHD-C group, superior frontal gyrus of ECN showed weaker FC. We speculate that this change may explain why ADHD-C patients are more
hyperactive than ADHD-I patients.

Conclusions
In conclusion, group ICA was interrelated analytical methods employed in the present study for evaluating FC of ADHD in adolescents. We found these major RSNs in both subtypes of ADHD patients showed FC changes compared with TD-C group, and there were also differences in FC between the two subtypes of ADHD patients. Our study is good at understanding the abnormal changes in the resting state network of different subtypes of adolescent ADHD patients, which is helpful for the management of adolescent ADHD patients. In the future, the researches combined multi-model imaging, such as structural MRI, diffusion tensor imaging and fMRI, were necessary to comprehensively investigate the brain changes in adolescents with ADHD. These further researches will contribute to the management and treatment of ADHD in adolescents.

Limitations
In this study, one of the limitations of our study was the absence of any psychological assessment of cognitive parameters associated with ADHD. And there was a big difference in the number of the three groups, which was likely to have an impact on the results of statistical analysis. On the other hand, the six RSN templates were created by WFU_PickAtlas in the SPM toolbox directory based on centroid coordinates and radii. There must be a certain difference between our templates and the actual anatomical RSNs, which would affect the accuracy of results.

Abbreviations
ADHD: attention-deficit/ hyperactivity disorder
ADHD-C: ADHD-Combined
ADHD-HI: ADHD-Hyperactive-impulsivity
ADHD-I: ADHD-Inattentive
AN: auditory network
DAN: dorsal attention network
DMN: default mode network
DSM-IV: the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders
ECN: executive control network
FA: flip angle
FC: functional connectivity
FOV: field of view
HIPAA: Health Insurance Portability and Accountability Act
ICA: independent component analysis
MRI: magnetic resonance imaging
ROI: region of interest
rs-fMRI: resting-state functional MRI
RSNs: resting-state brain networks
SMN: sensorimotor network
SN: salience network
TD-C: typically-developing controls
TE: echo time
TR: repetition time

Declarations
Ethics approval and consent to participate: In accordance with HIPAA guidelines and 1000 Functional Connectomes Project protocols, all datasets are anonymous, with no protected health information included.
Consent for publication: Not applicable.
Availability of data and material: The datasets analysed during the current study are available in the [ADHD-200 Global Competition] repository, [http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html]
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Tables

Table 1. Demographic characteristics of the samples.
|                      | TD-C(n=67)       | AC(n=56)       | AI(n=32)       | $F/c^2$ value | p value |
|----------------------|------------------|----------------|----------------|---------------|---------|
| Age                  | 12.10±2.92       | 10.98±2.57     | 12.30±2.67     | 3.400$^a$     | 0.036   |
| Gender (Female)      | 67(30)           | 56(45)         | 32(20)         | 17.147$^b$    | <0.001  |
| ADHD index           | 45.59±6.52       | 71.64±9.03     | 70.06±9.34     | 188.334$^a$   | <0.001  |
| Verbal IQ            | 112.13±13.92     | 108.79±13.23   | 107.88±19.07   | 1.285$^a$     | 0.280   |
| Performance IQ       | 106.88±14.18     | 102.95±14.09   | 106.75±14.98   | 1.323$^a$     | 0.269   |
| Full-Scale IQ        | 110.75±14.01     | 106.79±13.68   | 108.44±15.97   | 1.183$^a$     | 0.309   |

Notes: The data (except Gender) were shown in mean ± standard deviation, the Gender was shown in total (number of females);

a: one-way analysis of variance

b: chi-square test

Abbreviations: TD-C: Typically-Developing Controls; AC: ADHD-Combined patients; AI: ADHD-Inattentive patients; IQ, Intelligence Quotient.

Table 2. Analysis of Variance for all ICs

| RSNs | F-value | p-value |
|------|---------|---------|
| AN   | 7.9462  | 0.006   |
| ECN  | 6.8647  | 0.010   |
| DMN  | 9.5813  | 0.002   |
| DAN  | 16.6126 | 0.001   |
| SMN  | 5.8913  | 0.016   |
| SN   | 6.3573  | 0.013   |
Abbreviations: AN: auditory network; DAN: dorsal attention network; ECN: executive control network; SMN: sensorimotor network; SN: salience network.

Table 3. Regions exhibiting altered functional connectivity in ADHD patients

| Voxels | MNI | t    | p    | Region (AAL)             |
|--------|-----|------|------|--------------------------|
|        | x   | y    | z    |                          |

| AC<TD-C |          |      |      |                          |
|----------|----------|------|------|--------------------------|
| DAN      | 30       | -5   | -72  | -6 | -2.687 0.0041 Inferior occipital gyrus |
|          |          |      |      |          |
| DAN      | 28       | 2    | -69  | 4  | -3.139 0.0011 Superior occipital gyrus |
|          |          |      |      |          |
| ECN      | 10       | -3   | 21   | 4  | -2.730 0.0036 Supplementary motor area |
|          |          |      |      |          |
| SN       | 13       | -5   | -39  | 3  | -2.436 0.0081 Supramarginal gyrus |
|          |          |      |      |          |
| DMN      | 59       | -5   | -30  | -3 | -2.687 0.0041 Middle temporal gyrus |
|          |          |      |      |          |
| DMN      | 59       | -1   | 60   | 2  | -2.583 0.0055 Superior medial frontal gyrus |
|          |          |      |      |          |

| AI<TD-C |          |      |      |                          |
|----------|----------|------|------|--------------------------|
| DAN      | 28       | 2    | -72  | 5  | -3.002 0.0017 Superior parietal gyrus |
|          |          |      |      |          |
| DMN      | 59       | -6   | -27  | -3 | -2.347 0.0105 Middle temporal gyrus |
|          |          |      |      |          |

| AI>TD-C |          |      |      |                          |
|----------|----------|------|------|--------------------------|
| AN       | 15       | -5   | -24  | 2  | 2.845 0.0027 Supramarginal gyrus |
|          |          |      |      |          |
| SMN      | 17       | -3   | -21  | 5  | 2.893 0.0024 Precentral gyrus |
|          |          |      |      |          |
| Network | TD-C | AC<AI | AN | AC>AI | DMN | Superior medial frontal gyrus | p-value |
|---------|------|-------|----|-------|-----|------------------------------|---------|
| DMN     | 59   | 9     | 54 | 2     | 1.958 | 0.0265                      |         |
| AC<AI   |      |       |    |       |      |                              |         |
| AN      | 29   | -5    | -36| 1     | 2.550 | 0.0062                      |         |
| DAN     | 44   | -4    | -60| -6    | 3.023 | 0.0016                      |         |
| ECN     | 12   | -9    | 24 | 4     | 2.986 | 0.0018                      |         |
| DMN     | 59   | -1    | 51 | 2     | 2.450 | 0.0082                      |         |
| AC>AI   |      |       |    |       |      |                              |         |
| DMN     | 59   | -6    | -24| -9    | 2.627 | 0.0051                      |         |

Abbreviations: TD-C: Typically-Development Controls; AC: ADHD-Combined patients; AI: ADHD-Inattentive patients; AN: auditory network; DAN: dorsal attention network; ECN: executive control network; SMN: sensorimotor network; SN: salience network.

Figures
Figure 1

Six components obtained from all subjects and the corresponding resting state networks.

AN: auditory network. DAN: dorsal attention network. DMN: default mode network. ECN: executive control network. SMN: sensorimotor network. SN: salience network.
Figure 2

The results of ANOVA. AN: auditory network. DAN: dorsal attention network. DMN: default mode network. ECN: executive control network. SMN: sensorimotor network. SN: salience network.
The difference between ADHD-C patients and healthy controls. Significant clusters are depicted in red-yellow at a threshold of $p<0.05$. The clusters depicted in blue shows reduced functional connectivity.
The differences between ADHD-I patients and healthy controls. Significant clusters are depicted in red-yellow at a threshold of p<0.05. The clusters depicted in red (DMN (right), AN and SMN) shows the enhanced functional connectivity. And the reduced functional connectivity in DAN and DMN (left) is depicted in blue.
Figure 5

The difference between ADHD-C patients and ADHD-I patients. Significant clusters are depicted in red-yellow at a threshold of $p < 0.05$ The clusters depicted in blue (AN, DAN, ECN and DMN (right)) shows the reduced functional connectivity. And the enhanced functional connectivity in DMN (left) is depicted in red.