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Antisaccade-related brain activation in children with attention-deficit/hyperactivity disorder – A pilot study

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Abstract

While antisaccade paradigms invoke circuitry associated with cognitive control and attention-deficit/hyperactivity disorder (ADHD), there is a dearth of literature of functional magnetic resonance imaging (fMRI) investigations using antisaccade tasks among children with ADHD. Neural correlates associated with antisaccade performance were examined with fMRI in 11 children with ADHD (10 medicated) matched to 11 typically developing children. Significantly greater brain activation in regions in right dorsolateral prefrontal cortex and caudate nucleus was observed in children with ADHD relative to the control group. This pattern separated the children into their respective groups in a taxonomic manner. Sensitivity analyses probing comorbidity and medication-specific effects showed that results were consistent; however, the caudate nucleus difference was only detectable in the full sample, or in subsets with a more relaxed cluster threshold. Antisaccade performance did not significantly differ between the groups, perhaps as a result of greater brain activation or medication effects in the ADHD group. Thus, antisaccade paradigms may have sensitivity and specificity for the investigation of cognitive control deficits and associated neural correlates in ADHD, and may contribute towards the development of new treatment approaches for children with the disorder.

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Contributors

NFS collected the data, performed data analyses, interpreted the results, and wrote the manuscript. CEK, LC, DJS, JEP, and ALR helped with data collection and draft editing. ALW helped with data collection. CFW assisted with data analysis and draft editing. CHD confirmed ADHD diagnosis and calculated dose equivalents for the children's ADHD medication. BLM obtained funding, advised CLD on the study design, and calculated dose equivalents for the children's ADHD medication. CLD conceived the study, obtained funding, and supervised data analysis, interpretation, and draft editing. JEM conceived the study, obtained funding, supervised data analysis and interpretation, and co-wrote the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

Keywords

ADHD; Children; Cognitive control; Functional magnetic resonance imaging; fMRI; Stimulant medication

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is diagnosed by developmentally atypical levels of inattention, hyperactivity and/or impulsivity. ADHD is more frequently reported in boys, is less likely to be diagnosed in girls (Froehlich et al., 2007), and is associated with impaired academic and social functioning (Barkley, 2002) that can be improved with pharmacological treatment (Biederman and Faraone, 2005). The heterogeneous nature of the disorder is expressed in a range of difficulties with behavior and cognition, including cognitive control (CC) (Biederman and Faraone, 2005). CC supports flexible behavior through coordinating higher order cognitive processes and is essential for adaptive functioning (Miller and Cohen, 2001). The nature of CC disruptions in ADHD has been characterized by poorer performance across a range of tasks relative to control groups (Willcutt et al., 2005). Neural substrates associated with these deficits can be investigated with techniques such as functional magnetic resonance imaging (fMRI) (Bush et al., 2005).

The neural circuitry supporting CC tasks in individuals with ADHD generally resembles that of control groups with differences emerging in regions such as inferior, middle, and superior frontal gyri, anterior cingulate cortex, and striatum (Dickstein et al., 2006; Bush, 2011; Cortese et al., 2012). Reduced brain activation in these regions is frequently reported in unmedicated children and adolescents with ADHD when compared to control groups (Rubia et al., 1999; Tamm et al., 2004; Booth et al., 2005; Rubia et al., 2011a), although greater activation also has been observed (Durstun et al., 2003) and may indicate additional neural recruitment associated with augmented cognitive effort (Schulz et al., 2005; Fassbender and Schweitzer, 2006). Stimulant medication provides a mechanism to increase CC-related fronto-striatal activation and has been shown to reduce symptoms of ADHD (Faraone and Biederman, 2002; Faraone and Buitelaar, 2010) and enhance cognitive and motor control (Kempton et al., 1999; Klein et al., 2002).

Previous investigations have provided evidence for increased brain activation in the dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG), and striatum in children and adolescents with ADHD who received stimulant medication relative to unmedicated control groups (Vaidya et al., 1998; Shafritz et al., 2004; Rubia et al., 2011a; Rubia et al., 2011b). The efficacy of stimulant medication such as methylphenidate is suggested to stem, in part, from modulating dopamine transmission, resulting in increased extracellular dopamine and amplified cortico-striatal signal (Sonuga-Barke, 2005; Volkow et al., 2005; Swanson et al., 2007). Through this mechanism, methylphenidate is thought to increase the saliency of stimuli, enhance motivation and interest to engage in tasks, increase attention and decrease distractibility, all of which improve CC-related functions.

Eye movement paradigms such as antisaccade tasks have been used as simple and effective methods to examine both behavioral and neural correlates of CC in pediatric populations

(Hallett, 1978; Rommelse et al., 2008). Whereas a prosaccade is a glance towards a newly appearing peripheral visual stimulus, an antisaccade requires the inhibition of such a glance and a redirection of gaze to the mirror image location of the visual stimulus (i.e., same distance from center in the opposite direction). An initial glance towards the stimulus represents an error and may reflect problems with CC. Children with ADHD show worse performance on this task compared to typically developing children, including a greater number of antisaccade errors, and longer and more variable latencies of correct responses (Sweeney et al., 2004; Rommelse et al., 2008). Improved performance on task parameters such as reductions in antisaccade errors and latencies of correct responses have been observed with administration of stimulant medication (Klein et al., 2002; O'Driscoll et al., 2005; Goto et al., 2010), although not consistently (Aman et al., 1998). Prior studies (which did not report neuroimaging outcomes) have found a wide range of mean percent antisaccade errors and latency for correct responses, which overlap between unmedicated children with ADHD (23-59%, 331-382 ms), medicated children with ADHD (38-59%, 287 ms), and control groups (10-43%, 313-372 ms) (Aman et al., 1998; Mostofsky et al., 2001; Klein et al., 2002; Klein et al., 2003; Munoz et al., 2003; O'Driscoll et al., 2005; Hanisch et al., 2006; Goto et al., 2010). It should be noted that several antisaccade studies in children with ADHD included only boys (Rothlind et al., 1991; Aman et al., 1998; Klein et al., 2002; O'Driscoll et al., 2005), limiting generalizability to girls. Using neuroimaging techniques to complement studies of antisaccade performance in girls and boys with ADHD can provide additional information on alterations in the voluntary control of behavior and associated patterns of brain activation.

The neural circuitry underlying successful antisaccade performance in healthy adults has been thoroughly described (Gagnon et al., 2002; Dyckman et al., 2007; Ettinger et al., 2008; McDowell et al., 2008) and includes frontal and supplementary eye fields, posterior parietal cortex, as well as areas often associated with CC, such as dlPFC, anterior cingulate cortex, and striatum (Munoz and Everling, 2004; Sweeney et al., 2007; Krafft et al., 2012). A few fMRI studies have examined the neural correlates of antisaccade performance in typically developing children (Luna et al., 2001; Velanova et al., 2008, 2009). Findings indicate that basic saccadic circuitry is established in childhood but appears less well integrated compared to adults. Differences emerge in the right dlPFC where adults showed greater sustained brain activation compared to typically developing children (Velanova et al., 2009) and in the dorsal anterior cingulate cortex where typically developing children exhibited greater brain activation compared to adults (Velanova et al., 2008). An fMRI study examining antisaccade activation solely in healthy youth extended these findings, showing greater activation in right dlPFC and dorsal anterior cingulate cortex when blocks of antisaccades were contrasted with blocks of prosaccades (Fitzgerald et al., 2008).

There is a dearth of fMRI studies employing an antisaccade paradigm in children with ADHD. In adults with ADHD, a recent study reported greater activation in bilateral dlPFC for antisaccade execution and reduced activation in bilateral dlPFC and caudate nucleus (CN) for antisaccade errors in comparison to a control group (Hakvoort-Schwerdtfeger et al., 2012). Here, we sought to explore the neural circuitry associated with this task in children with ADHD (10/11) who maintained their regular pharmacological treatment relative to a matched control group. Antisaccade paradigms lend themselves to studying the neural

correlates of CC in children with ADHD as they provide direct neurophysiological indices, in the form of eye movements, of brain functions associated with the disorder (Reilly et al., 2008). We hypothesized that children with ADHD, particularly those who are medicated, would demonstrate greater brain activation in dlPFC, dorsal anterior cingulate cortex, and striatum in comparison to the control group. Furthermore, medicated children with ADHD were expected to perform at the level of the control group children.

2. Methods

2.1. Participants

Eleven children aged 8 to 11 years old and previously diagnosed with ADHD were recruited from public schools around Augusta, Georgia (U.S.A.). The diagnosis of ADHD for 10 children was confirmed using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (American Psychiatric Association, 2000). Nine of the participants met criteria for ADHD Combined Type and one for ADHD Predominantly Inattentive Type. Additional information was obtained through ratings on the Achenbach System of Empirically Based Assessment (Achenbach et al., 2003) and the Vanderbilt ADHD Parent and Teacher Rating Scales (Wolraich et al., 1998; Wolraich et al., 2003) provided by primary caregivers and teachers. Teacher ratings were averaged across all teachers who provided ratings for a given child. For each child, clinical significance of ADHD symptoms was defined with a T 63 for the Achenbach System. For the Vanderbilt rating scales, a count of at least 6 symptoms endorsed “often or very often” (2 or 3) on inattention and/or hyperactive-impulsive items indicates clinical significance. As part of study inclusion criteria, ten children were verified on stable medication for ADHD for at least one month prior to testing. Methylphenidate dose equivalents were calculated for nine participants (no adequate comparison could be made for one participant who took guanfacine). One boy had a history of seizures in early childhood and another boy had a tic disorder (eye blink). One girl was reported to have an anxiety disorder, oppositional defiant disorder and depression, and was on medication for complex partial seizures (levetiracetam 1500 mg/day) at the time of the scan. One other girl had oppositional defiant disorder and depression. Comorbidity with these disorders is common among children with ADHD (Spencer et al., 2007). One participant was recruited in a previous study (described below), before his ADHD diagnosis was discovered: he was included here because he had a parent-reported clinical diagnosis of ADHD (with no medication prescribed), and had undergone the same fMRI data collection procedures. The clinical diagnostic confirmation and Vanderbilt and Achenbach rating scales were not obtained in this case.

Participants in the control group were 8-11 years old and drawn from a study of overweight children carried out in the same time frame by this research group, and were recruited from similar schools as the children with ADHD (Krafft et al., 2014). Exclusion criteria included severe vision problems and a history of neurological or psychiatric disorders. Children in both groups were primarily African-American (except for one child in the ADHD group) and did not significantly differ in percent body fat as measured via dual-energy x-ray absorptiometry. Matching on percent body fat was carried out because adiposity and overweight have been associated with decreased cognitive function (Li et al., 2008; Davis

and Cooper, 2011). The groups also were matched on age, sex, and handedness, and did not significantly differ in socioeconomic status as indexed by the level of education of the primary caregiver, or in cognitive ability as assessed with the Full Scale score of the Cognitive Assessment System (Naglieri and Das, 1997). Sample characteristics are provided in Table 1. Children and primary caregivers provided informed assent and consent. All participants were given gift cards worth up to \$50 after study completion. Teachers received \$25 for providing behavior ratings for each child with ADHD. The study took place at Augusta University, where it was approved and monitored by the institutional review board in accordance with the Helsinki Declaration.

2.2. Paradigm

The task was presented in a blocked design alternating seven blocks of simple fixation with six blocks of antisaccade trials. During each antisaccade block, eight trials were presented, each lasting 3 s. A trial began with a blue filled circle at central fixation (1600 ms). Then the fixation target was extinguished and a cue presented in the periphery (1400 ms; $\pm 10^\circ$ of visual angle on the horizontal plane; half of the trials in each visual field). Participants were instructed to look at the target when it was in the middle of the screen but when the cue appeared at a peripheral location to look to the mirror image. Before entering the scanner, participants rehearsed the task using flash cards and were evaluated for understanding the requirements of the task. Research staff observed the children taking their usual medication before the scan.

Visual stimuli were generated using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, U.S.A.) and presented using a dual mirror system that both displayed visual stimuli on a rear projection screen and projected an image of the participant's eye to an MRI-compatible infrared camera system (IView X MRI-LR, SensoMotoric Instruments, Inc., Berlin, Germany). The system showed eye position in real time and recorded it digitally for future analysis. Two separate five-point runs allowed for the vertical and horizontal calibration of eye movements relative to the placement of visual stimuli.

Individual antisaccade trials were quantified and latencies for the correct, error and error correction responses generated using MATLAB (The Mathworks Inc., Natick, MA, U.S.A.) and procedures that have been previously used by our laboratory (Dyckman et al., 2007). Trials were eliminated from behavioral analysis if the reaction time was faster than 90 ms, a saccade was less than 10% of the distance to the target, there were blinks before saccades, there was no response, or the data were too noisy to be scored. Eye movements were recorded for all participants in both groups.

2.3. Analysis of behavioral data

Analysis was conducted in SPSS Version 20 (IBM, Armonk, NY, U.S.A.). Independent-sample t-tests were performed to investigate whether there were significant between-group differences in antisaccade performance. Alpha levels were set at $p < 0.05$ (two-tailed).

2.4. Scan acquisition

Images were acquired on a GE Signa Excite HDx 3 Tesla MRI system (General Electric Medical Systems, Milwaukee, WI) at Augusta University. For all MRI scans, head position was stabilized with a vacuum pillow and/or foam padding. High-resolution T1-weighted structural brain images were acquired using a 3D fast spoiled gradient-echo protocol (repetition time (TR)=9.436 ms, echo time (TE)=3.876 ms, flip angle=20°, field of view (FOV)=240 × 240 mm, acquisition matrix 512 × 512, 120 contiguous axial slices, slice thickness=1.3 mm, total scan time=3 min, 33 s). A functional scan of a single blocked antisaccade run (TR=3000 ms, TE=35 ms, flip angle=90°, FOV=240 × 240 mm, acquisition matrix=128 × 128, 30 interleaved axial slices, slice thickness=4 mm (skip 1 mm), 104 volumes) was collected. Volumes were acquired obliquely, with the slices aligned to the superior margin of the participant's anterior commissure and inferior margin of the posterior commissure. Four volumes were obtained and discarded before stimulus presentation began to allow for scanner stabilization. Participants listened to pre-recorded MRI sounds via earphones and practiced lying still before entering the scanner to assist with acclimation to the MRI environment.

2.5. Functional MRI analysis

All fMRI analyses and statistics were conducted using Analysis of Functional Neuroimages (AFNI) (Cox, 1996). For single subject analyses, the individual's T1-weighted structural MR image was transformed into standardized space based on a publicly available template (offered in AFNI) in Talairach space. For the functional run, individual slices were time-shifted and each volume registered to the third volume to correct for head movement. No participant was excluded due to excessive motion (threshold set at an absolute motion displacement of >3mm). The functional run was then aligned to the standardized T1-weighted image and voxels resampled to 1.75 mm (final voxel size). A 4-mm full-width at half-maximum Gaussian filter was applied and the raw time series scaled to a mean of 100.

Following preprocessing, the hemodynamic response function was generated convolving the stimulus timing of antisaccade trials with an incomplete gamma variate. The hemodynamic response function was then entered into a generalized least-squares regression model together with information on censored TRs (e.g., motion, outliers), six motion parameters, and three nuisance regressors modeling drift. The temporal autocorrelation in the residuals was estimated with an autoregressive moving average model (ARMA (1,1)) using restricted maximum likelihood.

Group differences in brain activation were investigated by performing a whole-brain mixed-effects analysis, modeling both between- and within-subject variability (Chen et al., 2012). To protect against false positives, resulting t-maps were thresholded using a voxel-wise $p < 0.02$ (preserving a cluster family-wise multiple comparison correction set at $\alpha p < 0.05$, two-tailed; inherent and applied spatial correlation of the data was taken into account) (Ward, 2000). A whole-brain effect size analysis was conducted to examine the strength of the group-level result. In addition, another four whole-brain mixed-effects analyses were carried out as sensitivity analyses between the control group and the ADHD group without the children who a) had seizures, b) mental health comorbidities, c) did not have a

Combined Type diagnosis, and d) without the unmedicated child with ADHD (using the same family-wise error correction as above). Group differences in average motion were investigated with independent t-tests (alpha set at $p=0.05$, two-tailed) in SPSS.

Pearson's correlation coefficient analyses were performed in SPSS to investigate possible relationships between brain activation in regions of significant between-group differences as well as relationships between these regions and antisaccade performance parameters. In the ADHD group, an association of brain activation and medication dose was examined. Alpha levels for all tests were set at $p<0.05$ (two-tailed).

3. Results

3.1. Behavioral results

The groups did not significantly differ on any of the antisaccade performance parameters (see Table 2).

3.2. Functional MRI results

Overall, both groups exhibited typical antisaccade-related circuitry in frontal- and supplementary eye fields, striatum, and posterior parietal cortex – regions associated with visual spatial attention, saccade generation, and inhibitory control (Ettinger et al., 2008; McDowell et al., 2008; Krafft et al., 2014). Significant group differences in brain activation were revealed in two clusters (see Fig. 1, Table 3 for descriptive statistics). The first cluster comprises right dlPFC, extending into IFG and superior frontal gyrus. The second cluster comprises right CN, extending into lentiform nucleus. Children with ADHD demonstrated greater brain activation compared to the control group in both of these regions.

No significant group difference in activation in dorsal anterior cingulate cortex was detected. There was no region showing greater brain activation in the control group compared to the ADHD group. Independent sample t-tests verified that the groups did not significantly differ in average motion of participants (all motion parameter $p>0.31$, average motion <2.2 mm in any of the three planes).

The effects size analysis supported the between-group differences in brain activation (effect size=0.8) in regions overlapping with the dlPFC and CN clusters. Sensitivity analyses excluding the children with ADHD who had a) seizures, b) mental health comorbidities, c) no Combined Type diagnosis, and d) without the unmedicated child with ADHD were mostly consistent although CN did not survive clustering in any of these analyses. The uniformity of this pattern across the sensitivity analyses (i.e., no significant difference between ADHD and control groups at the level of activation in CN) suggested reduced power due to decreased sample size rather than disorder- or medication-specific effects. In the case of the analysis excluding the unmedicated child with ADHD, both dlPFC and CN survived $p<0.02$ when using a cluster extent threshold of 260 voxels instead of the formally obtained threshold of 296 voxels to correct for multiple comparisons.

To investigate an association of brain activation between dlPFC and CN clusters, correlation analyses were performed. Brain activation in dlPFC did not correlate significantly with that

of CN in either group. Plotting the means of brain activation in dlPFC against those of CN for each participant, however, separated the groups in a taxonomic manner (Fig. 2). Specifically, mean brain activation in both regions was of predominantly greater magnitude in the ADHD group compared to the control group, and the combination of activation in dlPFC and CN essentially provided group classification. Antisaccade performance did not correlate with brain activation in either group. In the ADHD group, stimulant medication dose did not correlate with brain activation in either cluster, and the data from the one unmedicated child fell within the range of the other children with ADHD.

4. Discussion

The present study investigated whether children with ADHD differed in antisaccade-related brain activation compared to a matched control group of overweight typically developing children. In comparison to the control group, children with ADHD (10/11 of whom were maintained on their regular psychopharmacological treatment) demonstrated greater brain activation in two clusters covering prefrontal and striatal regions. The first cluster is located mainly within the right dlPFC, extending into IFG and superior frontal gyrus. The second cluster is located mainly in the right CN, extending into lentiform nucleus.

The locations of brain activation reported here are consistent with the literature on neural correlates of antisaccade paradigms. Greater activation in dlPFC is associated with inhibition of reflexive saccades (Pierrot-Deseilligny et al., 2003; McDowell et al., 2008), preparatory set before generating an antisaccade (DeSouza et al., 2003), and selection of the correct response (Ettinger et al., 2008). The additional recruitment of adjacent regions in IFG and superior frontal gyrus may support inhibitory saccade control (Velanova et al., 2009) and antisaccade preparation (Brown et al., 2007). Similar circuitry has been reported for fMRI studies of response inhibition, working memory, and motor control in related CC paradigms such as Go/No-Go (Durstun et al., 2003) and Stop-Signal tasks (Pliszka et al., 2006). The greater brain activation in prefrontal structures in children with ADHD reported in the current study may have facilitated task performance that is comparable to the control group. The groups did not significantly differ on any of the antisaccade performance parameters, including percent of correct trials and their latencies. The observed mean percent correct responses are consistent with prior literature, although their latencies are longer and appear more variable (Aman et al., 1998; Mostofsky et al., 2001; Klein et al., 2002; Klein et al., 2003; Munoz et al., 2003; Sweeney et al., 2004; O'Driscoll et al., 2005; Hanisch et al., 2006; Rommelse et al., 2008). In adults with ADHD, an earlier fMRI investigation of antisaccade performance revealed that bilateral dlPFC response was greater during execution of correct antisaccade trials relative to the control group and suggested to offset inadequate task set activation during the preparation of these trials (Hakvoort-Schwerdtfeger et al., 2012).

The greater activation in right CN and lentiform nucleus in children with ADHD in the present study may have sustained an anticipatory response set (Rubia, 2011), response timing (Gagnon et al., 2002), and the cognitive and motor control required for saccadic eye movements based on contextual cues (Sweeney et al., 1996; Munoz and Everling, 2004) that is necessary for correct task performance. Greater activation in striatum has been reported

for other CC tasks, particularly those that relate to response inhibition and working memory typically involved in the voluntary control of behavior (Durstun et al., 2003; Niendam et al., 2012). We note that CN did not survive clustering in our sensitivity analyses; however, the consistency of this pattern suggests a lack of power due to reduced sample size rather than a medication- or disorder-specific effect. Providing further support, the CN cluster survived when a more relaxed cluster extent (260 vs 296 voxels) was used. An extensive literature has provided evidence that frontostriatal circuitry plays an essential role in CC which we replicated for antisaccade performance in children with ADHD.

Stimulant medication, which acts on fronto-striatal circuitry, is a potential mechanism for the greater antisaccade-related brain activation observed in the ADHD group. FMRI investigations using placebo-controlled stimulant medication designs have shown normalized or greater brain activation in children and youths with ADHD who received methylphenidate compared to unmedicated control groups in regions associated with antisaccade performance, particularly right dlPFC, IFG, and striatum. These studies have used CC paradigms (Rubia et al., 2011a; Rubia et al., 2011b), including related Go/No-Go tasks (Vaidya et al., 1998). Similar findings have been reported using functional near-infrared spectroscopy (Monden et al., 2012). Medication dose did not correlate with activation in either of the two regions in the current study and the data from the one unmedicated participant with ADHD are clustered with those from the medicated children with ADHD. Nevertheless, we cannot rule out an effect of medication, as the literature reports greater activation in fronto-striatal circuitry in response to stimulant medication. Extending our results, future investigations may employ a randomized, double-blind, placebo-controlled, cross-over stimulant medication paradigm in medication-naïve participants with ADHD compared to a control group to further characterize fronto-striatal circuitry associated with antisaccade performance in children with ADHD, and the effects of pharmacological treatment.

CC-related brain activation in the right IFG (Aron and Poldrack, 2005; Schulz et al., 2005; Durstun et al., 2006) and the middle frontal gyrus has been shown to be responsive to methylphenidate (Monden et al., 2012) for the performance on Go/No-Go tasks. We also observed activation in right IFG/middle frontal gyrus for the performance on a related antisaccade task in children with ADHD, a pattern that classified the children into their respective groups. The behavioral and neural correlates of antisaccade paradigms on- and offmedication may provide sensitivity and specificity for ADHD (the Combined Type in particular), and may be useful in the development of new pharmaceutical treatment approaches for the disorder (Sweeney et al., 2004; Hutton and Ettinger, 2006; Reilly et al., 2008).

Our results replicate and extend previous literature in important ways; however, there are also limitations to the current study. While we hypothesized that children with ADHD would show greater activation in dorsal anterior cingulate cortex compared to children in the control group, we did not observe a difference. The design of our antisaccade task alternating blocks of fixation with blocks of antisaccades perhaps invoked a steady task-set and reduced cognitive effort. Future research should employ event-related designs and antisaccade gap trials to elucidate differences in the neural circuitry that underlies the

regulation of CC in children with ADHD. Furthermore, four children in the ADHD group were reported to have comorbid disorders, including oppositional defiant disorder, depression, anxiety, and seizure disorders. Previous studies of CC (Slaats-Willemse et al., 2003), including antisaccade tasks (Karatekin, 2006), have comprised individuals with ADHD who have similar comorbidities. None of the children in our study were outliers with respect to their brain activation, antisaccade performance, or scores on the Cognitive Assessment System. This is consistent with the proposal that deficits in CC exist independently from mental health comorbidities (Nigg et al., 2005; Willcutt et al., 2005). Our sensitivity analyses provided further support. As comorbid disorders are common, the group in our study may be more representative of the community and allow generalization of our results (Spencer et al., 2007). In addition, the small sample size in our investigation could have produced atypical results of brain activation. However, location and pattern of brain activation replicate findings in the literature, spanning neural circuitry associated with the disorder, CC, and antisaccade paradigms.

A distinct contribution of this study to the pediatric antisaccade and ADHD literature pertains to the demographics of the two groups. Several antisaccade studies only include boys (Rothlind et al., 1991; Aman et al., 1998; Klein et al., 2002; O'Driscoll et al., 2005), and more importantly, black children appear to be either unrepresented or largely underrepresented (Habeych et al., 2006). Information on behavioral and neural correlates associated with antisaccade performance may shed light on the development and efficacy of treatment approaches in this population, including girls and black children.

4.1. Conclusion

In sum, the neural correlates associated with an antisaccade task in a community sample of children with ADHD demonstrated activation in fronto-striatal circuitry that is in line with previous neuroimaging studies of CC in children with ADHD and suggested to underlie comparable group performance. Brain activation differed in right-lateralized regions in dlPFC and CN with diagnosed children exhibiting greater activation in both. The pattern of brain activation in dlPFC and CN separated the groups in a taxonomic manner which suggests that antisaccade paradigms may provide sensitivity and specificity for ADHD, with implications in the development and improvement of pharmaceutical treatment in children with the disorder.

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Highlights

- There are few studies using antisaccade tasks in children with ADHD
- Antisaccade fMRI data are shown (11 children with ADHD, 91% medicated; 11 controls)
- Children with ADHD had greater brain activation with similar performance to controls
- This pattern separated the children into their respective groups in a taxonomic way
- Antisaccade tasks may be sensitive to ADHD and useful in pharmacological research

Fig. 1.

Between-group whole-brain mixed-effects analysis for the antisaccade vs. fixation contrast revealed two clusters of significantly greater brain activation in the ADHD group relative to the control group. Shown are t-values (threshold set at $p < 0.02$, family-wise error corrected, and with units indicated by the scale) displayed on axial slices (from top left $z = -4$ through bottom right $z = 32$, spacing = 4 mm). 1 = dorsolateral prefrontal cortex (dIPFC) and 2 = caudate nucleus (CN). The images are in radiological orientation (right hemisphere (R) on left side of image and left hemisphere (L) on right side of image). The background image is an average of T1-weighted scans of all participants in Talairach space.

Fig. 2.

Dots illustrate the means of brain activation in the two clusters that survived family-wise error correction performed on the mixed effects whole-brain analysis, dorsolateral prefrontal cortex (dlPFC) plotted against caudate nucleus (CN), for each individual in both ADHD and control groups. The data point indicated with an “x” represents the unmedicated child in the ADHD group. The crosses demarcate the mean of dlPFC and CN in each group with ellipsoids drawn 1 and 2 standard deviations around the mean.

Table 1

Characteristics of participants

	ADHD (n = 11)	Control (n = 11)	Student's t-tests ^a
Demographics			
Race (Black)	10 (1 White)	11	n/a
Body fat (%)	24.9 (10.1)	31.9 (6.5)	t(20) = -1.92, p = 0.07
Age (years)	10.4 (1.2)	9.6 (0.8)	t(20) = 1.98, p = 0.06
Female (n)	4	4	n/a
Left-handed (n)	2	2	n/a
Primary caregiver education ^b	5.4 (1.2)	4.4 (1.5)	t(20) = 1.72, p = 0.10
Cognitive Assessment System – Full scale	100.2 (9.0)	96.1 (9.0)	t(20) = 1.06, p = 0.30
ADHD medication			
On treatment (n)	10	n/a	n/a
Methylphenidate dose equivalent (mg)	25 (8.7)	n/a	n/a
Achenbach System of Empirically Based Assessment ^c			
Primary caregiver – Internalizing	64.2 (8.9)	n/a	n/a
Primary caregiver – Externalizing	58.8 (14.1)	n/a	n/a
Primary caregiver – Total	64.4 (10.8)	n/a	n/a
Teacher – Internalizing	52.9 (9.2)	n/a	n/a
Teacher – Externalizing	54.4 (6.9)	n/a	n/a
Teacher – Total	55.7 (7.2)	n/a	n/a
Vanderbilt ADHD Parent and Teacher Rating Scales ^d			
Primary caregiver – Combined	8.7 (4.8)	n/a	n/a
Teacher – Combined	3.1 (2.9)	n/a	n/a

Note: Demographic variables are mean and standard deviation (SD) unless otherwise noted. ADHD = attention-deficit/hyperactivity disorder.

^aThe assumption of homogeneity of variances was met ($\alpha = 0.05$).

^bLevel of education with 4 = high school and 5 = partial college.

^cT-scores.

^dCount of symptoms endorsed "often or very often" for combined inattention and hyperactive/impulsive items.

Table 2

Antisaccade task performance of participants

	ADHD (n = 11)	Control (n = 11)	Student's t-tests ^a
Correct trials (%)	46 (25)	47 (26)	t(20) = -0.09, p = .93
Correct reaction time (ms)	451 (135)	455 (91)	t(19) = -0.08, p = .93
Error reaction time (ms)	344 (97)	320 (58)	t(20) = 0.71, p = .49
Errors corrected (%)	62 (31)	74 (25)	t(20) = -1.00, p = .33
Error correction reaction time (ms)	313 (69)	315 (66)	t(19) = -0.07, p = .95

Note: Results are represented in mean and standard deviation (SD).

^a Having met the t-test assumption of equal variance as indicated by non-significant Levene's tests for equality of variances.

Table 3

Descriptive statistics of brain activation for the ADHD > Control contrast derived from the whole-brain mixed-effects analysis (family-wise error corrected)

Anatomic location	Hemisphere	Number of voxels	Coordinates (x y z)		
Dorsolateral prefrontal cortex, extending into inferior and superior frontal gyri	R	408	-42.3	-30.9	+27.7
Caudate nucleus, extending into lentiform nucleus	R	298	-12.6	-20.5	0.0

Note: Coordinates are in Talairach space and demarcate the center of mass of each cluster.