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Quantitative MR analysis of caudate abnormalities in pediatric ADHD: Proposal for a diagnostic test

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A B S T R A C T

Most morphometric magnetic resonance imaging (MRI) studies of pediatric attention-deficit/hyperactivity disorder (ADHD) with appropriate sample sizes reveal a decreased right caudate nucleus volume. Recently, our group reported that this decrease is mainly due to a diminished right caudate body volume (rCBV). Here, we hypothesize that, employing either the total bilateral caudate volume (tbCV) or the bilateral caudate body volume (bCBV) as scaling variables, the rCBV/tbCV and rCBV/bCBV ratios could be found diminished and used as a basis of an imaging diagnostic test. Volumetric caudate nucleus data were obtained from a case-control morphometric MRI study with 39 ADHD subjects and 39 handedness- and IQ-matched controls, using a novel semi-automated caudate segmentation procedure. Student *t*-tests comparing each relevant ratio were conducted between the two samples. After splitting the samples into two groups, a receiving operator characteristic (ROC) analysis was conducted on the training group to determine the optimal cut-off. Its performance was then examined on the test group. The rCBV/bCBV ratio was found to be statistically different. For a value equal or inferior to 0.48, the specificity was 95.00%. We propose using the rCBV/bCBV ratio to assist in the diagnosis of ADHD in children.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in childhood. It is estimated that half of children with ADHD will display the disorder in adulthood. Yet the diagnosis is not straightforward. Although DSM-IV-TR (American Psychiatric Association, 2000) provides a well-structured criteria-based diagnosis, distinguishing ADHD from normal developmental levels of inattention, impulsivity and hyperactivity remains problematic. Further complications arise in integrating diagnostic data from different informants (e.g., parents and teachers; parents and children) and different settings (e.g., school, home). In these circumstances, a reliable ancillary test with high diagnostic accuracy is called for.

Increasingly, morphometric brain magnetic resonance imaging (MRI) studies show neuroanatomical abnormalities in pediatric ADHD. Our group recently published in this journal a study employing a semi-automated caudate nucleus segmentation procedure that replicated the right caudate volume abnormalities (Trèmols et al., 2008) reported in nearly all (3 out of 4) caudate nucleus morphometric MRI studies with appropriate sample sizes ($n>30$) (Castellanos et al., 1994, 1996, 2001). In addition, a significant decreased volume of the right caudate nucleus body (rCBV), with a medium effect size, was reported (Trèmols et al., 2008).

In light of this result, we hypothesize that employing either the total bilateral caudate volume (tbCV) or the bilateral caudate body volume (bCBV) as a scaling variable could reveal diminished rCBV/tbCV and rCBV/bCBV ratios, which could be used as a basis of an imaging diagnostic test in the ADHD pediatric population. To test this hypothesis and to determine the accuracy of quantitative MR imaging in diagnosing pediatric ADHD, we conducted a retrospective case-control study using the DSM-IV-TR based clinical diagnosis as the reference standard.

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2. Methods

2.1. Participants

The research ethics boards of both participating institutions approved our study. All parents signed a written informed consent and a verbal assent was obtained from all participants.

Our study included 39 subjects (35 boys and 4 girls) with ADHD according to DSM-IV-TR and 39 control subjects (27 boys and 12 girls). All participants were enrolled in the study between February 2003 and March 2004. The ADHD subjects were referred to us by the Unit of Child Psychiatry from a university hospital, whereas the control-group subjects were recruited from the Traumatology Department in the same hospital. Mean ages of the groups were 10.90 years (S.D.: 2.83) and 11.46 years (S.D.: 2.86), respectively. The subjects of both groups were matched according to their intelligence quotient (IQ). We used a Full Scale IQ based on the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1974) for ADHD (Verbal = 104, S.D.: 17.70; Performance = 104, S.D.: 13.60) and an estimated IQ based on a WISC-R subtest for controls (Vocabulary = 11.80, S.D.: 2.70; Block design = 11.20, S.D.: 2.90). Socioeconomic-status matching was determined through the Diagnostic Interview for Children and Adolescents-IV (DICA-IV; Reich et al., 1997), a semi-structured interview that evaluates parents' marital, professional and educational status. Table 1 summarizes the demographic data.

ADHD subjects were diagnosed by a team consisting of a psychologist and a psychiatrist. Scoring was based on parent and teacher rating scales, as well as a semi-structured clinical interview, which systematically reviewed DSM-IV-TR criteria for ADHD, oppositional-defiant disorder, conduct disorder, and depressive and anxiety disorders (DICA-IV). Exclusion criteria for both the ADHD and the control groups included: (a) IQ score on the WISC-R below 80, (b) severe psychiatric illness (including anxiety, mood disorders, developmental disorder, dissociative disorder), (c) brain damage, (d) neurological illness, (e) head trauma, (f) deafness, (g) blindness, (h) severe language delay, (i) cerebral palsy, (j) seizures, or (k) autism, as determined through interviews with parents. ADHD children did not present dyslexia or dyscalculia comorbidities, although some (23.7%) presented learning disabilities.

The patients were characterized by classroom teachers and parents using questions from the Conners' Teacher and Parent Rating Scale (Conners et al., 1998a,b), the Child Behavior Checklist (CBCL) (Achenbach and Ruffle, 2000) and the Edelbrock Scale (Edelbrock, 1983). At the time of original diagnosis, children with ADHD were further categorized into hyperactive–impulsive, inattentive and combined subtypes using DSM-IV-TR criteria.

All the ADHD subjects were receiving methylphenidate and were considered by their physicians (based on clinical and neuropsychological evaluations), parents, and teachers to have a positive response to the medication. None of the control-group subjects were receiving any medications.

Two psychologists ruled out ADHD in control-group subjects. Children were included in the control group if (a) they had no history of behavioral problems according to a semi-structured interview with parents and behavior rating scales (i.e., $T<70$ on CBCL) and (b) no scores in the clinical range on the CBCL subscales. Children with craniocerebral trauma were excluded.

2.2. MR imaging

Subjects were screened for relative and absolute contraindications before entering the MRI scanner. All subjects underwent a MRI examination with a 1.5 T system (Signa, General Electric, Milwaukee, WI, USA). We performed a volumetric fast spoiled gradient (FSPGR-T1 3D) axial sequence (TR = 13.2 ms; TE = 4.2 ms; FA = 15; NEX = 1; 256 × 256 matrix), with 2-mm partitions, and a dual-echo fast spin echo (FSE-DP-T2) axial sequence (TR = 3980 ms; TE = 20/100 ms; NEX = 2; 512 × 512 matrix), with 5-mm sections and a 2-mm gap.

Two neuroradiologists, blind to the clinical diagnosis, independently read and analyzed all MR images. The FSE-T2 sequence was employed to screen for incidental brain lesions. The FSPGR-T1 3D was used for the morphometric analysis. The axial T1 3D images were set in a plane parallel to the bicommissural line and processed with MRIcro software (version 1.37; http://www.mricro.com). Regions of interest (ROIs) were determined manually with MRIcro, which automatically provided each ROI volume (in voxels).

2.2.1. Background information on the caudate segmentation method

Several factors must be considered in the segmentation of the caudate nucleus. First, the caudate head should be distinguished from the accumbens nucleus (ventral striatum), which is involved in other neural networks (specifically, it receives afferencies from the hippocampus and the amygdala, and it thus sometimes has been called the emotional striatum). Second, the tail is not consistently discriminated ventrally from the pulvinar nucleus of the thalamus in conventional 1.5 T MR images (Schrimsher et al, 2002; Hokama et al, 1995). This is due to partial volume effects and insufficient spatial resolution. Because of this, attempts to include the whole tail may diminish measurement reliability. Third, the distinction between head and body should be replicable and should be consistent with the different neurobiological contributions to the fronto-subcortical circuits of both caudate regions. Fourth, the diagnostic test should be easy to implement and, eventually, to automate, making it practical in a time-constrained clinical setting.

As described in Trèmols et al. (2008) we have developed a novel caudate segmentation method that takes these considerations into account. In order to ease automatization of the method we have disregarded external anatomical landmarks and rely on internal morphological

Table 1
Demographic data.

	n	Sex	Age mean ± S.D. and range (years)	CBCL mean ± S.D.	Type	Laterality*	MFD mean ± S.D.	Conners' rating hyperactivity mean ± S.D.
ADHD	39	Boys = 35	10.90 ± 2.83 (6 to 16)	73.30 ± 10.30	*I* = 7	*R* = 27	0.60 ± 0.06	*F* = 18.71 ± 5.59 *M* = 19.63 ± 5.55 *T* = 19.25 ± 6.43
		Girls = 4			H-I = 8	L = 4	0.62 ± 0.06	*F* = 15.33 ± 2.52 *M* = 17.60 ± 3.97 *T* = 21.75 ± 5.85
					C = 24	CD = 8	0.61 ± 0.04	*F* = 17.00 ± 4.68 *M* = 19.60 ± 4.38 *T* = 19.65 ± 5.44
Control	39	Boys = 27 Girls = 12	11.46 ± 2.83 (6 to 17)	56.30 ± 3.40		R = 27 L = 3 CD = 10		

CBCL = Child Behavior Checklist (ages 6 to 16 years); I = inattention subtype; H-I = hyperactive–impulsive subtype; C = combined subtype; *Laterality measured with a battery of tests including Piaget's Test, Head's Test and Nadine Galifrast–Granjon's Test; R = right-handed; L = left-handed; CD = cross-dominance; MFD (mg/kg) = methylphenidate; S.D.= standard deviation.

features. Our method has a heuristic purpose rather than an anatomical one. It aims to aid in the identification of the biological bases of ADHD and eventually lead to an ancillary radiologic test for this disorder.

2.2.2. The caudate segmentation method

From the slab of T1 axial sections oriented parallel to the bicommissural line, we defined the caudate nucleus's head ROI, including all the caudate nucleus's 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, that is, excluding the ventral striatum (Fig. 1, part 1).
b) The last section to be measured is the one previous to the first section in which the caudate's antero-posterior diameter is more than two times larger than the latero-lateral diameter (Fig. 1, part 2).
c) In all measured sections, the caudate's antero-posterior diameter is taken to be the larger antero-posterior diameter parallel to the interhemispheric sulcus [see Fig. 1(a) diameter in the enlarged box of part 2]. The medio-lateral caudate's diameter is the larger medio-lateral diameter perpendicular to the caudate's antero-posterior diameter [see Fig. 1(b) diameter in the enlarged box of part 2].

We obtained the caudate body ROI based on the following criteria:

a) The first section measured 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, part 3).
b) The last dorsal section measured is previous to the one in which the caudate body cannot be visualized (Fig. 1, part 4).
c) The caudate's antero-posterior diameter is taken to be the larger antero-posterior diameter parallel to the interhemispheric sulcus [see Fig. 1(a) diameter in the enlarged box of part 3]. The medio-lateral caudate's diameter is the larger medio-lateral diameter perpendicular to the caudate's antero-posterior diameter [see Fig. 1(b) diameter in the enlarged box of part 3].

2.3. Statistical analyses

We had previously analyzed differences between the groups' ROIs using with the statistical package SPSS 11.5 (Trèmols et al., 2008). ROI

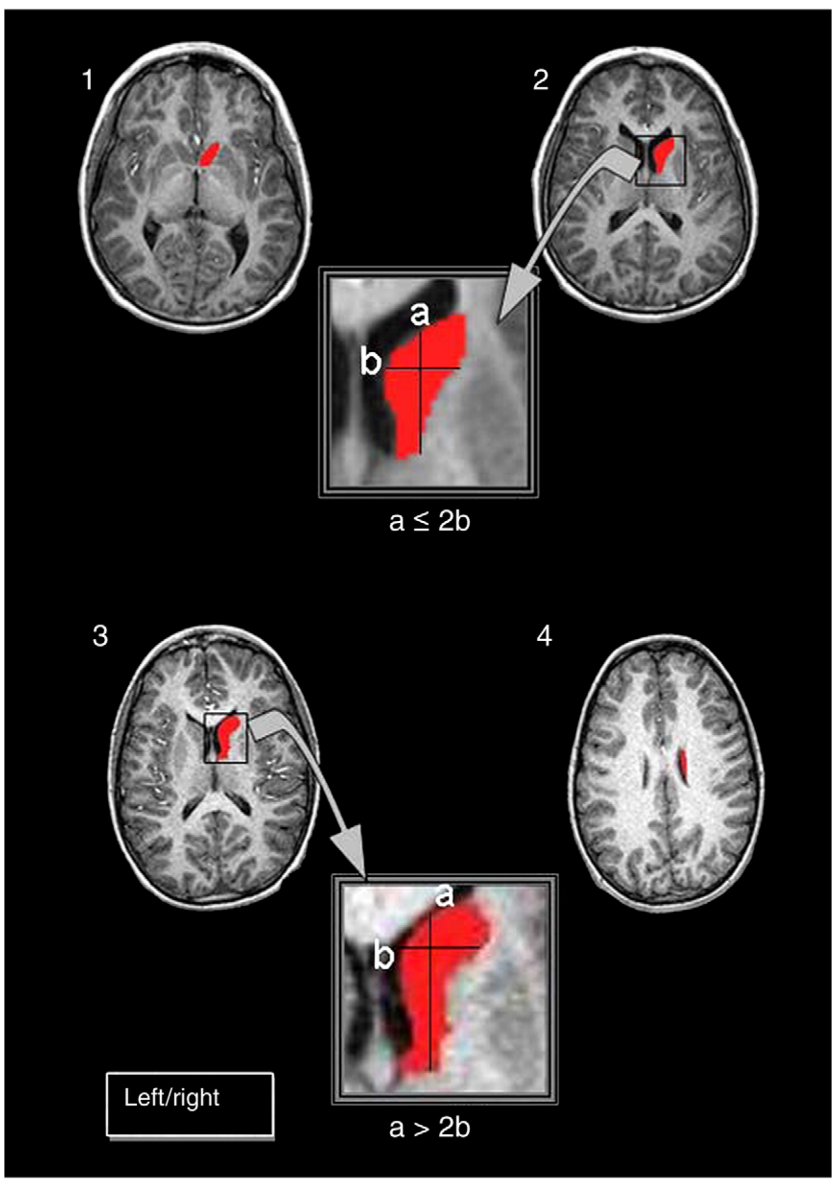

Fig. 1. Caudate segmentation procedure. T1 weighted images are oriented in a plane parallel to the bicommissural line. ROI is depicted in red. Refer to the text for description.

measures in voxels were transformed into cubic millimeters (mm^3) (ROIs total number of voxels multiplied by voxel dimensions).

To determine whether 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). To further investigate the differences in caudate head and body between the groups, we performed a three-way ANOVA with a between-groups factor (diagnostic group) and two repeated measures factors (hemisphere and caudate region). A decreased right caudate nucleus body (rCBV) was found in the ADHD sample with a medium effect size ($d = 0.42$). Results of this analysis are described in full in our previous article (Trèmols et al., 2008).

We selected a non-parametric receiving operator characteristic (ROC) analysis as a statistical approach, in order to evaluate diagnostic accuracy and determine the optimal cut-off.

In implementing a clinical diagnostic test, we first took into account the inter-individual differences in brain size correlated with factors unrelated to our hypothesis, such as the age range of the children; that is, we considered the scaling effect. In our previous study (Trèmols et al., 2008), we found a diminished rCBV but no statistically significant differences in the volumes of the left caudate body and right and left caudate head. It therefore seemed reasonable to employ either the total bilateral caudate volume (tbCV) or the bilateral caudate body volume (bCBV) as a scaling variable. By doing so, we hypothesized that the rCBV/tbCV and rCBV/bCBV ratios would target a biological variable deviant in the pediatric ADHD population and counterbalance the aforementioned scaling effect. To test our hypothesis, a Student *t*-test was conducted between the two samples, targeting both ratios. A Bonferroni correction for multiple comparisons was applied. To estimate the effect size, we applied Glass's delta statistic (Δ).

To determine the eventual diagnostic accuracy of the test, we performed an ROC analysis. First,we divided our samples into two groups: a training group (composed of 40 subjects) and a test group (composed of 38 subjects). Each group was made up of both a case subsample and an IQ-matched control subsample. The area under the curve (AUC) and its confidence intervals were estimated using a non-parametric method in the training group. To select the optimal test cut-off, we used the sensitivity function. We then calculated specificity, sensitivity, positive predictive value, negative predictive value and their respective confidence intervals for the test group. We also estimated the positive predictive value and the negative predictive value of our test in the general pediatric population by considering the widely agreed prevalence value of ADHD (Biederman and Faraone, 2005).

The intra-class correlation coefficient (ICC) was used too assess the inter-rater reliability of our caudate segmentation procedure. At the beginning of the study, we randomly selected five controls and five ADHD subjects. Those 10 participants (20 caudates) were used to calculate the ICC of the two tracers for the caudate head and for the caudate body. Later, we deleted all marks on the MR images, and they were pooled again in the common brain MRI sample. At the end of the study, we recalculated the ICC for the last five subjects. In assessing the inter-rater reliability at the beginning of the study, we obtained ICC = 0.87 for the caudate head and ICC = 0.89 for the caudate body. We obtained similar results at the end of the study: 0.89 for the caudate head and 0.91 for the caudate body.

All analyses were performed with the statistical package SPSS 15.0 and NCSS (2004).

3. Results

The rCBV/bCBV ratio was found to be statistically different in the two samples ($t = 3.16$, $P = 0.001$) with a high effect size ($\Delta = 0.84$), as shown in Table 2. The rCBV/tbCV ratio showed no statistically significant difference. Accordingly, we performed an ROC analysis for the rCBV/bCBV ratio in the training group.

Table 2
rCB-bCBV ratio.

	N	*M*	S.D.	*d*	*t*	*P*	$CI(95\%)_d$	*Δ*	$CI(95.\%)_\Delta$
Control	39	0.53	0.05	0.04	3.16	0.001	0.02 to 0.07	0.84	0.36 to 1.32
ADHD	39	0.49	0.07						

N, sample size; *M*, mean; S.D., standard deviation; *d*, mean difference; *t*, Student's *t* statistic; *P*, *P* value; CI, confidence interval of *d*; Δ, Glass's delta statistic; $CI(95.\%)_\Delta$, confidence interval of Δ at 0.95.

Table 3
Empirical ROC analysis.

	Value	CI(95%)	*z*	*P*
AUC	0.84	0.69 to 0.94	5.37	0.0001
Se	60.00	36.10 to 80.80		
Sp	95.00	75.10 to 99.20		

AUC, Area under the curve; Se, Sensitivity (in percent); Sp, Specificity (in percent).

The ROC analysis yielded an AUC of 0.84 ($CI_{0.95}$: 0.69 to 0.94) and $Z = 5.37$ ($P = 0.001$). The optimal cut-off value (OCOV) was: OCOV ≤ 0.4818. It provided a sensitivity of 60.00% ($CI_{0.95:}$ 36.10% to 80.00%) and a specificity of 95.00% ($CI_{0.95:}$75.10% to 99.20%). These results are presented in Table 3. The graph of the ROC curve is depicted in Fig. 2.

After applying the OCOV to our test group, we obtained a sensitivity of 42.11% ($CI_{0.95}$: 20.30 to 66.47), a specificity of 94.74% ($CI_{0.95}$: 73.90 to 99.12), a positive predictive value of 88.89% ($CI_{0.95}$: 52.51 to 98.30) and a negative predictive value of 62.07% ($CI_{0.95}$: 52.37 to 70.90). In the general pediatric population, assuming a prevalence of 10% (Biederman and Faraone, 2005), the estimated positive predictive value and the negative predictive value were 47.08% and 93.64%, respectively. Table 4 shows these results for prevalences ranging between 8 and 12%.

We also conducted four supplementary analyses on our test group, after excluding the female ADHD participants, the non-combined subtypes, the non-combined subtypes plus the female participants and the non-right-handed participants. This yielded the following sensitivities and a specificities: 47.06 ($CI_{0.95}$: 23.04 to 72.14) and 92.86 ($CI_{0.95}$: 66.06 to 98.01); 54.55 ($CI_{0.95}$: 23.50 to 83.08) and 94.74 ($CI_{0.95}$: 73.90 to 99.12); 66.67 ($CI_{0.95}$: 30.07 to 92.12) and 92.86 ($CI_{0.95}$: 66.06 to 98.81); and 50.00 ($CI_{0.95}$: 23.12 to 76.88) and 90.91 ($CI_{0.95}$: 58.67 to 98.49), respectively. Results can be seen in Table 5.

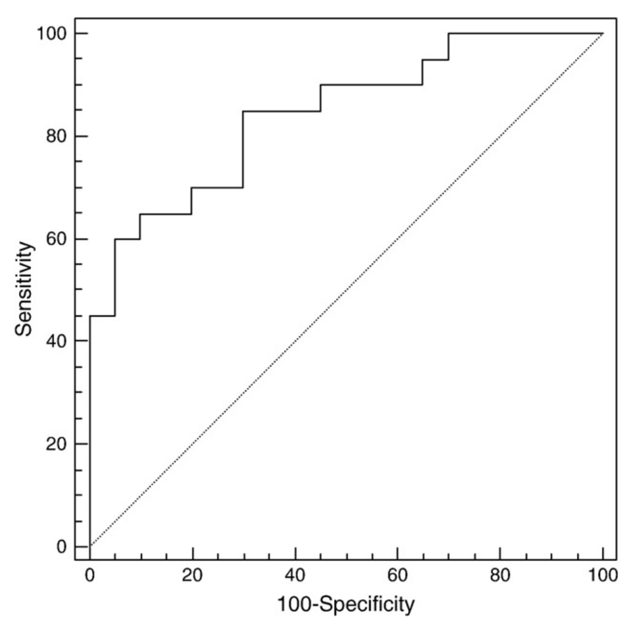

Fig. 2. ROC curve graphic.

Table 4
Predictive values at different levels of prevalence.

P	PPV	$CI(0.95)_{PPV}$	NPV	$CI(0.95)_{NPV}$
8	41.04	8.77 to 83.45	94.95	92.67 to 83.45
9	44.19	9.86 to 85.15	94.30	91.75 to 96.10
10	47.08	10.94 to 85.56	93.64	90.82 to 95.64
11	49.74	12.02 to 87.75	92.98	89.89 to 95.17
12	52.19	13.10 to 88.77	92.31	89.96 to 94.70
50	88.89	52.51 to 98.30	62.07	52.37 to 70.90

P, prevalence; PPV, positive predictive value; $CI(95\%)_{PPV}$, confidence interval at 0.95 of PPV; NPV, negative predictive value; $CI(0.95)_{NPV}$, confidence interval at 0.95 of NPV (all results are percentages).

4. Discussion

This study found a decreased rCBV/bCBV ratio in ADHD children. Using an ROC analysis to determine the optimal cut-off to discriminate between ADHD and control subjects, and applying this cut-off point to the test group, our method yielded a specificity of 94.74% and an estimated negative predictive value of 93.64% in the general pediatric population, given an estimated prevalence of 10%. These results suggest that there are grounds for considering this quantitative MRI test as an aid in the diagnosis of pediatric ADHD in a clinical setting, especially in those cases where DSM-IV-R based criteria are difficult to implement. The high NPV suggests that our method could be employed to either increase or decrease the likelihood of an ADHD diagnosis.

In our previous study, we found a decreased rCBV in the ADHD sample (Trèmols et al., 2008). To our knowledge, there had been no other previous published reports of a decreased rCBV or diminished rCBV/bCBV ratio in the pediatric ADHD population, although nearly all published MRI caudate morphometric studies in ADHD with an appropriate sample size ($n>30$) show a decreased total right caudate nucleus volume (Castellanos et al., 1994, 1996, 2001). In the sole study that does not report this finding, only the bilateral total caudate volume could be examined due to the automatized morphometric procedure employed (Castellanos et al, 2002). In a recent meta-analysis (Valera et al, 2007), the right caudate was found to be one of the regions most frequently assessed and showing the largest differences between AHDH and unaffected populations, in that its total volume was smaller in the ADHD samples. A decreased total right caudate nucleus volume was also found in our ADHD sample (Trèmols et al, 2008), but further analysis showed that it was entirely due to a decreased rCBV (Cohen's $d=0.59$). The fact that a decreased rCBV has not been reported in the aforementioned literature may be a consequence of the procedure by which the morphometric caudate nucleus analyses were conducted, in that these analyses were not designed to examine the body and head of the caudate nucleus separately.

Our findings—a decreased rCBV and a decreased rCBV/bCBV ratio in ADHD populations—underscore the pivotal role of the caudate nucleus in the neurobiology of ADHD.

In the main neuropsychological models of ADHD, impairment of executive functions is considered a key deficit of the disorder (Barkley, 1997; Pennington et al., 1996; Swanson, 2003; Denkla, 1996). The caudate nucleus is one of brain regions underlying these functions, mainly through its integration in the dorsolateral prefrontal circuit (Alexander et al., 1986, 1990). In an MRI morphometric study, Casey et al. demonstrated the implication of the right caudate nucleus in ADHD (Casey et al., 1997). Significant performance differences between ADHD subjects and normal controls in three inhibitory response tasks were observed in the study of Casey et al. As hypothesized, these differences correlated with the right caudate nucleus volume: smaller volumes in the ADHD sample were associated with poorer performance. More recently, in a functional MRI study (Vance et al., 2007), ADHD children engaged in a spatial working memory task (mental rotation) showed a hypoactivation in the right caudate nucleus, especially in the right caudate body, relative to a control group.

Table 5
Sensitivity and specificity for target subsamples.

Subsample	S	$CI(0.95)_S$	Sp	$CI(0.95)_{SP}$
Only males	47.06	23.04 to 72.14	92.86	66.06 to 98.01
Combined subtype	54.55	23.50 to 83.08	94.74	73.90 to 99.12
Males combined subtype	66.67	30.07 to 92.12	92.86	66.06 to 98.81
Right-handed	50.00	23.12 to 76.88	90.91	58.67 to 98.49

S, Sensitivity; $CI(95\%)_S$, confidence interval at 0.95 of S; Sp, Specificity; $CI(95\%)_{SP}$, confidence interval at 0.95 of Sp (all results are expressed in percent).

Our study provides a possible ancillary diagnostic test that combines ease of implementation with a high specificity and NPV. Furthermore, the study takes into account the proposals of the report on Standards for Reporting Diagnostic Accuracy (STARD) aimed at improving the quality of reporting in studies of diagnostic accuracy (Bossuyt and Reitsma, 2003; Bossuyt et al., 2003). Imaging techniques play a key role in the general medical practice. On their own or in conjunction with clinical and laboratory data, they provide a basis for widely employed diagnostic tests. In turn, diagnostic tests are expected to reliably identify a biological variable deviant from appropriate comparison groups of healthy subjects, thereby demonstrating potential clinical utility. Performance characteristics of a test should be assessed according to standardized statistical techniques (Boutros et al., 2005). We believe that the quantitative MRI test described here is based on an appropriate design, targets a possible biological marker of pediatric ADHD and offers satisfactory diagnostic accuracy. These factors suggest that this test may be clinically useful. Given the age range of our sample and the progressive "normalization" of the caudate volume in the ADHD samples around age 15 (Castellanos et al., 2002), the test could be expected to perform well in children from 7 to 15 years old.

Limitations of the present study include the use of a referred and medicated ADHD sample of methylphenidate responders. Ideally, the sample selection should be randomized. However, as is the case in almost all the published MRI morphometric studies concerning ADHD, the fact that the subjects are clinically referred could imply a bias towards more clinically severe cases of the disorder. Because all ADHD subjects in our study were medicated with methylphenidate and were considered to be responders to the pharmacotherapy, it could be the case that both independent variables are actually associated with specific neuroanatomic anomalies. Further investigation is needed to resolve this issue.

There exist contradictory reports about the association of neuroanatomical anomalies and medication in ADHD. Bussing et al. reported an augmented left and total caudate nucleus volume in a medicated ADHD sample in relation to a nonmedicated ADHD sample (Bussing et al., 2002). Castellanos et al. found a diminished total caudate bilateral volume in a medicated ADHD sample (Castellanos et al., 2002), whereas Semrud-Clikeman et al. observed no significant differences between these two samples (Semrud-Clikeman et al., 2006). We found no correlation between methylphenidate dosage and caudate volumetric measures in our ADHD sample. Moreover, as stated above, the total decreased volume of the right caudate is one of the most replicated findings in the ADHD morphometric MRI studies (which include medicated and nonmedicated samples). These facts suggest that there is little ground for hypothesizing a clear association between methylphenidate dosage and caudate volumetric measures, although this possibility cannot currently be ruled out. Only one study (Filipek et al., 1997) considered the eventual association between response to methylphenidate and neuronatomic anomalies, and it found no association between response to methylphenidate and caudate volumetric measures. Nonetheless, additional work is called for to firmly resolve this issue.

Another limitation of our study is that the ADHD sample is mainly composed of the combined DSM-clinical type, the most prevalent clinical type of the disorder. Additional statistical analyses in the combined subgroup yielded the same findings, but because of the small size of the inattentive and the hyperactive–impulsive type samples, we were unable to conduct independent statistical analyses on these groups. It would be desirable for other research groups to replicate our results using our method of caudate segmentation. Employing larger samples that include a sufficient number of each of the DSM-clinical types could lend further support to our findings, aid in understanding the disorder, and assess the clinical usefulness of our proposed test.

In addition, we should note that our groups have different male–female proportions, which could raise doubts regarding the internal validity of the present study. However, despite the scarcity of morphometric MRI studies on ADHD girls that examine the caudate nucleus, the study with the largest sample of ADHD girls (Castellanos et al., 2001) found a diminished total right caudate volume in comparison with a group of normal girls, thus replicating the finding reported in boys (Castellanos et al., 1994, 1996). Furthermore, we conducted supplementary analyses excluding the girls in both groups and found a diminished rCBV/bCBV ratio with similar effect size. This suggests that the different male–female proportions are not a confounding factor.

Finally, we would like to mention several potential criticisms of the method itself. Although proportions are not infrequently employed in brain volumetric studies, their use in manual measurements may increase error variance (Arndt et al., 1991; Mathalon et al., 1993). However, there is moderate agreement between the proportion method, the general lineal method and the analysis of variance approaches, and no method is obviously superior to the others (O'Brien et al., 2006).

Several factors should be taken into account in evaluating our choice of the scaling variable. Although total brain volume (TBV) is widely used in the proportion approach, we decided not to employ it for a number of reasons. TBV determination requires additional dedicated software and expertise, thus adding complexity to a test intended to be used in a clinical setting. On the other hand, TBV is also commonly diminished in ADHD samples (Seidman et al., 2005; Soliva and Vilarroya, 2009), which could affect test performance. However, our scaling variable also has its drawbacks. A recent study found a bilateral reduction in the caudate volume in an ADHD sample involving the left caudate body (Qiu et al., 2009). This finding could raise doubts about the external validity of our test, but it as yet remains unreplicated. As a final remark, we would like to mention that our procedure is, at present, semi-automated. Post-processing takes 20 min for each caudate nucleus once an adequate level of expertise has been accomplished. Semi-automated procedures also tend to be operator dependent. Full automatization of the procedure would be desirable.

In conclusion, we believe that quantitative MRI imaging, employing the bCBV-normalized rCBV obtained by our segmentation procedure, may serve as an ancillary test to assist in the diagnosis of ADHD in the pediatric population.

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