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The Effect of Stimulant Medication on Prefrontal Functional Connectivity during Working Memory in Attention-deficit/Hyperactivity Disorder

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Abstract

Objective—Recent theoretical and empirical work suggests that while unmedicated, children with Attention-deficit/Hyperactivity Disorder (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 (Sheridan et al. 2007). We examine the hypothesis that frontal-striatal connectivity and degree of PFC activation will be affected by stimulant medication.

Method—Functional magnetic resonance imaging (fMRI) was used during a working memory task for 5 adolescents with ADHD, aged 11–17 years, both on and off their usual dose of stimulant medication. We analyzed the degree of PFC and basal ganglia (BG) activation with anatomically defined ROIs and whole brain analysis. We additionally assessed functional connectivity between the PFC and all brain regions.

Results—On medication, adolescents with ADHD demonstrated less PFC activation and less functional connectivity between frontal and striatal regions compared to off medication.

Conclusions—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 BG function.

Keywords

ADHD; working memory; prefrontal cortex; basal ganglia; medication; stimulants

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Introduction

Attention-deficit/Hyperactivity Disorder (ADHD), a debilitating disorder of attention and inhibition that begins during childhood, is currently believed to affect between 5–8% of school-aged children in the United States, with serious implications for adolescent and adult outcomes for most (Fischer et al. 2007; Hinshaw et al., 2002; Nigg et al., 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 et al., 2002; for review see Durston, 2003, Giedd et al., 2001) and function (for review see Nigg & Casey, 2005; Halperin & Schulz, 2006; Durston, 2003) of the prefrontal cortex (PFC) and basal ganglia (BG). Particularly, the lateral prefrontal cortex (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 & Postel 2002). Although this analysis will focus on one area of prefrontal cortex, the middle frontal gyrus (MFG)—which 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 medial prefrontal cortex (Rubia et al. 1999). One of the major modulators of neural transmission in both the prefrontal cortex and basal ganglia is dopamine (DA; Grace, 1995), with some evidence that individuals with ADHD have increased dopamine transporter (DAT) in the BG (Dougherty et al., 1999). The primary medications used to treat ADHD are psychostimulants, which block DAT (Castellanos, 1999, Gatley et al., 1995, Volkow & Swanson, 2003; Volkow et al., 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 BG (Halperin & Schulz, 2006; Casey & Durston, 2006; Nigg & Casey, 2005; Volkow et al., 2005, 2007). In this model, the function of stimulant medication is to decrease the noise in signals from the BG to the PFC by increasing extracellular DA in the BG region (Volkow et al., 2005). In Volkow’s model of a ‘noisy’ system, the BG sometimes inappropriately signals the PFC, resulting in distractible behavior, and at other times does not signal the PFC when appropriate, resulting in perseveration or inattention. In support of these ideas, administering methylphenidate to unimpaired adults increases the salience of a difficult task through action on DA in the BG (Volkow et al., 2004). For individuals with ADHD, performance on an oddball paradigm is associated with under-activation of the BG to novel stimuli, as measured via functional magnetic resonance imaging (fMRI) (see Rubia et al., 2007; Tamm et al., 2006).

For other tasks, in which stimulus salience is paired with the need for cognitive control, individuals with ADHD overactivate the lateral PFC (specifically, the Middle and Inferior Frontal Gyrus) while off medication, relative to both (a) control subjects and (b) their own performance on medication (Schulz et al., 2004; Schulz et al., 2005; Durston et al., 2003; Schweitzer et al., 2003, 2004; Mehta et al., 2000). Increases in lateral PFC activation such as these have been conceptualized as “inefficient” (Sheridan et al., 2007) because individuals with ADHD activate prefrontal areas to a greater extent than control subjects even when performance is similar between groups. Additionally, within a group of adolescents with ADHD, as performance improves the lateral PFC is recruited to a greater extent, the opposite is true of adolescents without ADHD. Recent findings indicate that for both controls and individuals with ADHD, the amount of white matter connectivity between the PFC and BG—as measured as by diffusion tensor imaging—is correlated with performance on tasks demanding cognitive control (Liston et al., 2007; Casey et al., 2007). Combining the concepts of PFC inefficiency with Volkow’s concept of a “noisy” salience detector in the BG, we posit

that “noisy” BG function would lead to compensatory increases in activation in the PFC for adolescents with ADHD, in the context of equal behavioral or cognitive performance relative to normative controls.

In the current study we test these ideas by manipulating salience and cognitive control demands 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 BG function, the PFC will activate less while the participant is on medication, while producing the same or better performance. We also predict medication-related changes in (a) BG activity and (b) BG-PFC connectivity. Because, however, of the lack of fMRI research specifically assessing BG function in ADHD, and because of the lack of research on functional connectivity in this population, we do not make a prediction regarding the direction (e.g., increased vs. decreased activation) of any BG effects.

Methods and Materials

Participants

Participants were 5 adolescent girls (12–17 yrs) 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, and Hinshaw et al. 2006, 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 sub-sample. 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 subjects included in this sample have already been published elsewhere (Sheridan et al. 2007). Two subjects were taking a non-stimulant medication in addition to the stimulant. One was prescribed 100mg of Zoloft, another .05mg of Clonidine; these medications were held constant across scans, while their stimulant medication was manipulated.

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 Subjects, 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 subjects received medication during the first session and 2 subjects received medication during the second session. To address the potential confounder of practice effects, paired sample t-tests were conducted for both 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 one hour before the scan.

Cognitive Task

Adolescents performed a delayed match-to-sample task, using letter stimuli, with a memory load manipulation (high: 6 letters vs. low: 2 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 inter-trial interval was 13.2 seconds. The task was divided into 10 runs of 8 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 (for more information see Sheridan et al. 2007). Each functional volume acquisition was a whole brain volume, with $3.5 \times 3.5 \times 5.5$ mm voxels. Image processing and analysis were completed using a Statistical Parametric Mapping program (SPM2; Friston et al. 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 et al. 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.

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 Region of Interest (ROI) analysis was performed for two areas: bilateral middle frontal gyrus (MFG: Brodmann's Areas 8/9/46) and bilateral BG (caudate, putamen and 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.

Finally, to directly assess the relationship between the PFC and BG, medication-related differences in functional connectivity were explored (Rissman et al., 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 subjects. These ROIs were used as seed regions, and functional connectivity was assessed for every voxel in the brain volume during the encoding period of the delayed match-to-sample task (see Rissman et al., 2004, for a detailed description of this procedure). To test our hypothesis of changes in functional coupling between MFG and BG on medication, correlation *t* maps were thresholded at $t > 4.60$ ($p < 0.005$; 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 ($t(4)=2.92$, $p=.043$). 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.

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 2.

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, $F(1,4) 14.79$, $p=.018$, 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. The task period by medication interaction was not significant in the BG ($F(1,4) .881$, $p=.401$); but it was marginally significant for the MFG ($F(1,4) 5.8$, $p=.074$). 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 the same pattern at encoding but this finding, although the mean difference in activation on and off medication was large, it only approached significance (Figure 2; $t(4) =1.773$, $p=.151$). 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.

Second, a functional connectivity analysis was performed using correlation (Figure 3, Table 3; Rissman, et al., 2004). Connectivity during the encoding period was compared between medication conditions. Significantly stronger functional connectivity between the MFG and BG was found for subjects *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 during 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 BG may contribute to ADHD symptoms (Halperin & Schulz 2006; Volkow et al. 2005). Stimulant medications may increase the saliency of the BG signal to the PFC, specifically by increasing extracellular striatal DA (Volkow et al. 2005, 2004). This hypothesis is consistent with research

positing a role for DA function in the BG, regarding its signaling the PFC as to the importance or saliency of environmental stimuli (Grace 1995).

In the current fMRI study, we tested this theory using a small 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. We used an ROI analysis to test hypotheses concerning activation of the PFC and its connectivity to the BG. In both the ROI and whole brain analysis 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 (medial, middle frontal gyrus), consistent with previous literature identifying multiple areas of dysfunction in the PFC for individuals with ADHD (Schweitzer et al. 2003, 2004; Mehta et al. 2000; Schulz et al. 2004; 2005; Durston et al. 2003). This finding supports the hypothesis that increased PFC activation in individuals with ADHD serves a compensatory purpose, because medication improves task performance in our study, with a concomitant decrease in PFC activation.

Although we did not find statistically significant medication-related differences in BG activation, the large actual differences in activation between medication conditions in the BG (Figure 2) lead us to conclude the possibility of a Type II error..

We explicitly tested MFG-BG interactions on and off medication using two different methods. We correlated mean BOLD activity in these two regions and we investigated functional connectivity between the MFG and BG during the encoding period of the working memory task. Off medication, a stronger correlation was observed between the MFG and BG compared to on medication. In addition, stronger MFG-BG functional connectivity was observed off compared to on medication, supporting the idea that stimulant medication effects change in part by targeting the frontal-striatal system. However, other areas also showed increased functional connectivity with the MFG off medication. These findings may reflect increased demands on frontal circuitry off medication.

The primary limitation of this study is the small sample size due to restrictions on subject participation. Because of low statistical power, any null results should be interpreted cautiously. Despite this important limitation, this study serves as a test of the hypothesis that increased but inefficient activity in the prefrontal cortex, found for children with ADHD during certain task conditions, serves a compensatory function. Furthermore, this is the first direct exploration of hypothesized changes in PFC functional connectivity with stimulant medication in ADHD. Through this direct assessment, we obtained evidence supporting dysfunctional cortical (MFG) - subcortical (BG, hippocampus) and cortical (MFG)-cortical (temporal parietal junction, medial PFC) connectivity, which is modified by medication. Clearly, further research in this area is required before firm conclusions about the relationship between prefrontal function and the presence of a deficit in DA function can be drawn.

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Figure 1.

Reaction time (ms) and Accuracy for subjects on and off medication, at high (encoding of 6 letters) and low (encoding of 2 letters) load. For accuracy, there are significant main effects of medication condition and load but no medication by load interaction.

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 > 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>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. Additionally, results of paired t-test (On>Off Medication) show increases only in cerebellar vermis for participants with ADHD on medication.

Table 1

Presents, 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.

Subject	Hyper/ 9	Attn/9	Medication
1	0	8	18mg Concerta (time release Methylphenidate)
2	9	7	20mg Adderall (Amphetamine Salts) (100mg Zoloft)
3	5	9	54mg Concerta (time release Methylphenidate)
4	9	9	108mg Concerta (time release Methylphenidate) 10mg Ritalin (Methylphenidate) (.05mg clonidine)
5	9	8	54mg Concerta (time release Methylphenidate)

Table 2

Each period of the task was compared to baseline using a one sample t-test, results are reported separately for adolescents off and on medication. For each task period, activation off and on medication was directly compared using a paired t-test. Only the encoding period showed activation differences based on medication. These differences, areas more active for participants off medication compared to on medication during encoding, are reported here.

Off Medication				On Medication			
Encoding							
voxels	t-values	coordinates	Area	voxels	t-values	coordinates	Area
38	12.05	(-42 -54 -20)	L Cerebellum	23	13.04	(30 -60 22)	R Cuneus
26	14.06	(-32 -86 -12)	L Lingual gyrus	22	20.1	(-44 -10 32)	L Postcentral gyrus
28	16.14	(-32 -72 10)	L Middle Occipital gyrus	31	18.76	(-50 4 18)	L Precentral gyrus
27	20.74	(-50 -28 30)	L Tempo-Parietal junction	21	27.18	(-2 -8 24)	Anterior Cingulate cortex
35	60.4	(36 -52 44)	R Angular gyrus	20	18.48	(-10 20 26)	Middle Cingulate cortex
75	22.91	(-2 -6 28)	Anterior Cingulate cortex	73	25.61	(14 8 34)	Middle Cingulate cortex
59	19.17	(-8 16 44)	Middle Cingulate cortex				
49	21.18	(10 36 36)	Middle Cingulate cortex				
24	12.14	(20 32 32)	R Middle Frontal gyrus				
Probe				Probe			
20	12.74	(38 -58 -28)	R Cerebellum	43	12.25	(28 -50 -30)	R Cerebellum
21	17.68	(-48 -64 -20)	L Cerebellum	24	36.18	(-40 -70 -28)	L Cerebellum
28	29.94	(-54 -50 -16)	L Inferior Temporal gyrus	57	21.1	(0 -72 -16)	Cereblar Vermis
50	28.73	(28 -50 -26)	R Fusiform gyrus	32	17.05	(-8 -68 20)	Calcarine cortex
33	29.87	(-2 -42 -12)	Cerebellar Vermis	44	19.76	(34 -30 -2)	R Hippocampus
47	41.46	(-12 22 4)	L Thalamus	25	20.15	(4 -50 56)	Precuneus
21	24.03	(32 -46 26)	R Tempo-Parietal junction	64	25.78	(36 -26 34)	R Postcentral gyrus
41	19.71	(-4 -8 50)	Middle Cingulate cortex	25	16.99	(-4 18 28)	Anterior Cingulate cortex
33	38.57	(-36 -10 56)	L Precentral gyrus	56	25.25	(38 34 24)	R Middle Frontal gyrus
50	28.09	(44 -8 46)	R Precentral gyrus				
22	23.59	(0 14 54)	Supplementary Motor Area				
24	16.29	(-20 36 34)	L Middle Frontal gyrus				
OFF>ON Medication							

Off Medication				On Medication			
Encoding							
voxels	t-values	coordinates	Area	voxels	t-values	coordinates	Area
Encoding							
31	14.42	(12 40 40)	Medial Prefrontal Cortex				
21	23.15	(-6 -58 50)	Precuneus				

Table 3

Results of paired t-test (Off>On Medication; On>Off Medication) showing areas increased in functional connectivity with bilateral Middle Frontal Gyrus (MFG).

OFF>ON Medication			
Encoding			
voxels	t-values	coordinates	Area
41	26.15	-38 16 44	L Middle Frontal Gyrus
70	11.84	-4 24 42	L Superior Medial Prefrontal Cortex
214	17.12	24 14 20	R Insula
27	9.73	60 -22 34	R Temporal Parietal Junction
53	8.77	6 -22 20	R Caudate/Putamen
32	13.33	-28 -20 -16	L Hippocampus
32	14.27	-54 -52 -6	L Inferior Temporal
36	9.96	26 -46 -4	R Lingual Gyrus
ON>OFF			
84	14.89	2 -80 -14	Cerebellar Vermis