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An investigation of abnormal brain connectivity associated with regions implicated in ADHD

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AN INVESTIGATION OF ABNORMAL BRAIN CONNECTIVITY ASSOCIATED WITH REGIONS IMPLICATED IN ADHD

By
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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

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ABSTRACT

ROYA GORDJI: An investigation of abnormal brain connectivity associated with regions implicated in ADHD

Research into the unique etiology of attention deficit hyperactivity disorder (ADHD) has in recent years moved from a focus on dysfunction in brain regions to abnormalities in connectivity between those regions. In this study, we examined the connectivity in brain areas that were deemed to be of particular significance to the disease in terms of their function and already known discrepancies in morphology and connectivity from healthy individuals. The thalamic VA nucleus and the hippocampus were the regions investigated. The data, obtained from the ADHD-200 Sample, consisted of MRI, clinical, and demographic data and were made up of 215 individuals, 117 of whom were categorized as having ADHD. Data was preprocessed and Region of Interest (ROI) analyses were completed before voxelwise connectivity analyses were performed for each ROI. The results indicated increased connectivity between the VA nucleus and the right central opercular cortex in subjects with ADHD. There have been few investigations into the connections present between the thalamus and the opercular cortex, and we believe this is the first to identify a functional connectivity existing in the VA nucleus that compares individuals with ADHD to those without. The existence of the operculum in the cingulo-opercular network (CON) indicates its functioning in executive control and maintenance of attention, which are hallmarks of ADHD. This further
associates the opercular region with the disease. No abnormal connectivity involving the hippocampus was discovered.
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1. LIST OF ABBREVIATIONS

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<th>Abbr.</th>
<th>Definition</th>
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<tr>
<td>ADHD</td>
<td>attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>VA</td>
<td>ventral anterior</td>
</tr>
<tr>
<td>rs-fMRI</td>
<td>resting state functional magnetic resonance imaging</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood-oxygen-level-dependent</td>
</tr>
<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>TE</td>
<td>echo time</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>CON</td>
<td>cingulo-opercular network</td>
</tr>
</tbody>
</table>
2. INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a condition that may be characterized by a tendency for hyperactivity, an inability to modulate behavior, and difficulty remaining still and focusing on a task (Lange et al. 2010; Qiu et al. 2011; Batty et al. 2015). There are three subtypes of the disease: hyperactive/impulsive, inattentive, and combined. Individuals who are diagnosed as ADHD-combined possess both the hyperactive/impulsive and the inattentive symptoms. There are often working memory and executive function deficits present as well.

The Centers for Disease Control and Prevention report that the number of people diagnosed with ADHD increases each year, and at the last estimate was said to affect about 11% of children and adolescents aged 4 to 17 in the US. This prevalence rate puts it among the most common childhood disorders. ADHD may continue in individuals throughout adolescence, and in up to 60% of cases, persists through adulthood (Kessler et al. 2005).

In the past, the source of the issues present in individuals with ADHD was thought to be localized to specific regions of the brain. However, current research has shown that ADHD, among other neuropsychiatric disorders, implicates a number of interacting brain regions (Sergeant et al. 2003; Tian et al. 2006). As such, atypical connections between brain areas as opposed to dysfunction in those areas is believed to be among the causes of ADHD. This irregularity may be a result of hypo- or hyperactivity between various regions.
2.1 Thalamic role in ADHD

Pathways of particular significance are those surrounding the ventral anterior (VA) nucleus of the thalamus. The thalamus is a structure in the brain made up of deep gray matter. It is known as the relay center of the brain, and is responsible for transmitting sensory and motor signals to the cerebral cortex. Importantly, it has a key role in coordination and modulating bodily movements.

Resting state functional magnetic resonance imaging (rs-fMRI) has been used to identify brain regions that may be of interest for various neuropsychiatric disorders, such as multiple sclerosis and Alzheimer’s disease. With this procedure, changes in blood-oxygen-level-dependent (BOLD) signals are used to determine blood flow in the brain, making it a useful tool in detecting the amount of activity in or between specific regions. These tests are performed when the individual is not engaged in any particular task, providing information about brain activity when it is not in use.

With regard to ADHD, rs-fMRI studies have found that people with the disease possess an overall higher resting-state brain activity than healthy individuals. However, there have been mixed results about the thalamus specifically, with some finding activity to be less in people with ADHD and others finding it to be more (Qiu et al. 2011; Tian et al. 2008). Yet, there seems to be general agreement that the thalamus plays an important role in ADHD as nearly all information is routed through and processed by this structure before passing to the cerebral cortex, which is often the final destination for information transmitted through the thalamus.

The VA nucleus is a thalamic relay nucleus, and much of the input it receives comes from the basal ganglia. The basal ganglia are made up of a collection of
interconnected nuclei composing various structures throughout the brain. Major functions performed by the basal ganglia include the planning, coordinating, and executing of motor functions (Chakravarthy et al. 2010; Lanciego et al. 2012; Dudman and Krakauer, 2016) suggesting the VA nucleus has a role in mediating the coordination and initiation of movement. Rostral motor regions also project inputs onto the VA nucleus, which in turn projects onto caudal motor areas where motor outputs are subsequently affected (McFarland and Haber, 2002). The striatum, a component of the basal ganglia whose major role involves reward and motivation for carrying out specific actions, has a large number of projections originating from the VA nucleus (Kimura et al. 2004).

Individuals with ADHD have been found to exhibit atrophy within the VA nucleus that leads to reduced white matter connectivity of input and output projections from the thalamus. As a result of this atrophy, the decreased presence of connections between the VA nucleus and the striatum has been thought to be among the causes of the motor and attention deficits present in people with ADHD (Xia et al. 2012).

Based on these known results, further investigation of VA nucleus projections was deemed necessary to determine whether the atrophy in this region affected currently unknown regions. In this study, we examined input and output projections of the thalamic VA nucleus to determine whether it possesses any irregular connectivity. Based on the known presence of white matter atrophy in the thalamus of individuals with ADHD, it was hypothesized that there would be decreased connectivity in the pathways projecting from the VA nucleus.
2.2 Hippocampal role in ADHD

A second region of interest in this study was the hippocampus. The hippocampus is widely known for its function in the formation of long term memory, but its role in executive functioning is still under investigation. It has been said to be involved with selective attention and act as a motor program monitor (Wall and Messier, 2001) that oversees motor outputs.

Furthermore, healthy individuals show more activation in the hippocampus when attempting to answer difficult questions on a memory test or when making rational decisions than are people with the disease (Ernst et al. 2003). This supports the role of the hippocampus in executive functioning. With regard to hippocampal volume, an MRI study examining medication-naïve children with ADHD found it to be significantly reduced compared to the healthy control group (Posner et al. 2014). These results together suggest that the volume of the hippocampus is correlated to its use in executive functioning.

The executive function deficits present in individuals with ADHD coupled with known structural changes in the hippocampus support this as a region that requires further investigation. Due to these findings, it was believed that people with ADHD may present with abnormal connectivity in hippocampal projections. Because of the reduction in volume and decreased frequency of use in executive functioning compared to healthy individuals, it was hypothesized that people with the disease possess decreased resting-state activity in pathways traveling through the hippocampus.
3. METHODS

3.1 Data acquisition

All MRI, demographic and clinical data were obtained from the ADHD-200 Sample (http://fcon_1000.projects.nitrc.org/indi/adhd200/). From this dataset, the New York University Child Study Center subset was selected for use in this analysis. This subset contains 215 subjects for whom resting state and structural data were both available. Among these individuals, 117 had a diagnosis of ADHD (hereafter ADHD group), and 98 had no diagnosis of ADHD (control group).

MRI data in the dataset were acquired using a SIEMENS MAGNETOM Allegra syngo MR 2005A MRI. The resting state echo planner image volumes were 33 slices of 192 mm x 240 mm with 4 mm thickness (voxel size = 3 x 3 x 4 mm), with repetition time (TR) of 2000 ms and echo time (TE) of 15 ms. A total of 175 volumes (5 minutes and 50 seconds) were used in the analysis. High resolution structural T1 volume was acquired as 171 sagittal slices of 256 mm x 256 mm with 1.3 mm thickness (voxel size = 1.3 x 1 x 1.3 mm, TR = 2530 ms and TE = 3.25 ms).

3.2 Data processing

Script libraries (fcon) from the 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000; Biswal et al. 2010) were used for preprocessing and Region of Interest (ROI) analyses. Resting state images were first motion corrected and spatially smoothed 6 mm full width at half-maximum Gaussian
The structural T1 images were individually registered to the MNI152 2 mm brain. Through this registration, 12 affine parameters were created between rs-fMRI volume and MNI152 with a 2 mm space, so that a seed ROI could be later registered to each individual rs-fMRI space. The rs-fMRI time series were band-pass filtered (between 0.005 Hz and 0.1 Hz), and each resting state volume was regressed by white matter and cerebrospinal fluid signal fluctuations as well as the six motion parameters.

In conducting ROI connectivity analysis, ROIs were created from brain atlases in the MNI152 2 mm space. The hippocampal ROI was extracted from the Harvard-Oxford subcortical atlas. Ventral Anterior Nucleus was bilaterally extracted from the Oxford Thalamic Connectivity atlas (Behrens et al. 2003; Behrens et al. 2003) as the region 5. For each ROI, voxelwise connectivity analyses were conducted by the singlesubjectRSFC fcon script, whereby the time course is spatially averaged within the ROI so that correlations from the ROI to each individual voxel across the brain. The Z-scores representing the correlations between the ROI and a voxel were used for group level analyses.

The ADHD and control groups were compared by randomise script in FSL. Because the age distribution was significantly different between these two groups (Control **MEAN**SD**, ADHD **MEAN**SD**), age was first regressed before conducting a t-test between the two groups. Statistical thresholds were set at p < 0.05 (family-wise error corrected), with threshold free cluster enhancement.
4. RESULTS

4.1 Demographic and clinical characteristics

The participants with ADHD in the study consisted largely of males, while the control individuals were more evenly matched between males and females. The exact values are recorded in Table 1. There was a significant age difference, \( p < 0.05 \), between the ADHD group and the control group, in which the control group made up the older individuals (\( t(191) = 22, p = 0.028 \)). Significant differences in intelligence quotient (IQ) were also seen, with the control group scoring higher on both verbal IQ and full scale IQ (\( t(197) = 2.30, p = 0.023 \); \( t(193) = 2.04, p = 0.043 \)). Interestingly, there was no significant between group differences for performance IQ (\( t(190) = 1.51, p = 0.132 \)).

Measures of ADHD are listed in the table for reference, including inattentiveness and hyperactivity/impulsivity and an ADHD index. Co-morbid diagnoses are also listed, the most common of which are learning disabilities and specific phobias. Some individuals presented with more than one secondary disease. No members of the control group had a clinical diagnosis.

Although the study did not include the specific form of ADHD for all participants, the most prevalent that showed up in the study was combined, in which individuals present with both hyperactivity/impulsivity and inattentiveness. The hyperactive/impulsive form of ADHD was the least common, showing up in only two trial participants.
<table>
<thead>
<tr>
<th></th>
<th>ADHD group mean</th>
<th>Control group mean</th>
<th>df</th>
<th>Test Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.27</td>
<td>12.17</td>
<td>191</td>
<td>2.22</td>
<td>0.028</td>
</tr>
<tr>
<td>Gender</td>
<td>F = 27 M = 90</td>
<td>F = 52 M = 46</td>
<td></td>
<td></td>
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<tr>
<td>ADHD index</td>
<td>71.31</td>
<td>45.23</td>
<td>203</td>
<td>-25.61</td>
<td>1.65E-65</td>
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<td>Verbal IQ</td>
<td>107.12</td>
<td>111.62</td>
<td>197</td>
<td>2.30</td>
<td>0.023</td>
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<tr>
<td>Performance IQ</td>
<td>104.05</td>
<td>107.18</td>
<td>190</td>
<td>1.51</td>
<td>0.132</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>106.52</td>
<td>110.60</td>
<td>193</td>
<td>2.04</td>
<td>0.043</td>
</tr>
<tr>
<td>Inattentive</td>
<td>70.45</td>
<td>45.27</td>
<td>196</td>
<td>-24.10</td>
<td>1.63E-60</td>
</tr>
<tr>
<td>Hyperactive/Impulsive Diagnosis</td>
<td>68.09</td>
<td>46.25</td>
<td>167</td>
<td>-17.52</td>
<td>1.17E-39</td>
</tr>
<tr>
<td>Medication statusa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication naive</td>
<td>30</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Not medication naive</td>
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<td>0</td>
<td></td>
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<tr>
<td>Secondary diagnosis</td>
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<td>LD</td>
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<td>0</td>
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<td>Specific phobia</td>
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<td>ODD</td>
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<tr>
<td>Dysgraphia</td>
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<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past major depressive episode</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: LD = learning disability. ODD = oppositional defiant disorder. a The medication status of some ADHD participants in the trial is unknown. Only the known statuses have been recorded.
4.2 **Thalamic connectivity**

Analysis of thalamic connectivity with the rest of the brain indicated the ventral lateral anterior nucleus had significantly higher connectivity to the right central opercular cortex (cluster center MNI: 32, 6 14) in the ADHD group compared to the control group. Figure 1 illustrates the location of the right central opercular cortex, to which there is increased connectivity. There was no significantly lower connectivity from the ventral lateral anterior nucleus in the ADHD group.

![Figure 1](image)

**Figure 1.** The right central opercular cortex, highlighted above, shows increased connectivity from the VA nucleus in the ADHD sample group compared to the control group.

4.3 **Hippocampal connectivity**

Voxelwise connectivity analysis of the hippocampus showed no statistically significant differences between the ADHD group and the control group. As both afferent and efferent projections between the hippocampus and the entirety of the
brain were investigated, this result indicates that in this region there is a lack of impairment in functional connectivity for individuals with ADHD.
5. DISCUSSION

5.1 Analysis of thalamic-opercular connectivity

Based on rs-fMRI data, the results indicate that there is significant hyperconnectivity in the projections from the VA nucleus to the right central opercular cortex. The major function of the VA nucleus in initiating and coordinating movements as they are carried out endorses their predicted role in ADHD, in which connectivity dysfunction was proposed in this study. However, the results were in contrast to the hypothesized decreased activity in pathways from the VA nucleus.

The opercular cortex is a region of the brain made up of overlapping pieces of cerebral matter, which surrounds the insula. The opercula and insula are anatomically very close to one another and so historically, there was difficulty in differentiating the projections that are specific to each region.

This issue was addressed in a primate study, in which the various pathways from the opercular/insular region were isolated and the area the thalamic projections terminated on was identified. Using retrograde degeneration, the operculum and the insula were lesioned in various trials. It was determined that lesioning of the insula did not cause degeneration in the thalamus and therefore did not impact thalamic nuclei, leading to the conclusion that there were very few, if any, connections present between the insula and the thalamus (Locke, 1967). Among the specific thalamic regions that remained unaffected was the VA nucleus. In trials that deeply lesioned the operculum and spared the insula almost entirely, there was profound degeneration throughout the VA
nucleus. This study then supports the existence of anatomical connectivity between the operculum and the thalamus, underlying the finding of a functional connectivity in our study.

The operculum’s role in ensuring the accessibility of cognitive resources may help to explain the variance between the hypothesized hypoactivity and the measured hyperactivity in the connections leading from the VA nucleus to the opercular cortex. The operculum is closely affiliated with the cingulate cortex in what is known as the cingulo-opercular network (CON). This network is responsible for tonic alertness, including maintaining attention to a task and allowing for the performance of more complicated tasks involving executive control (DeGutis and Van Vleet, 2010; Sadaghiani and D’Esposito, 2015). Increasing task activity is positively correlated with CON activity. Thus, the CON system is instrumental in maintaining the availability of cognitive capacities that may at any moment be called upon (Sadaghiani and D’Esposito, 2015). Therefore, it is possible that the hyperconnectivity identified between the VA nucleus and opercular cortex in this study is a result of needing increased tonic alertness in order to maintain attention to a task.

5.2 Analysis of hippocampal connectivity

In contrast to our hypothesis, the rs-fMRI connectivity studies of the hippocampus showed no significant differences between the ADHD group and the healthy control group. The hippocampus was selected as a region to investigate due to evidence that support its role in selective attention and executive functioning, which are both areas that individuals with ADHD encounter problems with. However, the results indicate that there
is no issue with functional connectivity when an individual is not performing a task, or in other words when the person is at rest.

The variation between our hypothesis and the findings may be explained by the method used to evaluate the hippocampal connectivity. Because the individuals were tested using rs-fMRI, the hippocampal issues known to arise due to ADHD are not apparent. A study using a tool such as task-based fMRI, in which hippocampal ADHD issues like selective attention and executive functioning can be monitored, may be better suited to identifying connectivity abnormalities.
6. CONCLUSIONS

The findings involving the VA nucleus show correlation between individuals that have an impaired ability to focus and maintain attention, such as those in our study with ADHD, and increased signaling to the opercular cortex. Based on this data alone, it is not clear whether it is the impairments that cause the hyperconnectivity in order to promote the functioning of that region, or if the increased connectivity may be causing the impairments. Other output projections from the VA nucleus showed no difference in activity from the healthy control group.

To our best knowledge, this is the first study performed in which functional connectivity from the VA nucleus was compared between individuals with and without ADHD. Therefore, this finding in which increased connectivity between the VA nucleus and right central opercular cortex was identified in individuals with ADHD introduces an avenue through which the study of the disease may be pursued. For instance, further investigation is required to determine whether the hyperconnectivity seen between these regions is a cause of the disease or a consequence of it.

With regard to the hippocampus, although our results indicate there are no significant differences in connectivity with the rest of the brain between our two sample groups, this area requires more research. The consistency in hippocampal connectivity measured using rs-fMRI in subjects with and without ADHD does not fully rule out the possibility that hippocampal connectivity issues could be present. Future investigations
may examine whether any abnormal connectivity exists if the subject is performing a task-based assignment, rather than simply being at rest, as in this study.
7. REFERENCES


