Stimulant Medication and Prefrontal Functional Connectivity During Working Memory in ADHD

A Preliminary Report

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Objective: Recent theoretical and empirical work suggests that while unmedicated, children with ADHD have a deficit in subcortical processing that leads to greater and more varied prefrontal cortical (PFC) activation, compared to (a) age-matched control participants and (b) their own brain activity while on stimulant medication. This pattern has been described elsewhere as inefficient. Method: Functional magnetic resonance imaging (fMRI) and functional connectivity analyses were used during a working memory task for five female adolescents with ADHD, aged 11 to 17 years, both on and off their usual dose of stimulant medication. Results: On medication, adolescents with ADHD demonstrated less PFC activation and less functional connectivity between frontal and subcortical regions compared to off medication. Conclusions: Because of the small sample size, results are presented as preliminary findings which await replication in a larger sample. However, these findings lend support to the idea that remediation of inefficiencies in PFC function for individuals with ADHD by stimulant medication may be related, in part, to frontal-subcortical connectivity. (J. of Att. Dis. 2010; 14(1) 69-78)

Keywords: ADHD; working memory; prefrontal cortex; striatum; basal ganglia; inefficiency; brain development

Introduction

ADHD is a debilitating disorder of attention and inhibition that begins during childhood, and is currently believed to affect between 5% and 8% of school-aged children in the United States, with serious implications for adolescent and adult outcomes for most (Fischer, Barkley, Smallish, & Fletcher, 2007; Hinshaw, 2002; Nigg, Blaskey, Stawicki, & Sachek, 2004). One of the most effective therapies for ADHD symptomatology is stimulant medication (Greenhill et al., 2002).

Despite a large and growing body of literature about this disorder, there continues to be a substantial debate about the neuropathophysiology underlying ADHD. Studies of individuals with ADHD show differences from control participants in the structure (Castellanos & Tannock, 2002; for review see Durston, 2003; Giedd, Blumenthal, Molloy, & Castellanos, 2001) and function (for review see Durston, 2003; Halperin & Schulz, 2006; Nigg & Casey, 2005) of the prefrontal cortex (PFC) and striatum. Particularly, the lateral PFC (middle and inferior frontal gyrus) has been linked to ADHD symptomatology and the kinds of executive functioning with which individuals with ADHD experience difficulties (Aron & Poldrack, 2005; D’Esposito & Postle, 2002). Although this analysis will focus on one area of prefrontal cortex, the middle frontal gyrus (MFG)—which

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69
is most relevant for the task used in this study (see below)—there is evidence that other areas of prefrontal cortex may also be affected in ADHD, most notably, the anterior cingulate cortex (ACC; Bush et al., 1999). One of the major modulators of neural transmission in both the prefrontal cortex and basal ganglia (BG) is dopamine (DA; Grace, 1995). There is some evidence that individuals with ADHD have increased dopamine transporter (DAT) in the BG (Dougherty et al., 1999) and the primary medications used to treat ADHD are psychostimulants, which block DAT (Castellanos, 1999; Volkow & Swanson, 2003; Volkow, Wang, Fowler, & Ding, 2005).

Recently, investigators have suggested that well-known differences in PFC function in ADHD are the downstream sequelae of deficits in subcortical structures, such as the striatum, or cerebellum (Casey & Durston, 2006; Halperin & Schulz, 2006; Nigg & Casey, 2005; Volkow et al., 2005, 2007). In one model, the function of stimulant medication would be to decrease the noise in signals from the striatum to the PFC by increasing extra-cellular DA in the striatal region (Volkow et al., 2005). In this model of a “noisy” system the striatum sometimes fire to nonsalient, novel, or relevant stimuli. The PFC is one target of striatal output and this firing could result in irrelevant shifts of attention or irrelevant updating in working memory, resulting in distractible behavior. At other times the striatum would not fire to relevant novel or salient stimuli, resulting in the appearance of perseveration or inattention. Basic support of this concept comes from a study which demonstrated that administering methylphenidate to unimpaired adults increases the salience of a difficult task through action on DA in the striatum (Volkow et al., 2004). In addition, in individuals with ADHD, performance on an oddball paradigm is associated with underactivation of the striatum to novel stimuli, as measured via functional magnetic resonance imaging (fMRI; see Rubia, Smith, Brammer, & Taylor, 2007; Tamm, Menon, & Reiss, 2006).

For other tasks, in which stimulus salience is paired with the need for cognitive control, individuals with ADHD activate the lateral PFC to a greater degree (specifically, the Middle and Inferior Frontal Gyrus) while off medication, relative to both (a) control participants and (b) their own performance on medication (Durston et al., 2003; Mehta et al., 2000; Schulz et al., 2004, 2005; Schweitzer et al., 2003, 2004). Increases in lateral PFC activation such as these have been conceptualized as “inefficient” (Sheridan, Hinshaw, & D’Esposito, 2007) because individuals with ADHD activate prefrontal areas to a greater extent than control participants even when performance is similar between groups. Recent findings indicate that for both controls and individuals with ADHD, the amount of white matter connectivity between the PFC and striatum—as measured as by diffusion tensor imaging—is correlated with performance on tasks demanding cognitive control (Casey et al., 2007; Liston et al., 2006). Combining the concepts of PFC inefficiency with the concept of low dopamine in the striatum leading to a “noisy” salience detector, we posit that poor striatal function would lead to compensatory increases in activation of the PFC for adolescents with ADHD, in the context of equal behavioral or cognitive performance relative to normative controls. We lay out this conceptual relationship for the striatum and PFC, however other areas thought to be affected in ADHD, such as the cerebellum, may have a similar relationship whereby deficits in subcortical areas lead to compensatory activation in the PFC.

In the current pilot study we test these ideas during the encoding period of a delayed match-to-sample task. During encoding, failure to selectively attend to and remember the relevant stimuli should result in failure on that trial of the task. We hypothesize that, while adolescent participants are on stimulant medication relative to off medication, PFC activity will decrease. That is, if medications remediate inefficient subcortical function, the PFC will activate less when the participant is on medication, while producing the same or better performance. We also predict medication-related changes in (a) striatum activity and (b) striatal-PFC connectivity. This is a pilot study and given the lack of fMRI research specifically assessing striatal function in ADHD, and/or functional connectivity, we make no prediction regarding the direction (e.g., increased vs. decreased activation) of any striatal effects.

Method and Materials

Participants. Participants were five adolescent girls (12-17 years) with ADHD (mean age = 14.8, SD = 2.4). All participants had been initially evaluated and diagnosed when they attended a research summer camp program approximately 5 years earlier, with diagnoses reconfirmed prior to the current study (see Hinshaw, 2002, for details). Participants had Verbal (Avg. = 110.6) and Performance (Avg. = 112.6) IQs in the normal range (WISC-III; Wechsler, 1991). Rigorous exclusion criteria, ensuring medical and neurological normality, were used (see Sheridan et al., 2007 for details), greatly limiting the fMRI subsample. Seven possible adolescents were eligible for inclusion and were willing to participate. One subject was excluded because of excessive movement and one because of technical difficulties. Data from the
off-medication scans for two of the participants included in this sample have already been published elsewhere (Sheridan et al., 2007). Two participants were taking a nonstimulant medication in addition to the stimulant. One was prescribed 100 mg of Zoloft, another 0.05 mg of Clonidine. These medications were held constant across scans, while their stimulant medication was manipulated. It was considered appropriate to include these participants despite their additional medications because, as this is a within subject design, that variable could be held constant across scans. In addition, individual variance added by the other medications would serve primarily to decrease the likelihood of finding a stimulant medication related effect.

All participants came to the Henry H. Wheeler, Jr. Brain Imaging Center at the University of California, Berkeley with a parent. Parents read and signed a consent form, approved by the University of California, Berkeley Committee for the Protection of Human participants, allowing their daughter to participate in the study. Adolescents read and signed a similar, but more simply written, assent form that described study procedures.

**Medication.** For stimulant medications a simple calculation of mg/kg is not likely to result in an appropriate dose (Denney & Rapport, 1999). Thus, in the current study, we administered the participant’s own dose of medication, previously titrated by her physician or psychiatrist (see Table 1 for doses). Three participants received medication during the first session and two participants received medication during the second session. To address the potential confounder of practice effects, paired sample t-tests were conducted for both region of interest (ROI) and behavioral data analysis with session order as the independent variable. Consistent with other findings, order or practice effects on this task were not significant. Prior to the “off medication” scan, participants were medication free for 24 hours. For the “on medication” scan participants took their usual dose of medication approximately 1 hour before the scan.

**Cognitive task.** Adolescents performed a delayed match-to-sample task, using letter stimuli, with a memory load manipulation (high: six letters vs. low: two letters; Sternberg, 1966) that was fully counterbalanced within runs of the task. Load did not interact with stimulant medication and is therefore reported in only a limited way below. A single trial consisted of three periods: encoding (2.2 seconds), delay (13.2 seconds), and retrieval (2.2 seconds). The intertrial interval was 13.2 seconds. The task was divided into 10 runs of eight trials each for the purpose of fMRI scanning.

**Behavioral analysis.** Four girls with ADHD were included in the analysis of the behavioral data. One participant was excluded because of technical problems with the recording of her behavioral responses. For the remainder, mean reaction time and accuracy were computed for each trial type. These means were then entered into a 2 (medication: on, off) by 2 (load: high, low) repeated measures ANOVA.

**Imaging analysis.** Images were acquired using a 4.0 T Varian INOVA MR scanner using standard scanning procedures. Whole brain volumes were acquired, with 3.5 × 3.5 × 5.5 mm voxels. Image processing and analysis were completed using a Statistical Parametric Mapping program (SPM2; Friston, Frith, Liddle, & Frackowiak, 1991) using linear combinations of the covariates modeling each task period and load condition. Motion correction was accomplished using a 6-parameter rigid-body transformation algorithm (Friston, Frith, Frackowiak, & Turner, 1995). Prior to individual analysis, data were normalized to Montreal Neurological Institute (MNI) space. Any run containing more than 3 mm of movement was excluded from analysis; number of runs was held constant across medication condition. Movement parameters were included as covariates in each individual’s analysis. When possible, only correct trials were used in statistical analyses of fMRI data.

### Table 1
**For Each Subject, the Dose of Their Medication and the Number of Hyperactive and Inattentive Symptoms Endorsed by Their Primary Caregiver on a Structured Interview (DISC-IV, Shaffer et al., 2000) Where 9 is the Maximum Number of Hyperactive (Hyper/9) and Inattentive (Attn/9) Symptoms Which can be Endorsed on This Measure**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Hyper/9</th>
<th>Attn/9</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>8</td>
<td>18 mg Concerta (time release methylphenidate)</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>7</td>
<td>20 mg Adderall (Atphetamine salts) (100 mg Zoloft)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>9</td>
<td>54 mg Concerta (time release methylphenidate)</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>9</td>
<td>108 mg Concerta (time release methylphenidate) 10 mg Ritalin (methylphenidate) (0.05 mg clonidine)</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>8</td>
<td>54 mg Concerta (time release methylphenidate)</td>
</tr>
</tbody>
</table>
The results of the individual analyses were combined into a group analysis. Blood oxygen level dependent (BOLD) signal for adolescents on medication during each task period and condition was directly compared to off medication values, using paired-sample t-tests. Significance for the map-wise random effects analysis was set at \( p = .001 \) with a required voxel extent of 20, which is commensurate with thresholds used in similar patient studies (Bush et al., 1999; Durston et al., 2003; Schweitzer et al., 2000).

A group-level ROI analysis was performed for two areas: bilateral MFG (Brodmann’s Areas 8/9/46) and bilateral basal ganglia, including the striatum (caudate and putamen) and the globus pallidus. ROIs were determined anatomically, using a MNI normalized automated anatomical labeling (AAL) map (Tzourio-Mazoyer et al., 2002), and analysis was performed using the MarsBaR toolbox in SPM. Brain activation was entered into a 2 (medication: on, off) by 3 (task period: encoding, delay, probe) repeated measures ANOVA with condition as the within-subjects factor. The results of the individual analyses were combined into a group analysis. Blood oxygen level dependent (BOLD) signal for adolescents on medication during each task period and condition was directly compared to off medication values, using paired-sample t-tests. Significance for the map-wise random effects analysis was set at \( p = .001 \) with a required voxel extent of 20, which is commensurate with thresholds used in similar patient studies (Bush et al., 1999; Durston et al., 2003; Schweitzer et al., 2000).

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Finally, to directly assess the relationship between the PFC and striatum, medication-related differences in functional connectivity were explored (Rissman, Gazzaley, & D’Esposito, 2004). For this analysis bilateral functional ROIs were defined in the left (15 voxels, \(-28 44 18, t = 5.23\)) and right (215 voxels, \(36 26 32, t = 6.93\)) MFG based on encoding activity across medication condition for all participants. These ROIs were used as seed regions, and functional connectivity was assessed for every voxel in the brain during the encoding period of the delayed match-to-sample task. For each participant, a set of single trial activity estimates, or \( b \) series, were derived independently for every brain voxel, based on a separate GLM in which each task phase from each trial was modeled as a unique event (see Rissman et al., 2004, for a detailed description of this functional connectivity analysis procedure, and see Buchsbaum et al., 2005, and Gazzaley et al., 2004, for further examples of its application). For each condition, a seed \( b \) series, averaged across all voxels of the seed ROI, was generated for each participant, and the correlation of each brain voxel’s \( b \) series with that of the seed was determined. The resulting condition-specific correlation maps were compared between conditions at the group level using \( t \) tests for paired samples. To test our hypothesis of changes in functional coupling between MFG and BG on medication, correlation \( t \) maps were threshold at \( t > 4.60 \) (\( p < .005; 20 \) voxel extent).

**Results**

**Behavioral Data**

A significant main effect of medication condition was found for accuracy \( F(1, 4) = 8.496, p = .043 \) but not for response times \( F(1, 4) = 2.083, p = .22 \). Regardless of load, participants were significantly more accurate on stimulant medication than off medication \( (t(4) = 2.92, p = .043) \). Effect size was calculated for the medication effect on accuracy \( (\text{Cohen’s } d = .42) \) yielding a medium effect size. Effect size was calculated here and in future analyses by treating the groups independently because there is controversy in the field and this is the most conservative way to calculate effect size (Dunlap, Cortina, Vaslow, & Burke, 1996). There was also a significant main effect of load on accuracy \( F(1, 4) = 10.73, p = .03 \) but not on response times \( F(1, 4) = 2.5, p = .188 \). Both on and off medication, participants performed more accurately at low load \( (t(4) = 3.28, p = .031) \). There was no medication by load interaction for accuracy \( (F(1, 4) = 1.86, p = .24) \) or response time \( (F(1, 4) = 1.385, p = .30) \). Figure 1 presents the behavioral data and Table 2 presents the medication effect on accuracy and response time for each participant separately.

**Imaging Data**

**Whole Brain Analysis**

In the whole brain analysis, neural activity for each task period was first assessed separately for adolescents on and off stimulant medication and then directly compared to assess the effect of medication. For a complete list of activations found in the whole brain analysis, see Table 3. The effect of medication on brain activity was assessed using paired sample \( t \)-tests for each task period and load condition. During encoding, participants activated the PFC and precuneus more off than on medication. No medication effects were found during the other task periods.

**ROI Analysis**

In the BG and MFG there was no main effect of medication, \( F(1, 4) .013, p = .913 \), and \( F(1, 4) 4.49, p = .101 \), respectively, but there was a main effect of task period, \( F(1, 4) 14.79, p = .013 \), and \( F(1, 4) 20.06, p = .011 \), respectively, whereby both regions were more active at encoding and probe than delay regardless of
medication condition. When the effect of medication was examined within each task period and ROI separately, only the MFG during encoding showed a significant effect ($t(4) = 3.397, p = .027$). As predicted, during the encoding period, participants activated the MFG more during off-medication than on-medication trials (Figure 2). The BG followed a similar pattern, where the BG were more active off relative to on medication but this finding was not significant (Figure 2; $t(4) = 1.773, p = .151$). The effect size was calculated for the medication effect in the MFG (Cohen’s $d = 1.75$) and BG (Cohen’s $d = .86$) both yielding respectably large differences in contrast value on and off medication. Because for both the whole brain analysis and the ROI analysis, effects of medication were strongest at encoding, and because of the importance of cognitive control over salience during this time period, we performed the connectivity analysis only during encoding. See Table 2 for the medication effect on contrast values at encoding for each participant.

A functional connectivity analysis was performed using correlation (Figure 3, Table 4; Rissman et al., 2004). Connectivity during the encoding period was compared between medication conditions. Significantly stronger functional connectivity between the MFG and striatum was found for participants off medication compared to on medication. Increased connectivity with bilateral MFG off compared to on medication was also observed for areas in the left MFG, medial prefrontal cortex, left hippocampus, left inferior temporal gyrus,
right temporal parietal junction, right insula, and right lingual gyrus. Increased connectivity with the MFG on-medication compared to off-medication period was found only for the cerebellar vermis.

**Discussion**

It has been argued recently that DA deficiency within subcortical structures such as the striatum may contribute to ADHD symptoms (Halperin & Schulz, 2006; Volkow et al., 2005). This hypothesis is consistent with research positing a modulatory role for DA in the striatum in its response to the salient or novel stimuli (Grace, 1995).

In this pilot fMRI study, we tested this theory using a sample of adolescent girls with ADHD who were tested on and off their own dose of stimulant medication during performance of a working memory task. In both the whole brain and ROI analyses we found support for our hypothesis that the PFC would be more active when participants were off medication. Increased recruitment of the PFC was identified in more than one region (ACC, middle frontal gyrus), consistent with previous literature identifying multiple areas of dysfunction in the PFC for individuals with ADHD (Durston et al., 2003; Mehta et al., 2000; Schulz et al., 2004; Schweitzer et al., 2003, 2004, 2005). This finding serves as a minor replication, in a population of female adolescents, of previous findings that PFC activation decreases for individuals with ADHD on medication accompanying an increase in accuracy.

We explicitly tested PFC/striatal interactions on and off medication by assessing functional connectivity for...
bilateral regions in the MFG during the encoding period of the working memory task. Stronger MFG/striatal functional connectivity was observed off medication compared to on medication, supporting the idea that stimulant medication effects change in part by targeting the frontal-striatal system. However, other cortical and subcortical areas also showed increased functional connectivity with the MFG off medication. These findings may reflect increased demands on frontal circuitry off medication. One area, in the cerebellar vermis, was more correlated with MFG activity on medication, suggesting the potential importance of the vermis for ADHD symptomology, hypothesized elsewhere (Halperin & Schulz, 2006).

This was a pilot study, aimed at establishing the potential use of functional connectivity to assess hypothesized circuit dysfunction in ADHD. As such, the primary limitation of this study is the small sample size. Because of low statistical power, null results should not be interpreted. Despite this important limitation, this study serves as an initial test of the hypothesis that increased but inefficient activity in the prefrontal cortex serves a compensatory function. Through the use of functional connectivity, we obtained evidence supporting dysfunctional cortical MFG—subcortical (striatum, hippocampus, cerebellum)

**Figure 2**

Blood oxygen level dependent signal (BOLD) in middle frontal gyrus (MFG), basal ganglia (BG), and inferior frontal gyrus (IFG) regions of interest during encoding off medication compared to on medication.

This graph demonstrates the increase in MFG and BG activation for encoding off medication, but the difference between medication conditions is significant only for the MFG at (*p < .05).

**Figure 3**

Results of paired t-test (off medication compared to on medication) showing increases in functional connectivity between bilateral middle frontal gyrus (MFG) and left MFG, hippocampus, medial prefrontal cortex, and inferior temporal gyrus.

And correlation between bilateral MFG and right striatum, insula, lingual gyrus, and temporal parietal junction for both on and off medication collapsed across load. In addition, results of paired t-test (on medication compared to off medication) show increases only in cerebellar vermis for participants with ADHD on medication.
and cortical MFG-cortical (temporal parietal junction, medial PFC) connectivity, which is modified by medication. Since the majority of hypotheses concerning neural dysfunction in ADHD, posit deficits in circuitry (frontal striatal dysfunction), or neurotransmitters DA which act to modulate multiple areas across the brain, use of functional connectivity analyses could prove to be an important tool in the future of ADHD research.

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Margaret A. Sheridan received her PhD from the University of California, Berkeley in December, 2008 in Psychology with an emphasis in clinical psychology. She was mentored by Drs. Stephen Hinshaw and Mark D’Esposito. She completed a clinical internship at Bellevue/NYU Child Study Center and is currently a Robert Wood Johnson Health and Society Scholar at Harvard School of Public Health. Her current research mentor is Charles Nelson, a professor at Harvard Medical School and faculty at Children’s Hospital Boston. Her graduate research focused on the neural correlates of working memory and inhibition in adolescents with ADHD as measured by functional magnetic resonance imaging (fMRI). While at Berkeley she also examined the neural correlates of learning and inhibition in children from low and high socioeconomic status (SES) backgrounds using fMRI. She is the first author of peer-reviewed publications published in major research journals including a paper which described the results of an fMRI study of adolescents with ADHD published in *Journal of the American Academy of Child and Adolescent Psychiatry*.

Stephen Hinshaw is a full professor at the University of California, Berkeley. He is well respected for his longitudinal studies of females with ADHD and his work on the multimodal
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