Asymmetry of basal ganglia in children with attention deficit hyperactivity disorder

P. Uhlíková 1, I. Paclt 1, M. Vaněčková 1, T. Morcinek 1, Z. Seidel 2, J. Krášenský 2 & J. Daneš 2

1. Department of Psychiatry, 1st Faculty of Medicine, Charles University, Prague, Czech Republic
2. Department of Radiology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Correspondence to: Assoc. Prof. Ivo Paclt, MD., PhD.
Department of Psychiatry, 1st Faculty of Medicine, Charles University,
Ke Karlovu 11, 128 02 Prague 2, Czech Republic
PHONE: +420-2-224-965-316
FAX: +420-2-224-910-577
EMAIL: vsemerad@volny.cz

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatry disorder with several key symptoms, such as inattentiveness, impulsivity and hyperactivity. Neuropsychiatry studies have implicated the frontostriatal circuit in the pathological physiology of the disorder. Using magnetic resonance imaging (MRI), we examined the basal ganglia in 13 ADHD patients and eight unaffected comparison children. The volume of caudate, putamen and globus pallidus was measured. In the ADHD patients, we detected an increased left > right asymmetry of the basal ganglia. This reversal of asymmetry in the globus pallidus and caudate nucleus were statistically significant. These finding provide further evidence of morphological brain abnormalities in ADHD.

INTRODUCTION

Factors implicated in the etiology of ADHD generally fall into a small number of categories: (1) family and genetic factors [26], (2) prenatal/perinatal factors, (3) chemical toxins, (4) exacerbating psychosocial stressors and combined factors.

Still (1902) [34], following the theories formulated by William (1890) [37], hypothesized that the deficits in inhibitory volition, moral control, and sustained attention were causally related to each other and to the same underlying neurological deficiency (current DSM-IV terminology includes ADHD with conduct disorder co morbidity). Shirley (1939) [32], studied association, cognitive and behavioral impairments, including the triad of ADHD symptoms and "birth trauma". Blau (1936) [4] and Lewin (1938) [22] noted striking similarity between the symptoms exhibited by hyperactive children and the behavioral sequel of frontal lobe lesions in primates. Several investigators, such as Lewin (1938) [22], would use these similarities to postulate that severe restlessness in children was most likely the result of pathological defects in the forebrain structures. Based on contemporary knowledge acquired by neuroimaging methods, it is assumed that dysfunction in the frontostriatal circuit plays a critical role in ADHD [6]. Recent studies are indicating a role for the basal ganglia in a variety of neuro-psychiatric conditions, involving motor
and attention dysfunction. These functionally segregated loops contribute respectively to motor somatosensory, oculomotor executive, emotion and motivation function in ADHD children. Essential ADHD symptoms are connected with basal ganglia and cerebellum activity. These structures play a key role in the control of movement and they are very rich in dopamine receptors. One variant of the dopamine hypothesis of ADHD is based on assumed dopamine deficits, which corresponds to compensatory hyperactivity in these structures [21,24].

The basal ganglia are comprised of structures such as the caudate nucleus, putamen, globus pallidus, subthalamic nucleus and ventral mesencephalon [29,27,17]. According to the most current studies, in convergence with findings from magnetic resonance imaging (MRI) studies of brain anatomy, it has been established that attention deficit hyperactivity disorder characterized by a slightly smaller (4%) total brain volume (both white and gray matter [28]). MRI images can be used to estimate the size of structures in the brain by outlining each slice of the MRI. Swanson and Castellanos (2002) [35] summarized data and concluded that the reduction in size of some brain regions as compared to healthy controls of the same age is as follows: frontal lobes –3.6–12.7%; cerebellar vermis –11.1–12.3%; basal ganglia 5.4–19.0%; corpus callosum 5.7–12.2%).

In the normal population, the volume of the right hand-side basal ganglia is typically larger than that of the left hand one. A reversal of asymmetry in the basal ganglia has been previously described in ADHD patients [10,18].

In the first study to examine the caudate volumes in ADHD, Hynd et al., 1993 [18], studied 11 children with ADHD (8 males and 3 females, ages not reported) and 11 normal controls (6 males and 5 females, ages not reported) and found a decrease in the size of the head of the left caudate nucleus. The controls showed a left larger than right pattern of asymmetry whereas ADHD children showed a right larger than left asymmetry. Fillipek et al., 1997 [15] compared the volume of total caudate and caudate heads in 15 boys with ADHD (ages 12.4±3.4) without co morbid diagnosis with 15 healthy controls (age 14.4±3.4). The ADHD subjects had smaller total left caudate and their caudate head volumes failed to show the normal left predominant asymmetry seen controls. In the largest MRI study of ADHD, Castellanos et al., [1996b] [10] compared the caudate volumes of 57 boys with ADHD (mean age 11.7; range 5.8–17.8) with 55 healthy controls (mean age 12.0; range 5.5–17.8). They found a reduced right caudate volume in the ADHD subjects, with a loss of the right predominant asymmetry observed in the normal controls.

Alterations in the globus pallidus structure and function have been observed in boys with ADHD as compared to normal controls [2,10,11] and in boys with ADHD and comorbid Tourette's syndrome (TS) [2]. Aylward et al., (1996) [2] also found a decrease in the total and left globus pallidus volumes smaller than the right in boys with ADHD (10; mean age 11.2±1.62) as compared to normal controls (11; mean age 10.7±1.98), with no significant differences seen between boys with ADHD and boys with ADHD and TS (16, mean age 11.3±1.46). Castellanos et al., (1996b) [10], found a significant reduction in the volume of the right globus palidus in boys with ADHD, as compared to the normal controls.

We hypothesized that a subject selection between the ages of 6–11 may help to provide an age-undisturbed limit of distinct clinical symptoms for research. The symptoms of ADHD in this age group are clearer than in older subjects. Cross-sectional analysis of age groups also suggests that the normal developmental course of decreasing caudate size may not occur in ADHD children, so by late adolescence, the size difference between ADHD subjects and controls may not be maintained [10,11]. This possibility of developmental and age-related changes in caudate size defines an extremely important area of research.

All co-morbidities (learning disabilities, conduct disorder, Tourette's syndrome) may complicate the interpretation of results further and was excluded here. We hypothesized that a change in volume and asymmetry of basal ganglia would be found in our ADHD sample.

Our research sample included boys and girls, which corresponds to the incidence of ADHD in the general population. A recent paper by Biederman et al., (2005) [3] did not suggest a different clinical picture and pharmacology in boys and girls.

Comparable studies include both children with stimulants treatment and children without drug therapy. The results are identical [13,11,12,28]. In a FMR study with strong control conditions and the number of key presses similar in the go and the no-go task blocks, methylphenidate did not significantly activate the caudate nucleus [36]. We included children with methylphenidate therapy for a short time (no more than two months), because we concluded from past papers that only chronic stimulant therapy might change the MRI findings on basal ganglia.

SUBJECTS AND METHODS

Thirteen patients with ADHD, 10 boys (77%) and 3 girls (23%), age range from 6 to 11 (mean standard deviation = 8.2±1.4), were investigated. School psychologists for hyperactivity and attention disorder identified these children. Two independent psychiatrists blind to patients diagnostic status evaluated subjects by DSM-IV. Inclusion criteria were the diagnosis of ADHD, combined type, according to the DSM-IV and parent questionnaire (CPQ), greater than two standard deviations above age mean [14,20]. Exclusion criteria: co morbid psychiatric and physical disorders, IQ lower than 80 and higher than 120.

Seven patients were treated by a stimulant (methylphenidate, 10–50 mg daily) at the time of the study and
six patients were without any pharmacological therapy. Wechsler’s IQ test was applied again after previous tests one year or more.

The control group comprised of eight healthy children, 6 boys (75%) and 2 girls (25%), age range of 6.0–11.0 (average age 9.0±1.6), with no evidence of ADHD. Volunteer teachers identified them. No parents of children in the control group described any ADHD symptoms. (Clinical examination by two independent psychiatrists by DSM-IV, Conner’s parent questionnaire results smaller one standard deviation, IQ higher than 80 and lower 120.) Exclusion criteria: co morbidity psychiatric and physical disorders. These children and parents were from identical schools like ADHD subjects and they were not identified in psychiatry and psychology setting.

All parents and children older 10 years signed informed consent.

MRI was used to examine all subjects and the volumes of selected structures of the basal ganglia (caudate nucleus, globus pallidus and putamen) were measured. Scans were performed on the Philips Gyroscan NT 15 (1.5 T) device. We made transversal Ti WI-IR (Ti weighted image-inversion recovery) with the following parameters: TR 1800, TE 25, TI 400, FLIP 90, FOV 270, thickness of slices THK 2.0/0, matrix 256×205 and TI WI/FFE (Ti weighted image/ fast field echo) with parameters: TR 25.05 ms, TE 5, FLIP 30, FOV 266, THK 1.0/0.1 mm, matrix 256×205. The coronary sections were TI WI/FFE with the following parameters: TR 25.05 ms, TE 5, FLIP 30, FOV 266, THK 1.0/0 mm and matrix 256×205. The IR sequence provides a high degree of contrast between the white and gray matter and was chosen as the most suitable for volumetric analyses. The structures of interest were outlined semi automatically using the Scan View application on each individual section [5]. The total volumes of the selected structures (nucleus caudate, globus pallidus, putamen) were then calculated. The Scan View application is able to distinguish the contrast in boundary surfaces among structures in central nervous system and enables additional editing. Size of structures is measured with an accuracy calculated at 0.3%. Measurement objectivity is based on repeating the measurement with the same parameters 3 times. Measurement was performed with the same conditions (contrast and enlargement). Using the semiautomatic region selection of the slice, it is not possible to bias the automatically computed volume. A filter enhancing the boundaries of anatomic structures by means of different signal intensity was used first. As the next step, semiautomatic boundary tracing was used, using the difference in the signal intensity.

In the evaluation of the MM results, the index of symmetry (the difference between the right and left side divided by the average of the right and left side) was calculated. When the Index of symmetry is higher than zero, the right side is larger than the left side. Because the reliability of ratios such as the index of symmetry can be negatively influenced by high correlation between the numerator and the denominator [1], correlation coefficient were calculated.

**Statistical analysis**

Confidence intervals were used to examine possible left-right asymmetry. Independent sample t-test was used to examine the possible difference between subjects and controls in the index of symmetry for each structure. The variables fulfilled criteria for parametric tests. Results were considered significant at the level α=0.05. Because of multiple testing we recalculate this level using Bonferroni method. For the six confidence intervals we used 0.05/6=0.0083 as significance criterion, for the three t-tests we used 0.05/3=0.017 as significance criterion.

**RESULTS**

The correlation coefficient r between the numerator and denominator of index of symmetry was 0.09–0.22 and –0.30 for caudate, putamen and globus pallidus, none of these correlations were significant. Such correlation can be considered as low and influencing the reliability of indexes of symmetry only a little.

The symmetry indexes are summarized in Table 1.

Figure 1 shows the 99.17% confidence intervals of the index of symmetry for each measured basal ganglia region, separately for the ADHD and the control group. From these 99.17% confidential intervals, we can conclude that the left globus pallidus in the ADHD group was larger than the right one at a significant level of α=0.05 (Figure 1).

Results testing the difference between subjects and controls in the index of symmetry for each basal ganglia are given in Table 2. A significant difference was found for the globus pallidus, where mean index of symmetry is negative in patients (–0.06) and positive in controls (0.05). The p-value for caudate nucleus (p=0.014) was closed to the significant value of p<0.017. No significant difference was found for putamen.

These findings support our hypothesis that the right globus pallidus and caudate nucleus in controls are larger than the left ones and that there is a reversal of asymmetry in patients suffering from ADHD. A trend indicating a difference in the index of symmetry was found for caudate nucleus. The putamen did not demonstrate any differences between the groups with regards to asymmetry.

**DISCUSSION**

Our results in 13 children with ADHD without co morbidity (10 boys and 3 girls aged between 6 and 11) show the loss of normal symmetry of caudate nucleus in 9 from 13 children (p<0.017) and the reversal asymmetry of globus pallidus (at p<0.005).

Castellanos et al., (1996b) [10] found a reduction in the volume of globus pallidus in 57 ADHD patients (age 5.7 to 17.8), where 29 patients had the symptoms of co-
Table 1. Index of symmetry of basal ganglia in ADHD group and control group.

<table>
<thead>
<tr>
<th>INDEX OF SYMMETRY</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Caudate nucleus</th>
<th>Putamen</th>
<th>Globus Pallidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD 01</td>
<td>10.0</td>
<td>m</td>
<td>-0.046</td>
<td>-0.095</td>
<td>-0.080</td>
</tr>
<tr>
<td>ADHD 02</td>
<td>8.8</td>
<td>m</td>
<td>-0.022</td>
<td>-0.022</td>
<td>-0.049</td>
</tr>
<tr>
<td>ADHD 03</td>
<td>8.8</td>
<td>m</td>
<td>0.176</td>
<td>0.144</td>
<td>-0.034</td>
</tr>
<tr>
<td>ADHD 04</td>
<td>8.8</td>
<td>m</td>
<td>0.041</td>
<td>0.071</td>
<td>-0.040</td>
</tr>
<tr>
<td>ADHD 05</td>
<td>10.4</td>
<td>m</td>
<td>-0.029</td>
<td>-0.006</td>
<td>-0.028</td>
</tr>
<tr>
<td>ADHD 06</td>
<td>8.6</td>
<td>f</td>
<td>-0.014</td>
<td>-0.081</td>
<td>-0.140</td>
</tr>
<tr>
<td>ADHD 07</td>
<td>7.4</td>
<td>m</td>
<td>0.020</td>
<td>-0.084</td>
<td>-0.031</td>
</tr>
<tr>
<td>ADHD 08</td>
<td>5.4</td>
<td>m</td>
<td>-0.007</td>
<td>0.066</td>
<td>-0.044</td>
</tr>
<tr>
<td>ADHD 09</td>
<td>9.2</td>
<td>f</td>
<td>-0.073</td>
<td>0.023</td>
<td>-0.163</td>
</tr>
<tr>
<td>ADHD 10</td>
<td>7.3</td>
<td>m</td>
<td>-0.017</td>
<td>-0.002</td>
<td>-0.084</td>
</tr>
<tr>
<td>ADHD 11</td>
<td>6.4</td>
<td>m</td>
<td>-0.045</td>
<td>0.071</td>
<td>-0.108</td>
</tr>
<tr>
<td>ADHD 12</td>
<td>7.1</td>
<td>f</td>
<td>-0.009</td>
<td>-0.102</td>
<td>-0.003</td>
</tr>
<tr>
<td>ADHD 13</td>
<td>8.5</td>
<td>m</td>
<td>-0.054</td>
<td>0.001</td>
<td>-0.006</td>
</tr>
<tr>
<td>Mean</td>
<td>8.2</td>
<td></td>
<td>-0.006</td>
<td>-0.001</td>
<td>-0.062</td>
</tr>
<tr>
<td>Control 01</td>
<td>11.1</td>
<td>m</td>
<td>0.049</td>
<td>0.033</td>
<td>0.015</td>
</tr>
<tr>
<td>Control 02</td>
<td>7.2</td>
<td>m</td>
<td>0.174</td>
<td>0.049</td>
<td>-0.019</td>
</tr>
<tr>
<td>Control 03</td>
<td>9.5</td>
<td>f</td>
<td>0.072</td>
<td>-0.056</td>
<td>0.106</td>
</tr>
<tr>
<td>Control 04</td>
<td>7.3</td>
<td>m</td>
<td>-0.018</td>
<td>-0.021</td>
<td>0.180</td>
</tr>
<tr>
<td>Control 05</td>
<td>7.6</td>
<td>m</td>
<td>0.076</td>
<td>-0.040</td>
<td>0.004</td>
</tr>
<tr>
<td>Control 06</td>
<td>10.0</td>
<td>m</td>
<td>0.039</td>
<td>-0.067</td>
<td>0.072</td>
</tr>
<tr>
<td>Control 07</td>
<td>8.8</td>
<td>f</td>
<td>0.065</td>
<td>-0.032</td>
<td>-0.048</td>
</tr>
<tr>
<td>Control 08</td>
<td>10.8</td>
<td>m</td>
<td>0.073</td>
<td>-0.065</td>
<td>0.080</td>
</tr>
<tr>
<td>Mean</td>
<td>9.0</td>
<td></td>
<td>0.066</td>
<td>-0.025</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Figure 1. 99.17% Confidence Interval for Index of Symmetry.
Table 2. Index of Symmetry: T-test of the difference between ADHD and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Mean</th>
<th>t-value</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nucleus</td>
<td>-0.0060</td>
<td>0.0662</td>
<td>-2.71</td>
<td>19</td>
<td>0.0139</td>
</tr>
<tr>
<td>Putamen</td>
<td>-0.0012</td>
<td>-0.0248</td>
<td>0.80</td>
<td>19</td>
<td>0.4350</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>-0.0624</td>
<td>0.0487</td>
<td>-4.11</td>
<td>19</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

morbidity (ODD n=20, CD n=9, anxiety n=2, specific learning dysfunctions n=9). According to the comparison with 55 healthy boys of the corresponding ages, a loss in normal symmetry of caudate nucleus and a reduction of the volume of right globus pallidus was found, but Mataro et al., (1997) [23] described a volume reduction of right caudate nucleus without signs of reversal asymmetry in 11 children (aged 14 to 16) without co morbidity in the clinical sample. Mataro et al., (1997) [23] and Filipek et al., (1997) [31] compared the volume of total caudate and caudate heads in 15 boys with ADHD aged 12.4±3.4 with controls. The subjects with ADHD had smaller left total caudate and caudate head.

Despite convergence across some of these results, there are differences that complicate the interpretation of these findings. First, the initial reports of differences in two sub regions (genual and splenium) of the corpus callosum [19] have been questioned. Subsequent studies reported significant differences between the ADHD and the control groups, but not for the same sub regions. Giedd et al., (1994) [16] suggested the rostrum and rostrum body but not the splenium, and Semrud-Clique-man et al., (1994) [31], suggested only the splenium. The most problematic fact is that the initial finding by one team [16] was not replicated in the largest sample yet studied [10]. Castellanos et al., (1996b) [10], have also demonstrated smaller volumes of the globus pallidus in a sample of 57 male children and adolescents with ADHD; although in a more recent study of girls with ADHD [9], they found less the abnormalities in frontal and striatal structure less characteristic, especially after using a case-control comparison for effects of verbal IQ. Other study describes decrease of the volume of the left globus pallidus in 11 boys (age 11.26±1.62) examined by MRI in comparison with controls [2].

The patients’ age could also influence the results of studies [33]. Morphological and psychopathological changes are experienced during development of a hyper kinetic patient. We suppose that to take account of patients’ age is a contribution. MRI longitudinal changes during childhood and adolescence did not differ in any other way between 73 ADHD subjects and 75 matched controls studied prospectively, with 2 and 4 years follow-up rescan [28].

Overmeyer et al., (2001) [25], applied new image analysis techniques to estimate the volume of each issue class represented by each voxel in each subject’s MRI dataset and to identify spatial clusters of voxels that demonstrate a significant difference in gray or white matter volume between patient and control groups [7,8]. Overmeyer et al., (2001) [25] identified three main loci of regional deficit, medial superior frontal gyrus, posterior cingulated gyrus and retrosplenial cortex, and putamen and globus pallidus in spatially distributed gray matter deficit in the right hemisphere. This method will be sensitive enough to detect a difference in anatomy that may be smaller than, or may cross the boundaries between, the regions of interest adopted a priori by cerebral parcellation schemes such as that used by [9].

Differences in imaging methodology, subject selection and co morbidity may account for this discrepancy. Also, the subtlety of the asymmetry and developmental-related anatomic variability in this structure may have contributed to the lack of consistency in the findings [30,17].

The physiological and clinical meaning of reverse asymmetry (left>right) is at this time unclear. Changes in the asymmetry in ADHD children may have an adaptive significance or may serve as a marker for altered regulatory function of the frontostriatal system [6]. They may be connected to changes of laterality and motor functions.

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REFERENCE

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