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Caudate asymmetry is related to attentional impulsivity and an objective measure of ADHD-like attentional problems in healthy adults

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Abstract

Case-control studies comparing ADHD with typically developing individuals suggest that anatomical asymmetry of the caudate nucleus is a marker of attention deficit hyperactivity disorder (ADHD). However, there is no consensus on whether the asymmetry favors the right or left caudate nucleus in ADHD or whether the asymmetry is increased or decreased in ADHD. The current study aimed to clarify this relationship by applying a dimensional approach to assessing ADHD symptoms that, instead of relying on clinical classification, utilizes the natural behavioral continuum of traits related to ADHD. Structural T1-weighted MRI were collected from 71 adults between 18 and 35 years old and analyzed for caudate asymmetry. ADHD-like attentional symptoms were assessed with an objective measure of attentional problems, the ADHD score from the Test of Variables of Attention (TOVA). Impulsivity, a core feature in ADHD, was measured using the Barratt Impulsiveness Scale, a self-report measure that assesses attentional, nonplanning, and motor features of impulsivity. We found that larger right relative to left caudate volumes correlated with both higher attentional impulsiveness and worse ADHD scores on the TOVA. Higher attentional impulsiveness also correlated with worse ADHD scores, establishing coherence between the objective measure and the self-report measure of attentional problems. These results suggest that a differential passage of information through frontal-striatal networks may produce instability leading to attentional problems. The findings also demonstrate the utility of a dimensional approach to understanding structural correlates of ADHD symptoms.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Keywords

caudate asymmetry; attention deficit hyperactivity disorder; impulsivity; Test of Variables of Attention (TOVA); and Barratt Impulsiveness Scale

INTRODUCTION

Problems with attention and impulsivity are major hindrances to academic and occupational success. When severe enough to cause impairment, such problems often lead to a diagnosis of attention deficit hyperactivity disorder (ADHD), which is one of the most commonly diagnosed mental disorders arising in childhood in the United States (Froehlich et al., 2007). With a few exceptions (Schrimsher et al., 2002, Shaw et al., 2011, Ducharme et al., 2012), attempts to understand the neural substrates of attentional deficits have focused on case-control designs contrasting typically developing individuals and patients who meet DSM criteria for ADHD. However, because of the complexity and heterogeneous nature of ADHD, such studies are not necessarily ideal for identifying and teasing apart specific brain-behavior correlates. The problems associated with such case-control designs have featured heavily in recent calls for studies examining relations between brain circuits and specific symptom dimensions. This trend is reflected in the Research Domain Criteria Initiative sponsored by the National Institute of Mental Health (Insel et al., 2010).

In the present study, we sought to examine the relation of two specific symptom dimensions of ADHD to a particular biological variable that has previously been suggested to be related to ADHD. Of the several possible neural markers of ADHD (Shaw and Rabin, 2009, Cortese and Castellanos, 2012), we focused here on the level of asymmetry in the volume of the caudate nucleus because the caudate nucleus is one of the most consistently identified areas in structural and functional case-control studies that contrast children with ADHD and typically developing children (Schneider et al., 2006, Cubillo et al., 2012). Previous studies have shown that patients with caudate nucleus dysfunction and animals with caudate nucleus lesions are impaired at tasks assessing attention processes (Cools et al., 2001b, Crofts et al., 2001), and neuroimaging studies using these attention demanding tasks commonly demonstrate activation in the caudate nucleus (Simon et al., 2002, Sylvester et al., 2003, Monchi et al., 2006). Although caudate asymmetry differences have been identified repeatedly as a possible signature of ADHD, consensus on the nature of this asymmetry remains elusive. A few studies have reported that children with ADHD have a larger right caudate relative to the left caudate but others have observed the opposite pattern (Hynd et al., 1993, Pueyo et al., 2000, Semrud-Clikeman et al., 2000, Uhlikova et al., 2007). Furthermore, there is no consensus on whether ADHD is associated with increased or decreased asymmetry relative to control samples (Castellanos et al., 1996, Filipek et al., 1997, Castellanos et al., 2002, Uhlikova et al., 2007).

While the source of the above discrepancies is unclear, we wondered if an examination of more narrow symptom domains would help clarify the relation between caudate asymmetry and ADHD relevant symptoms. We also wondered whether treatment of these variables as continuous dimensions rather than binary categorical diagnostic features would prove useful.

ADHD symptoms are arguably dimensional phenomena spanning the range from normal to abnormal. Reducing a continuous variable to a binary present-absent classification, as is typically done in ADHD diagnosis, may hinder both our understanding of ADHD phenomena and their relationship to brain structure. Indeed, the arbitrary nature of cutoff points has long been a concern when considering differential rates of ADHD diagnosis (Brown et al., 2001, Froehlich et al., 2007).

The present study examined the relationship between caudate asymmetry and ADHD features by using both an objective measure of attentional problems and a self-report measure of the individual's perception of impulsivity and attentional symptoms. For an objective measure of ADHD-like attentional problems, we used the Test of Variables of Attention (TOVA), a computerized task that is sensitive to dysfunction of attention and is commonly used in clinical settings to aid diagnosis of ADHD (Leark et al., 2008). The Barratt Impulsiveness Scale (BIS-11) served as the self-report measure (Patton et al., 1995). We chose the BIS-11 as it taps components of impulsivity that appear as core features of ADHD (Newcorn et al., 2001), including problems in attentional control (attentional impulsivity), nonplanning, and motor impulsiveness. Inclusion of both measures allowed us to test the coherence between the objective measure and the self-report questionnaire and to increase confidence in our findings if both measures showed similarities in the relationship between caudate asymmetry and ADHD-like problems. All measures were analyzed as continuous variables to determine whether the level of caudate asymmetry was linearly related to ADHD-behavioral continuum. Rather than using clinical definitions to guide brain-behavior investigations, our approach seeks to understand the neurobiological substrates underlying ADHD relevant dimensions. In the present study we focused on a young adult population in order to minimize effects of delayed developmental trajectories on caudate volumes in ADHD populations (Castellanos et al., 2002, Nakao et al., 2011), and we limited the study to individuals with no history of psychostimulant treatment given evidence that psychostimulants can increase caudate volume (Nakao et al., 2011).

METHODS

Subjects

Seventy-one subjects between 18 and 35 years old (mean age: 21.7±2.9 years, 35 females, 4 left-handed) were included in this study. Subjects were recruited as part of two related studies with overlapping measures. 47 of the subjects came from a study with an age range of 18 to 35 while the remaining subjects came from a study with a narrower age range of 18 to 25. Subjects were excluded if they reported any history of psychiatric illness on screening interview (a Structural Interview for Clinical DSM-IV Diagnosis was available for almost all subjects and confirmed no history of major Axis I disorders) (First et al., 1997), any history of head trauma, any significant medical condition, or any condition that would interfere with MRI (e.g. extreme obesity, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, pregnancy, anemia, and metallic body inclusions or other metal implanted in the body which may interfere with MRI scanning). Subjects were also excluded if they reported a history of substance abuse, current tobacco use, alcohol consumption greater than 8 ounces of whiskey or equivalent per week, use of

psychostimulants (excluding caffeine) more than twice at any time in their life or at all in the past 6 months, or any psychotropic medication in the last 6 months other than occasional use of benzodiazepines for sleep. Any illicit drug use in the last 2 months was grounds for exclusion, even in subjects who did not otherwise meet criteria for substance abuse. Urine drug tests were available during the screening for the majority of subjects, with any positive tests for the presence of amphetamines, cocaine, marijuana, PCP, opiates, benzodiazepines, or barbiturates reflecting grounds for exclusion. Written informed consent was obtained from all subjects. This study was approved by the Institutional Review Board at Vanderbilt University and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Schedule of Procedures

Subjects completed the TOVA prior to completing either the BIS-11 or the MRI. The MRI was scheduled approximately 2 weeks after the TOVA session. The BIS-11 was completed during a separate session, whenever possible during the two weeks separating the TOVA session and the scheduled MRI, but in some cases it was completed following the MRI.

Test of Variables of Attention (TOVA)

The TOVA by The TOVA Company is a computerized test of attention often used to aid clinical diagnosis of attention disorders. The TOVA consists of two test conditions: the target infrequent condition, which assesses the ability to maintain attention during a repetitive task, and the target frequent condition, which measures the ability to inhibit responses. In both conditions, subjects are asked to respond to each target, with each failure to respond to a target recorded as an error of omission, and each response to nontargets recorded as an error of commission. In the target infrequent condition, 1 geometric target appears for every 3.5 geometric nontargets, while in the target frequent condition, 3.5 targets were presented for every 1 nontarget. This frequency manipulation leads to differential rates of errors of omission and commission. The TOVA ADHD score was developed by determining which combination of elements from the tests were most predictive in discriminating between diagnosed individuals with ADHD and a large sample of healthy controls. The TOVA's ADHD score indicates how similar the subject's performance is to the performance profile of an ADHD sample. The formula for the ADHD score is mean response time Z-score on the target infrequent condition + D′ Z-score on the target frequent condition + response time variability Z-score on both conditions. A more negative ADHD Score indicates performance closer to the profile of a diagnosed ADHD sample (Leark et al., 2008).

Barratt Impulsiveness Scale (BIS-11)

The Barratt Impulsiveness Scale measures three forms of impulsiveness: attentional, nonplanning, and motor. Attentional impulsiveness combines questions on attention (e.g. "I don't 'pay attention'") and cognitive instability (e.g. "I have 'racing' thoughts"). Nonplanning impulsiveness is a measure of self-control (e.g. 'I say things without thinking') and cognitive complexity (e.g. 'I get easily bored when solving thought problems'). Motor impulsiveness is a composite measure of motor (e.g. 'I do things without thinking') and perseverance (e.g. 'I change jobs')(Patton et al., 1995). A paper and pencil measure was

used with the first recruitment sample (n = 47), while the remaining 24 subjects completed an online version of the scale through REDCap (project-redcap.org), which is a secure, web-based application designed exclusively to collect data for research studies. REDCap was initiated at Vanderbilt University and is now utilized by more than 70 institutional partners. No significant differences emerged in terms of scores between the paper and pencil and online versions of the scale.

MRI Scanning

All MRI scans were performed on two identically configured 3 Tesla Phillips Achieva scanners located at the Vanderbilt University Institute for Imaging Science. T1-weighted high-resolution 3D anatomical scans were obtained for each participant (FOV 256x256, 1x1x1mm resolution). Additionally, fast spin echo axial spin density weighted (TE=19, TR=5000, 3 mm thick) and T2-weighted (TE=106, TR=5000, 3 mm thick) scans were obtained to identify subjects for exclusion due to structural abnormalities.

Caudate Nucleus Segmentation

The caudate nucleus was defined using FMRIB's Integrated Registration and Segmentation Tool (FIRST) implemented in FSL. FIRST automatically segments the subcortex using Bayesian models constructed from prior manually segmented images (Patenaude et al., 2011). Figure 1 shows the segmentation of one subject's caudate by FIRST. Each segmentation was visually checked by L.C.D., who is experienced at manual segmentation of the caudate (Dang et al., 2012). All but two subjects (19 year old male, 24 year old female) passed the visual check. Attempts to correct the two segmentations using existing algorithmic procedures were not successful. These subjects were consequentially excluded from the analysis.

Caudate volumes were calculated for the left and right caudate separately. Caudate asymmetry was assessed as the ratio of right to left caudate volumes. We note that this ratio is independent of total brain volumes because the division of right caudate volume/total brain volume by left caudate volume/total brain volume is mathematically equal to right caudate volume/left caudate volume. The majority of the volume of the caudate lies in the head of the caudate rather than its tail, with the volume anterior of the anterior commissure comprising about 80% of the measured volume. To confirm that the results of analyses were related to the anterior aspects of the caudate, in post-hoc analyses we limited the caudate ratio calculation to only the volume anterior to the anterior commissure. These post-hoc analyses produced near identical results as analyses using the whole caudate volume ratio, indicating that the results could be accounted for by anterior sections of the caudate that receive projections from lateral prefrontal and premotor cortices.

Statistical Analyses

Multiple regressions were performed using R (Team, 2011) to examine the relation between caudate asymmetry and ADHD-score or BIS-11 scores. Age, gender, and handedness were included as covariates in all analyses and adjusted for in all graphs presented here.

RESULTS

ADHD Score and Caudate Asymmetry

The TOVA ADHD score can range from −6 to 6, with scores of −1.8 or lower indicating statistically significant evidence of attentional problems suggestive of ADHD. In the present sample, scores ranged from −6 to +6, with a mean score ± SD of 0.30±2.7. Although the present sample was generally high functioning, with no reported history of ADHD diagnosis, 20% of subjects had scores below −1.8. The ratio of asymmetry was expressed so that scores greater than 1.0 reflected greater right caudate volume and scores less than one reflecting greater left caudate volume. The sample showed a mean asymmetry score of 1.01±0.8. 17% of the sample showed a 5% or greater left than right caudate volume, 35% showed a 5% or greater right than left caudate volume, while the remaining subjects showed minimal differences.

Analysis of the relationship between caudate asymmetry and ADHD score revealed a significant inverse correlation between the two measures, with larger right relative to left caudate volumes associated with worse attentional performance (more negative ADHD score), $r = -0.27$, $p = 0.03$ (Fig. 2).

Barratt Impulsiveness Scale and Caudate Asymmetry

Means and standard deviations on the BIS-11 were 15.7±4.3 for attentional impulsiveness, 21.9±4.2 for nonplanning impulsiveness, and 23.2±4.8 for motor impulsiveness.

Larger right relative to left caudate volume correlated with higher attentional impulsiveness, $r = 0.34$, $p = 0.004$, the composite measure of cognitive instability and attention. Cognitive instability is assessed with questions about racing thoughts and thought insertions. The attention component includes questions about the ability to focus on the task at hand. Caudate asymmetry correlated with both cognitive instability and attention, but the correlation was particularly strong for cognitive instability, $r = 0.40$, $p = 0.0009$, relative to the attention component, $r = 0.23$, $p = 0.06$ (Fig. 3).

No significant relationship was observed between caudate asymmetry and nonplanning, $r = 0.06$, $p = 0.63$, or motor, $r = 0.19$, $p = 0.12$, impulsiveness.

In post hoc analyses, we also examined whether the volume of the right caudate or left caudate (corrected for total intracranial volume) were independently related to the TOVA scores or BIS-11 scores. Neither left nor right caudate volume correlated with the ADHD score, $r = 0.09$, $p = 0.45$ and $r = -0.07$, $p = 0.58$, respectively. We also did not observe significant relationships between the left or right caudate with nonplanning or motor impulsiveness. Right but not left caudate volume correlated positively with attentional impulsiveness, $r = 0.26$, $p = 0.03$. However, this correlation should be interpreted with caution given the number of post-hoc correlations performed.

Barratt Impulsiveness Scale and ADHD Score

ADHD Score correlated with all three forms of impulsiveness: attentional, $r = -0.33$, $p = 0.005$, nonplanning, $r = -0.37$, $p = 0.002$, and motor, $r = -0.30$, $p = 0.012$, (Fig. 4). Both

components of attentional impulsiveness were similarly correlated with ADHD Score: cognitive instability, r = −0.29, p = 0.02, and attention, r = −0.29, p = 0.02.

Gender

Males had more negative ADHD score, $t_{67} = -2.62$, p = 0.011, and a trend for higher attentional impulsiveness, $t_{67} = 1.77$, p = 0.081. There was no effect of gender on caudate asymmetry, $t_{67} = -1.12$, p = 0.265. Interaction analysis with gender as a factor revealed that the relationship between caudate asymmetry and attentional impulsiveness was modestly stronger for males but the correlation did not reach statistical significance, r = 0.20, p = 0.091. There was no significant interaction between gender and caudate asymmetry on the ADHD score, r = −0.04, p = 0.751.

Mediation Analyses

The results above show a three-way relationship between caudate asymmetry, ADHD score, and attentional impulsiveness. To test whether the relationship between caudate asymmetry and ADHD score is explained by variance in the self-report measure of attentional impulsiveness, we performed separate mediation analyses with ADHD score and attentional impulsiveness as the dependent measure. With attentional impulsiveness as the dependent measure, its relationship to caudate asymmetry remained significant after controlling for ADHD score, indicating that its relation with caudate asymmetry was not mediated by its relation to the ADHD score. By contrast, when ADHD score served as the dependent measure, the relationship between caudate asymmetry and ADHD score was no longer significant after controlling for its relationship with attentional impulsivity (Fig. 5). This indicates that the relationship between caudate asymmetry and ADHD-like attentional problems was significantly mediated by attentional impulsivity.

DISCUSSION

We found that asymmetry in the volume of the caudate significantly predicted ADHD-like attentional deficits and attentional impulsiveness in a sample of young adults. Specifically, larger right relative to left caudate volume correlated with higher self-reported attentional impulsiveness and showed a similar relation to attentional problems indexed with the TOVA ADHD score. Although not statistically significant, the relationship between caudate asymmetry and attentional impulsiveness was slightly stronger for males, possibly reflecting the higher prevalence of attention deficits in males (Cuffe et al., 2005). Higher self-reported attentional impulsiveness also correlated with worse ADHD scores. This finding establishes coherence between a self-report measure and an objective measure of attention that is often used to aide clinical diagnosis of ADHD, providing additional validation for both measures.

The present study highlights the value of a dimensional approach to examining ADHD-relevant symptom domains. By not categorically dividing subjects into ADHD and non-ADHD groups, we were able to examine linear effects of caudate asymmetry on specific features of the natural behavioral continuum of ADHD-relevant domains to further understand brain-behavior relationships without the constraint of clinical classification. Other researchers in the field have also adopted this approach in more recent investigations

of relations between ADHD symptoms and brain structures (Shaw et al., 2011, Ducharme et al., 2012). The observed association of caudate asymmetry with attentional problems converges remarkably well with one of the few prior studies to explicitly report on caudate volumetric asymmetry and dimensional measures of ADHD. Schrimsher et al. (2002) reported that the degree of right relative to left caudate volume selectively predicted parent-ratings of inattentive behaviors in a nonreferred sample of children. However, to our knowledge, the present study is the first study to show this relationship between caudate asymmetry and an objective measure of ADHD-like attentional deficits. Given that the TOVA is often used in clinical settings to aid diagnosis of ADHD and to track the effect of treatment, this finding has significant translational potential.

Studies with cognitive probes have previously revealed a critical role for the caudate nucleus in attention processing (Cools et al., 2001a, Crofts et al., 2001). The caudate nucleus is thought to influence attention through its membership in a key frontostriatal circuit. The caudate nucleus receives direct projections from the prefrontal cortex, modulates the signal it receives, and sends its output back to the prefrontal cortex through the pallidum and thalamus (Alexander et al., 1990). Imaging data from ADHD children and typically developing children reveal significant anatomical and functional differences in this frontostriatal network (Cubillo et al., 2012), with declines in the microstructural integrity of fronto-caudate white matter tracts associated with ADHD (Wu et al., 2012).

Caudate asymmetry could affect attentional processing in two ways. Some authors have proposed that caudate asymmetry may reflect general asymmetric dysfunction in ADHD (Stefanatos and Wasserstein, 2001). In other words, besides the caudate, other structures in the cortex would also be unilaterally affected in ADHD (Heilman et al., 1991, Carter et al., 1995). Support for this hypothesis comes from observations that individuals with ADHD show abnormal activity in one hemisphere but not the other during different tasks that are sensitive to ADHD (Pliszka et al., 2000, Gumenyuk et al., 2005). For example, compared to control participants, individuals with ADHD showed reduced ERP activity in the right hemisphere on a task assessing response inhibition (Pliszka et al., 2000) and reduced activity in the left hemisphere on an involuntary attention task (Gumenyuk et al., 2005). Within a dimensional model and a relatively healthy sample, the term “dysfunction” or “abnormality” risks over-pathologization of the neural findings. Nevertheless, caudate asymmetry could reflect broader asymmetric structural and functional issues.

We propose a different, more functionally specific interpretation of the effect of caudate asymmetry that centers on the function of the caudate nucleus within the frontostriatal circuit. The caudate, as part of the basal ganglia, is thought to perform a gating function, filtering signals coming into the cortex and updating current cortical representations (Cools and Robbins, 2004, Marklund et al., 2009). Tractography of white matter tracts between the caudate nucleus and the cortex reveals that connections are predominantly ipsilateral (Leh et al., 2007). Grey matter volume correlates with white matter volume (Zhang and Sejnowski, 2000), so a larger right caudate with more white matter connections to the right hemisphere may allow more signals to travel to the right hemisphere, which is dominant for attention, particularly stimulus-driven attention (Shulman et al., 2010). Increased stimulus-driven signals reaching the right hemisphere may result in unnecessary updating of current cortical

representations, leading to instability in attentional processing. Our finding that the cognitive instability component of attentional impulsiveness is particularly correlated with caudate asymmetry is intriguing in this context, as it includes specific items on having “extraneous thoughts when thinking” and racing thoughts.

Our mediation analyses suggest that the effect of caudate asymmetry on ADHD score is closely linked to features of attentional impulsivity. ADHD score correlated with all three forms of impulsiveness in the BIS-11: attentional, nonplanning, and motor. However, caudate asymmetry only correlated with attentional impulsiveness. The correlation between caudate asymmetry and ADHD score was no longer significant when attentional impulsiveness was included as an independent variable in the model. These results together imply that the relationship between caudate asymmetry and ADHD score is secondary to the relationship between caudate asymmetry and attentional impulsiveness. This result is striking in that the TOVA ADHD score avoids the inherent biases of self-report data but in fact appears closely predicted by a self-report measure, indicating that individuals are relatively accurate in assessing their deficits.

Several caveats are warranted in interpreting the present results. First and foremost, the extension of the present results to a disordered population is uncertain, as none of our subjects reported a prior diagnosis of ADHD and we did not perform further assessments to determine if any of the subjects met DSM-IV or DMS-V criteria for ADHD. Nevertheless, there were multiple subjects whose ADHD-scores were in the clinical range. Future studies that use a dimensional approach to analysis but explicitly include individuals who meet clinical criteria would be valuable. Additionally, studies with younger subjects would be valuable given the developmental features of ADHD. These developmental features may be particularly critical, as the majority of case control studies have assessed children. Whereas data in younger subjects have indicated caudate volume reductions (or right relative to left reductions) (Castellanos et al., 1996, Pliszka et al., 2006), several studies have shown that relationships between ADHD features and brain structure are highly dynamic before adulthood (Castellanos et al., 2002, McAlonan et al., 2009, Nakao et al., 2011, Shaw et al., 2011, Ducharme et al., 2012). Some of these studies reported that abnormalities in the caudate observed in children with ADHD disappeared with age, but it is unclear whether adults with abnormal caudate asymmetry reflect a subgroup of children whose caudate abnormalities fail to mature to the level of healthy controls or whose caudate maturation, once reaching the level of healthy controls, fails to pause and, as a result, overshoots the level found in healthy controls (Castellanos et al., 2002, Nakao et al., 2011). It is notable in this regard that while reduced caudate volumes have been observed in multiple studies of pediatric ADHD (Filipek et al., 1997, Pliszka et al., 2006, Qiu et al., 2009), a meta-analysis of voxel based morphometry studies observed significant increases in right, but not left striatal volume, with age in pediatric ADHD samples (Nakao et al. 2011). This would fit with both the direction of asymmetry observed in the present sample as well as the post-hoc observation that right caudate volume was positively associated with self-reported impulsivity. In addition to age-related changes in caudate structure, presentation of symptoms associated with ADHD also changes. Impulsivity, for example, has been found to decline with age (Steinberg et al., 2008). These developmental changes may explain the current lack of consensus on the relation between caudate asymmetry and symptoms of

ADHD, as most studies were performed in pediatric sample groups. Our focus on young adults in this study allowed us to examine the relationship between caudate asymmetry and attention processing in a more developmentally stable and homogenous age range. Longitudinal data on the relation between caudate asymmetry and attention measures from childhood to young adulthood will be essential if the present findings are to be extrapolated to a younger age range.

Another interesting follow up to this study involves examining the neurochemistry underlying these effects of caudate asymmetry. The caudate nucleus is a major site for innervation from dopamine neurons in the midbrain (Bjorklund and Dunnett, 2007), and relationships between attention and the dopamine system are well documented (Monchi et al., 2006). Studies using PET with dopamine receptor tracers show that grey matter density in the caudate positively correlates with dopamine receptor availability, and asymmetry in dopamine receptor availability correlates with individual differences in personality traits (Tomer et al., 2008, Woodward et al., 2009). Future studies investigating relationships between dopamine activity and caudate asymmetry would greatly enhance our understanding of attention and ADHD features.

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References

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. Prog Brain Res. 1990; 85:119–146. [PubMed: 2094891]

Bjorklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci. 2007; 30:194–202. [PubMed: 17408759]

Brown RT, Freeman WS, Perrin JM, Stein MT, Amler RW, Feldman HM, Pierce K, Wolraich ML. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. Pediatrics. 2001; 107:E43. [PubMed: 11230624]

Carter CS, Krener P, Chaderjian M, Northcutt C, Wolfe V. Asymmetrical visual-spatial attentional performance in ADHD: evidence for a right hemispheric deficit. Biol Psychiatry. 1995; 37:789–797. [PubMed: 7647163]

Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Lange N, Kaysen D, Krain AL, Ritchie GF, Rajapakse JC, Rapoport JL. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry. 1996; 53:607–616. [PubMed: 8660127]

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA. 2002; 288:1740–1748. [PubMed: 12365958]

Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson’s disease as a function of dopaminergic medication and task demands. Cereb Cortex. 2001a; 11:1136–1143. [PubMed: 11709484]

Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson’s disease. Brain. 2001b; 124:2503–2512. [PubMed: 11701603]

Cools R, Robbins TW. Chemistry of the adaptive mind. Philos Transact A Math Phys Eng Sci. 2004; 362:2871–2888.

Cortese S, Castellanos FX. Neuroimaging of attention-deficit/hyperactivity disorder: current neuroscience-informed perspectives for clinicians. Curr Psychiatry Rep. 2012; 14:568–578. [PubMed: 22851201]

Crofts HS, Dalley JW, Collins P, Van Denderen JC, Everitt BJ, Robbins TW, Roberts AC. Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. Cereb Cortex. 2001; 11:1015–1026. [PubMed: 11590111]

Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex. 2012; 48:194–215. [PubMed: 21575934]

Cuffe SP, Moore CG, McKeown RE. Prevalence and correlates of ADHD symptoms in the national health interview survey. J Atten Disord. 2005; 9:392–401. [PubMed: 16371662]

Dang LC, Donde A, Madison C, O'Neil JP, Jagust WJ. Striatal Dopamine Influences the Default Mode Network to Affect Shifting between Object Features. J Cogn Neurosci. 2012; 24:1960–1970. [PubMed: 22640392]

Ducharme S, Hudziak JJ, Botteron KN, Albaugh MD, Nguyen TV, Karama S, Evans AC. Decreased regional cortical thickness and thinning rate are associated with inattention symptoms in healthy children. J Am Acad Child Adolesc Psychiatry. 2012; 51:18–27. e12. [PubMed: 22176936]

Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology. 1997; 48:589–601. [PubMed: 9065532]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Washington, D.C: American Psychiatric Publishing, Inc; 1997.

Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. Arch Pediatr Adolesc Med. 2007; 161:857–864. [PubMed: 17768285]

Gumenyuk V, Korzyukov O, Escera C, Hamalainen M, Huotilainen M, Hayrinen T, Oksanen H, Naatanen R, von Wendt L, Alho K. Electrophysiological evidence of enhanced distractibility in ADHD children. Neurosci Lett. 2005; 374:212–217. [PubMed: 15663965]

Heilman KM, Voeller KK, Nadeau SE. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. J Child Neurol. 1991; 6(Suppl):S76–81. [PubMed: 2002218]

Hynd GW, Hern KL, Novey ES, Eliopulos D, Marshall R, Gonzalez JJ, Voeller KK. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J Child Neurol. 1993; 8:339–347. [PubMed: 8228029]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]

Leark, RA.; Greenberg, LK.; Kindschi, CL.; Dupuy, TR.; Hughes, SJ. Test of Variables of Attention: Professional Manual. Los Alamitos: The TOVA Company; 2008.

Leh SE, Ptito A, Chakravarty MM, Strafella AP. Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. Neurosci Lett. 2007; 419:113–118. [PubMed: 17485168]

Marklund P, Larsson A, Elgh E, Linder J, Riklund KA, Forsgren L, Nyberg L. Temporal dynamics of basal ganglia under-recruitment in Parkinson's disease: transient caudate abnormalities during updating of working memory. Brain. 2009; 132:336–346. [PubMed: 19036762]

McAlonan GM, Cheung V, Chua SE, Oosterlaan J, Hung SF, Tang CP, Lee CC, Kwong SL, Ho TP, Cheung C, Suckling J, Leung PW. Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder. Br J Psychiatry. 2009; 194:123–129. [PubMed: 19182173]

Monchi O, Ko JH, Strafella AP. Striatal dopamine release during performance of executive functions: A [(11)C] raclopride PET study. Neuroimage. 2006; 33:907–912. [PubMed: 16982202]

Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry. 2011; 168:1154–1163. [PubMed: 21865529]

Newcorn JH, Halperin JM, Jensen PS, Abikoff HB, Arnold LE, Cantwell DP, Conners CK, Elliott GR, Epstein JN, Greenhill LL, Hechtman L, Hinshaw SP, Hoza B, Kraemer HC, Pelham WE, Severe JB, Swanson JM, Wells KC, Wigal T, Vitiello B. Symptom profiles in children with ADHD: effects of comorbidity and gender. J Am Acad Child Adolesc Psychiatry. 2001; 40:137–146. [PubMed: 11214601]

Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage. 2011; 56:907–922. [PubMed: 21352927]

Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995; 51:768–774. [PubMed: 8778124]

Pliszka SR, Lancaster J, Liotti M, Semrud-Clikeman M. Volumetric MRI differences in treatment-naive vs chronically treated children with ADHD. Neurology. 2006; 67:1023–1027. [PubMed: 17000972]

Pliszka SR, Liotti M, Woldorff MG. Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. Biol Psychiatry. 2000; 48:238–246. [PubMed: 10924667]

Pueyo R, Maneru C, Vendrell P, Mataro M, Estevez-Gonzalez A, Garcia-Sanchez C, Junque C. Attention deficit hyperactivity disorder. Cerebral asymmetry observed on magnetic resonance. Rev Neurol. 2000; 30:920–925. [PubMed: 10919186]

Qiu A, Crocetti D, Adler M, Mahone EM, Denckla MB, Miller MI, Mostofsky SH. Basal ganglia volume and shape in children with attention deficit hyperactivity disorder. Am J Psychiatry. 2009; 166:74–82. [PubMed: 19015232]

Schneider M, Retz W, Coogan A, Thome J, Rosler M. Anatomical and functional brain imaging in adult attention-deficit/hyperactivity disorder (ADHD)--a neurological view. Eur Arch Psychiatry Clin Neurosci. 2006; 256(Suppl 1):i32–41. [PubMed: 16977550]

Schrimsher GW, Billingsley RL, Jackson EF, Moore BD 3rd. Caudate nucleus volume asymmetry predicts attention-deficit hyperactivity disorder (ADHD) symptomatology in children. J Child Neurol. 2002; 17:877–884. [PubMed: 12593459]

Semrud-Clikeman M, Steingard RJ, Filipek P, Biederman J, Bekken K, Renshaw PF. Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry. 2000; 39:477–484. [PubMed: 10761350]

Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, Greenstein D, Evans A, Rapoport J, Giedd J. Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder. Am J Psychiatry. 2011; 168:143–151. [PubMed: 21159727]

Shaw P, Rabin C. New insights into attention-deficit/hyperactivity disorder using structural neuroimaging. Curr Psychiatry Rep. 2009; 11:393–398. [PubMed: 19785981]

Shulman GL, Pope DL, Astafiev SV, McAvoy MP, Snyder AZ, Corbetta M. Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. J Neurosci. 2010; 30:3640–3651. [PubMed: 20219998]

Simon SR, Meunier M, Piettre L, Berardi AM, Segebarth CM, Boussaoud D. Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI. J Neurophysiol. 2002; 88:2047–2057. [PubMed: 12364527]

Stefanatos GA, Wasserstein J. Attention deficit/hyperactivity disorder as a right hemisphere syndrome. Selective literature review and detailed neuropsychological case studies. Ann N Y Acad Sci. 2001; 931:172–195. [PubMed: 11462741]

Steinberg L, Albert D, Cauffman E, Banich M, Graham S, Woolard J. Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model. Dev Psychol. 2008; 44:1764–1778. [PubMed: 18999337]

Sylvester CY, Wager TD, Lacey SC, Hernandez L, Nichols TE, Smith EE, Jonides J. Switching attention and resolving interference: fMRI measures of executive functions. Neuropsychologia. 2003; 41:357–370. [PubMed: 12457760]

Team RDC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2011.

Tomer R, Goldstein RZ, Wang GJ, Wong C, Volkow ND. Incentive motivation is associated with striatal dopamine asymmetry. Biol Psychol. 2008; 77:98–101. [PubMed: 17868972]

Uhlikova P, Paclt I, Vaneckova M, Morcinek T, Seidel Z, Krasensky J, Danes J. Asymmetry of basal ganglia in children with attention deficit hyperactivity disorder. Neuro Endocrinol Lett. 2007; 28:604–609. [PubMed: 17994006]

Woodward ND, Zald DH, Ding Z, Riccardi P, Ansari MS, Baldwin RM, Cowan RL, Li R, Kessler RM. Cerebral morphology and dopamine D2/D3 receptor distribution in humans: a combined [18F]fallypride and voxel-based morphometry study. Neuroimage. 2009; 46:31–38. [PubMed: 19457373]

Wu YH, Gau SS, Lo YC, Tseng WY. White matter tract integrity of frontostriatal circuit in attention deficit hyperactivity disorder: Association with attention performance and symptoms. Hum Brain Mapp. 2012

Zhang K, Sejnowski TJ. A universal scaling law between gray matter and white matter of cerebral cortex. Proc Natl Acad Sci U S A. 2000; 97:5621–5626. [PubMed: 10792049]

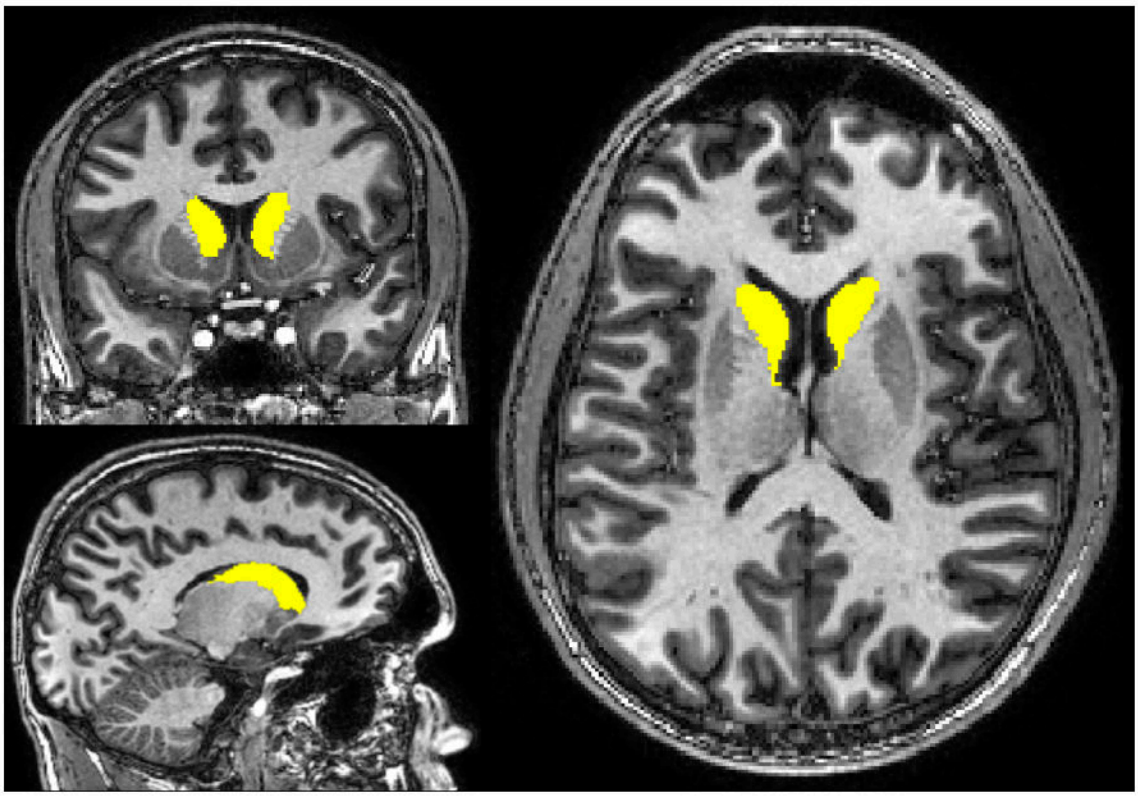

Fig. 1.
Caudate segmentation. An example of one subject's caudate as defined by FIRST, FSL's segmentation tool

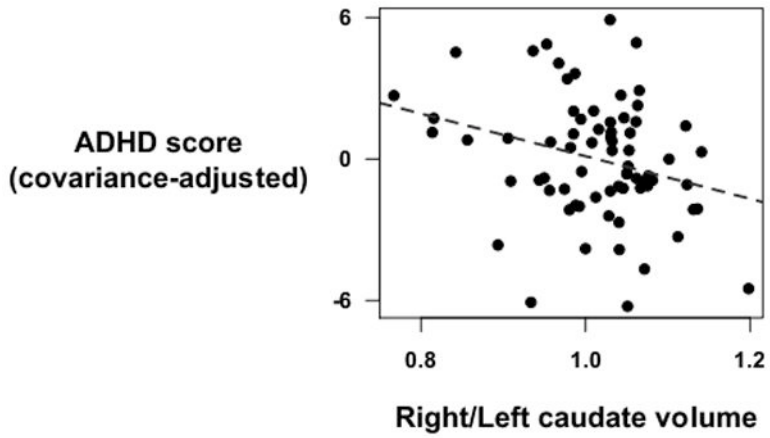

Fig. 2.

ADHD score and caudate asymmetry. Larger right relative to left caudate volume correlated with lower ADHD score on the TOVA, $r = -0.27$, $p = 0.03$, indicating more attentional problems

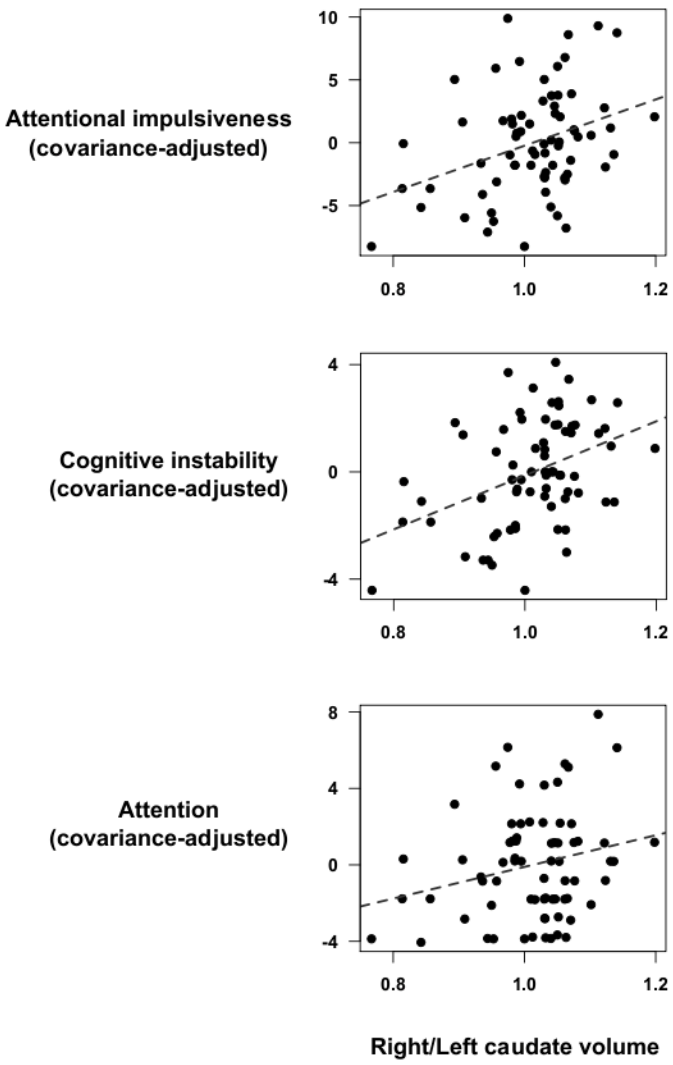

Fig. 3.

Attentional impulsiveness and caudate asymmetry. Larger right relative to left caudate volume correlated with higher attentional impulsiveness on the Barratt Impulsiveness Scale, $r = 0.34$, $p = 0.004$. Larger right to left caudate volume ratio also correlated with cognitive instability, $r = 0.40$, $p = 0.0009$, and attention, $r = 0.23$, $p = 0.06$, the two components of attentional impulsiveness

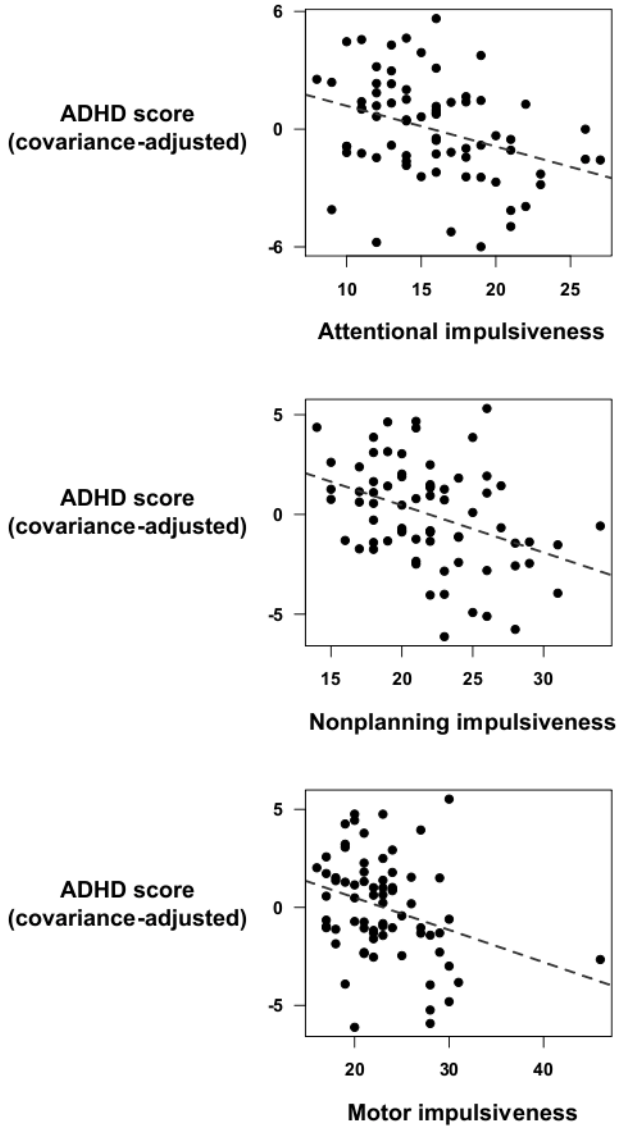

Fig. 4.

Barratt Impulsiveness Scale and ADHD score. Lower ADHD score correlated with higher attentional impulsiveness, $r = -0.33$, $p = 0.005$, higher nonplanning impulsiveness, $r = -0.37$, $p = 0.002$, and higher motor impulsiveness, $r = -0.30$, $p = 0.012$

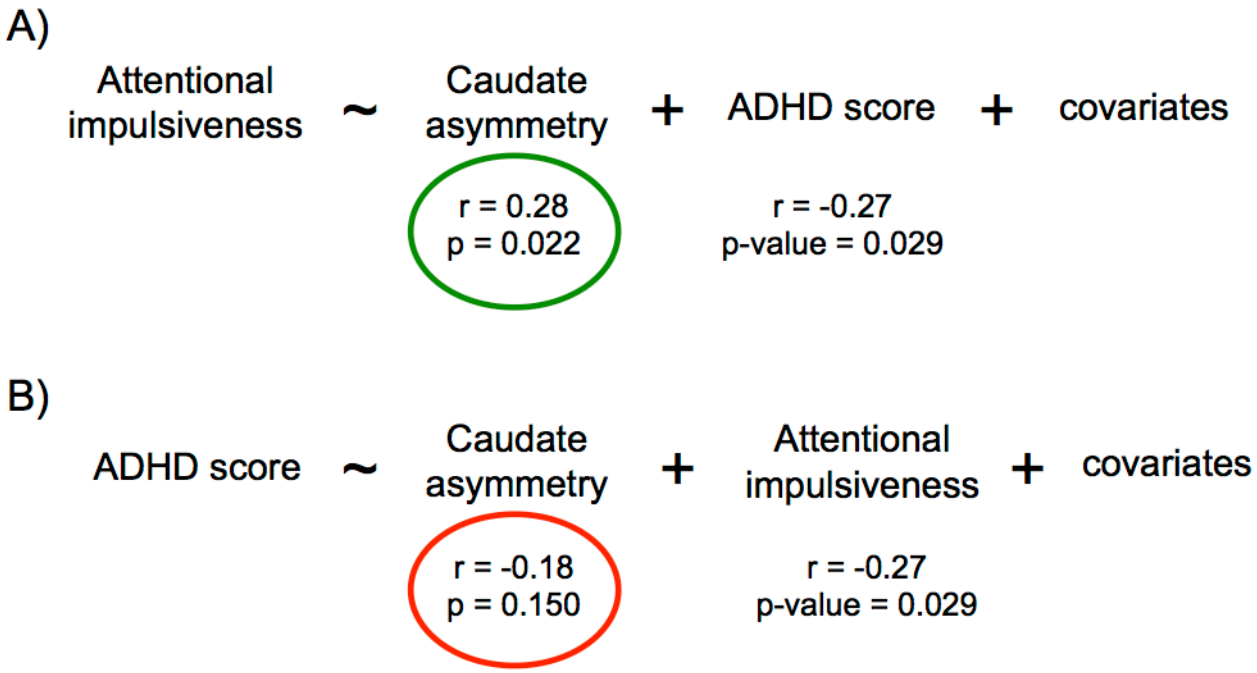

Fig. 5.

Mediation analyses. A) The correlation between caudate asymmetry and attentional impulsiveness remained significant after controlling for ADHD score. B) The correlation between caudate asymmetry and ADHD score was no longer significant after controlling for attentional impulsiveness