Effect of Methylphenidate on Executive Functioning in Adults with Attention-Deficit/Hyperactivity Disorder: Normalization of Behavior but Not Related Brain Activity

Julie B. Schweitzer, Douglas O. Lee, Russell B. Hanford, Caroline F. Zink, Timothy D. Ely, Malle A. Tagamets, John M. Hoffman, Scott T. Grafton, and Clinton D. Kilts

Background: *We examined the effect of prolonged methylphenidate (MPH) treatment on the functional neuroanatomy of executive functioning in adult men with attention-deficit/hyperactivity disorder (ADHD).*

Methods: *Positron emission tomography with [^{15}O] water measured alterations of regional cerebral blood flow (rCBF) during the Paced Auditory Serial Addition Task and a control task in 10 ADHD and 11 normal control men. Attention-deficit/hyperactivity disorder men were imaged unmedicated and after a clinically optimal dose of MPH for 3 weeks.*

Results: *Methylphenidate improved ADHD task performance, reduced rCBF in the prefrontal cortex (PFC), and increased rCBF in the right thalamus and precentral gyrus. Comparisons between the ADHD and normal control groups showed that normal control participants exhibited greater anterior cingulate cortex and temporal gyrus rCBF than ADHD participants under both conditions. Executive functioning was associated with greater subcortical (basal ganglia and cerebellar vermis) activation in the ADHD than normal control group under both conditions.*

Conclusions: *Methylphenidate does not normalize task-related activity in ADHD. Task-related rCBF decreases in the PFC may be due to improved filtering out of task-irrelevant stimuli by way of MPH-mediated dopamine release in the PFC.*

Key Words: PET, ADHD, methylphenidate, executive function, working memory, PASAT

While therapeutic doses of methylphenidate (MPH) in humans appear related to increased extracellular dopamine in the striatum due to inhibition of the reuptake by dopamine transporters (Volkow et al 2001), little is known about the cognitive correlates of MPH in patients with attention-deficit/hyperactivity disorder (ADHD). The animal literature on MPH suggests the involvement of both dopaminergic and noradrenergic systems (e.g., Arnsten 2001; Kuczenski and Segal 2001; Porrino and Lucignani 1987). Studies in animals have shown intact catecholaminergic functioning is crucial to supporting functions associated with the prefrontal cortex (PFC), such as working memory (WM) and other executive functioning (EF) processes (Arnsten et al 1994; Brozoski et al 1979; Sawaguchi and Goldman-Rakic 1991, 1994; Tunbridge et al 2004). Accumulating evidence suggests altered catecholaminergic transmission in the PFC disrupts executive functioning in clinical populations, such as in schizophrenia (Abi-Dargham et al 2002; Egan et al 2001; Mattay et al 2003) and Parkinson disease (Mattay et al 2002).

There is increasing support for alterations in structure and function of the PFC in ADHD, including 1) smaller PFC volumes (Castellanos et al 1996; Filipek et al 1997; Sowell et al 2003); 2) altered PFC function in imaging studies (Durston et al 2003; Ernst et al 1997; Kim et al 2002; Rubia et al 1999; Schweitzer et al 2000; Vaidya et al 1998; Zametkin et al 1990); 3) decreased fluorodopa uptake by catecholamine neurons in the PFC in adults with ADHD (Ernst et al 1998); and 4) improvement in EF deficits thought to be mediated by the PFC with stimulants (Bedard et al 2004; Tannock et al 1995).

Prefrontal cortex impairment in the form of EF difficulties is present in both children (Anastopoulos et al 1994; Barnett et al 2001; Mariani and Barkley 1997; McInnes et al 2003) and adults with ADHD (Barkley et al 1996; Dowson et al 2004; Kovner et al 1998; Lovejoy et al 1999; Lufi and Cohen 1985; Murphy et al 2001). Working memory, or the ability to hold information in mind, manipulate it, and use it to guide behavior (Baddeley 1996), is a specific component of EF and may be linked to difficulties that the individual with ADHD encounters in the classroom, work setting, or even social relationships. We proposed that individuals with ADHD use alternative strategies and brain regions during WM tasks due to impaired PFC functioning (Schweitzer et al 2000). We found adults with ADHD were more likely to report using visual strategies and activation of brain regions associated with visual imagery, while healthy control participants showed greater activation of regions associated with verbal strategies (e.g., left superior temporal gyrus, Brodmann's area [BA] 22).

Methylphenidate improves EF function in ADHD (e.g., Bedard et al 2004; Tannock et al 1995); however, the physiologic basis for this improvement in ADHD is not well known. In normal adults, improvement in EF in the form of a spatial WM task with acute MPH administration was associated with reductions in task-related activation in the PFC, supplementary motor area, and posterior parietal cortex (Mehta et al 2000). The current study assessed the effects of prolonged MPH treatment on EF in adults with ADHD using the Paced Auditory Serial Addition Task (PASAT) (Gronwall 1977; Levin et al 1988; Staffen et al 2002) to tap EF composed of WM, attention, response inhibition, and speed of information processing. We hypothesized that MPH would alter PASAT-related PFC functioning in the PFC based on

From the Maryland Psychiatric Research Center (JBS, MAT) and the Division of Child Psychiatry (JBS), University of Maryland School of Medicine, Baltimore, Maryland; Department of Psychiatry and Behavioral Sciences (DOL, RBH, CFZ, TDE, CDK), Emory University School of Medicine, Atlanta, Georgia; National Cancer Institute (JMH), National Institutes of Health, Bethesda, Maryland; and Center for Cognitive Sciences (STG), Dartmouth College, Hanover, New Hampshire.

Address reprint requests to Julie Schweitzer, Ph.D., MPRC, University of Maryland School of Medicine, PO Box 21247, Catonsville, MD 21228; E-mail: jschweit@mprc.umaryland.edu.

Received December 30, 2003; revised July 8, 2004; accepted July 13, 2004.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2004.07.011

Table 1. Demographic and Clinical Characteristics of Adults with ADHD and NC Participants

Measure	ADHD Mean	ADHD ±SD	Control Mean	Control ±SD	p^a
Age	31.5	±8.2	29.2	±7.4	ns
Years of Education	16.3	±2.4	16.6	±2.3	ns
Full-Scale WAIS IQ	122.0	±10.2	118.4	±13.5	ns
WRAT-Reading SS	112.3	±5.6	110.0	±7.2	ns
WRAT-Arithmetic SS	111.4	±10.9	114.7	±12.2	ns
Adult ADHD DSM-IV Rating scale					
Self-current[b]	33.6	±7.4	2.5	±2.1	.0001
Significant other/friend	27.5	±10.9	3.3	±3.7	.0001
Self-child retrospective	37.7	±8.1	2.6	±2.5	.0001
Mother retrospective	32.0	±8.6	3.1	±3.5	.0001

ADHD, attention-deficit/hyperactivity disorder; NC, normal control; WAIS, Wechsler Adult Intelligence Scale; IQ, intelligence quotient; WRAT, Wide Range Achievement Test; SS, subscale; ns, not significant.

[a] *t* test.

[b] Cutoff score for clinical significance on Adult ADHD DSM-IV Rating Scale for current behavior is 23.6.

studies with varying methodologies showing MPH modifies frontal lobe activity (Kim et al 2001; Matochik et al 1993, 1994; Mehta et al 2000; Vaidya et al 1998). We hypothesized that MPH would also alter subcortical (e.g., basal ganglia, cerebellar) brain activation. Studies in children with ADHD suggest MPH either increases subcortical activation or alters it in relationship to the MPH dose or the activity level of the child (Anderson et al 2002; Kim et al 2001; Lou et al 1989; Teicher et al 2000; Vaidya et al 1998). In contrast, MPH in adults, including a study in normal control subjects (Volkow et al 1997), suggests MPH decreases basal ganglia activation (Matochik et al 1994; Schweitzer et al 2003; Volkow et al 1997). The current study assessed the effect of MPH on the neural correlates of EF in ADHD adults after prolonged (≥3 weeks) treatment and determined if MPH normalized neural correlates of EF deficits.

Methods and Materials

Participants

The initial subject sample consisted of 13 men diagnosed with ADHD, combined type (American Psychiatric Association 1994), and a group of 11 healthy normal control (NC) subjects matched for age, gender, and general intelligence (Table 1). Two of the ADHD men in the unmedicated condition did not participate in the medicated condition, and brain positron emission tomography (PET) data from one of the ADHD participants in the off-medication condition was incomplete. Therefore, the final ADHD sample was composed of 10 men with complete PET data sets for both the on-medication and off-medication conditions. All participants were right hand dominant (Raczkowski and Kalat 1974) and following thorough discussion of the protocol, gave written informed consent to participate in a protocol approved by the Human Investigations Committee and the Radiation Safety Committee at the Emory University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki. Subject recruitment was based on referrals from a university-based adult ADHD clinic and responses to local advertisements. A licensed, Ph.D. level psychologist (JBS) interviewed each participant. Participants also completed a computerized structured psychiatric interview (Mini-Structured Clinical Interview for DSM-IV [Mini-SCID]) (First et al 1996) and the Symptom Checklist-90, Revised (SCL-90-R) (Deragotis 1986) to screen for non-ADHD psychiatric disorders.

Investigators screened each participant using a semistructured interview, the Adult ADHD DSM-IV Rating Scale (Murphy and Barkley 1996), available past psychiatric records, and grade school report cards. Spouses or close friends of the participants rated current behavior. Participants and their parents rated participants' childhood behavior on the ADHD DSM-IV Rating Scale to confirm the presence of the disorder during childhood (Table 1). All ADHD participants fulfilled DSM-IV diagnostic criteria for ADHD at initial diagnosis (JBS) and at diagnostic confirmation (DOL).

The Wechsler Adult Intelligence Scale-III (WAIS) (Wechsler 1997) assessed intellectual functioning. The reading and arithmetic subtests of the Wide Range Achievement Test–Third Edition (WRAT-3) (Wilkinson 1993) measured academic achievement and was used in conjunction with the WAIS to exclude participants with a potential reading or mathematic learning disability.

Volunteers were excluded for the following reasons: clinically significant chronic medical conditions, history of brain injury, presence of metal or a prosthesis in the body, mental retardation (full scale intelligence quotient [IQ] < 75), Axis I disorders (with the exception of ADHD for the ADHD participants), history of nonstimulant pharmacotherapy within 2 months of the study, or any history of antipsychotic medication. All participants received a neurologic exam (DL) and the results were negative for any focal abnormalities. In addition, we excluded NC subjects if they or their first-degree family members met DSM-IV criteria for any psychiatric disorder.

Four of the ADHD participants had a prior history of MPH administration, two participants as children and two as adults. Participants medicated as children had been stimulant-free for approximately 10 years. One adult had been stimulant-free for several months and the other had been stimulant-free for 8 days before the off-medication images were collected.

Medication Conditions

During the treatment condition, ADHD participants received MPH (Ritalin) on a three times a day dosing schedule and were started at .5 mg/kg/d for the first week, .75 mg/kg/d for the second week, and up to 1.0 mg/kg/d for the third week, unless adverse side effects precluded further dose titration. Methylphenidate dose was increased until the clinically optimal dose was achieved. Dosing was based on weekly evaluations by a psychiatrist (DOL), including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale (National Institute of Mental Health 1985) with improvement defined as a score of 1 or 2 (very much or much improved), completion of the Side Effects Rating Scale for psychostimulants (Barkley 1981) that showed participants had minimal to no side effects, and reduction of 30% or greater on Adult ADHD DSM-IV Rating Scale scores (Murphy and Barkley 1996) completed by the participant and a significant other or friend of the participant. Nine of the ADHD participants were imaged unmedicated for the first scan and medicated for the second scan after a minimum of 3 weeks on an optimal MPH dose. One participant was imaged in reverse order. On the day of the medicated imaging sessions, participants ingested their optimal dose of medication 60 minutes before scanning began.

PET Imaging Conditions

The PASAT (Gronwall 1977), used as an EF measure, relies on allocation and coordination of attention, active stimulus manipulation, retrieval, and interference control in a speeded format. Many of the processes required by the PASAT are impaired in ADHD (Barkley 1998). One major advantage of the task is its ability to detect impairment in an adult population that is relatively high functioning, in contrast to tasks used with ADHD children or populations with greater functional impairments. Each participant practiced the task until demonstrating 100% accuracy on three consecutive brief series of numbers before the PET acquisitions. During the PASAT, 50 single-digit, computer-generated random numbers (1–9) were presented binaurally through earphones, 1 every 200 milliseconds. Participants were instructed to add each number to the preceding number and vocalize their answers. As a self-paced control condition, participants were told to generate and vocalize single or double-digit random numbers. The number-generate task was intended to control for the contribution of arousal, motor, verbal production (auditory stimulation), and short-term (nonworking) memory to the regional cerebral blood flow (rCBF) changes associated with the PASAT. Numbers generated from the number-generate control task were tape-recorded and rate of production was scored. A third condition consisted of a resting state.

Within a session, each participant completed a total of two resting, three number-generate, and three PASAT conditions for a total of eight PET acquisitions. The order of the tasks was the same across participants, with each PASAT condition paired with a number-generate control condition. The rest conditions occurred at the beginning and end of the PET acquisitions. Attention-deficit/hyperactivity disorder participants were imaged twice (during the on-medication and off-medication conditions) and NC subjects once.

A ECAT 951 PET scanner (Siemens, Knoxville, Tennessee) acquired PET images under dim ambient lighting. The scanner collected 31 contiguous 3.375-mm-thick slices with an intrinsic resolution of 6 mm at the center of the field of view. Head movement was minimized using a thermoplastic face mask affixed to a customized head holder. The PASAT and number-generate conditions began 10 seconds before bolus intravenous administration of 45 mCi of [^{15}O] water. Ninety-second, single frame studies were initiated by the detection of head radioactivity and acquired in a two-dimensional mode. Participants closed their eyes in all conditions.

PET Imaging and Data Analysis

We used statistical parametric mapping 99 (SPM99) (Wellcome Department of Cognitive Neurology, London, England; http://www.fil.ion.ucl.ac.uk/spm) (Friston et al 1996) to process and analyze the PET images. The participant's first scan was used to realign the remaining scans for each participant. After realignment, the images were transformed into a standard anatomical space (Talairach and Tournoux 1988) and smoothed to a final isotropic resolution of 10 mm at full-width at half maximum before generating the statistical parametric map.

After normalization by proportional scaling to the global mean of each image, we analyzed task-related changes in rCBF between the number-generate control task and the PASAT for the ADHD group on medication and off medication. The analyses also contrasted images from the NC group to images from the ADHD group under the unmedicated and medicated conditions.

Masking. Significant differences between conditions and groups can be generated by both increases or decreases in blood flow between cognitive states or between groups. Masking can aid in the detection of differences in task-related neural activity by assigning direction to the differences found between conditions and groups. For the between-group analysis and the unmedicated versus medicated ADHD comparisons, the images were masked in two ways to isolate changes in rCBF related to the PASAT only and not the other conditions. The first mask was done to exclude areas that were significant in the number-generate minus PASAT conditions. For example, for the NC versus ADHD contrast, the mask excluded voxels that were significantly increased in the number-generate minus PASAT contrast for the ADHD group. The second mask was used to control for MPH effects on the number-generate condition that might alter the PASAT minus number-generate results. This second mask was accomplished by masking activation related to the comparison of the "on" versus "off" MPH conditions for the number-generate minus rest contrast. Significant sites of activation were defined by a voxel intensity of $p < .001$, uncorrected for multiple comparisons for difference images related to the PASAT condition after both masks.

Behavioral Data Analysis

We collected behavioral outcome measures for all PASAT trials and number-generate conditions. Paced Auditory Serial Addition Task performance (i.e., response accuracy, response time) and number generation rates were averaged over three imaging sessions. A paired *t* test compared ADHD off-medication and on-medication scores and an independent sample *t* test compared ADHD performance with NC using two-tailed significance tests.

Results

MPH Effects on ADHD Symptoms and PASAT Performance

The mean daily dose of MPH was 19 mg (SD = 9.07) administered over a mean of 2.9 (SD = .74) divided doses per day. Methylphenidate pharmacotherapy was statistically effective in reducing ADHD symptoms as measured by the CGI and self and other's ratings on the Adult ADHD DSM-IV Rating Scale (Table 2). Methylphenidate improved PASAT performance accuracy of 82% (SD = 12.90) at baseline to 89% (SD = 6.15) at end point ($t = 2.73$, $df = 9$, $p = .02$). The NC group performed significantly better on the PASAT (mean = 93% correct, SD = 6.42) than the ADHD group at baseline ($t = 2.65$, $df = 19$, $p = .02$) but not at end point. Mean response time (MRT) on the PASAT decreased significantly under the MPH condition from 750 milliseconds (SD = 10 milliseconds) to 690 milliseconds (SD = 9 milliseconds) seconds ($t = 3.68$, $df = 7$, $p = .008$) based on complete data sets from eight ADHD subjects (data from two ADHD subjects and one NC subject were lost due to computer malfunction). Mean response time between the ADHD and NC subjects (mean = 640 milliseconds, SD = 25 milliseconds) seconds did not differ significantly under either medication condition. Rates of generating random numbers during the number-generate condition did not vary between the medication conditions of the ADHD group or between the ADHD conditions and the NC group. During the unmedicated condition, the ADHD group generated random numbers on an average of .59 (SD = .12) numbers per second, during the medicated condition .58 (SD = .11) numbers per second, and the NC group on the average of .60 (SD = .11) numbers per second. This rate compares with a rate of response every .50 numbers per second for the PASAT during the PASAT condition.

Table 2. Symptom Ratings for the ADHD Participants at Baseline and End Point of the MPH Medication Trial

Measure	Baseline Rating		End of Treatment Rating			
	Mean	±SD	Mean	±SD	*t*-value	*p*
CGI[a]	4.4	±.70	1.9	±.57	9.30	.0001
ADHD Rating Scale–Self[b]	34.5	±7.1	8.7	±3.7	9.7	.0001
ADHD Rating Scale–Other[b]	27.5	±10.9	8.0	±4.5	4.5	.002

ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; CGI, Clinical Global Impressions Scale.
[a]Global Severity of Illness Subscale of the Clinical Global Impression (CGI) Scale.
[b]Scale scores can range from 0–54.

Within Group Analyses: PASAT Versus Number Generation Conditions

Normal Control Participants. Consistent with the results of a previous PET study (Schweitzer et al 2000), the PASAT-related activation of the largest spatial extent was in the left superior temporal gyrus (BA 22) with additional activations in the right superior (BA 22) and left middle temporal gyrus (BA 21). Significant PASAT-related activations were noted also in the right PFC (BA 11, 46), ventral anterior cingulate cortex (BA 24), precuneus, fusiform gyrus (BA 20), and hippocampus (Table 3).

Unmedicated ADHD Participants. Similar to the NC subjects, participants with ADHD showed significant increases in rCBF during the PASAT condition in the left superior temporal sulcus (BA 22), right middle temporal gyrus (BA 21), left hippocampus, and precuneus (BA 7) (Table 4). The ADHD participants showed unique PASAT-related activations, however, that included the cerebellar vermis, midbrain, left thalamus, left globus pallidus, right lenticulate, and left middle frontal gyrus (BA 46) (Table 4). Unlike the NC subjects, the ADHD participants did not activate the right PFC or anterior cingulate cortex.

Methylphenidate-Medicated ADHD Participants. Following a therapeutic regimen of MPH administration, the ADHD participants activated many of the same regions as when untreated, including the posterior cerebellum vermis (VIII), bilateral superior temporal gyrus (BA 22/42), left thalamus, bilateral basal ganglia, left hippocampus, and precuneus (BA 7). Only the MPH-treated ADHD participants, however, demonstrated PASAT-related activation of the right precentral and postcentral gyrus (Table 5).

Between Condition Analyses: PASAT Versus Number Generation Conditions

Unmedicated ADHD Versus Medicated ADHD Condition. This analysis compared the task-related rCBF changes between the untreated and treated conditions using volumes of interest defined by subtraction of the number-generate control condition from the PASAT condition (Figure 1). In the unmedicated ADHD condition, the PASAT was associated with greater activation of the right middle (BA 9, Talairach coordinates x = 52, y = 34, and z = 36 mm, z score = 3.49) and medial (BA 10, x = 14, y = 50, and z = 2 mm, z score = 3.22] frontal gyrus compared with the medicated condition. Methylphenidate administration was associated with PASAT activation of the right thalamus (x = 24, y = −30, and z = 16 mm, z score = 3.76) and precentral gyrus (BA 4, x = 56, y = −12, and z = 54 mm, z = 3.57) compared with the medication-free condition.

Between Group Analyses: PASAT Versus Number Generation Conditions

Normal Control Participants Versus Unmedicated ADHD Participants. We compared the NC group with the untreated ADHD group for the PASAT versus number-generate conditions to identify the influence of ADHD on the neural correlates of EF (Table 6, Figure 2A). The most prominent differences were greater activations of the inferior frontal (BA 45/47) and superior temporal gyri (BA 40, 22) and the ventral anterior cingulate cortex (BA 24) in NC participants. Conversely, the ADHD participants exhibited greater PASAT-related activation of primarily subcortical regions (i.e., midbrain, pons, right caudate nucleus,

Table 3. Localization of Changes in Normalized rCBF in NC Group During PASAT Versus Number-Generate Conditions

Anatomical Region	Site of Activation		Analysis	
	BA	x, y, z	*Z*	k_E[c]
Superior Temporal Gyrus, Left	22	−58, −48, 14	6.72	4097[a]
Middle temporal gyrus, left	21	−64, −2, −8	5.14	4097[a,b]
Superior Temporal Gyrus, Right	22	72, −26, 2	5.79	3216[a]
Superior Frontal Gyrus, Right	11	16, 60, −14	3.51	322
Precuneus	7	2, −52, 34	3.45	388
Inferior Frontal Gyrus, Right	45/46	34, 26, 8	3.42	177
Anterior Cingulate	24	0, 20, −6	3.41	531
Hippocampus, Left		−22, −34, −10	3.30	126
Fusiform Gyrus, Right	20	42, −20, −20	3.12	72
Fusiform Gyrus, Left	20	−46, −42, −20	3.11	77
Posterior Cerebellum, Right		10, −84, −22	3.02	91

rCBF, regional cerebral blood flow; NC, normal control; PASAT, Paced Auditory Serial Addition Task; BA, Brodmann area.
[a]Clusters with voxels significant at .05 after correcting for multiple comparisons.
[b]Secondary peak in cluster.
[c]Cluster extent.

Table 4. Localization of Changes in Normalized rCBF in the Unmedicated ADHD Group During PASAT Versus Number-Generate Conditions

	Site of Activation		Analysis	
Anatomical Region	BA	x, y, z	*Z*	k_E[c]
Superior Temporal Gyrus, Left	22	−68, −22, 4	5.12	1731[a]
Superior Temporal Gyrus, Left	22	−56, −54, 14	4.48	1731[a,b]
Posterior Cerebellum Vermis, VIIIA, Right		4, −64, −34	4.97	2469[a]
Midbrain, Right		4, −32, −16	4.35	2469[a,b]
Middle Temporal Gyrus, Right	21	68, −16, −2	4.91	1811[a]
Superior Temporal Gyrus, Right	22	64, −34, 10	4.55	1811[a,b]
Globus Pallidus, Left		−12, 4, −4	3.99	454
Caudate/Putamen, Right		12, 12, −6	2.99	454[b]
Middle Frontal Gyrus, Left	46	−48, 36, 30	3.37	93
Thalamus, Left		−24, −26, 6	3.36	357
Hippocampus, Left		−28, −28, −6	3.35	357[b]
Precuneus	7	−2, −58, 34	3.30	231

rCBF, regional cerebral blood flow; ADHD, attention-deficit/hyperactivity disorder; PASAT, Paced Auditory Serial Addition Task; BA, Brodmann area.
[a]Clusters with voxels significant at .05 after correcting for multiple comparisons.
[b]Secondary peak in cluster.
[c]Cluster extent.

and cerebellar vermis), as well as the left middle frontal gyrus (BA 46/9) (Figure 3A).

Normal Control Participants Versus Medicated ADHD Participants. Comparisons were made between the NC participants and the MPH-medicated ADHD participants to determine if MPH treatment normalized EF-related changes in rCBF. This analysis demonstrated that PASAT-related brain regions continued to differ between medicated ADHD and NC participants (Table 7). The activation with the largest spatial extent that differentiated the groups (NC > ADHD; Figure 2B) was in the anterior cingulate cortex (BA 32), extending to the orbitofrontal cortex (BA 11). The NC participants also activated the inferior (BA 20) and middle temporal (BA 39) gyri more than the ADHD participants. Conversely, for the medicated ADHD participants, the PASAT was associated with greater activation of sensory and motor areas (BA 3), the cerebellar vermis, and bilateral basal ganglia compared with NC participants (Figure 3B). Additional significant activations (ADHD > NC) included the right middle frontal gyrus (BA 10), left inferior occipital lobe (BA 18), right insula, and left inferior frontal gyrus (BA 47).

Discussion

Similar to Mehta et al (2000), we found that MPH administration reduced EF-related activity in the PFC. We speculate that reductions in rCBF in the PFC are due to the release of dopamine by MPH in the PFC that, in turn, act on dopamine D1 and D2 receptors. Increases in dopamine have been shown to cause reductions in the firing activity of PFC neurons (Isacson et al 2004; Parfitt et al 1990; Zhou and Hablitz 1999). Dopamine,

Table 5. Localization of Changes in Normalized rCBF in the MPH-Treated ADHD Group During PASAT Versus Number-Generate Conditions

	Site of Activation		Analysis	
Anatomical Region	BA	x, y, z	*Z*	k_E[c]
Posterior Cerebellum Vermis, VIIIB		2, −66, −38	5.76	2485[a]
Superior Temporal Gyrus, Right	22/42	74, −20, 6	5.17	3646[a]
Inferior Parietal Lobe, Right	39	68, −54, 24	4.83	3646[a]
Superior Temporal Gyrus, Left	22	−66, −44, 14	5.16	3570[a]
Putamen, Right		28, 6, 14	4.72	1192[a]
Globus Pallidus, Right		14, −2, −2	3.55	1192[a,b]
Caudate Nucleus, Left		−4, 10, −2	3.88	870[d]
Lenticulate, Left		−14, −6, 8	3.59	870[b,d]
Thalamus, Left		−10, −12, 16	3.12	870[b,d]
Precentral Gyrus, Right	4	50, −10, 56	3.74	249
Hippocampus, Left		−22, −32, 0	3.58	334
Precuneus	7	2, −58, 34	3.33	253
Postcentral Gyrus, Right	5	36, −40, 64	3.22	85

rCBF, regional cerebral blood flow; MPH, methylphenidate; ADHD, attention-deficit/hyperactivity disorder; PASAT, Paced Auditory Serial Addition Task; BA, Brodmann area.
[a]Clusters with both voxel intensity and cluster size significant at .05 after correcting for multiple comparisons.
[b]Secondary peak in cluster.
[c]Cluster extent.
[d]Clusters with cluster size significant at $p < .05$ after correcting for multiple comparisons.

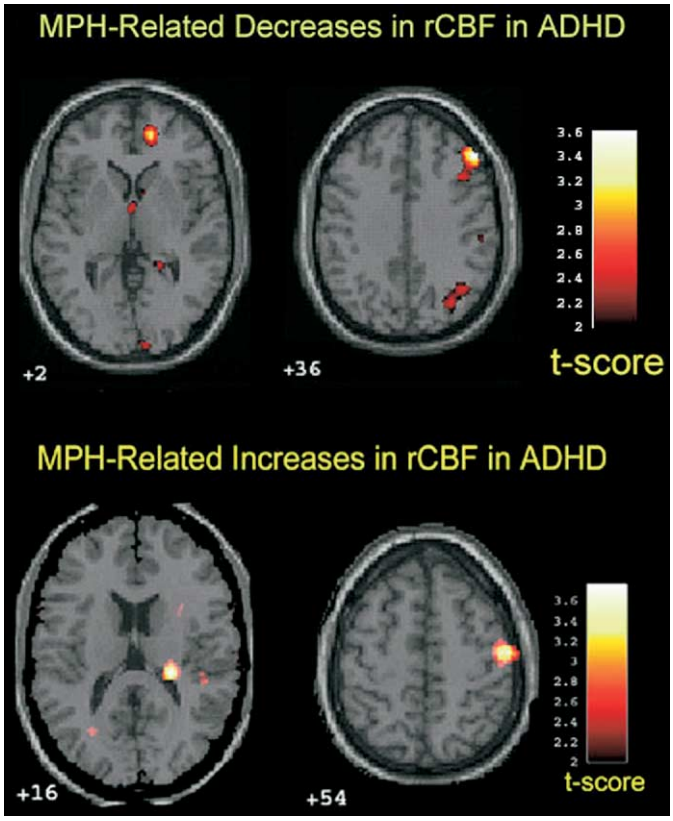

Figure 1. The top row displays relative rCBF PASAT-related decreases in on-MPH versus off-MPH conditions in men with ADHD. The bottom row displays relative rCBF PASAT-related increases in on-MPH versus off-MPH conditions in men with ADHD. The image illustrates that MPH is associated with significant increases in brain activity in the right thalamus and precentral gyrus during the PASAT. For this figure as well as Figure 2 and Figure 3, the sites of activation displayed are significant at a voxel level of $p < .001$ uncorrected for multiple comparisons. The number beneath the image indicates the millimeters above or below the bicommisural plane. The image illustrates that MPH is associated with significant decreases in brain activity in the right medial and middle frontal gyrus during an EF task. For this figure as well as Figures 2 and 3, the sites of activation displayed are significant at a voxel level of $p < .001$ uncorrected for multiple comparisons. The number beneath the image indicates the mm above or below the bicommisural plane. rCBF, regional cerebral blood flow; PASAT, Paced Auditory Serial Addition Task; MPH, methylphenidate; ADHD, attention-deficit/hyperactivity disorder; EF, executive functioning.

acting through D1 receptors, appears to inhibit local excitatory connections among layer V pyramidal cells in the PFC (Gao et al 2001; Williams and Goldman-Rakic 1995) during WM tasks. These actions likely account for the rCBF reductions we have observed. More specifically, a neural modeling study (Wang et al 2004) has suggested a pivotal role for cortical interneurons in the microcircuit of WM and how they may work to enhance resistance against distractors. Dopamine has been reported to modulate inhibitory circuits involving fast-spiking and non–fast-spiking cells onto the perisomatic domains on layer V pyramidal cells (Gao et al 2003). The net effect of dopamine on synaptic inhibition mediated by the two types of cells is postulated to enhance resistance against distractors in a WM paradigm, thus boosting EF performance. Our task, the PASAT, requires active inhibition of distracting stimuli, such as the answer for the total from the previous two stimuli, to effectively maintain online the new stimulus to be recalled for each trial. Methylphenidate may enhance task performance by directly improving the ability of the interneurons to filter out distractors.

Alterations in PFC activations associated with MPH also might be related to the difficulty level of the task and task-specific operations (e.g., importance of inhibiting distractors), as recent studies have demonstrated hypofunctioning and hyperfunctioning in the PFC depending on the difficulty level of the task and baseline functioning of the subject (Callicott et al 1999, 2000, 2003; Mattay et al 2003). We suspect the MPH action of decreasing PFC activity applies to some EF tasks without clear WM components, as PFC decrements have also been shown with a continuous performance task (Matochik et al 1993). In contrast, others have found increases in PFC activation (Kim et al 2001; Vaidya et al 1998) or no change (Matochik et al 1994) with MPH. Differences in PFC-MPH findings may be due to a number of variables, including the imaging techniques used, child versus adult subjects, flexible versus fixed dose medication regimens, chronic versus acute dosing conditions, task or resting state conditions, type and difficulty level of the task, ADHD diagnostic issues (e.g., subtype of ADHD included, screening for comorbidity), patient versus normal control subjects, and the role of novelty of the task. Future research will need to systematically test the impact of these factors on PFC-MPH interactions.

Practice effects cannot be ruled out as another possible explanation for reduced PFC activity (e.g., Beauchamp et al 2003; Petersen et al 1998; Qin et al 2003, 2004) associated with MPH. We suspect, however, that practice effects for the ADHD participants between the scanning days were negligible, because the ADHD participants demonstrated no improvement in performance between the three PASAT scans within each day of testing under the unmedicated or medicated conditions (data not shown). Perhaps training the participants on the PASAT to criterion before the imaging sessions reduced learning effects on the task. Future studies controlling for order effects will need to investigate this possibility.

We are speculating the only cortical region to show rCBF increases associated with MPH, the primary motor area (BA 4), might be related to increased preparatory efforts to respond rapidly to task-relevant stimuli, enabled by less demand on the frontal cortex to respond to irrelevant distractors. The other region to increase with MPH administration, the right thalamus, may be in response to increased norepinephrine (NE) release and reflect the drug's effects on NE at both α-1 (Rogawski and Aghajanian 1980) and β-receptors that work to increase the responsiveness of thalamic neurons to stimuli sensed from the environment (Berridge 2001). This may be a non–task-specific effect, as increases in thalamic activity appeared in a resting state MPH study in ADHD children as well (Kim et al 2001).

The anterior cingulate is a region that appeared to be grossly unaffected by MPH, as we found it to be underactive in the ADHD group in comparison with the NC group under both conditions. This region has been consistently found to be underactive in both children and adults with ADHD (Bush et al 1999; Ernst et al 2003; Rubia et al 1999; Schweitzer et al 2000). The absence of significant anterior cingulate cortex activation, as demonstrated in the within-group contrasts, suggests that the ADHD group may be relying on other regions, perhaps motor regions, to assist in the traditional role of inhibiting responding and managing conflict between the ongoing PASAT stimuli (Braver et al 2001; Rubia et al 2001; van Veen et al 2001).

Consistent with Mehta et al (2000), we did not find task-related cerebellar activation with MPH in this study. Methylphenidate clearly has non–task-related effects of increasing rCBF

Table 6. Localization of Differences in Normalized rCBF between NC and Unmedicated ADHD Groups for the PASAT Minus Number-Generate Contrast

Anatomical Region	Site of Activation		Analysis	
	BA	x, y, z	*Z*	k_E[a]
Areas of Activation Greater in NC Than ADHD Groups				
Inferior Frontal Gyrus, Left	45/47	−54, 38, 0	3.74	34
Supramarginal Gyrus, Left	40	−62, −46, 28	3.45	157
Superior Temporal Sulcus, Left	22	−40, −44, 10	3.34	70
Anterior Cingulate Gyrus	24	0, 20, −6	3.31	92
Middle Temporal Lobe, Left	21	−60, −2, 4	3.04	70
Insula, Left	13	−36, 18, 8	3.04	38
Middle Occipital Gyrus, Left	37	−50, −68, 4	3.01	41
Areas of Activation Greater in ADHD Than in NC Groups				
Midbrain/Pons, Right		4, −32, −16	3.61	127
Caudate Nucleus, Right		22, −6, 22	3.32	65
Anterior Cerebellum, Vermis, XIII		4, −58, −28	3.18	119
Middle Frontal Gyrus, Left	46/9	−38, 28, 30	3.18	33

rCBF, regional cerebral blood flow; NC, normal control; ADHD, attention-deficit/hyperactivity disorder; PASAT, Paced Auditory Serial Addition Task; BA, Brodmann area.
[a]Cluster extent.

in the cerebellar vermis both in ADHD participants (Anderson et al 2002; Schweitzer et al 2003) and normal control participants (Mehta et al 2000; Volkow et al 1997), most likely by enhancing extracellular concentrations of norepinephrine (Kuczenski and Segal 2001).

Although MPH does not appear to have a direct effect on task-related brain activation in the cerebellum, it is targeting a brain region that is altered in volume (e.g., Berquin et al 1998; Castellanos et al 2002; Mostofsky et al 1998) and, our data suggest, in function. Contrasts in the present study found greater PASAT-related activity in the cerebellar vermis in the ADHD group in comparison with the NC group for either medication condition. Perhaps as Arnsten (2001) has speculated, PFC dysfunction has relegated control of behavior to subcortical structures such as the cerebellum (and perhaps the basal ganglia) to compensate for the PFC dysfunction.

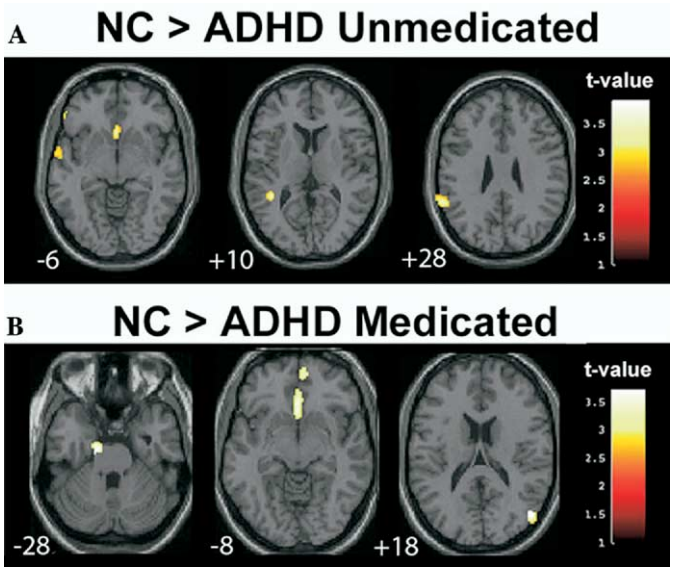

Figure 2. Contrasts between NC participants versus men with ADHD during different medication conditions versus normal control participants. **(A)** The top row displays images from relative rCBF PASAT-related increases in brain activity in NC participants versus unmedicated men with ADHD versus NC participants. **(B)** The bottom row displays images from relative rCBF PASAT-related increases in brain activity in NC participants versus MPH medicated men with ADHD. ADHD, attention-deficit/hyperactivity disorder; rCBF, regional cerebral blood flow; PASAT, Paced Auditory Serial Addition Task; NC, normal control; MPH, methylphenidate.

The basal ganglia is another subcortical region that showed PASAT-related increases in rCBF under both the unmedicated and medicated conditions in comparisons between the ADHD and NC groups. Basal ganglia activation may reflect preferential use of visual/spatial strategies to perform the PASAT and guide motor preparation (Postle and D'Esposito 1999; 2003) over brain regions associated with verbal/phonological strategies (e.g., left temporal gyrus) that were more active in the NC group. Our data suggest that MPH may alter activity within the basal ganglia, but future studies with better spatial resolution are needed to more finely localize the effects of MPH on the subcomponents of the basal ganglia. An earlier PET study in ADHD adults suggested possible MPH-induced decreases in the putamen (Matochik et al 1994); however, studies in ADHD children (Kim et al 2001; Lou et al 1989; Teicher et al 2000; Vaidya et al 1998) found MPH increased activity in the basal ganglia. Of note, in the child studies, brain activity was significantly lower in the basal ganglia in ADHD participants than NC participants during nondrug conditions. In contrast, imaging studies in ADHD adults suggest increased task-related caudate and putamen activity relative to NC subjects (Bush et al 1999; Schweitzer et al 2000). The discrepancy between the child and adult findings may be due to the same potential methodological factors that are responsible for inconsistencies in PFC findings or it may be directly related to developmental changes in the caudate (Castellanos et al 2002). There may be functional implications related to differences in the developmental trajectory of the caudate nucleus in individuals with ADHD who appear to have a smaller caudate nucleus in childhood in comparison with normal control subjects that normalizes by mid-adolescence (Castellanos et al 2002).

The results of this study suggest adults with ADHD use an alternative neural pathway to perform EF tasks and that prolonged MPH administration only marginally alters this pattern. While MPH improved PASAT performance, it did not "normalize" task-related neuronal activity. In contrast to the ADHD group under either medication condition, the NC group generally

Table 7. Differences in Normalized rCBF between NC and Medicated ADHD Groups in PASAT Minus Number-Generate Condition

Anatomical Region	Site of Activation BA	Site of Activation x, y, z	Analysis *Z*	Analysis k_E [b]
Areas of Activation Greater in NC Than ADHD Groups				
Inferior temporal gyrus, left	20	−14, −14, −28	3.58	160
Middle temporal gyrus, right	39	50, −72, 18	3.56	64
Anterior cingulate	32	2, 22, −8	3.33	452
Medial frontal gyrus, right	11	6, 54, −12	3.20	452[a]
Fusiform gyrus, right	20	40, −18, −22	3.01	60
Superior temporal gyrus, right	22	62, 8, 0	2.97	23
Inferior temporal gyrus, left	20	−14, −14, −28	3.58	160
Areas of Activation Greater in ADHD Than in NC Groups				
Postcentral gyrus, right	3	58, −12, 52	3.86	87
Middle frontal gyrus, right	10	36, 52, 19	3.68	60
Anterior cerebellum, vermis (IV/V)		0, −54, −20	3.51	502
Anterior cerebellum, vermis (V)		2, −62, −2	3.36	502[a]
Inferior occipital gyrus, left	18	−24, −80, −2	3.45	113
Putamen, right		24, −8, 14	3.27	154
Insula, right		42, 12, 4	3.25	56
Inferior frontal gyrus, left	47	−22, 30, −20	3.15	420
Lenticulate, left		−16, −4, 8	3.02	420[a]
Caudate body, left		−6, 6, 8	3.00	420[a]
Anterior cerebellum, right (VI)		28, −46, −28	3.06	25

rCBF, regional cerebral blood flow; NC, normal control; ADHD, attention-deficit/hyperactivity disorder; PASAT, Paced Auditory Serial Addition Task; BA, Brodmann area.

[a]Secondary peak in cluster.

[b]Cluster extent.

activated brain regions consistent with the cognitive processes involved in the PASAT (Ahmad et al 2003; Braver et al 2001; Carter et al 2000; Durston et al 2002; Pinel et al 1999, 2001; van Veen et al 2001). In contrast, we found ADHD participants were less likely to use regions traditionally associated with EF and efficient allocation to subsidiary brain regions for EF tasks (Baddeley 1996) and instead relied more on regions associated with motor preparation. Normal control participants may be better at performing EF tasks because they use the anterior cingulate and PFC more effectively to recruit brain regions and strategies to match given task demands as they arise. Perhaps MPH improves performance in ADHD by boosting the PFC ability to block the effects of distractors (Wang et al 2004), but the absence of anterior cingulate activation and well-worn use of subcortical motor structures cannot be modified within a few weeks of medication in adult participants.

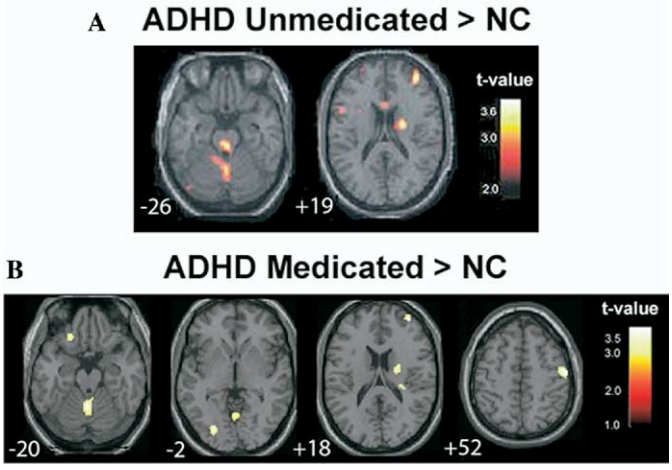

Figure 3. Contrasts between men with ADHD and NC participants during different medication conditions. **(A)** The top row displays images from relative rCBF PASAT-related increases in brain activity in unmedicated men with ADHD versus NC participants. **(B)** The bottom row displays images from relative rCBF PASAT-related increases in brain activity in MPH medicated participants versus NC participants. NC, normal control; ADHD, attention-deficit/hyperactivity disorder; rCBF, regional cerebral blood flow; PASAT, Paced Auditory Serial Addition Task; MPH, methylphenidate.

Future studies might use a double-blind crossover design in a larger number of participants to determine the effect of MPH on brain activity and separate out changes due to practice and time. A control task that can better parse out the operations involved in the PASAT could strengthen future analyses and help identify how subcomponents of EF are altered in ADHD. We also recommend that noninvasive neuroimaging studies attempt to replicate these findings in children to determine if our findings are applicable to a younger age group. Future treatment studies should consider assessing the effect of a neuropsychological treatment (e.g., cognitive training program) on EF in individuals with ADHD to determine if other treatments similarly affect brain functioning.

This research was supported in part by the National Institute of Mental Health (K08 MH01053 and RO3 MH55550) and the William K. Warren Foundation.

We thank Delecia Votaw, B.S., CNMT, Michael White, B.S., CNMT, and Margie Jones, B.S., CNMT of the Emory Center for PET and the participants and their spouses, friends, and family members for completion of rating scales. We also thank Deborah Medoff, Ph.D., Carol Tamminga, M.D., and Henry Holcomb, M.D. for their insightful discussions and support.

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, et al (2002): Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 22:3708–3719.

Ahmad Z, Balsamo LM, Sachs BC, Xu B, Gaillard WD (2003): Auditory comprehension of language in young children: Neural networks identified with fMRI. *Neurology* 60:1598–1605.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association.

Anastopoulos A, Spisto M, Maher M (1994): The WISC-III freedom from distractibility factor: Its utility in identifying children with attention deficit hyperactivity disorder. *Psychol Assess* 2:368–371.

Anderson CM, Polcari A, Lowen SB, Renshaw PF, Teicher MH (2002): Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in boys with ADHD. *Am J Psychiatry* 159:1322–1328.

Arnsten AFT (2001): Dopaminergic and noradrenergic influences on cognitive functions mediated by prefrontal cortex. In: Solanto MV, Arnsten AFT, Castellanos FX, editors. *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience*. New York: Oxford University Press.

Arnsten AFT, Cai JX, Murphy BL, Goldman-Rakic PS (1994): Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. *Psychopharmacology (Berl)* 116:143–151.

Baddeley A (1996): The fractionation of working memory. *Proc Natl Acad Sci U S A* 26:13468–13472.

Barkley RA (1981): *Hyperactive Children: A Handbook for Diagnosis and Treatment*. New York: Guilford Press.

Barkley RA (1998): *Attention Deficit Hyperactivity Disorder*, 2nd ed. New York: Guilford Press.

Barkley RA, Murphy K, Kwasnik D (1996): Psychological adjustment and adaptive impairments in young adults with ADHD. *J Atten Disord* 1:41–54.

Barnett R, Maruff P, Vance A, Luk ES, Costin J, Wood C, et al (2001): Abnormal executive function in attention deficit hyperactivity disorder: The effect of stimulant medication and age on spatial working memory. *Psychol Med* 31:1107–1115.

Beauchamp MH, Dagher A, Aston JA, Doyon J (2003): Dynamic functional changes associated with cognitive skill learning of an adapted version of the Tower of London task. *Neuroimage* 20:1649–1660.

Bedard AC, Martinussen R, Ickowicz A, Tannock R (2004): Methylphenidate improves visual-spatial memory in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 43:260–268.

Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, et al (1998): Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology* 50:1087–1093.

Berridge CW (2001): Arousal- and attention-related actions of the locus coeruleus-noradrenergic system: Potential target in the therapeutic actions of amphetamine-like stimulants. In: Solanto MV, Arnsten AFT, Castellanos FX, editors. *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience*. New York: Oxford University Press, 158–184.

Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A (2001): Anterior cingulate cortex and response conflict: Effects of frequency, inhibition and errors. *Cereb Cortex* 11:825–836.

Brozoski TJ, Brown RM, Rosvold HE, Goldman PS (1979): Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science* 205:929–932.

Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, et al (1999): Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biol Psychiatry* 45:1542–1552.

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, et al (2002): Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proc Natl Acad Sci U S A* 99:523–528.

Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, et al (2000): Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* 10:1078–1092.

Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, et al (1999): Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 9:20–26.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR (2003): Complexity of prefrontal cortical dysfunction in schizophrenia: More than up or down. *Am J Psychiatry* 160:2209–2215.

Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, et al (2000): Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proc Natl Acad Sci U S A* 97:1944–1948.

Castellanos F, Giedd J, Marsh W, Hamburger S, Vaituzis A, Dickstein D, et al (1996): Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psych* 53:607–616.

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al (2002): Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 288:1740–1748.

Deragotis LR (1986): *Symptom Checklist-90-R: Administration, Scoring, and Procedures Manual, 3rd ed*. Minneapolis: National Computer Systems, Inc.

Dowson JH, McLean A, Bazanis E, Toone B, Young S, Robbins TW, et al (2004): Impaired spatial working memory in adults with attention-deficit/hyperactivity disorder: Comparisons with performance in adults with borderline personality disorder and in control subjects. *Acta Psychiatr Scand* 110:45–54.

Durston S, Thomas KM, Worden MS, Yang Y, Casey BJ (2002): The effect of preceding context on inhibition: An event-related fMRI study. *Neuroimage* 16:449–453.

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, et al (2003): Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* 53:871–878.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al (2001): Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A* 98:6917–6922.

Ernst M, Kimes AS, London ED, Matochik JA, Eldreth D, Tata S, et al (2003): Neural substrates of decision making in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 160:1061–1070.

Ernst M, Zametkin AJ, Matochik J, Schmidt M, Jons PH, Liebenauer LL, et al (1997): Intravenous dextroamphetamine and brain glucose metabolism. *Neuropsychopharmacology* 17:391–401.

Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM (1998): DOPA decarboxylase activity in attention deficit disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. *J Neurosci* 18:5901–5907.

Filipek P, Semrud-Clikeman M, Steingard R, Renshaw P, Kennedy DJB (1997): Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* 48:589–601.

First M, Gibbon MWJ, Spitzer RL (1996): *SCID Screen PQ*. North Tonawanda, NY: Multi-Health Systems.

Friston KJ, Poline J-B, Holmes AP, Frith CD, Frackowiak RSJ (1996): A multivariate analysis of PET activation studies. *Hum Brain Mapp* 4:140–151.

Gao WJ, Krimer LS, Goldman-Rakic PS (2001): Presynaptic regulation of recurrent excitation by D1 receptors in prefrontal circuits. *Proc Natl Acad Sci U S A* 98:295–300.

Gao WJ, Wang Y, Goldman-Rakic PS (2003): Dopamine modulation of perisomatic and peridendritic inhibition in prefrontal cortex. *J Neurosci* 23: 1622–1630.

Gronwall D (1977): Paced auditory serial addition task: A measure of recovery from concussion. *Percept Mot Skills* 44:367–373.

Isacson R, Kull B, Wahlestedt C, Salmi P (2004): A 68930 and dihydrexidine inhibit locomotor activity and d-amphetamine-induced hyperactivity in rats: A role of inhibitory dopamine D(1/5) receptors in the prefrontal cortex? *Neuroscience* 124:33–42.

Kim BN, Lee JS, Cho SC, Lee DS (2001): Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/hyperactivity disorder. *Yonsei Med J* 42:19–29.

Kim BN, Lee JS, Shin MS, Cho SC, Lee DS (2002): Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. Statistical parametric mapping analysis *Eur Arch Psychiatry Clin Neurosci* 252:219–225.

Kovner R, Budman C, Frank Y, Sison C, Lesser M, Halperin J (1998): Neuropsychological testing in adult attention deficit hyperactivity disorder: A pilot study. *Int J Neurosci* 96:225–235.

Kuczenski R, Segal DS (2001): Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: Relative roles of dopamine and norepinephrine. *J Pharmacol Exp Ther* 296:876–883.

Levin HS, High WM, Goldstein FC, Williams DH (1988): Sustained attention and information processing speed in chronic survivors of severe closed head injury. *Scand J Rehabil Med Suppl* 17:33–40.

Lou H, Henriksen L, Bruhn P, Borner H, Nielsen J (1989): Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch Neurol* 46:48–52.

Lovejoy DW, Ball JD, Keats M, Stutts ML, Spain EH, Janda L, et al (1999): Neuropsychological performance of adults with attention deficit hyperactivity disorder (ADHD): Diagnostic classification estimates for mea-

sures of frontal lobe/executive functioning. *J Int Neuropsychol Soc* 5:222–233.
Lufi D, Cohen A (1985): Attentional deficit disorder and short-term visual memory. *J Clin Psychol* 41:265–267.
Mariani M, Barkley R (1997): Neuropsychological and academic functioning in preschool boys with attention deficit hyperactivity disorder. *Dev Neuropsychol* 13:111–129.
Matochik J, Liebenauer L, King C, Szymanski H, Cohen R, Zametkin A (1994): Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment. *Am J Psychiatry* 151:658–664.
Matochik JA, Nordahl TE, Gross M, Semple WE, King AC, Cohen RM, et al (1993): Effects of acute stimulant medication on cerebral metabolism in adults with hyperactivity. *Neuropsychopharmacology* 8:377–386.
Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al (2003): Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A* 100:6186–6191.
Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, et al (2002): Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Ann Neurol* 51:156–164.
McInnes A, Humphries T, Hogg-Johnson S, Tannock R (2003): Listening comprehension and working memory are impaired in attention-deficit hyperactivity disorder irrespective of language impairment. *J Abnorm Child Psychol* 31:427–443.
Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW (2000): Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci* 20:RC65.
Mostofsky SH, Reiss AL, Lockhart P, Denckla MB (1998): Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *J Child Neurol* 13: 434–439.
Murphy KR, Barkley RA (1996): Prevalence of DSM-IV ADHD symptoms in an adult community sample of licensed drivers. *J Atten Disord* 1:147–161.
Murphy KR, Barkley RA, Bush T (2001): Executive functioning and olfactory identification in young adults with attention deficit-hyperactivity disorder. *Neuropsychology* 15:211–220.
National Institute of Mental Health (1985): Clinical Global Impression Scale. *Psychopharmacol Bull* 21:839–844.
Parfitt KD, Gratton A, Bickford-Wimer PC (1990): Electrophysiological effects of selective D1 and D2 dopamine receptor agonists in the medial prefrontal cortex of young and aged Fischer 344 rats. *J Pharmacol Exp Ther* 254:539–545.
Petersen SE, van Mier H, Fiez JA, Raichle ME (1998): The effects of practice on the functional anatomy of task performance. *Proc Natl Acad Sci U S A* 95:853–860.
Pinel P, Dehaene S, Riviere D, LeBihan D (2001): Modulation of parietal activation by semantic distance in a number comparison task. *Neuroimage* 14:1013–1026.
Pinel P, Le Clec'H G, van de Moortele PF, Naccache L, Le Bihan D, Dehaene S (1999): Event-related fMRI analysis of the cerebral circuit for number comparison. *Neuroreport* 10:1473–1479.
Porrino LJ, Lucignani G (1987): Different patterns of local brain energy metabolism associated with high and low doses of methylphenidate. Relevance to its action in hyperactive children *Biol Psychiatry* 22:126–138.
Postle BR, D'Esposito M (1999): Dissociation of human caudate nucleus activity in spatial and nonspatial working memory: An event-related fMRI study. *Brain Res Cogn Brain Res* 8:107–115.
Postle BR, D'Esposito M (2003): Spatial working memory activity of the caudate nucleus is sensitive to frame of reference. *Cogn Affect Behav Neurosci* 3:133–144.
Qin Y, Carter CS, Silk EM, Stenger VA, Fissell K, Goode A, et al (2004): The change of the brain activation patterns as children learn algebra equation solving. *Proc Natl Acad Sci U S A* 101:5686–5691.
Qin Y, Sohn MH, Anderson JR, Stenger VA, Fissell K, Goode A, Carter CS (2003): Predicting the practice effects on the blood oxygenation level-dependent (BOLD) function of fMRI in a symbolic manipulation task. *Proc Natl Acad Sci U S A* 100:4951–4956.
Raczkowski D, Kalat J (1974): Reliability and validity of some handedness questionnaire items. *Neuropsychologia* 12:43–47.
Rogawski MA, Aghajanian GK (1980): Activation of lateral geniculate neurons by norepinephrine: Mediation by an alpha-adrenergic receptor. *Brain Res* 182:345–359.
Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, et al (1999): Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. *Am J Psychiatry* 156:891–896.
Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, et al (2001): Mapping motor inhibition: Conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage* 13:250–261.
Sawaguchi T, Goldman-Rakic PS (1991): D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science* 251:947–950.
Sawaguchi T, Goldman-Rakic PS (1994): The role of D1-dopamine receptor in working memory: Local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J Neurophysiol* 71:515–528.
Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD (2000): Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *Am J Psychiatry* 157:278–280.
Schweitzer JB, Lee DO, Hanford RB, Tagamets MA, Hoffman JM, Grafton ST, et al (2003): A positron emission tomography study of methylphenidate in adults with ADHD: Alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology* 28:967–973.
Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS (2003): Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet* 362:1699–1707.
Staffen W, Mair A, Zauner H, Unterrainer J, Niederhofer H, Kutzelnigg A, et al (2002): Cognitive function and fMRI in patients with multiple sclerosis: Evidence for compensatory cortical activation during an attention task. *Brain* 125:1275–1282.
Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Thieme.
Tannock R, Ickowicz A, Schachar R (1995): Differential effects of methylphenidate on working memory in ADHD children with and without comorbid anxiety. *J Am Acad Child Adolesc Psychiatry* 34:886–896.
Teicher MH, Anderson CM, Polcari A, Glod CA, Maas LC, Renshaw PF (2000): Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nat Med* 6:470–473.
Tunbridge EM Bannerman DM, Sharp T, Harrison PJ (2004): Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. *J Neurosci* 24:5331–5335.
Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, et al (1998): Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proc Natl Acad Sci U S A* 95:14494–14499.
van Veen, V, Cohen JD, Botvinick MM, Stenger VA, Carter CS (2001): Anterior cingulate cortex, conflict monitoring, and levels of processing. *Neuroimage* 14:1302–1308.
Volkow ND, Wang G, Folwer JS, Logan J, Gerasinov M, Maynard LDY, et al (2001): Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J Neurosci* 21: RC121.
Volkow ND, Wang GJ, Fowler JS, Logan J, Angrist B, Hitzemann R, et al (1997): Effects of methylphenidate on regional brain glucose metabolism in humans: Relationship to dopamine D2 receptors. *Am J Psychiatry* 154: 50–55.
Wang X-J, Tegnér J, Constantinidis C, and Goldman-Rakic PS (2004): Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory. *Proc Natl Acad Sci U S A* 101:1368–1373.
Wechsler D (1997): *Wechsler Adult Intelligence Scale*, *3rd ed*. San Antonio, TX: Psychological Corp.
Williams GV, Goldman-Rakic PS (1995): Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376:572–575.
Wilkinson G (1993): *The Wide Range Achievement Test*, *3rd ed*. Wilmington, DE: Wide Range, Inc.
Zametkin A, Nordahl T, Gross M, King A, Semple W, Rumsey J, et al (1990): Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med* 323:1361–1366.
Zhou FM, Hablitz JJ (1999): Dopamine modulation of membrane and synaptic properties of interneurons in rat cerebral cortex. *J Neurophysiol* 8:967–976.