Altered Resting-state Functional Connectivity Patterns of Several Frontal and DMN Related Areas in Children with Attention Deficit Hyperactivity Disorder

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Attention Deficit Hyperactivity Disorder (ADHD) affects nearly 5% of school-aged children and generally it continues to adulthood. Neural basis of ADHD has been a matter of debate in recent decades. In this study a group independent component analysis based study has been done on 21 ADHD individuals and 21 control group. Spatial maps have been derived using dual regression method. Several differences have been found in frontal pole (specifically anterior cingulate cortex and inferior frontal gyrus). Posterior components of DMN, cerebellum and brainstem (pons) in the form of decreased activation compared to control group.

Key words: Children with attention deficit, DMN, Patterns of several frontal.

Age-inappropriate symptoms of inattention, impulsiveness and hyperactivity are main characteristic of Attention Deficit Hyperactivity Disorder (ADHD). It affects nearly 5% of school-aged children and generally it continues to adulthood. Variety of studies has been conducted in order to understand neural basis of ADHD. Structural and functional studies have been attributed to study underlying neural basis of ADHD. Earlier Positron Emission Tomography studies suggested general reduction in neural activity of brain; however recent studies have shown differences in a variety of regions. Underactivation of dorsal anterior cingulate cortex (ACC) and changeless network of fronto-striatal-insular have been suggested as an effective basis for inattention and impulsivity in patient with ADHD. Structural studies have suggested reduced volume and cortical thickness in several frontal brain regions, in parietal temporal areas, the basal ganglia, posterior cingulated (PCC), the cerebellum and the splenium of the corpus callosum.

Functional magnetic resonance studies provide a valuable technique for studying neural basis of ADHD. Several studies of fMRI have been dedicated to studying different regions of brain in task related paradigms. Children with ADHD have been studied during vigilant, selective and flexible attention, tasks with temporal processing, “hot” executive functions, reward expecting tasks and very few in emotion processing tasks. In these task-related experiments brain activity patterns are derived by dynamic changes between task experiment and baseline. The differences of patterns caused by the disorder are then studied based on comparing ADHD patients with their age matched controls. Various evidences have been provided to show under-activation in the DLPFC/IFC, ACC, Caudate, supplementary motor area (SMA) compared to control group. Furthermore there are convergent evidence toward
FMRI studies which are done in rest state are quite different from task based experiments. This kind of FMRI studies provides further information about brain dynamics. In rest state studies results can be compared through different studies. However few studies have been dedicated to study fMRI data of ADHD children in rest state. The purpose of this study was to compare functional connectivity network between ADHD individuals and control group using rest state fMRI images. We were looking for differences in patterns of neural activity underlying the disorder.

METHODS

Subjects

The subject group comprised 21 ADHD individuals in the age of 8.5±2 and 21 age matched controls from typically developing individuals. All participants had a Full Scale IQ of 80 or higher and were checked with the Symptom-Checklist-90-Revised (SCL-90 R) in order to avoid other psychiatric disorders. The criteria for individuals evaluation included: 1. Lifetime history of psychotic, bipolar or substance use disorders, 2) current history of mood, psychotic, anxiety, or substance use disorders, 3) lifetime history of treatment with psychotropic other than stimulants (for ADHD group). They had no history of language disorder or a Reading Disability (RD) either screened out before a visit or based on school assessment completed within 1 year of participation. RD was based on a statistically significant discrepancy between a child’s FSIQ score and his/her Word Reading subtest score from the Wechsler Individual Achievement Test-II [Wechsler, 2002], or a standard score below 85 on the Word Reading subtest, regardless of IQ score. Participants with visual or hearing impairment, or history of other neurological or psychiatric disorder were excluded. Psychiatric diagnoses were based on evaluations with the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV, 1997), a structured parent interview based on DSM-IV criteria; the Conners’ Parent Rating Scale-Revised, Long Form (CPRS-R), and the DuPaul ADHD Rating Scale-IV (Reid, 1998). Intelligence was evaluated with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and academic achievement was assessed with the Wechsler Individual Achievement Test-II [Wechsler, 2002]. Children assigned to the ADHD group met criteria for ADHD on the DICA-IV and either had a T-score of 65 or greater on the CPRS-R Long Form (DSM-IV Inattentive) and/or M (DSM-V Hyperactive/Impulsive) or met criteria on the DuPaul ADHD Rating Scale IV (six out of nine items scored 2 or 3 from Inattentive items and/or six out of nine scored 2 or 3 from the Hyperactivity/Impulsivity items). Children with DSM-IV diagnoses other than Oppositional Defiant Disorder or Specific Phobias were excluded.

Children with ADHD taking psychoactive medications other than stimulants were excluded. Children who were taking stimulant medication were removed from these medications the day before and the day of testing.

TDC participants were required to have T-scores of 60 or below on the DSM-IV Inattention (L) and DSM-IV Hyperactivity (M) subscales of CPRS-R and no history of behavioral, emotional, or serious medical problems. Additionally, TDC individuals were not included if there was a history of school-based intervention services as established by parent interview, or if they met DSM-IV psychiatric disorder except specific phobia as reported on the DICA-IV.

MRI Scanning

Each participant underwent one resting state scan consisting of 128 contiguous whole-brain functional volumes using echo planar imaging on a Siemens 3.0 Tesla Allegra (TR=2500 ms; TE=30 ms; flip angle=90, 47 slices, matrix=84*81; FOV=256*256 , 141 mm; acquisition voxel size=3×3×3mm; 6.4 min). Each subject lay supine with the head snugly fixed by a belt and foam pads. Participants were verbally instructed to relax and during the resting-state fMRI sessions, the subjects were asked to remain still as much as possible, keep their eyes closed and try not to think systematically. A high-resolution T1-weighted magnetization prepared gradient echo sequence was also obtained.

Data Preprocessing

The first few fMRI image volumes of subjects were discarded and the rest were utilized for data analysis. Images were used for one level of motion correction using MCFLIRT using FSL (www.fmrib.ox.ac.uk/fsl).
and spatial smoothing using FWHM (5mm) and also a high pass temporal filtering were used. FMRI resting state images were first registered to their high resolution anatomical image by normal 6 DoF transformation and then registered to standard Montreal Neurological Institute (MNI152) template using 12 DoF affine transform by normal search using resampling resolution of 4mm. The registration phase is necessary in order to overcome the problem of different shapes of head through participants.

**Functional Connectivity Analysis**

Spatial connectivity maps and their relative time series were derived using group ICA method by MELODIC toolbox. Using this method spatial maps are assumed to be independent. Resulting independent components were used to derive results using dual regression method. The set of spatial maps from the group-average analysis was used to generate subject-specific versions of the spatial maps, and associated time series, using dual regression\(^1\). First, for each subject, the group-average set of spatial maps is regressed (as spatial regressor in a multiple regression) into the subject’s 4D space-time dataset. This results in a set of subject-specific time series, one per group-level spatial map. Next, those time series are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. We then tested for group differences using FSL’s randomize permutation - testing tool\(^2\).

**RESULTS**

**Between Group Resting State Network Comparison**

Several Resting state networks resulted from the group ICA which was done by the MELODIC toolbox. The aim was to find obvious differences between ADHD and control group. By using dual regression and randomizing the results several meaningful differences between patterns were found. Reduction in activity in different parts of frontal lobe including Subcallosal cortex and cingulate cortex were seen. Additionally reduced neural activity pattern was seen in ADHD group compared to controls in superior division of lateral occipital cortex in parietal lobe, angular gyrus, Inferior temporal gyrus, Cerebellum, Inferior Temporal gyrus, Occipital fusiform gyrus and Anterior Cingulate (Table 1). These areas were thresholded to have a minimum amount of voxels as well as meaningful value of p. X, Y and Z values are reported in MNI152 coordinates (Figure 1, Table1).

### Table 1. Areas of different connectivity patterns in ADHD individuals

<table>
<thead>
<tr>
<th>Regions</th>
<th>Brodman’s area BA</th>
<th>P value</th>
<th>No. of Voxels</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD&lt;Controlol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal pole/Right cerebral cortex</td>
<td>10, 11</td>
<td>&gt;.02</td>
<td>570</td>
<td>34</td>
<td>45</td>
<td>16</td>
</tr>
<tr>
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<td>511</td>
<td>22</td>
<td>43</td>
<td>12</td>
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<td>Inferior temporal gyrus/superior parietal lobule/Precuneus</td>
<td>7</td>
<td>0.01</td>
<td>484</td>
<td>25</td>
<td>9</td>
<td>28</td>
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<tr>
<td>Cerebellum</td>
<td>-</td>
<td>0.05</td>
<td>385</td>
<td>22</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Occipital pole/lateral occipital cortex</td>
<td>17,18</td>
<td>0.01</td>
<td>160</td>
<td>29</td>
<td>8</td>
<td>13</td>
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<td>Inferior division/ Occipital fusiform gyrus</td>
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<td></td>
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<td></td>
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<tr>
<td>Temporal pole/Temporal fusiform gyrus</td>
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<tr>
<td>Inferior temporal gyrus</td>
<td>20, 38</td>
<td>&gt;0.01</td>
<td>141</td>
<td>15</td>
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<tr>
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<td>0.02</td>
<td>122</td>
<td>15</td>
<td>47</td>
<td>26</td>
</tr>
</tbody>
</table>

**DISCUSSION**

By analyzing and comparing the functional connectivity of control and ADHD group, the activity patterns underlying whole brain neural activity were used to find the differences between...
Fig. 1. Areas of difference: a) Frontal pole/Right cerebral cortex b) Frontal medial cortex c) Inferior temporal gyrus/superior parietal lobule/Precuneus d) Cerebellum e) Occipital fusiform gyrus f) Temporal fusiform gyrus g) Frontal pole

two groups. Frontal areas have been widely implicated in the control of attention the right inferior frontal gyrus has been proven to participate in stimulus-driven modulating the attention and right middle frontal gyrus has effective rule in manipulating the contents of working memory in attention process. Furthermore the anterior cingulate cortex has effects on detecting and resolving processing conflicts.

Default mode network has been considered as one of important resting state networks which affect brain activity in rest state. Our findings support the decreased activity in default mode network related areas both in frontal areas including anterior cingulate cortex (ACC) and posterior parts. Precuneus, one of the well-known areas of DMN, has also been found to have different activity pattern between two groups. Our results are congruous with literature and also morphometric findings of decreased cortical thickness in precuneus.

The ADHD individuals showed decreased connectivity in cerebellum compared to typically growing control group. Cerebellum has been found to be involved in a number of autonomic cardiovascular response representation and conditioned cardiovascular control, and performs the major role acting as a functional mediate between cortex and brainstem to perform cortical modulation of brainstem autonomic nuclei.

CONCLUSION
In summary we found different connectivity patterns in the areas of frontal pole (specifically anterior cingulate cortex and inferior frontal gyrus), posterior components of DMN, cerebellum and brainstem (pones) in the form of decreased activation compared to control group. These areas have been proven to have relatively high relationship with attention.

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REFERENCES


