BRAIN ACTIVATION ASSOCIATED WITH ANTISACCADE PERFORMANCE IN CHILDREN WITH ADHD - A FUNCTIONAL MRI STUDY

by

NICOLETTE FRANÇOISE SCHWARZ

(Under the Direction of Jennifer E. McDowell)

ABSTRACT

Individuals with attention-deficit/hyperactivity disorder (ADHD) demonstrate deficits in cognitive control (CC). Using functional magnetic resonance imaging, patterns of brain activation associated with performance on an antisaccade task were examined in eleven predominantly black children with ADHD (10 medicated) who were matched to eleven typically developing black children. Results indicated significantly greater brain activation in two right-lateralized regions located mainly in dorsolateral prefrontal cortex and caudate nucleus in children with ADHD compared to children in the control group. Although comparable on behavioral measures, the groups differed in the recruitment of neural circuitry in support of task performance. Interestingly, the pattern of brain activation in these regions separated the participants into their respective groups, suggesting a role of antisaccade paradigms as a biomarker for the investigation of deficits in CC and associated neural correlates in children with ADHD.

INDEX WORDS: ADHD, cognitive control, antisaccade, fMRI, obesity, fitness, children

BRAIN ACTIVATION ASSOCIATED WITH ANTISACCADE PERFORMANCE IN CHILDREN WITH ADHD - A FUNCTIONAL MRI STUDY

by

NICOLETTE FRANÇOISE SCHWARZ

B.A., Northwestern University, 2007

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2013

BRAIN ACTIVATION ASSOCIATED WITH ANTISACCADE PERFORMANCE IN CHILDREN WITH ADHD - A FUNCTIONAL MRI STUDY

by

NICOLETTE FRANÇOISE SCHWARZ

Major Professor:	Jennifer E. McDowell
Committee:	Catherine L. Davis Brett A. Clementz

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
August 2013

ACKNOWLEDGEMENTS

I would like to thank my advisor for her support. I would also like to thank the other members of my committee, Dr. Brett Clementz and Dr. Catherine L. Davis for their valuable input. Furthermore, I would like to thank Cynthia E. Krafft, Lingxi Chi, and Qingyang Li for teaching me data collection and analysis procedures and Tram Ngoc Bao Van in assisting with analyses. Finally, I thank my mother and will patiently translate this work for her should she be patient enough to listen. This research was supported by the NIH (RO1 HL087923) and MCG Child Health Discovery Institute Advanced Pilot Award.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most pervasive neurodevelopmental disorder in childhood with reports suggesting a prevalence rate of approximately 5-12% in children worldwide (Association & DSM-IV., 1994; Biederman & Faraone, 2005; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). ADHD is diagnosed by developmentally atypical levels of inattention, hyperactivity and impulsivity, and for more than half of diagnosed children symptoms will persist into adulthood (Association & DSM-IV., 1994; Faraone, Biederman, & Mick, 2006). Individuals typically present with a combination of symptoms that are classified into a predominantly inattentive, predominantly hyperactive-impulsive, and a combined subtype. Comorbidities are common and include oppositional defiant disorder (ODD), conduct disorder, mood disorders, anxiety disorders, and learning disabilities (Faraone, et al., 2006; Rubia, 2011; Spencer, Biederman, & Mick, 2007). Like other mental disorders, ADHD is characterized by considerable heterogeneity in the nature of impairments that goes beyond the diagnostic symptoms and has ramifications in social, emotional, and cognitive domains. Reduced academic achievement, attenuated peer and family relations, lower occupational and socioeconomic status, increased involvement in traffic accidents and violations, and elevated rates of substance abuse are frequently reported (Barkley & Cox, 2007; Biederman & Faraone, 2005). These problems are associated with ADHD-related symptoms such as impulsivity and indicate a deficit in the voluntary control of behavior.

Cognitive control (CC) supports flexible behavior through coordinating a range of higher-order cognitive processes and is considered essential for adaptive functioning (Miller & Cohen, 2001). Working memory, action initiation, set switching, and response inhibition are all CC constructs necessary for voluntary behavior (Alvarez & Emory, 2006; Niendam, et al., 2012)

Worse performance across a range of CC paradigms has illuminated deficits in children with ADHD compared to typically developing children (TDC) (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). While weaknesses in CC are clearly documented so is a substantial overlap in task performance with that of TDC and suggestive of an underlying heterogeneous psychopathology that is manifested as CC deficits in subsamples of the disorder rather than being universal to all diagnosed individuals (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Willcutt, et al., 2005).

Stimulant medications such as methylphenidate (MPH) are shown to improve performance on tasks of motor control and cognition (Kempton, et al., 1999; Klein, Fischer, & Hartnegg, 2002; Posner, et al., 2011; Vaidya, et al., 1998) and reduce symptoms of ADHD (Faraone & Biederman, 2002; Faraone & Buitelaar, 2010). Stimulant medication is implicated in catecholaminergic neurotransmitter systems that are theorized to play a role in the neuropathophysiology of ADHD, especially dopaminergic pathways (Sonuga-Barke, 2005; Swanson, et al., 2007). The efficacy of MPH may stem, in part, from correcting alterations in dopamine (DA) transmission (Volkow, Wang, Fowler, & Ding, 2005). MPH blocks DA transporter (DAT), effectively preventing re-uptake of DA into the presynaptic neuron, increasing its synaptic availability, and therefore amplifying DA signal which may strengthen corticostriatal signals (Swanson, et al., 2007; Volkow, et al., 2005). In this way, administration of MPH is suggested to increase saliency of stimuli, supports formation of predictions about future outcomes, enhances motivation and interest to engage in tasks, increases attention and decreases distractibility, all of which improve CC-related functions. Structural magnetic resonance imaging studies have reported reduced volume (Valera, Faraone, Murray, & Seidman, 2007) and grey matter (Ellison-Wright, Ellison-Wright, & Bullmore, 2008) in right striatum in individuals with ADHD. MPH blocks DAT prominently in the striatum, a region associated with the neuropathophysiology of ADHD and CC (Volkow, et al., 2005).

The neural substrates of CC can be investigated with techniques such as functional magnetic resonance imaging (fMRI) which records changes in blood-oxygen-level-dependent signal considered a proxy for underlying brain activation (Ogawa, Lee, Kay, & Tank, 1990). Widespread circuitry with nodes in prefrontal cortex (PFC), including inferior-, middle-, and superior frontal gyri (IFG, MFG, SFG), anterior cingulate and parietal cortices, and subcortical structures such as striatum appear to be co-recruited in adults (Niendam, et al., 2012). The neural circuitry in support of CC in TDC is largely similar to that of adults but less well integrated (Casey, Tottenham, Liston, & Durston, 2005; Durston, et al., 2006; Houdé, Rossi, Lubin, & Joliot, 2010). Developmental shifts in the pattern of brain activation are characterized by diffuse activation that becomes fine-tuned in relevant neural systems and likely underlie improvements in task performance from childhood to adulthood.

The pattern of CC-related neural circuitry of individuals with ADHD resembles that of typically developing samples with differences emerging in regions such as MFG, IFG, SFG, and ACC, as well as striatum (Castellanos & Proal, 2011; Cortese, et al., 2012; Dickstein, Bannon, Castellanos, & Milham, 2006). While greater brain activation has been reported in some areas for several tasks (Cortese, et al., 2012; Dickstein, et al., 2006), the majority of studies show reduced activation in PFC, ACC, and/or striatum on paradigms of CC including Go/No-Go (Booth, et al., 2005), Attention Network Test (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006), Simon (Rubia, Halari, Cubillo, et al., 2011), and Mental Rotation (Silk, et al., 2005) tasks. Reduced brain activation in fronto-striatal circuitry is linked to difficulties with voluntary behavior and ADHD (Biederman & Faraone, 2005; Cubillo, Halari, Smith, Taylor, & Rubia, 2012). As such, tasks that contain volitional components may further elucidate the neuropathophysiology in ADHD.

Simple and effective models to examine both neural and behavioral correlates of CC in pediatric populations are available via well-studied eye movement paradigms such as antisaccade tasks (Hallett, 1978). An antisaccade requires the inhibition of a glance to a newly

appearing, prepotent visual stimulus in the periphery and a voluntary redirection of gaze to its mirror image location (i.e., same distance from center in the opposite direction). An initial glance (reflexive saccade) towards the stimulus represents an antisaccade error and may reflect problems with CC. Antisaccade performance is relatively stable, sensitive to different psychiatric populations, and can be quantified as percentage of antisaccade errors, proportion of errors corrected, and saccade latency (i.e., reaction time) for correct and error responses (Rommelse, Van der Stigchel, & Sergeant, 2008; Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004). Children with ADHD show worse performance on this task, including a greater number of antisaccade errors and longer and more variable antisaccade latency compared to TDC. Task performance of children with ADHD can illuminate the voluntary control of behavior and provide information on the integrity of associated neural correlates, such as PFC.

The neural circuitry underlying successful antisaccade performance in adults has been thoroughly described (Dyckman, Camchong, Clementz, & McDowell, 2007; Ettinger, et al., 2008; Gagnon, O'Driscoll, Petrides, & Pike, 2002; McDowell, Dyckman, Austin, & Clementz, 2008; O'Driscoll, et al., 2005). Included in this circuitry are regions in PFC, including frontal- (FEF) and supplementary (SEF) eyefields, and posterior parietal cortex (PPC), thalamus, and areas often identified with CC, such as dorsolateral PFC (dlPFC), ACC, and striatum (Krafft, et al., 2012; Munoz & Everling, 2004; Sweeney, Luna, Keedy, McDowell, & Clementz, 2007). Pediatric fMRI studies are less numerous and show that basic saccadic circuitry is established in childhood but appears less well integrated compared to adults (Fitzgerald, et al., 2008; Luna, et al., 2001; Velanova, Wheeler, & Luna, 2008; Velanova, Wheeler, & Luna, 2009). One of the few studies examining neural correlates of antisaccade performance in TDC reports greater brain activation in children's right dlPFC in comparison to adults and greater activation in striatum for both groups (Velanova, et al., 2008). The only fMRI study examining brain activation solely in TDC extended these findings, showing greater activation in right dlPFC and dACC when blocks of antisaccades were contrasted with blocks of prosaccades (Fitzgerald, et al.,

2008). To our knowledge, neural correlates of antisaccade tasks in children with ADHD have not been investigated using fMRI. Given that antisaccade tasks recruit neural circuitry associated with CC and worse performance of children with ADHD is indicative of deficits in CC, examining the neural correlates associated with this paradigm may provide further information on the neuropathophysiology in ADHD (Ettinger, et al., 2008).

Chronic disorders such as ADHD are affiliated with health complications that may have an influence on brain function and CC. For instance, elevated rates of overweight and obesity have been reported in this population (Altfas, 2002; Holtkamp, et al., 2004). A cross-sectional study in overweight and sedentary TDC related higher aerobic fitness to better cognitive performance and overweight and lower aerobic fitness to deficits in CC (Davis & Cooper, 2011; Holtkamp, et al., 2004). Another study in this population showed that participation in a 3-month aerobic exercise program improved CC in a dose-dependent manner, increased antisaccade-related activation in bilateral dlPFC and decreased in activation bilateral PPC (Davis, et al., 2011). As aerobic exercise appears to enhance CC and increase antisaccade-related brain activation in bilateral dlPFC in overweight and sedentary TDC, similar benefits may be derived in children with ADHD. A small body of literature investigated whether physical activity can improve cognitive and behavioral impairments in ADHD (Berwid & Halperin, 2012; Gapin, Labban, & Etnier, 2011; Halperin & Healey, 2011) and preliminary evidence indicates improved functioning in cognitive and behavioral domains in children who are diagnosed with ADHD (Gapin & Etnier, 2010; Verret, Guay, Berthiaume, Gardiner, & Béliveau, 2012) or display symptoms of ADHD (Smith, et al., 2013). While stimulant medication improves CC in many individuals with the disorder, physical activity may be a useful adjunct treatment approach.

The current investigation sought to explore neural circuitry associated with an antisaccade task in children with ADHD (who maintained their normal pharmacological treatment) as compared to a matched group of TDC. First, we hypothesize that children with ADHD will demonstrate reduced brain activation in dlPFC, dACC, and striatum that is related to

worse antisaccade performance. Second, it is hypothesized that measures of CC will be positively related to fitness and negatively related to adiposity in both the TDC and ADHD groups.

CHAPTER 2

METHODS

Participants

Eleven children diagnosed with ADHD were recruited from public schools around Augusta, GA. The diagnosis of ADHD for each child was confirmed by a developmental behavioral pediatrician (CHD) based on a clinical interview with the child and primary caregiver. Nine of the participants were diagnosed with the combined subtype, one with the inattentive subtype, and information for another participant was unavailable. Symptom severity was assessed by the primary caregiver and teachers using the Achenbach System of Empirically Based Assessment (ASEBA) (Achenbach & McConaughy, 2003) and the Vanderbilt ADHD Parent and Teacher Rating Scales (VAN) (Achenbach & McConaughy, 2003; Wolraich, Feurer, Hannah, Baumgaertel, & Pinnock, 1998; Wolraich, et al., 2003). Ratings on the ASEBA scales assessing Internalizing and Externalizing problems as well as the Total scale (Internalizing, Externalizing-, Social-, Thought-, and Attention problems) surpassed clinical significance ($T \geq 63$; standardized T score with mean of 50 and standard deviation (SD) of 10) as reported by primary caregivers and on the Total and Internalizing subscales reported by teachers. Primary caregivers and teachers also provided ratings on the VAN Combined scale (Inattention and Hyperactivity/Impulsivity), indicating clinically significant symptoms as those ratings represent a count of symptoms endorsed "often or very often". See Table 1 for more information. As part of study inclusion, ten children were verified on stable medication for ADHD for at least one month prior to testing. One participant, who was added to the current study from a larger control sample (described below) after discovery of a previous ADHD diagnosis, did not take medication. Methylphenidate dose equivalents were calculated by a developmental behavioral pediatrician (CHD) according to literature and medication guides for nine participants (one

participant took Tenex for which no adequate comparison could be made). For two children, parents reported co-morbid ODD and depression. One of these children was also indicated to have an anxiety disorder and complex partial seizures. Another child had a history of seizures and an additional child had a tic disorder (eye blink).

Participants in the control group were 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., in press). Exclusion criteria for the control group included severe vision problems and a history of neurological or psychiatric disorders. Children in both groups were 8-11 years old and predominantly black (except for one child in the ADHD group), matched on percent body fat, age, gender, and handedness, and did not differ in socioeconomic status as indexed by the level of education of the primary caregiver or cognitive ability as assessed with performance on the Full Scale score of the Cognitive Assessment System (described below). While children in the ADHD and control group were matched on percent body fat, they differed on BMI z-scores, with the ADHD group having lower BMI values than the control group. Percent body fat is a more sensitive measure of body composition than BMI z-scores. The groups differed on levels of fitness where children with ADHD (data available for n=9/11 participants) demonstrated higher peak VO_2 than children in the control group. Sample characteristics are provided in Table 2. Children and parents provided informed assent and consent. All participants were offered gift cards worth up to $50 after completing testing. Teachers received $25 for providing behavior ratings for each child with ADHD, and $5 for each child in the control group. The study was reviewed and approved in accordance with the Human Assurance Committee of the Georgia Regents University (GRU). The study took place at GRU.

Procedures

Health, Cognitive, and Symptom Measures

Health Measures

Health and fitness measures were obtained from each child. All children in the control group had a Body Mass Index (BMI) ≥ 85th percentile. While four participants in the ADHD group had a BMI of ≥ 85th percentile, this criterion was relaxed to include children with lower BMI in order to complete recruitment. Percent body fat, a more sensitive index of body composition, was measured with a dual-energy x-ray absorptiometry scan using a Discovery W (Hologic Inc., Bedford, MA). Aerobic fitness (VO_2 peak, ml/kg/min) was measured with a treadmill test (Modified Balke Protocol for Poorly Fit Children; Cardiac Science TM65 treadmill, Bothell, WA with Parvo Medics TrueOne 2400 Metabolic Measurement System, Sandy, UT) (Medicine, 2000).

Cognitive Measures

Participants in both groups completed the Cognitive Assessment System (CAS) (Naglieri, Goldstein, Iseman, & Schwebach, 2003) which is a standardized individual assessment of children's cognitive abilities. The Full Scale score takes into account scores from four test scales: Planning (developing strategies to solve problems), Attention (selectively attending to specific stimuli while inhibiting attention to competing stimuli), Simultaneous (integrating separate verbal and non-verbal items into single groups), and Successive Processing (repeating/comprehending sequences of items), each of which includes 3 subtests. The normative mean for Standard Scores on all scales of the CAS is 100, with a SD of 15.

The Behavioral Rating Inventory of Executive Function (BRIEF) was completed by up to four teachers per child (Gioia, Isquith, Guy, & Kenworthy, 2000). This questionnaire provides a standardized measure of CC behaviors in the school environment, with higher scores reflecting worse performance (i.e., a higher degree of CC dysfunction). Of interest were the Behavioral Regulation Index, Metacognition Index, and the Global Executive Composite (which comprises the two prior indices). The BRIEF was completed by an average of 2.6 (SD=1.1) teachers for the ADHD group and 1.1 (SD=0.3) teachers in the control group, with significantly

more teachers providing ratings for the ADHD group than control group ($t(19)=4.48$, $p<.05$). The normative mean for Standard T Scores on all scales of the BRIEF is 50, with a SD of 10.

Data Collection and Analyses

Data Collection

Functional Magnetic Resonance Imaging Acquisition

Images were acquired on a GE Signa Excite HDx 3 Tesla MRI system (General Electric Medical Systems, Milwaukee, WI) at MCG. For all MRI scans, head positions were stabilized with a vacuum pillow and/or foam padding. High-resolution T1-weighted structural brain images were acquired using a 3D FSPGR protocol (repetition time (TR)=9.436 ms, echo time (TE)=3.876 ms, flip angle=20°, field of view (FOV)=240 x 240 mm, acquisition matrix 512 x 512, 120 contiguous axial slices, slice thickness=1.3 mm, total scan time=3 min, 33 sec). A functional scan of a single blocked antisaccade run (TR=3000 ms, TE=35 ms, flip angle=90°, FOV=240 x 240 mm, acquisition matrix=128 x 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.

Antisaccade Task

The task was presented in a blocked design alternating blocks of simple fixation (7 blocks; 24 sec each) and antisaccade trials (6 blocks, 24 sec each). During fixation blocks, participants were asked to look at a target (a blue filled circle) at central fixation. During each antisaccade block, 8 trials were presented, each lasting 3 seconds (48 total trials across the run; Figure 1). A trial began with a blue filled circle at central fixation (1600 milliseconds). Then fixation was extinguished and a cue presented in the periphery (1400 ms; ±10° 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 (opposite side of the screen, the same distance from the center). Prior to entering the scanner, participants rehearsed the task using flash cards and were evaluated for understanding of task requirements. Participants also listened to pre-recorded MRI sounds via earphones and practiced laying still before entering the scanner to assist with acclimation to the MRI environment.

Visual stimuli were generated using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) 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. Prior to the antisaccade task, eye position was calibrated.

Individual antisaccade trials were scored as a correct or an error response based on eye direction relative to target direction. Error corrections also were quantified and consisted of an initial incorrect movement toward the target which was then self-corrected by the participant to make the appropriate response. Latencies for the correct, error and error correction responses were generated using MATLAB (The Mathworks Inc., Natick, MA) 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, when a saccade was less than 10% of the distance to the target, when there were blinks before saccades, if there was no response, or if the data were too noisy to be scored. Eye movements were recorded for all participants in both groups. On average, 59% (range 22 - 94%) of trials were scorable in the ADHD group and 57% (range 35 - 81%) in the control group.

Analyses

Cognitive and Antisaccade Performance Data Analyses

Analysis was conducted in SPSS Version 20 (IBM, Armonk, NY). Independent-sample *t*-tests were performed to investigate whether there were significant between-group differences in

cognitive measures (CAS and BRIEF) and antisaccade performance. Alpha levels were set at p=.05.

MRI Data Analysis

All fMRI analyses and statistics were conducted using Analysis of Functional Neuroimages (AFNI) (Cox, 1996). For single subject analyses, individual slices of the functional run were time-shift and outliers computed for inclusion in later analysis. The individual's T1-weighted structural MR image was transformed into a standardized space based on a publicly available template (TT_N27; offered in AFNI) in Talaraich space. Each volume in the functional run was registered to the third volume to correct for head movement. The functional run was then resampled to 1.75 x 1.75 x 1.75 mm and aligned to the standardized T1-weighted image. A 4-mm full-width at half-maximum (FWHM) Gaussian filter was applied and time series were scaled to a mean of 100.

Following preprocessing, the hemodynamic response function (HRF) was represented convolving the stimulus timing of antisaccade blocks with a gamma variate. The HRF was then entered into a generalized least-squares model together with information on censored TRs (e.g., motion, outliers), six motion parameters (rotation and displacement in each of 3 planes), and nuisance regressors detrending for linear, quadratic, and cubic drift. Specifically, generalized linear regression on the convolved HRF in each voxel was performed and the temporal autocorrelation in the residuals estimated with an autoregressive moving average model (ARMA (1,1)) using restricted maximum likelihood.

To identify basic neural circuitry associated with the antisaccade task, a one-sample *t*-test of the task-related beta coefficients collapsed across groups was performed in AFNI. Significant group differences in brain activation were investigated by performing a whole-brain, mixed-effects analysis, modeling both between- and within-subject variability (Chen, Saad, Nath, Beauchamp, & Cox, 2012). In this approach, within-subject variability was estimated using the *t*-values of the task-related beta coefficient (e.g., larger *t*-values indicate less variability and

associated beta coefficients receive more weight). Participants were treated as random effects. To protect against false positives, resulting *t*-maps were thresholded using a family-wise error correction as follows: smoothness in the data was estimated from the residuals of the individual time series fit taking both inherent smoothness in the data and the applied FWHM kernel into account (Ward, 2000). Then Monte Carlo simulations with 10,000 iterations were conducted on the whole brain to obtain a nearest-neighbor cluster threshold with a connectivity radius of 2.5 mm. Based on these simulations, a family-wise alpha of 0.02 (two-tailed) was preserved with three-dimensional clusters comprising a minimum volume of 296 voxels. Group differences in average motion were investigated with independent *t*-tests (alpha set at p=.05) in SPSS Version 20 (IMB, Armonk, NY) using the absolute values of motion generated from volume registration parameters at each time point.

Correlations of Brain Activation, Cognitive, and Health Measures

Pearson's correlation coefficient analyses were performed in SPSS to investigate possible relationships between brain activation and measures of CC as well as relationships between measures of health and measures of CC. In the ADHD group, an association of brain activation and medication dose was examined. Alpha levels for all tests were set at p=.05.

Table 1. ADHD Symptom Severity.

Symptom Severity in the ADHD group		
	Primary Caregiver	***Teacher***
ASEBA - Total	60%	20%
ASEBA - Internalizing	70%	10%
ASEBA - Externalizing	60%	0%
VAN - Total	8.7 (4.8)	3.1 (2.9)

Achenbach System of Empirically Based Assessment (ASEBA): percents indicate ratings that exceed the clinically significant threshold (T ≥ 63). Vanderbilt Assessment Scale (VAN): mean and SD of items endorsed "often or very often".

Table 2. Characteristics of Participants.

		ADHD group	***Control group***
	N	11	11
Demographics	Female	4	4
	Age (years)	10.4 (1.2)	9.6 (0.8)
	Race (Black)	10 (1 White)	11
	Left-handed	2	2
	Primary Caregiver Education°	5.4 (1.2)	4.4 (1.5)
	ADHD Medication Status	10	n/a
	Methylphenidate Dose Equivalent (mg)	25 (8.7)	n/a
Health	Body Fat (%)	25.9 (10.2)	31.5 (6.7)
	BMI z-score*	0.1 (1.5)	1.9 (0.4)
	VO_2 (ml/kg/min)^ *	36.3 (5.1)	30.8 (3.5)
Cognitive Assessment System	Full Scale	100.2 (9.0)	96.1 (9.0)
	Planning	96.6 (11.8)	94.5 (12.3)
	Attention	100.5 (11.5)	94.6 (5.9)
	Simultaneous Processing	105.5 (11.2)	100.3 (11.2)
	Successive Processing	98.5 (9.5)	99.9 (8.5)
Behavioral Rating Inventory of Executive Function	Global Executive Composite^{+}	63.2 (16.8)	52 (10.9)
	Behavioral Regulation Index^{+}	61.9 (15.9)	51.7 (10.3)
	Metacognition Index^{+}	62.3 (16.5)	50.9 (11.2)
Antisaccade Performance	Correct Trials (%)	46 (25)	50 (25)
	Correct Reaction Time (ms)	410 (187)	444 (90)
	Error Reaction Time (ms)	344 (97)	341 (58)
	Errors Corrected (%)	62 (31)	76 (26)
	Error Correction Reaction Time (ms)	284 (115)	297 (47)

Mean and SD where applicable. * $p<.05$. $^{+}$ missing data of one individual in the ADHD group.

^ missing data of two individuals in the ADHD group. ° level of education with 4=high school and 5=part college.

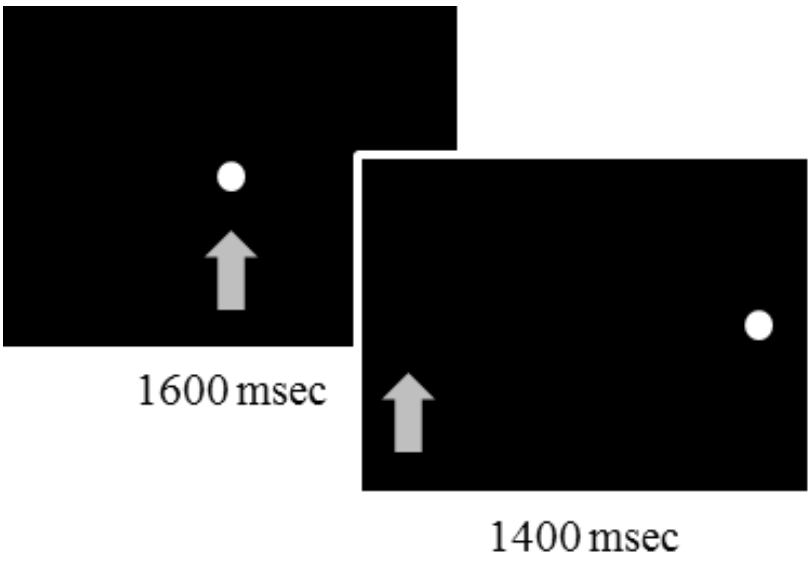

Figure 1. Antisaccade Task. The participant was instructed to fixate on the cue when it was in the middle of the screen. When the cue appeared at a peripheral location, the participant was instructed to the mirror image location (opposite side of the screen, the same distance from center). The arrow did not appear on the screen but is shown in this figure to illustrate correct eye position.

CHAPTER 3

RESULTS

Cognitive and Antisaccade Performance Measures

Performance on the test scales of the CAS did not differ between the groups nor did they differ on any of the antisaccade performance parameters (see Table 1).

Antisaccade Imaging Results

Expected saccadic circuitry, including areas that support vision, visuo-spatial attention, inhibitory control, saccade generation, and motor regions, was revealed performing a one-sample *t*-test collapsed across groups contrasting antisaccade with fixation blocks (Figure 2) (Ettinger, et al., 2008). Included are bilateral FEF, SEF, PPC, thalamus, as well as dlPFC, ACC, and striatum.

Significant group differences in brain activation were investigated by applying the cluster threshold described above on the *t*-maps obtained from the whole-brain mixed-effects analysis and revealed two clusters that differed between groups. The first cluster comprises right dlPFC, extending into IFG and SFG. The second cluster comprises right caudate nucleus (CN), extending into lentiform nucleus (LN). Children with ADHD demonstrated greater brain activation compared to the control group in both of these regions (Figure 3). See Table 3 for descriptive statistics and Figure 4 for the group means of brain activation in both clusters.

There was no region showing greater brain activation in the control group compared to the ADHD group. No significant group difference in activation in dACC was detected. In the ADHD group, stimulant medication dose did not correlate with brain activation in either cluster. As for between group analysis, independent sample *t*-tests verified that the groups did not significantly differ in average motion of participants (all motion parameters $p>.31$; absolute average motion < 2.2 mm in any of the three planes for all participants).

In order to investigate an association of brain activation between dlPFC and CN, correlation analyses were performed. Results show that 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 taxonic manner (Figure 5).

Correlations of Brain Activation, Cognitive, and Health Measures

Correlation analyses between brain activation in dlPFC and CN with scales of the CAS did not yield significant results in either group. Scores on some CAS scales were associated with obesity and fitness, however, in the ADHD group. Higher scores on the Attention scale were associated with lower percent body fat and greater fitness (i.e., higher VO_2 max). In addition, higher scores on the Planning scale were associated with greater fitness. No significant correlations between health and fitness measures and brain activation variables emerged in the control group.

Table 3. Descriptive Statistics of Brain Activation.

Brain Activation		
	Number of Voxels	***Coordinates of Center of Mass (x, y, z)***
1. R Dorsolateral Prefrontal Cortex, Extending Into Inferior and Superior Frontal Gyri	408	-42.3 -30.9 +27.7
2. R Caudate Nucleus, Extending Into Lentiform Nucleus	298	-12.6 -20.5 0.0

Number of voxels and coordinates of center of mass of each cluster derived from the whole-brain, mixed-effects analysis. R=right hemisphere.

Table 4. Correlations of Health Measures with Scales of the Cognitive Assessment System.

		ADHD	***Control***	***ADHD***	***Control***
Health and fitness		Body fat (%)		VO_2* (ml/kg/min)	
CAS	Plan	*n/s*	*n/s*	*r*(9)=.658, p=.05	*n/s*
	Attention	*r*(11)=-.626, p=.04	*n/s*	*r*(9)=.709, p=.03	*n/s*
	Simultaneous Processing	*n/s*	*n/s*	*n/s*	*n/s*
	Successive Processing	*n/s*	*n/s*	*n/s*	*n/s*

CAS=Cognitive Assessment System. * denotes missing data of two individuals in the ADHD group.

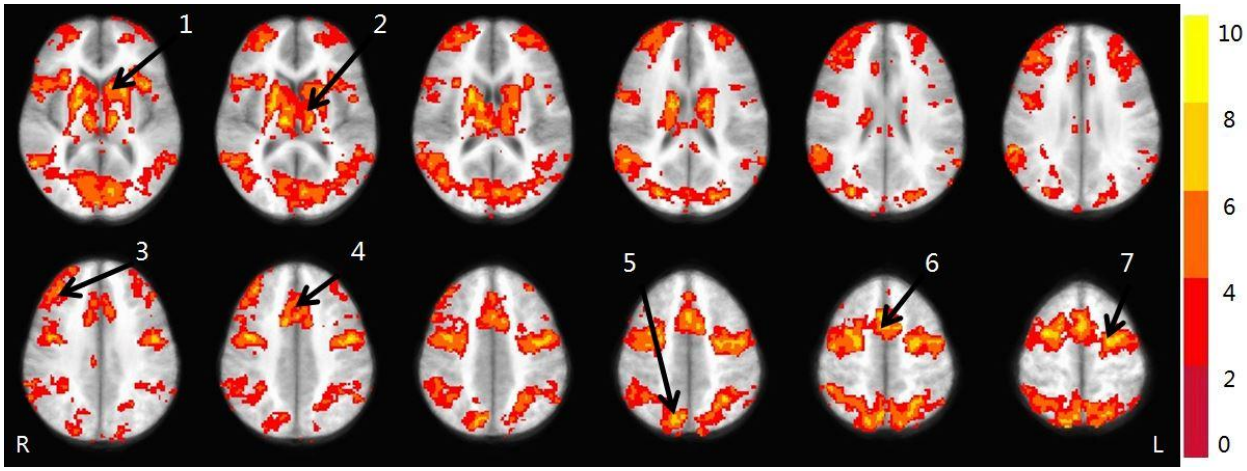

Figure 2. General Antisaccade Circuitry (Antisaccade > Fixation). Axial slices (top left z=7 through bottom right z=51, spacing=4mm) displaying significant antisaccade-related activation collapsed across the groups with warmer colors indicating greater brain activation (only positive *t*-values are shown at p=.05, uncorrected, *t*-values are indicated by the scale). 1=striatum, 2=thalamus, 3=dorsolateral prefrontal cortex, 4=anterior cingulate cortex, 5=posterior parietal cortex, 6=supplementary eye field, 7=frontal eye fields. The background image is an average of T1-weighted images of all participants in TLRC space.

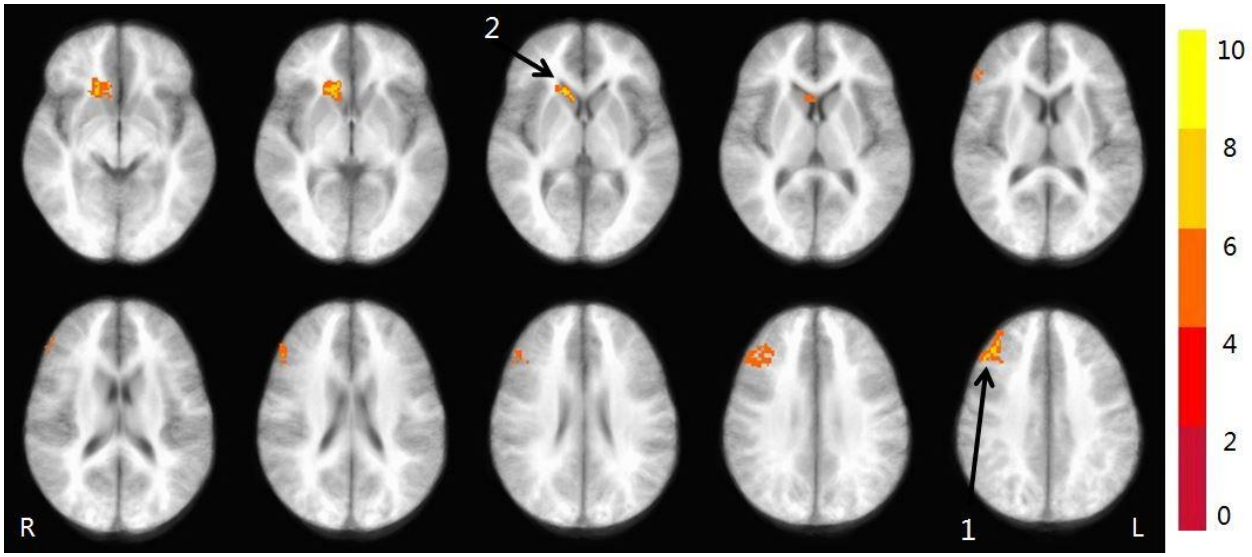

Figure 3. Whole-Brain Between-Group Comparison (Antisaccade > Fixation). Axial slices (top left z=-4 through bottom right z=32, spacing=4mm) displaying two clusters with significantly greater activation in the ADHD group compared to the control group with warmer colors indicating greater brain activation (*t*-values are shown at p=.02, corrected, *t*-values are indicated by the scale). 1=dorsolateral prefrontal cortex, 2=caudate nucleus. The background image is an average of T1-weighted images of all participants in TLRC space.

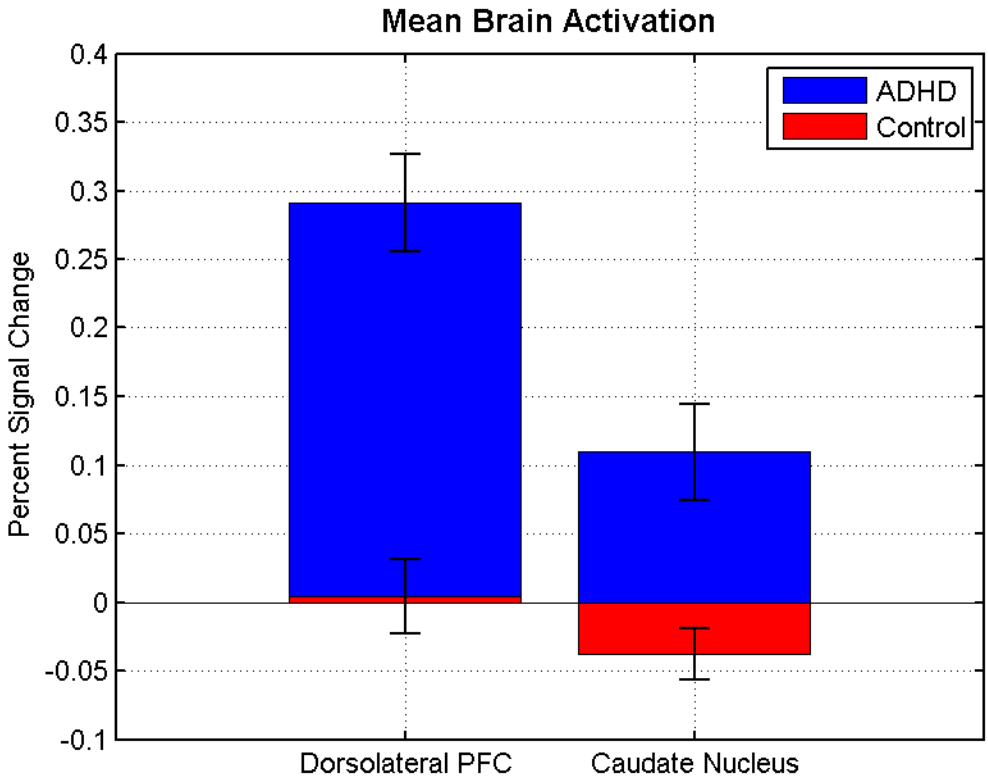

Figure 4. Group Mean Brain Activation. Mean brain activation based on percent signal change for the antisaccade > fixation contrast.

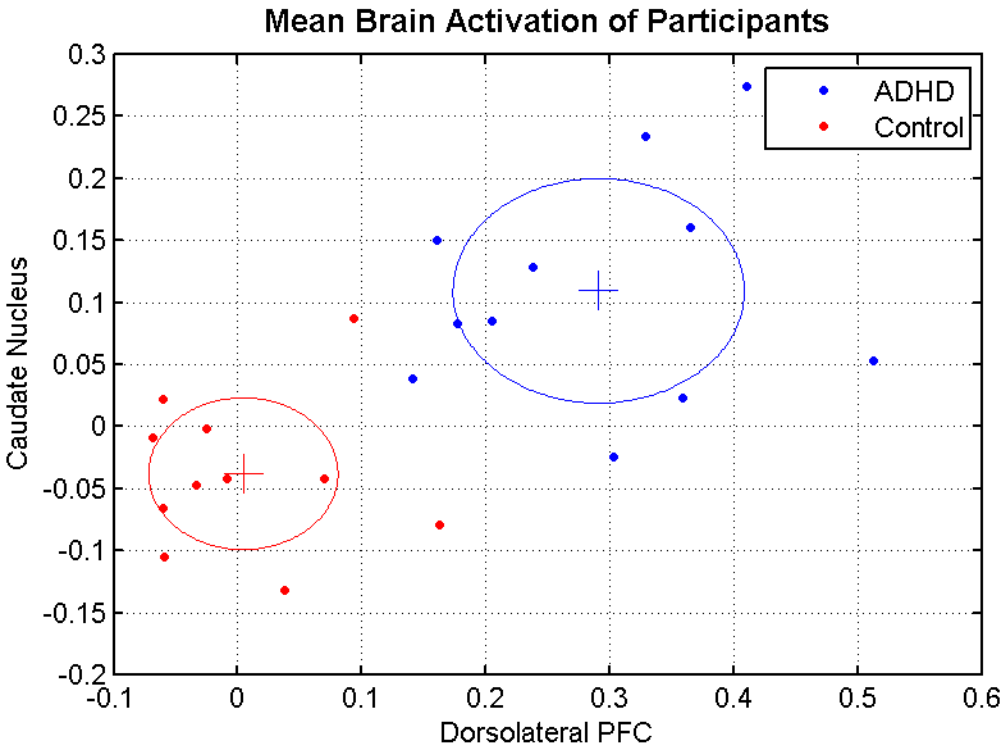

Figure 5. Individual Mean Brain Activation. Dots denote the means of brain activation in dorsolateral prefrontal cortex plotted against caudate nucleus for each individual in both groups. Means were obtained from the whole-brain between-group analysis. The cross demarcates the mean of dlPFC and CN in each group with an ellipsoid drawn one SD around the mean.

CHAPTER 4

DISCUSSION

The present study investigated whether children with ADHD differed in antisaccade-related brain activation compared to TDC. Collapsed across groups, typical brain activation patterns were observed in regions including FEF, SEF, PPC, and thalamus as well as dlPFC, ACC, and striatum (Luna, et al., 2001; Velanova, et al., 2008). In comparison to the TDC and contrary to our hypothesis, medicated children with ADHD demonstrated greater brain activation in two clusters in prefrontal and striatal regions. The first cluster is located mainly within the right dlPFC, and extending into IFG and SFG. The second cluster is located mainly in the right CN and extending into LN. The right-lateralization of neural activation in these regions is consistent with previous studies employing antisaccade tasks (McDowell, et al., 2002) as well as other paradigms associated with CC (Garavan, Ross, & Stein, 1999).

The locations of brain activation presented here fit well with the literature on neural correlates of antisaccade and other CC paradigms. Greater activation in dlPFC is affiliated with general task control over inhibition of reflexive saccades (Pierrot‐Deseilligny, et al., 2003), preparatory set prior to generating an antisaccade (DeSouza, Menon, & Everling, 2003), and selection of correct responses (Ettinger, et al., 2008). The additional recruitment of adjacent regions in SFG and IFG may be supportive of antisaccade preparation (Brown, Vilis, & Everling, 2007) and inhibitory saccade control (Velanova, et al., 2009; Walker, Husain, Hodgson, Harrison, & Kennard, 1998). The role of right IFG in inhibitory control has been emphasized (Aron & Poldrack, 2005) and suggested as a neurofunctional biomarker in medicated children with ADHD (Monden, et al., 2012). Similar circuitry as observed in the current study has been reported for fMRI studies of response inhibition, working memory, and motor control in related

CC paradigms such as Go/No-Go (Casey, et al., 1997; Durston, et al., 2003) and Stop-Signal tasks (Pliszka, et al., 2006).

The greater activation in right CN and LN in the ADHD group may have sustained an anticipatory response set (Luna & Sweeney, 2004), response timing (Gagnon, et al., 2002), preparation of antisaccades (Hakvoort Schwerdtfeger, et al., 2013), and the cognitive and motor control required for saccadic eye movements based on contextual cues (Munoz & Everling, 2004; Sweeney, et al., 1996) that is necessary for 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 (Durston, et al., 2003; Niendam, et al., 2012). An extensive literature has provided evidence that fronto-striatal circuitry plays an essential role in CC which we replicated for antisaccade performance in medicated children with ADHD.

While we hypothesized that TDC would show greater activation in dACC compared to children with ADHD, we did not observe a group difference. A role of conflict monitoring between simultaneous and competing response options has been ascribed to greater activation in dACC and adjusted task performance (C. Carter & Veen, 2007; C. S. Carter, et al., 1998). Greater activation in this region was reported for correct and error antisaccade trials, consistent with a conflict monitoring function between reflexive versus voluntary responses that are inherent in antisaccade task design (Polli, et al., 2005; Velanova, et al., 2008). The degree of conflict imposed by task demand may have precluded group differences in dACC activation observed in the current investigation. Antisaccade paradigms that vary in degrees of conflict may elucidate neural circuitry underlying the regulation of CC allocation in children with ADHD compared to TDC.

Across groups, behavioral measures of antisaccade performance did not differ. The greater brain activation in prefrontal structures in children with ADHD may have facilitated task performance that is comparable to TDC. A prior fMRI investigation of antisaccade performance

in adults with ADHD revealed that bilateral dlPFC response was reduced during preparation and greater during execution of correct antisaccade trials in comparison to the control group (Hakvoort Schwerdtfeger, et al., 2013). Increased cognitive effort could be a source for greater activation in dlPFC and necessary to counteract reflexive saccades that may arise from inadequate preparatory set due to reduced activation in this region. The block design we employed did not allow an investigation of brain activation for correct and error trials separately, as such, future research should dissociate the neural circuitry associated with the preparation and execution of antisaccade trials to illuminate increased CC effort at the level of brain function.

Stimulant medication, which acts on fronto-striatal circuitry associated with CC, may be another mechanism for the observed greater antisaccade-related brain activation in our medicated ADHD group. FMRI investigations have shown patterns of increased brain activation in youths with ADHD off and on medication in regions associated with antisaccade performance, particularly right dlPFC, IFG, and striatum, on Go/No-Go tasks (Monden, et al., 2012; Vaidya, et al., 1998) and other CC paradigms (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011). While medication dose did not correlate with activation in either of the two regions in the current study, our findings are reflective of the literature reporting greater activation in fronto-striatal circuitry in response to stimulant medication.

Brain activation in dlPFC and CN observed here showed an interesting pattern of separating the groups in a taxonic manner; specifically, mean brain activation in both regions was of predominantly greater magnitude in the ADHD group compared to the control group. The identification of neuropsychological measures that provide sensitivity and specificity to CC deficits and alterations in related neural circuitry has important implications in the early diagnosis and improvement of treatment outcome in children with ADHD. Antisaccade tasks involve a direct stimulus-response relationship with eye movements representing neurophysiological indices of directly targeted brain functions or cognitive systems (Reilly,

Lencer, Bishop, Keedy, & Sweeney, 2008). Performance parameters can be reliably measured, quantified, and manipulated; all of which are features that make this task a potential candidate as a biological marker (biomarker). Biomarkers are typically considered physiological processes that can be measured in-vivo and provide information on a disease state or pharmacologic intervention (Schmidt, Shelton, & Duman, 2011).

Antisaccade performance as an oculomotor biomarker may be useful in the development, monitoring, and/or selection of pharmacological treatments that target and mitigate CC deficits in the disorder (Reilly, et al., 2008) as stimulant medication was shown to improve task performance in adolescents with ADHD (Klein, et al., 2002). Patterns of brain activation may serve as functional biomarker for drug monitoring in regions associated with antisaccade performance, such as right IFG and MFG. A previous study demonstrated normalized brain activation in these regions with administration of stimulant medication for the performance of a Go/No-Go task in children with ADHD compared to a control group (Monden, et al., 2012). We also report right IFG/MFG as well as a pattern of brain activation that classified the children into their respective groups. The children with ADHD in our study were medicated and performed an antisaccade task which is similar to Go/No-Go paradigms. Response inhibition is a component of antisaccade performance and may serve as a diagnostic biomarker as it is suggested to be a potential cognitive endophenotype (intermediary between behavior and genetic susceptibility for the disorder) for ADHD (Aron & Poldrack, 2005; Slaats-Willemse, Swaab-Barneveld, De Sonneville, Van Der Meulen, & Buitelaar, 2003). A single biomarker is unlikely to provide sensitivity and specificity for ADHD but a group of diagnostic and treatment biomarkers may increase clinical helpfulness (Schmidt, et al., 2011). As such, antisaccade paradigms may be useful aiding diagnosis of ADHD and monitor treatment in medicated children as well illuminating CC and genetic dispositions to the disorder.

Other explanations of our findings should be considered. Deficits in CC are not universal to individuals with ADHD as many perform similar to control participants (Castellanos, Sonuga-

Barke, Milham, & Tannock, 2006; Nigg, et al., 2005; Sonuga-Barke, 2005). Both groups showed a large number of antisaccade errors and scored at (ADHD) or below (control) average on the CAS. Ratings on the BRIEF suggested deficits in CC in TDC. In sedentary and overweight TDC, previous research reported lower levels of aerobic fitness to correspond to worse CC (Davis & Cooper, 2011). While the groups in the current study were matched on percent body fat, children in the ADHD group were fitter than the children in the control group. We cannot rule out that greater aerobic fitness in the ADHD group has supported better CC and greater brain activation, or conversely, that lower aerobic fitness has impaired CC in the lesser fit control group.

Our results provide interesting approaches for future research to isolate the effects of increased cognitive demand, stimulant medication, and fitness on fronto-striatal circuitry associated with CC and antisaccade performance in children with ADHD. An approach to this may incorporate an extended, event-related antisaccade task in combination with a randomized, double-blind, placebo-controlled, cross-over stimulant medication paradigm in medication-naive participants with ADHD and a control group matched on adiposity and fitness. As aerobic fitness interventions have been linked to improved task performance and augmented neural correlates associated with CC in TDC, children treated for ADHD who maintain residual deficits in CC may benefit from aerobic exercise.

While our results are consistent with previous literature, there are limitations to the current investigation. Four children in the ADHD group were reported to have comorbid disorders, including ODD, depression, anxiety, and seizure disorders. However, none of these children were outliers with respect to their brain activation, antisaccade performance, or scores on the CAS which is consistent with the proposal that comorbidities may only have a limited effect as deficits in CC seem to exist independently (Cortese, et al., 2012; Nigg, et al., 2005; Willcutt, et al., 2005). In general, individuals with ADHD commonly present with comorbid disorders and as such, the sample in our study may be representative of the community and

approximate more naturalistically a given population of individuals with ADHD. In addition, the small sample size in our investigation could have produced atypical results of brain activation. However, location and pattern replicate findings in the literature, spanning neural circuitry associated with the disorder, CC, and antisaccade paradigms.

Conclusions

The neural correlates associated with an antisaccade task in a community sample of medicated children with ADHD demonstrated activation in fronto-striatal circuitry that is suggested to underlie comparable group performance. Brain activation differed in right-lateralized clusters in dlPFC and CN with diagnosed children exhibiting greater activation in both. We demonstrated atypical neural circuitry in line with previous neuroimaging studies of CC in participants with ADHD. An interesting pattern emerged when mean brain activation in dlPFC was compared with that of CN in that it separated the groups in a taxonic manner that may provide vantage points of antisaccade paradigms for investigations of biomarkers, drug development, and adjunct treatment approaches in medicated children with ADHD.

REFERENCES

Achenbach, T. M., & McConaughy, S. (2003). The Achenbach system of empirically based assessment. *Handbook of psychological and educational assessment of children: Personality, behavior, and context, 2*, 406-432.

Altfas, J. R. (2002). Prevalence of attention deficit/hyperactivity disorder among adults in obesity treatment. *BMC psychiatry, 2*(1), 9.

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology review, 16*(1), 17-42.

Aron, A. R., & Poldrack, R. A. (2005). The Cognitive Neuroscience of Response Inhibition: Relevance for Genetic Research in Attention-Deficit/Hyperactivity Disorder. [doi: 10.1016/j.biopsych.2004.10.026]. *Biological Psychiatry, 57*(11), 1285-1292.

Association, A. P., & DSM-IV., A. P. A. T. F. o. (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV*: Amer Psychiatric Pub Inc.

Barkley, R. A., & Cox, D. (2007). A review of driving risks and impairments associated with attention-deficit/hyperactivity disorder and the effects of stimulant medication on driving performance. *Journal of safety research, 38*(1), 113-128.

Berwid, O. G., & Halperin, J. M. (2012). Emerging Support for a Role of Exercise in Attention-Deficit/Hyperactivity Disorder Intervention Planning. *Current psychiatry reports, 14*(5), 543-551.

Biederman, J., & Faraone, S. V. (2005). Attention-deficit hyperactivity disorder. *Lancet, 366*(9481), 237-248.

Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D., et al. (2005). Larger deficits in brain networks for response inhibition than for visual selective

attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry, 46*(1), 94-111.

Brown, M. R. G., Vilis, T., & Everling, S. (2007). Frontoparietal Activation With Preparation for Antisaccades. *Journal of Neurophysiology, 98*(3), 1751-1762.

Carter, C., & Veen, V. (2007). Anterior cingulate cortex and conflict detection: An update of theory and data. *Cognitive, Affective, & Behavioral Neuroscience, 7*(4), 367-379.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior Cingulate Cortex, Error Detection, and the Online Monitoring of Performance. *Science, 280*(5364), 747-749.

Casey, B. J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain: what have we learned about cognitive development? [doi: 10.1016/j.tics.2005.01.011]. *Trends in Cognitive Sciences, 9*(3), 104-110.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., et al. (1997). A Developmental Functional MRI Study of Prefrontal Activation during Performance of a Go-No-Go Task. [doi: 10.1162/jocn.1997.9.6.835]. *Journal of Cognitive Neuroscience, 9*(6), 835-847.

Castellanos, X. F., & Proal, E. (2011). Large-scale brain systems in adhd: beyond the prefrontal–striatal model. *Trends in Cognitive Sciences*.

Castellanos, X. F., Sonuga-Barke, E. J. S., Milham, M. P., & Tannock, R. (2006). Characterizing cognition in ADHD: beyond executive dysfunction. [doi: 10.1016/j.tics.2006.01.011]. *Trends in Cognitive Sciences, 10*(3), 117-123.

Chen, G., Saad, Z. S., Nath, A. R., Beauchamp, M. S., & Cox, R. W. (2012). FMRI group analysis combining effect estimates and their variances. [doi: 10.1016/j.neuroimage.2011.12.060]. *NeuroImage, 60*(1), 747-765.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., et al. (2012). Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies. *American Journal of Psychiatry*.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research, 29*(3), 162-173.

Cubillo, A., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). 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. [doi: 10.1016/j.cortex.2011.04.007]. *Cortex, 48*(2), 194-215.

Davis, C. L., & Cooper, S. (2011). Fitness, fatness, cognition, behavior, and academic achievement among overweight children: Do cross-sectional associations correspond to exercise trial outcomes? [doi: 10.1016/j.ypmed.2011.01.020]. *Preventive Medicine, 52, Supplement*(0), S65-S69.

Davis, C. L., Tomporowski, P. D., McDowell, J. E., Austin, B. P., Miller, P. H., Yanasak, N. E., et al. (2011). Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. *Health Psychol, 30*(1), 91-98.

DeSouza, J. F. X., Menon, R. S., & Everling, S. (2003). Preparatory Set Associated With Pro-Saccades and Anti-Saccades in Humans Investigated With Event-Related fMRI. *Journal of Neurophysiology, 89*(2), 1016-1023.

Dickstein, S. G., Bannon, K., Castellanos, X. F., & Milham, M. P. (2006). The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *Journal of Child Psychology and Psychiatry, 47*(10), 1051-1062.

Durston, S., Davidson, M. C., Tottenham, N., Galvan, A., Spicer, J., Fossella, J. A., et al. (2006). A shift from diffuse to focal cortical activity with development. *Developmental Science, 9*(1), 1-8.

Durston, S., Tottenham, N. T., Thomas, K. M., Davidson, M. C., Eigsti, I.-M., Yang, Y., et al. (2003). Differential patterns of striatal activation in young children with and without ADHD. [doi: 10.1016/S0006-3223(02)01904-2]. *Biological Psychiatry, 53*(10), 871-878.

Dyckman, K. A., Camchong, J., Clementz, B. A., & McDowell, J. E. (2007). An effect of context on saccade-related behavior and brain activity. [doi: 10.1016/j.neuroimage.2007.03.023]. *NeuroImage, 36*(3), 774-784.

Ellison-Wright, I., Ellison-Wright, Z., & Bullmore, E. (2008). Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC psychiatry, 8*(1), 51.

Ettinger, U., ffytche, D. H., Kumari, V., Kathmann, N., Reuter, B., Zelaya, F., et al. (2008). Decomposing the Neural Correlates of Antisaccade Eye Movements Using Event-Related fMRI. *Cerebral Cortex, 18*(5), 1148-1159.

Faraone, S. V., & Biederman, J. (2002). Efficacy of Adderall® for attention-deficit/hyperactivity disorder: A meta-analysis. *Journal of Attention Disorders, 6*(2), 69-75.

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological medicine, 36*(2), 159-166.

Faraone, S. V., & Buitelaar, J. (2010). Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European Child & Adolescent Psychiatry, 19*(4), 353-364.

Fitzgerald, K. D., Zbrozek, C. D., Welsh, R. C., Britton, J. C., Liberzon, I., & Taylor, S. F. (2008). Pilot study of response inhibition and error processing in the posterior medial prefrontal cortex in healthy youth. *Journal of Child Psychology and Psychiatry, 49*(9), 986-994.

Gagnon, D., O'Driscoll, G. A., Petrides, M., & Pike, G. B. (2002). The effect of spatial and temporal information on saccades and neural activity in oculomotor structures. *Brain, 125*(1), 123-139.

Gapin, J. I., & Etnier, J. L. (2010). The relationship between physical activity and executive function performance in children with attention-deficit hyperactivity disorder. *Journal of sport & exercise psychology, 32*(6), 753.

Gapin, J. I., Labban, J. D., & Etnier, J. L. (2011). The effects of physical activity on attention deficit hyperactivity disorder symptoms: the evidence. *Preventive Medicine, 52*, S70-S74.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences, 96*(14), 8301-8306.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Behavior rating inventory of executive function. *Child Neuropsychology: A Journal On Normal And Abnormal Development In Childhood And Adolescence, 6*(3), 235-238.

Hakvoort Schwerdtfeger, R. M., Alahyane, N., Brien, D. C., Coe, B. C., Stroman, P. W., & Munoz, D. P. (2013). Preparatory neural networks are impaired in adults with attention-deficit/hyperactivity disorder during the antisaccade task. *NeuroImage: Clinical, 2*(0), 63-78.

Hallett, P. (1978). Primary and secondary saccades to goals defined by instructions. *Vision research, 18*(10), 1279-1296.

Halperin, J. M., & Healey, D. M. (2011). The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: Can we alter the developmental trajectory of ADHD? *Neuroscience & Biobehavioral Reviews, 35*(3), 621-634.

Holtkamp, K., Konrad, K., Müller, B., Heussen, N., Herpertz, S., Herpertz-Dahlmann, B., et al. (2004). Overweight and obesity in children with Attention-Deficit/Hyperactivity Disorder. *International journal of obesity, 28*(5), 685-689.

Houdé, O., Rossi, S., Lubin, A., & Joliot, M. (2010). Mapping numerical processing, reading, and executive functions in the developing brain: an fMRI meta-analysis of 52 studies including 842 children. *Developmental Science, 13*(6), 876-885.

Kempton, S., Vance, A., Maruff, P., Luk, E., Costin, J., & Pantelis, C. (1999). Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. *Psychological medicine, 29*(3), 527-538.

Klein, C., Fischer, B., & Hartnegg, K. (2002). Effects of methylphenidate on saccadic responses in patients with ADHD. *Experimental Brain Research, 145*(1), 121-125.

Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., & Herpertz-Dahlmann, B. (2006). Dysfunctional Attentional Networks in Children with Attention Deficit/Hyperactivity Disorder: Evidence from an Event-Related Functional Magnetic Resonance Imaging Study. *Biological Psychiatry, 59*(7), 643-651.

Krafft, C. E., Schwarz, N. F., Chi, L., Li, Q., Schaeffer, D. J., Rodrigue, A. L. P., Jordan E, et al. (2012). The location and function of parietal cortex supporting of reflexive and volitional saccades, a meta-analysis of over a decade of functional MRI data. *Horizons of neuroscience research, 9*, 131-153.

Krafft, C. E., Schwarz, N. F., Chi, L., Li, Q., Weinberger, A. L., Schaeffer, D. J., et al. (in press). An 8-month Exercise Intervention Alters Brain Activation in Overweight Children. *Obesity*.

Luna, B., & Sweeney, J. A. (2004). The emergence of collaborative brain function: FMRI studies of the development of response inhibition. *Ann N Y Acad Sci, 1021*, 296-309.

Luna, B., Thulborn, K. R., Munoz, D. P., Merriam, E. P., Garver, K. E., Minshew, N. J., et al. (2001). Maturation of widely distributed brain function subserves cognitive development. *NeuroImage, 13*(5), 786-793.

McDowell, J. E., Brown, G. G., Paulus, M., Martinez, A., Stewart, S. E., Dubowitz, D. J., et al. (2002). Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. [doi: 10.1016/S0006-3223(01)01204-5]. *Biological Psychiatry, 51*(3), 216-223.

McDowell, J. E., Dyckman, K. A., Austin, B. P., & Clementz, B. A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: Evidence from studies of humans. [doi: 10.1016/j.bandc.2008.08.016]. *Brain and Cognition, 68*(3), 255-270.

Medicine, A. C. o. S. (Ed.). (2000). *ACSM's guidelines for exercise testing and prescription* (6th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience, 24*(1), 167-202.

Monden, Y., Dan, H., Nagashima, M., Dan, I., Tsuzuki, D., Kyutoku, Y., et al. (2012). Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: An fNIRS study. [doi: 10.1016/j.nicl.2012.10.001]. *NeuroImage: Clinical, 1*(1), 131-140.

Munoz, D. P., & Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. [Article]. *Nature Reviews Neuroscience, 5*(3), 218-228.

Naglieri, J. A., Goldstein, S., Iseman, J. S., & Schwebach, A. (2003). Performance of children with attention deficit hyperactivity disorder and anxiety/depression on the WISC-III and Cognitive Assessment System (CAS). *Journal of Psychoeducational Assessment, 21*(1), 32-42.

Niendam, T., Laird, A., Ray, K., Dean, Y., Glahn, D., & Carter, C. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective, & Behavioral Neuroscience, 12*(2), 241-268.

Nigg, J. T., Willcutt, E. G., Doyle, A. E., & Sonuga-Barke, E. J. S. (2005). Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biological Psychiatry, 57*(11), 1224-1230.

O'Driscoll, G. A., Dépatie, L., Holahan, A.-L. V., Savion-Lemieux, T., Barr, R. G., Jolicoeur, C., et al. (2005). Executive Functions and Methylphenidate Response in Subtypes of Attention-Deficit/Hyperactivity Disorder. [doi: 10.1016/j.biopsych.2005.02.029]. *Biological Psychiatry, 57*(11), 1452-1460.

Ogawa, S., Lee, T., Kay, A., & Tank, D. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences, 87*(24), 9868-9872.

Pierrot‐Deseilligny, C., Müri, R. M., Ploner, C. J., Gaymard, B., Demeret, S., & Rivaud‐Pechoux, S. (2003). Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain, 126*(6), 1460-1473.

Pliszka, S., Glahn, D., Semrud-Clikeman, M., Franklin, C., Perez Iii, R., Xiong, J., et al. (2006). Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *American Journal of Psychiatry, 163*(6), 1052-1060.

Polanczyk, G., de Lima, M., Horta, B., Biederman, J., & Rohde, L. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry, 164*(6), 942-948.

Polli, F. E., Barton, J. J., Cain, M. S., Thakkar, K. N., Rauch, S. L., & Manoach, D. S. (2005). Rostral and dorsal anterior cingulate cortex make dissociable contributions during

antisaccade error commission. *Proceedings of the National Academy of Sciences of the United States of America, 102*(43), 15700-15705.

Posner, J., Maia, T. V., Fair, D., Peterson, B. S., Sonuga-Barke, E. J., & Nagel, B. J. (2011). The attenuation of dysfunctional emotional processing with stimulant medication: An fMRI study of adolescents with ADHD. *Psychiatry Research: Neuroimaging, 193*(3), 151-160.

Reilly, J. L., Lencer, R., Bishop, J. R., Keedy, S., & Sweeney, J. A. (2008). Pharmacological treatment effects on eye movement control. *Brain and Cognition, 68*(3), 415-435.

Rommelse, N. N. J., Van der Stigchel, S., & Sergeant, J. A. (2008). A review on eye movement studies in childhood and adolescent psychiatry. [doi: 10.1016/j.bandc.2008.08.025]. *Brain and Cognition, 68*(3), 391-414.

Rubia, K. (2011). “Cool” inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus “hot” ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. *Biological Psychiatry, 69*(12), e69-e87.

Rubia, K., Halari, R., Cubillo, A., Smith, A. B., Mohammad, A.-M., Brammer, M., et al. (2011). Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naive boys with attention-deficit hyperactivity disorder. *Neuropsychopharmacology, 36*(8), 1575-1586.

Rubia, K., Halari, R., Mohammad, A.-M., Taylor, E., & Brammer, M. (2011). Methylphenidate Normalizes Frontocingulate Underactivation During Error Processing in Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry, 70*(3), 255-262.

Schmidt, H. D., Shelton, R. C., & Duman, R. S. (2011). Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. *Neuropsychopharmacology, 36*(12), 2375-2394.

Silk, T., Vance, A., Rinehart, N., Egan, G., O'Boyle, M., Bradshaw, J. L., et al. (2005). Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. *The British Journal of Psychiatry, 187*(3), 282-283.

Slaats-Willemse, D., Swaab-Barneveld, H., De Sonneville, L., Van Der Meulen, E., & Buitelaar, J. (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry, 42*(10), 1242-1248.

Smith, A. L., Hoza, B., Linnea, K., McQuade, J. D., Tomb, M., Vaughn, A. J., et al. (2013). Pilot physical activity intervention reduces severity of ADHD symptoms in young children. *Journal of Attention Disorders, 17*(1), 70-82.

Sonuga-Barke, E. J. (2005). Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biological Psychiatry, 57*(11), 1231-1238.

Spencer, T. J., Biederman, J., & Mick, E. (2007). Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *Ambulatory Pediatrics, 7*(1), 73-81.

Swanson, J., Kinsbourne, M., Nigg, J., Lanphear, B., Stefanatos, G., Volkow, N., et al. (2007). Etiologic Subtypes of Attention-Deficit/Hyperactivity Disorder: Brain Imaging, Molecular Genetic and Environmental Factors and the Dopamine Hypothesis. *Neuropsychology review, 17*(1), 39-59.

Sweeney, J. A., Luna, B., Keedy, S. K., McDowell, J. E., & Clementz, B. A. (2007). fMRI studies of eye movement control: Investigating the interaction of cognitive and sensorimotor brain systems. [doi: 10.1016/j.neuroimage.2007.03.018]. *NeuroImage, 36, Supplement 2*(0), T54-T60.

Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., et al. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *Journal of Neurophysiology, 75*(1), 454-468.

Sweeney, J. A., Takarae, Y., Macmillan, C., Luna, B., & Minshew, N. J. (2004). Eye movements in neurodevelopmental disorders. *Current Opinion in Neurology, 17*(1), 37-42.

Vaidya, C. J., Austin, G., Kirkorian, G., Ridlehuber, H. W., Desmond, J. E., Glover, G. H., et al. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proceedings of the National Academy of Sciences, 95*(24), 14494-14499.

Valera, E. M., Faraone, S. V., Murray, K. E., & Seidman, L. J. (2007). Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 61*(12), 1361-1369.

Velanova, K., Wheeler, M. E., & Luna, B. (2008). Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cerebral Cortex, 18*(11), 2505-2522.

Velanova, K., Wheeler, M. E., & Luna, B. (2009). The Maturation of Task Set-Related Activation Supports Late Developmental Improvements in Inhibitory Control. *The Journal of Neuroscience, 29*(40), 12558-12567.

Verret, C., Guay, M.-C., Berthiaume, C., Gardiner, P., & Béliveau, L. (2012). A Physical Activity Program Improves Behavior and Cognitive Functions in Children With ADHD An Exploratory Study. *Journal of Attention Disorders, 16*(1), 71-80.

Volkow, N. D., Wang, G.-J., Fowler, J. S., & Ding, Y.-S. (2005). Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1410-1415.

Walker, R., Husain, M., Hodgson, T. L., Harrison, J., & Kennard, C. (1998). Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. *Neuropsychologia, 36*(11), 1141-1159.

Ward, B. D. (2000). Simultaneous inference for fMRI data. *AFNI 3dDeconvolve Documentation, Medical College of Wisconsin*.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. [doi: 10.1016/j.biopsych.2005.02.006]. *Biological Psychiatry, 57*(11), 1336-1346.

Wolraich, M. L., Feurer, I. D., Hannah, J. N., Baumgaertel, A., & Pinnock, T. Y. (1998). Obtaining systematic teacher reports of disruptive behavior disorders utilizing DSM-IV. *Journal of abnormal child psychology, 26*(2), 141-152.

Wolraich, M. L., Lambert, W., Doffing, M. A., Bickman, L., Simmons, T., & Worley, K. (2003). Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. *Journal of Pediatric Psychology, 28*(8), 559-568.