Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder

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Abstract

The aim of the study is to present a new method for the segmentation of the caudate nucleus and use it to compare the caudate heads and bodies of an attention deficit-hyperactivity disorder (ADHD) group with those of a control group. We used a 1.5-T system to acquire magnetic resonance brain scans from 39 children with ADHD, as defined by DSM-IV TR, and 39 age, handedness and IQ matched controls. The new method for caudate head and body segmentation was applied to obtain semi-automatic volumes and asymmetric patterns. Bilateral volumetric measures of the head, body, and head-body of the caudate nuclei were compared within groups and between ADHD and control groups. Although the group factor was not significant, there were first and second order interactions. The analysis of simple effects showed that the right body and right head+body of the ADHD group was significantly smaller than in the control group, although the ADHD right caudate head was bigger. No ADHD within-group caudate differences were found. Controls showed a significantly larger left caudate head and a significantly bigger caudate right body and right head+body. Our new method for segmenting the caudate nucleus detected differential abnormalities of the right caudate head and body in the ADHD group, explaining previous heterogeneous findings in the literature.

Keywords: ADHD; MRI; Caudate nucleus; Morphometry; Volumetry

1. Introduction

The caudate nucleus is a critical brain region implicated in the pathophysiology of attention deficit-hyperactivity disorder (ADHD) (Barkley, 1997; Sergeant, 1990; Swanson et al., 1998). Structural neuro-
imaging studies have confirmed abnormalities in such a structure in ADHD patients, though with somewhat conflicting results. In caudate-nuclei morphometry studies, some authors found that ADHD populations had a smaller left caudate head (Filipek et al., 1997; Hynd et al., 1993; Semrud-Clikeman et al., 2000) in comparison with control samples. One study showed a left caudate total volume reduction (Filipek et al., 1997), while the study with the largest ADHD sample (Castellanos et al., 1996) found smaller right total caudate volumes in comparison with control samples. In intragroup comparisons, the ADHD population was found to present a right-caudate head asymmetry (right bigger than left) (Hynd et al., 1993) and total right caudate asymmetry, while the largest sample study (Castellanos et al., 1994, 1996) found a total caudate symmetry. In addition, another study (Schrimsher et al., 2002) found that a greater degree of right caudate asymmetry predicted subclinical inattentive behaviour in the general population.

Such discordant results may in part stem from methodological differences. Some studies use automatic measures, and others apply manual techniques. The studies using automatic techniques lack a standard method to segment automatically the brain structures implicated in the disorder, and the manual techniques have not provided a clear way of establishing the frontier between the caudate head and body. Besides, the samples, with the exception of those of Castellanos (Castellanos et al., 1994, 1996), Hill (Hill et al., 2003) and Durston (Durston et al., 2004) are rather small.

Two points are critical to confirm or disprove the results obtained so far in caudate nuclei. Firstly, manual measures are required to complement the automatic methods employed and, secondly, the size of the sample studied must be increased. There is nevertheless an additional point that may be more critical to detect specific abnormalities. One important difference among extant studies is between those that measure the caudate nucleus in toto, and those that segment the head and the rest of the nucleus. In our opinion, the measures of total caudate volumes may screen off differential abnormalities of the caudate head and body.

The fact is that the head, body and tail of the caudate nucleus seem to participate in different pathways, and hence in different functions. The caudate head is integrated in the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate circuits of Alexander (Alexander et al., 1986). The body of the caudate is integrated in Alexander’s oculomotor circuit. Functionally, the head of the caudate nucleus has been related to multi-modal information and inhibition processes. Lesions in the head of the caudate nucleus can result in sensory neglect, agitation, hyperactivity, distractibility and, in some cases, manic or schizo-affective psychosis (Aylward et al., 1996; Caplan et al., 1990; Castellanos et al., 1994; Richfield et al., 1987). In recent studies, the head of the caudate nucleus has been associated with feedback processing, while the caudate body has been implicated in successful classification learning (Seger and Cincotta, 2005).

Therefore, if the striatal pathway is dysfunctional in ADHD, and this dysfunction affects in different ways the head and the body of the caudate nucleus, then there may be morphometric abnormalities in the disorder showing a differential implication of each of these caudate areas. However, there is no extant method for segmenting the caudate head from the body. The aim of this study is to introduce a caudate segmentation method and to use it to compare the caudate heads and bodies of an ADHD group with those of a control group.

2. Methods

2.1. Participants

The study population (Table 1) included 39 children (35 boys and 4 girls) with ADHD according to DSM-IV

<table>
<thead>
<tr>
<th>Sample</th>
<th>n</th>
<th>Sex</th>
<th>Age (years) mean±S.D.</th>
<th>Handedness *</th>
<th>Type</th>
<th>MPH mean±S.D.</th>
<th>CBCL Hyperactivity mean±S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>39</td>
<td>Boys=35 Girls=4</td>
<td>10.8±2.9</td>
<td>R=27; L=4; CD=8</td>
<td>I=8</td>
<td>0.6±0.05</td>
<td>73.3±10.3</td>
</tr>
<tr>
<td>Control</td>
<td>39</td>
<td>Boys=27 Girls=12</td>
<td>11.7±2.9</td>
<td>R=27; L=3; CD=9</td>
<td>NA</td>
<td>NA</td>
<td>56.3±3.4</td>
</tr>
</tbody>
</table>

* Handedness measured with a battery that includes Piaget’s Test, Head’s Test and Nadine Galifраст–Grannjon’s Test.

I=Inattention subtype; H-I=Hyperactive-impulsive subtype; C=Combined subtype. R=right-handed; L=left-handed; CD=cross-dominance. MPH (mg/kg)=methylphenidate. NA=not applicable. CBCL: Child Behavior Checklist (ages 6 to 16 years).
(referred from the Unit of Child Psychiatry at Vall d’Hebron Hospital) and 39 control subjects (27 boys and 12 girls) recruited from the community. One previous study of our group (Carmona et al., 2005) was performed with a subgroup of the present sample. Mean ages were 10.8 (S.D.: 2.9) and 11.7 (S.D.: 3), respectively. Both groups were matched for IQ level. Full Scale IQ based on the WISC-R (Wechsler, 1974) for ADHD (Verbal =104, S.D.: 17.7; Performance =104, S.D.: 13.6) and estimated IQ, based on WISC-R subtest, for controls (Vocabulary =11.8, S.D.: 2.7; Block design =11.2, S.D.: 2.9). Matching for socioeconomic status was based on a semi-structured interview that evaluated parents’ marital, professional and educational status. The institutional ethics committee approved the study, and parental informed consent was obtained from all the participants.

Children with ADHD received a consensus diagnosis by a team consisting of a licensed psychologist and a psychiatrist, based on parent and teacher rating scales as well as a clinical interview systematically reviewing DSM-IV TR (American Psychiatric Association, 2000) criteria for ADHD, oppositional defiant disorder, conduct disorder, and depressive and anxiety disorders. Exclusion criteria for both the ADHD and the control groups included an IQ scores on the WISC-R (Wechsler, 1993) below 80, severe psychiatric illness (including anxiety, mood disorders, developmental disorder, dissociative disorder), brain damage, neurological illness, head trauma, deafness, blindness, severe language delay, cerebral palsy, seizures, or autism, as determined through interviews with parents. ADHD children did not present dyslexia or dyscalculia comorbidities, although some of them (23.7%) presented learning disabilities.

The patients were examined by classroom teachers and parents using questions from the Conners’ Teacher and Parent Rating Scale (Conners et al., 1998a,b; Goyette et al., 1978), the Child Behaviour Checklist (CBCL) (Achenbach and Ruffle, 2000) and the Edelbrock Scale (Edelbrock, 1983). Children with ADHD were further categorized into hyperactive-impulsive, inattentive and combined subtypes using DSM-IV TR criteria at the time of original diagnosis.

All the children with ADHD were receiving stimulant medication (methylphenidate), and all were considered positive responders by their physicians (based on clinical and neuropsychological evaluations), parents and teachers; no control children were receiving any medications. No children received sustained-release amphetamines.

Control children were selected from the Traumatology Department as a sample of convenience. Two neuropsychologists excluded ADHD diagnosis in the control group. Children were included in the control group if they had no history of behavioural problems according to semi-structured interview with parents and parent behaviour rating scales (i.e., T<70 on subscales of the Conners’ Rating Scale: Parent Version) and no significant elevations on subscales of the CBCL.

2.2. MRI acquisition

All subjects were screened for metal implants before undergoing brain MRI examination with a 1.5-T system (Signa, General Electric, Milwaukee, WI, USA). We used an FSPGR (fast spoiled gradient) T1 3D axial sequence (TR=13.2 ms; TE=4.2 ms; FA=15; NEX=1; 256×256 matrix; FOV=24 cm), with 2-mm partitions and without a gap, and a FSE-PD-T2 axial sequence (TR=3980 ms; TE=20/100 ms; TF=16; NEX=2; 512×512 matrix; FOV=24 cm), with 5-mm sections and a 2-mm gap.

2.3. MRI analyses

Two neuroradiologists set the axial IR (inversion recovery) T1 3D images in a plane parallel to the bicommissural plane and processed them with MRicro (freeware: http://www.sph.sc.edu/comd/rorden/mricro.html). The regions of interest (ROI) were identified manually with MRicro, which automatically provided each ROI volume (in voxels). The FSPGR-T1 3D sequence was used for the morphometric analysis. A measure of total brain volume for each subject was obtained with SPM2 (Wellcome Department of Imaging Neuroscience, London, United Kingdom).

2.4. Caudate segmentation method

The caudate nucleus has three components: head, body and tail. The head and body are involved in distinct fronto-subcortical circuits (Alexander et al., 1986, 1990). Although there is agreement that the head is the ovoid rostral part and the tail is its elongated, backward prolongation, the boundary between the head and body is arbitrary. Monro’s interventricular foramen is used for this purpose by some authors (Duvernoy, 1991), while others have used the corpus callosum (Filipek et al., 1997) or the optic chiasm (Pineda et al., 2002). In our opinion, the main drawbacks of these methods are that they are complex (needing a thorough understanding of neuroradiology) and time-consuming, and that they do not address critical issues, such as the delimitation between the caudate and accumbens nuclei. There have also been other segmentation methods (Dreifuss et al., 2001).
However, the method that we present here has an heuristic purpose rather than an anatomical one, that is, to provide a simple, and reliable procedure for distinguishing the head from the body of the caudate nucleus.

2.4.1. Delimitation of the ROI for the head of the caudate nucleus

We defined the ROI for the head of the caudate nucleus, including all the areas presented in the axial images, according to the following criteria (see Fig. 1):

(a) The first section to be measured is the first in which the caudate nucleus can be separated from the putamen nucleus, hence, excluding the ventral striatum (Fig. 1, a).

(b) The next sections to be measured should follow the ventro-dorsal direction.

(c) The last section is previous to that in which the caudate’s antero-posterior diameter is more than two times larger than the medio-lateral diameter (Fig. 1, b).

(d) The caudate’s antero-posterior diameter should be the larger antero-posterior diameter parallel to the interhemispheric sulcus (see Fig. 1, y in the enlarged box of b). The medio-lateral caudate’s diameter should be the larger medio-lateral diameter perpendicular to the caudate’s antero-posterior diameter (see Fig. 1, x in the enlarged box of b).

2.4.2. Delimitation of the ROI for the body of the caudate nucleus

We obtained the ROI for the body of the caudate nucleus according to the following criteria:

(a) The first section is that in which the caudate’s antero-posterior diameter is more than two times larger than the caudate’s medio-lateral diameter (Fig. 1, c).

(b) The next sections to be measured should follow the ventro-dorsal direction.

(c) The last dorsal section is that previous to that in which the caudate body cannot be visualized (Fig. 1, d).

(d) The caudate’s antero-posterior diameter should be the larger antero-posterior diameter parallel to the interhemispheric sulcus (see Fig. 1, y in the enlarged box of c). The medio-lateral caudate’s diameter should be the larger medio-lateral diameter perpendicular to the caudate’s antero-posterior diameter (see Fig. 1, x in the enlarged box of c).

Measurements of the ROIs were performed by two experienced tracers. Intraclass correlation coefficients (ICC) were used to assess interrater reliability: caudate head, ICC=0.87; caudate body, ICC=0.89.

2.5. Statistical analyses

Differences between the groups’ ROIs were analyzed with the statistical package SPSS 11.5. ROI measures in voxels were transformed into cubic millimetres (mm³) (ROI’s total number of voxels multiplied by voxel dimensions).

To determine whether or not the total caudate volume differed in the two groups, we conducted a two-way analysis of variance (ANOVA) with a between-groups
factor (diagnostic group) and a repeated measures factor (hemisphere) for the total caudate volume (dependent variable). Additionally, to investigate the differences between groups I the head and body of the caudate nucleus, we also performed a three-way ANOVA with a between-groups factor (diagnostic group) and two repeated measures factors (hemisphere and caudate region).

In order to examine the symmetry patterns, we calculated asymmetry indices (AIs) for each caudate region. The use of AI is widespread in the scientific literature of ADHD morphometric analyses, and hence they allow us to compare our results with previous findings.

We defined the AIs as follows: For the total caudate volumes, we applied the following AI (AIt), which includes right total caudate volume (RCV) and left total caudate volume (LCV):

$$A_{It} = \frac{\left[ (RCV_{mm^3} - LCV_{mm^3})/RCV_{mm^3} \right] \times 100}{1 + LCV_{mm^3}}$$

For the head of the caudate volumes, we applied the following AI (AIh), which includes right head caudate volume (RHCV) and left head caudate volume (LHCV):

$$A_{Ih} = \frac{\left[ (RHCV_{mm^3} - LHCV_{mm^3})/RHCV_{mm^3} \right] \times 100}{1 + LHCV_{mm^3}}$$

For the body of the caudate volumes, we applied the following AI (Alb), which includes right body caudate volume (RBCV) and left body caudate volume (LBCV):

$$A_{Ib} = \frac{\left[ (RBCV_{mm^3} - LBCV_{mm^3})/RBCV_{mm^3} \right] \times 100}{1 + LBCV_{mm^3}}$$

To analyze eventual differences among the AIs between the two groups, we conducted a two-way ANOVA (diagnostic group and caudate region).

### 3. Results

The results of the two separate ANOVAs are shown in Table 2. The first ANOVA examines caudate volume as a whole, evaluating the effects of the ‘group’ and ‘hemisphere’ factors, as well as the interaction between them. When group is considered as the principal effect, the caudate volume differences between groups are not significant in the analyzed sample. However, the statistically significant interactions point to the presence of a combined or conjoint effect of some of the factors included in the analysis, justifying the interaction effects analysis in terms of conditional or simple effects. As shown in Table 2, there is a significant group-by-hemisphere interaction effect ($F=5.370; P=0.023$). The nature of the interaction is explored in a simple-effect analysis (Table 3), which shows a significantly decreased right total caudate volume for the ADHD group ($P=0.02$).

The three-way ANOVA (Table 2), in which the ‘region’ factor was introduced, thus distinguishing between caudate head and body, shows a significant second order interaction effect, group-by-region-by-hemisphere ($F=10.63; P=0.002$). The simple effect analysis, shown in Table 3, breaks down the interaction as a significantly decreased right body volume ($P=0.01$) in the ADHD group, with a moderate–high effect size ($d=0.59$). The statistical analyses did not reveal any significant effect of the different gender proportion in the samples.

Regarding the within-group comparisons, the right total caudate volume was found to be larger than the left in the control group (Table 3). Interestingly, when we take into account the head/body segmentation, the previous pattern in the control group breaks down into a left larger than right caudate head volume, and a right larger than left caudate body volume (Table 3). In other words, the caudate head and body volumes show inverse volumetric patterns in the control group, whereas the ADHD patients show no significant right/left volume differences.

Developing these findings, the AI two-way ANOVA reveals a significant group-by-region interaction effect ($F=11.039; P=0.001$). The simple effect analysis reveals significant differences in the head and body AIs between the two groups (see Fig. 2). In other words, an asymmetry pattern arises for the ADHD group that is the inverse of the control pattern, namely, right asymmetry (right larger than left) for the ADHD caudate head, and left asymmetry (left larger than right) for the ADHD caudate body.
(Fig. 2). As supplementary material for the electronic version, we provide the same two- and three-way ANOVAs for the subsample of boys.

4. Discussion

The aim of this study was to introduce a method for segmenting caudate head from body, and to compare volumetric measures of both structures between a group of ADHD patients and a control group. The rationale behind this objective was that the differential implication of the caudate head and body regions must be elucidated to improve our understanding of ADHD pathophysiology.

The caudate segmentation method that we present here is anatomically coherent, and conforms to previous volumetric data. First, it captures the common anatomical understanding of the structures and, furthermore, the two caudate parts segmented, anterior and posterior, coincide with the head (rostro-ventral part) and body (dorso-posterior part) of the caudate nucleus, respectively. Moreover, our results square with previous findings in the scientific literature, backing our claim that we are measuring the same structures (total caudate) and their same main regions (head and body). In this sense, and concerning total caudate volume in the ADHD sample (left: 4.7 cm³; right: 4.7 cm³), our measures fall between those of Ayward et al. (1996) and those of Castellanos et al. (1996) and Filipek et al. (1997). Regarding the caudate head volume in the ADHD sample, data are still scarce. Nevertheless, our measures fall between those of Pineda et al. (2002) and those of Filipek et al. (1997).

Although the group factor in the ANOVA was not significant, there were first and second order interactions. The analysis of simple effects showed that ADHD patients present statistically significant caudate volumetric differences as compared with the control group. Besides, our method of segmentation allows us to unravel the differential implication of the caudate head and body. The right body and right head + body of the ADHD group are significantly smaller than in the control group, even if the right ADHD caudate head is larger than that of the controls. It therefore appears that

Table 3
Within- and between-groups comparisons of caudate volumes

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=39)</th>
<th>ADHD (n=39)</th>
<th>Mean difference</th>
<th>T</th>
<th>df</th>
<th>P value</th>
<th>CI (0.95) of means (mm³)</th>
<th>Effect size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate head+body</td>
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<tr>
<td></td>
<td>Mean volume±S.D. (mm³)</td>
<td>Mean volume±S.D. (mm³)</td>
<td>(mm³)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5056±613</td>
<td>4722±713</td>
<td>336</td>
<td>2.22</td>
<td>76</td>
<td>0.02</td>
<td>35 to 635</td>
<td>0.50</td>
</tr>
<tr>
<td>Left</td>
<td>4888±592</td>
<td>4719±787</td>
<td>169</td>
<td>1.07</td>
<td>76</td>
<td>0.28</td>
<td>−145 to 483</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Mean difference</td>
<td>F</td>
<td>df₁, df₂</td>
<td>P value</td>
<td>CI (0.95)</td>
<td>Effect size</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>168</td>
<td>11.054</td>
<td>1, 38</td>
<td>0.001</td>
<td>0.27</td>
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<tr>
<td>Right vs. left</td>
<td></td>
<td>−128</td>
<td>4.086</td>
<td>1, 38</td>
<td>0.047</td>
<td>−0.19</td>
<td>−252 to −2</td>
<td>−0.094</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>−37 to 213</td>
<td></td>
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<tr>
<td>Caudate head</td>
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<tr>
<td></td>
<td>Mean volume±S.D. (mm³)</td>
<td>Mean volume±S.D. (mm³)</td>
<td>(mm³)</td>
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<tr>
<td>Right</td>
<td>2507±715</td>
<td>2593±930</td>
<td>−86</td>
<td>−0.45</td>
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<td>0.05</td>
<td>−460 to 289</td>
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<tr>
<td>Left</td>
<td>2635±613</td>
<td>2505±944</td>
<td>130</td>
<td>0.72</td>
<td>76</td>
<td>0.47</td>
<td>−230 to 490</td>
<td>0.16</td>
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<tr>
<td></td>
<td>Mean difference</td>
<td>F</td>
<td>df₁, df₂</td>
<td>P value</td>
<td>CI (0.95)</td>
<td>Effect size</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>−128</td>
<td>4.086</td>
<td>1, 38</td>
<td>0.047</td>
<td>−0.19</td>
<td>−252 to −2</td>
<td>−0.094</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>−37 to 213</td>
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</tr>
<tr>
<td>Right vs. left</td>
<td></td>
<td>295</td>
<td>15.323</td>
<td>1, 38</td>
<td>&lt;0.001</td>
<td>0.42</td>
<td>145 to 445</td>
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<td>−236 to 64</td>
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</tbody>
</table>

the right caudate nucleus in ADHD patients is characterized by a caudate head at least as big as that of the controls, while the body of the same side is much smaller. Additionally, our method permits us to examine the asymmetry patterns of both caudate regions, and to detect an inverse asymmetry pattern in the ADHD group (right larger than left caudate head volume, and a left larger than right caudate body volume), which is actually the opposite pattern to that in the control group.

These findings are important for the study of ADHD pathophysiology for various reasons. First, our study substantially contributes to the evaluation of the caudate MR images, providing a new method for segmenting the head and body of the caudate nucleus, as well as helping to detect the differential abnormalities between these two areas. Secondly, we provide one of the largest samples in an ADHD group (39 ADHD and 39 controls) in which morphometric manual measures have been performed. Manual measures are suitable for complementing the automatic measures of other studies, because they allow the examination of MR images without the normalization processes inherent in all automatic or semi-automatic measures. As has been shown to be the case for other psychiatric conditions (Hakala et al., 2004), any conclusion about the pathophysiology of a brain-development disorder such as ADHD needs to be, at least partially, based on direct measures of brain images. Third and last, our results confirm previous data and explain some heterogeneous findings. Our total with those of Castellanos (Castellanos et al., 1996), who found a reduced right total caudate volume in the ADHD patients in the study with the biggest sample until now. Additionally, we also found a tendency towards a right-sided asymmetry of the head of the caudate nucleus and a tendency towards a reduced size of the left head of the caudate, which is concordant with findings of other studies (Hynd et al., 1993; Filipek et al., 1997; Semrud-Clikeman et al., 2000).

In sum, there seems to be a critical distinction between the abnormalities in the head and the body of the caudate nuclei of ADHD patients. Specifically, the heads of the caudate on the right side are slightly enlarged and show a right-sided asymmetry, whereas the right caudate bodies are greatly reduced and show a left-sided asymmetry in the ADHD group. The volumes of the ADHD caudate heads (enlarged) and the ADHD caudate bodies (reduced) produce a nearly symmetric total caudate. In contrast, the control groups shows a right caudate head+body asymmetry. All of these findings could account for the discrepancy in the studies where total caudate measures were considered (Castellanos et al., 1994, 1996) relative to those where the caudate head was differentiated (Filipek et al., 1997; Hynd et al., 1993; Pueyo et al., 2000). In future work, we intend to supplement our manual measures with automatic methods based on our caudate segmentation protocol. The use of automatic methods such as the voxel-based morphometry protocol, has already provided interesting results in ADHD populations (Carmona et al., 2005).

To conclude, our study provides a new method for segmenting the caudate nucleus. This method has allowed us to show that ADHD patients have striatal volumetric abnormalities in comparison with a control group, affecting in a differential way the caudate head and body. ADHD patients present a smaller right caudate body, a right caudate head asymmetry and a left caudate body asymmetry. These abnormalities confirm the role of the striatum in the pathophysiology of ADHD. Our results explain previous heterogeneous findings in the literature, and provide new and complementary methods for studying brain structures in these patients.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psyneuen.2007.04.017.

References


