Neuropsychopharmacology (2003) 28, 967–973

www.neuropsychopharmacology.org

A Positron Emission Tomography Study Of Methylphenidate in Adults with ADHD: Alterations in Resting Blood Flow and Predicting Treatment Response

Julie B Schweitzer*[,1], Douglas O Lee[2], Russell B Hanford[2], Malle A Tagamets[1], John M Hoffman[3,4], Scott T Grafton[5] and Clinton D Kilts[2]

[1]Maryland Psychiatric Research Center and Division of Child Psychiatry, University of Maryland School of Medicine, USA; [2]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, USA; [3]Departments of Neurology and Radiology, Emory University School of Medicine, USA; [5]Center for Cognitive Sciences, Dartmouth College, USA

A hallmark symptom of attention-deficit hyperactivity disorder (ADHD) is an excess of motoric behavior or hyperactivity. Methylphenidate (MPH) is known to reduce hyperactivity in individuals with ADHD. Yet little is known about how it alters neural activity and how this relates to its clinical effects. The goal of this study is to examine MPH-induced changes during resting brain metabolism, and to examine how these changes correlate with measures of behavioral response to the drug. Measures of regional cerebral blood flow (rCBF) using positron emission tomography (PET) were acquired at rest for ten adult subjects with ADHD during both an unmedicated state and after a 3-week period of chronic dosing with a clinically optimal dose of MPH. Compared with the on-MPH condition, the off-MPH condition was associated with relative increases in rCBF bilaterally in the precentral gyri, left caudate nucleus, and right claustrum. The on-MPH condition was associated with relative increases in rCBF in the cerebellar vermis. A correlational analysis measured the relation between rCBF in the off-medication condition to change in ADHD ratings between the off- and on-MPH condition to identify brain regions associated with treatment response. The degree of change in the ratings was negatively correlated with rCBF increases in the midbrain, cerebellar vermis, and the precentral and middle frontal gyri in the off-MPH condition. The majority of these brain regions are involved in the planning and execution of motor behavior. These data suggest that MPH modulates brain regions associated with motor function to achieve a reduction in ADHD symptoms.
Neuropsychopharmacology (2003) **28,** 967–973, advance online publication, 26 March 2003; doi:10.1038/sj.npp.1300110

Keywords: ADHD; methylphenidate; positron emission tomography; treatment response; cerebellar vermis

INTRODUCTION

Methylphenidate (MPH) is the drug of choice for the treatment of attention-deficit/hyperactivity disorder (ADHD) (Safer and Malever, 2000). MPH reduces the symptoms of situationally inappropriate and high levels of motor activity, poor sustained attention, and increased impulsivity (see eg Borcherding *et al*, 1989; Rapport *et al*, 1985; van der Meere *et al*, 1995). Although approximately 11 million MPH prescriptions are written per year in the United States (Woodworth, 2000) the mechanisms of MPH effects beyond its molecular actions, and the biological basis of poor response, remain poorly understood. Noninvasive *in vivo* imaging methods have emerged as a promising tool to explore the nonpharmacological effect of psychotropic drugs on regional brain activity (Salmeron and Stein, 2002).

A review of the literature on stimulants and ADHD suggests that the effectiveness of MPH is owing to its actions on both the dopamine and norepinephrine systems (Solanto, 1998). There is a growing body of research on the effects of MPH on the dopamine system in humans. Therapeutic oral doses of MPH appear to block the function of the dopamine transporter protein (DAT, Volkow *et al*, 1998) and increase brain extracelluar dopamine levels (Volkow *et al*, 2001). An imaging positron emission tomography (PET) study using MPH labeled with carbon-11 (^{11}C) in normal volunteers showed selective binding of MPH in striatum in humans (Volkow *et al*, 1995). Most of what is known about the effects of MPH on the norepineperine system is based on nonhuman studies and these show an effect of drug on extracellular concentrations

*Correspondence: Dr J Schweitzer, Maryland Psychiatric Research Center, White Building, PO Box 21247, Baltimore, MD 21228, USA, Tel: +1 410 402 6027; Fax: +1 410 788 3394,
[4]Current address: National Cancer Institute, National Institute of Health, USA
E-mail: jschweit@mprc.umaryland.edu
Received 28 May 2002; revised 08 August 2002; accepted 31 October 2002
Online publication: 06 November 2002 at http://www.acnp.org/citations/Npp110602427

of NE (Kuczenski and Segal, 2001), in addition to the well-known effects on dopamine.

Imaging studies on the effects of MPH on blood flow in children and adults with ADHD implicate dysfunction of the striatum. Several different brain-imaging techniques have shown that MPH increases neuronal activity in the striatum in children and adults treated with MPH (Lou *et al*, 1984; Teicher *et al*, 2000; Vaidya *et al*, 1998).

The frontal cortex is also implicated as a substrate for ADHD and MPH with accumulating evidence pointing to abnormalities in structural volume (Castellanos *et al*, 1996) and function (Bush *et al*, 1999; Rubia *et al*, 1999; Schweitzer *et al*, 2000; Vaidya *et al*, 1998; Zametkin *et al*, 1990) in this region in subjects with ADHD. Early PET-imaging studies on stimulant administration (acute oral, chronic oral, and intravenous administration) showed a lack of effect on frontal glucose metabolism in adults with ADHD (Ernst *et al*, 1994, 1997; Matochik *et al*, 1994). Recent functional magnetic resonance imaging fMRI studies (Vaidya *et al*, 1998), however, suggest that MPH increases frontal cortical activity in children with ADHD (Teicher *et al*, 1996).

In addition to interest in striatum and frontal cortex, ADHD researchers are now focusing more attention on the cerebellum. Structural imaging studies in ADHD have repeatedly shown abnormalities in the cerebellum in children with ADHD (Berquin *et al*, 1998; Castellanos *et al*, 2001; Mostofsky *et al*, 1998). A recent fMRI study expanded knowledge of the relation between stimulants and the cerebellum (Anderson *et al*, 2002). Anderson and colleagues measured the effects of MPH on steady-state blood volume on the cerebellar vermis and demonstrated a dose-dependent effect of the drug in children with ADHD (Anderson *et al*, 2002). This study revealed that the direction of the effect of MPH on blood flow depends on the basal rate of motor activity of the child.

Little is known about the methods for predicting response to MPH. A review of the studies on predicting positive MPH response suggests that at best, only weak associations exist between either behavioral measures or neurochemistry and drug response (Gray and Kagan, 2000). Functional brain imaging as yet has not been looked to as a method for predicting drug response to MPH, although these techniques have yielded novel insights into the pharmacotherapy of major depression (Mayberg *et al*, 2000). The current study uses a pharmacological PET (phPET) approach to address the question of how MPH alters rCBF in adults with ADHD and what patterns of rCBF alteration correspond to improvement in ADHD symptoms.

The specific goals of the present study were two-fold: (1) To define the anatomy of regional cerebral blood flow (rCBF) responses related to MPH in men with ADHD and (2) to identify resting patterns of rCBF in unmedicated participants that might predict response to MPH. The study reported here differs from previous PET and most fMRI studies of pharmacological effects (Salmeron and Stein, 2002) in that the rCBF responses were determined at rest, and therefore unconfounded by interactions between a cognitive activation task and drug effect. This resting study is part of a more extensive study that does include cognitive activation tasks, and forms a baseline for the interpretation of subsequent studies that use cognitive activation paradigms to define the effects of MPH on ADHD.

METHODS

Subjects

Participants included ten men diagnosed with ADHD, combined type (American Psychiatric Association, 1994). To be diagnosed with ADHD, combined type participants had to meet the DSM-IV criteria: having at least six of nine symptoms of inattention and six of nine symptoms of hyperactivity and/or impulsivity. Furthermore, the symptoms had to have arisen in childhood and persisted over development into adulthood. Four of the ADHD subjects had a prior history of MPH treatment, two subjects as children and two as adults. The subjects medicated as children had been stimulant free for approximately 10 years. One adult had been stimulant free for several months and the other for 8 days before the off-medication images were collected.

A school of medicine-based adult ADHD clinic and local advertisements were used to recruit the participants. The screening process included a thorough review of childhood and adult psychological and educational history, family psychiatric history; completion of the Mini-SCID for DSM-IV (First *et al*, 1996) and the Symptom Checklist-90, Revised (Deragotis, 1986) to screen for non-ADHD psychiatric disorders. Completion of a semi-structured interview based on the DSM-IV criteria for ADHD, the Adult ADHD DSM-IV Rating Scale (Murphy and Barkley, 1996) represented the primary diagnostic instruments used to establish the presence of ADHD. Multiple sources completed the ADHD Rating Scale for DSM-IV including two self-report versions (current behavior and behavior between the ages of 5 and 12); a current observer (eg spouse, close friend); and the mother of the potential participant reviewing behavior between the ages of 5 and 12. The Wechsler Adult Intelligence Scale—3rd Edition (WAIS-III; Wechsler, 1997) assessed Full Scale intellectual functioning and was combined with the Wide Range Achievement Test—3rd Edition (WRAT-3; Wilkinson, 1993) to rule out learning disabilities in subjects. The mean ($\pm$ SD) age for the participants was 31.5 (8.2) and the mean ($\pm$ SD) IQ was 122 (10.2).

We excluded prospective participants for the following reasons: presence of any clinically significant medical condition, history of brain injury, mental retardation (Full Scale IQ <75), other Axis I disorders, and/or history of nonstimulant pharmacotherapy for greater than 3 weeks. All participants were right-hand dominant (Raczkowski and Kalat, 1974). All subjects had normal neurological histories and exams (DL). Following description of the study and its associated risks, participants gave written informed consent for a protocol approved by the Human Investigations and Radiation Safety Committees of the Emory University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki.

MPH Treatment

Subjects were started on an MPH dose of 0.5 mg/kg/day for the first week, escalating to 0.75 mg/kg/day for the second week, and up to 1.0 mg/kg/day for the third week, unless adverse side effects were noted, until the optimal dose for each subject was found. Dose selection was based on weekly evaluations that included an interview with a review of

symptoms and side effects by a psychiatrist (DL), completion of the clinical global impression scale (NIMH, 1985) by the psychiatrist (DL), and completion of the side effect scale for psychostimulants (Barkley, 1981) and ADHD rating scale (Murphy and Barkley, 1996) by the subject and a significant other or friend of the subject. Subjects ingested their dose of MPH 60 min before scanning on the day of the imaging at the imaging center. Subjects were administered an average daily dose of 19 mg ($\pm$ 9.1, SD) given as a divided dose (TID). All subjects but one were imaged in the unmedicated condition first and then imaged a second time after achieving optimal behavioral changes on the MPH. One subject was imaged in the medication condition first and then in the unmedicated condition. A review of the data from this one subject does not suggest that the results from this subject differ from the other subjects.

Study Conditions

During PET scanning subjects were instructed to relax and close their eyes during the acquisition of two $[^{15}O]H_2$ resting PET scans of 90-s duration and spaced 60 min apart. Each subject also performed two different cognitive tasks in separate scans, which are not reported here. Data from the activation tasks will be the subject of a separate report.

A Siemens ECAT 951 PET scanner (Knoxville, TN) acquired images under dim ambient lighting following the bolus intravenous administration of 45 mCi of $[^{15}O]H_2$ The scanner collects 31 contiguous 3.375-mm-thick slices with an intrinsic resolution of 6 mm at the center of the field of view. Images were collected parallel to the canthomeatal line. Head movement was minimized by use of a thermoplastic face mask affixed to a customized head holder (TruScan restraint system®).

PET Imaging and Data Analysis

PET images were reconstructed using a measured attenuation correction. The PET images were analyzed using statistical parametric mapping 99 (Wellcome Department of Cognitive Neurology, 1999). Scans from each subject were realigned to each subject's first scan to control for head movement. The PET scans for each condition were averaged, spatially normalized, normalized for global blood flow by proportional scaling, and coregistered to a population representative PET cerebral blood flow atlas centered in Talairach coordinates (Talairach and Tournoux, 1988). PET images were smoothed to a final isotropic resolution of 10 mm FWHM. Smoothed PET images were normalized to each other by proportional scaling of global activity. A within-subject model was used to calculate the comparisons between the averaged unmedicated from the medicated images using a subtraction analysis. In a separate analysis, the difference scores between unmedicated and medicated self-ratings of ADHD symptoms were correlated with whole-brain rCBF volumes from the unmedicated PET scans. This yields a map of regions that predict expected response to the medication. SPM whole-volume contrasts were thresholded at a voxel level of $p < 0.001$ uncorrected. Significant sites of activation were then defined as contiguous clusters at a threshold of $p < 0.05$, corrected for multiple comparisons. Only clusters meeting these criteria are reported in Tables 1 and 2.

RESULTS

Behavioral Data

According to self ratings and ratings by spouses and significant others, subjects improved significantly on the ADHD DSM-IV rating scale between the off-medication and on-medication conditions. Group-averaged self-ratings of ADHD symptoms decreased by 25.8 points (scale ranged from 0 to 54; $t = 9.68$, $p < 0.0001$, one-tailed) and ratings by others decreased by 19.5 points (scale ranged from 0 to 54; $t = 4.42$, $p < 0.002$). Ratings on the CGI decreased significantly from the off-medication condition (mean of 4.40;

Table 1 Changes in rCBF[a] Related to Chronic Methylphenidate Administration in Men with ADHD

	Site of activation[b]			
Anatomical region	**BA**	**Coordinates (x, y, z)**	**z**	**Volume[c]**
Unmedicated–medicated condition				
Left precentral gyrus	6	−46, 4, 8	4.91	1448*
Right precentral gyrus	4	44, −10, 54	4.45	276
Left precentral gyrus	4	−40, −14, 50	4.25	213
Left caudate nucleus		−8, 10, 14	4.07	640
Right claustrum		42, 4, 0	3.74	441
Medicated–unmedicated condition				
Cerebellum, posterior (VII/VIII)		−6, −68, −30	4.96	1587*

[a]rCBF indicates regional cerebral blood flow.
[b]Values represent the stereotaxic location of voxel maxima or minima with coordinates in Talairach space (Talairach and Tournoux, 1988) in millimeters lateral to midline (*x*), anterior/posterior to the anterior commissure (*y*), and superior/inferior to the commissural line (*z*).
[c]SPM whole volume contrasts were thresholded at a voxel level of $p < 0.001$ uncorrected.
Significant sites of activation were then defined as contiguous clusters at a threshold of $p < 0.05$, corrected for multiple comparisons.
*Intensity of voxels significant at $p < 0.05$ after correcting for multiple comparisons.

Table 2 Negative Correlations between Changes in rCBF[a] and ADHD Ratings

Anatomical region	Site of activation[b] BA	Coordinates (x, y, z)	z	Volume[c]
Midbrain		−2, −8, −12	5.84	3213*
Cerebelllum, posterior (Crus II)		4, −86, −26	5.65	600*
Left middle frontal gyrus	9	−24, 6, 40	4.27	210

[a]rCBF indicates regional cerebral blood flow.
[b]Values represent the stereotaxic location of voxel maxima or minima with coordinates in Talairach space (Talairach and Tournoux, 1988) in millimeters lateral to midline (*x*), anterior/posterior to the anterior commissure (*y*), and superior/inferior to the commissural line (*z*).
[c]SPM whole volume contrasts were thresholded at a voxel level of $p<0.001$ uncorrected.
Significant sites of activation were then defined as contiguous clusters at a threshold of $p<0.05$, corrected for multiple comparisons.
*Intensity of voxels significant at $p<0.05$ after correcting for multiple comparisons.

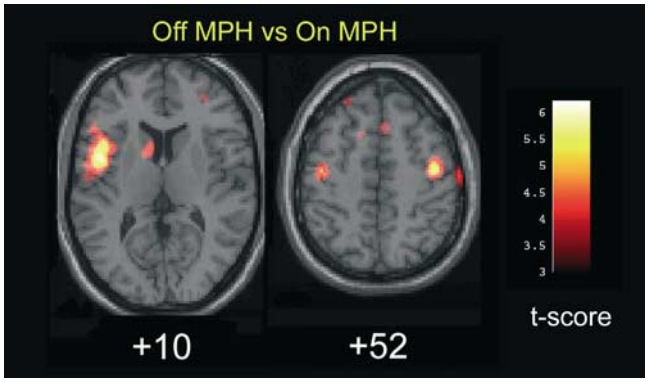

Figure 2 Relative rCBF increases in off-MPH *vs* on-MPH condition in 10 men with ADHD. The image illustrates the significant activation in the unmedicated condition bilaterally in the precentral gyrus, left caudate nucleus, and the right claustrum.

SD = 0.70) to the on-medication condition (mean of 1.90; SD = 0.57; $t = 9.30$, df = 19, $p = 0.0001$). The side effect scale revealed minimal side effects during the on-medication condition.

PET Data (Subtraction Analysis): Changes in rCBF because of MPH

Compared with the off-medication condition, MPH treatment was associated with increases in rCBF in the posterior cerebellum (lobules VII/VIII). The greatest increases were noted in the vermis and a site lateral to the vermis in the right cerebellar hemisphere (see Table 1 and Figure 1). The effect of the MPH was strikingly localized to deep brain structures. Compared with the on-medication condition, the off-medication condition was associated with widespread increases in rCBF throughout the brain. The off-medication condition increases in rCBF were in regions superior to those seen in the on-medication condition, including the bilateral precentral gyrus (BA 4), the left caudate nucleus, and the right claustrum (see Figure 2).

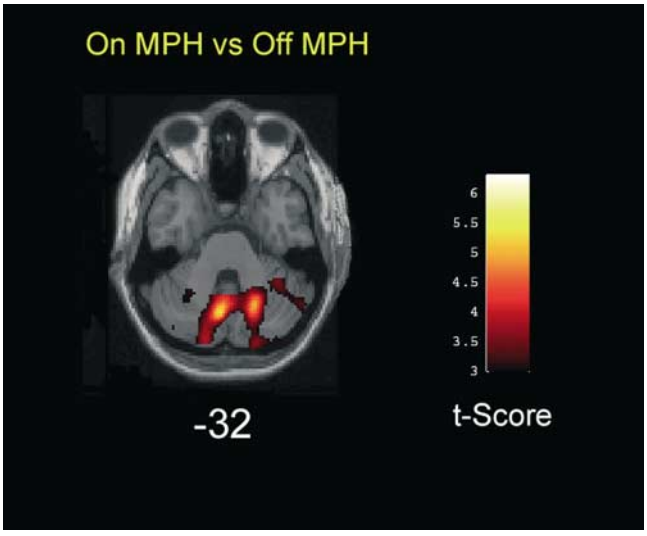

Figure 1 Relative rCBF increases in on-MPH *vs* off-MPH condition in 10 men with ADHD. For this figure as well as Figures 2 and 3, the sites of activation displayed are significant at a voxel level of $p<0.001$ uncorrected and thresholded at $p<0.05$, corrected for multiple comparisons at the cluster level. The number beneath the image indicates the mm above or below the bicommisural plane. The image illustrates the significant activation in the cerebellum.

PET Data (Correlation Analysis): MPH-Related Improvement on ADHD Ratings and rCBF

Subjects with greater improvement in ADHD symptom ratings from the unmedicated to the medicated condition showed lower resting rCBF in the off-medication condition in the midbrain, posterior cerebellum (vermis-Crus II), and left middle frontal gyrus (BA 9). These negative correlations are presented in Table 2 and Figure 3. The activation at the left precentral gyrus was significant at $p<0.05$ after correcting for multiple comparisons for intensity of voxels. There were no significant positive correlations between MPH-related changes in the ADHD symptom ratings and rCBF.

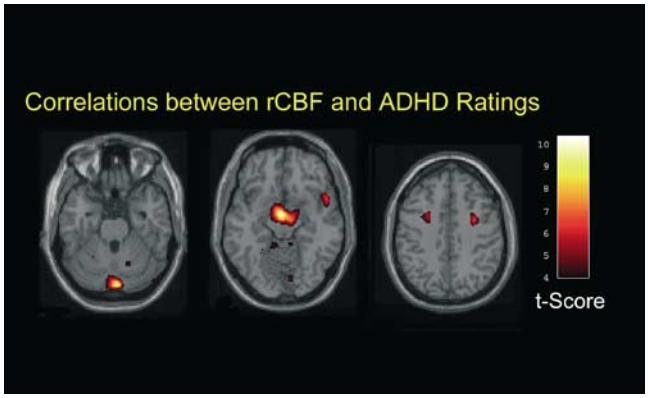

Figure 3 Location of brain activity negatively correlated with change in the ADHD rating scale from the off-MPH to on-MPH condition and rCBF activity in the off-MPH condition.

DISCUSSION

These data identify the anatomical targets of MPH's effect on ADHD and support theories of ADHD based on dysfunctional frontal–striatal circuitry that is influenced by cerebellar and midbrain function (Giedd *et al*, 2001). A consistent finding in our data is that chronic MPH administration increases rCBF in the cerebellar vermis, suggesting that it may specifically target this structure. Volkow *et al*'s (1997) finding that MPH consistently increased glucose metabolism in the cerebellum of normal control adult participants suggests that MPH targets this structure in healthy individuals as well. Additional support for the contention that MPH treats ADHD symptoms through the cerebellum was shown in a recent study by Anderson *et al* (2002) who demonstrated using fMRI that MPH decreases blood volume in the cerebellar vermis in ADHD children with greater symptoms of hyperactivity. Structural data also suggest that the cerebellar vermis may be implicated in ADHD with findings suggesting that the vermis is smaller in children with ADHD compared with healthy children (Berquin *et al*, 1998).

MPH is an inhibitor of the norepinephrine and serotonin transporters, in addition to the dopamine transporter. The human cerebellum receives a rich noradrenergic input (Powers *et al*, 1989) and MPH has been shown to enhance markedly extracellular concentrations of norepinephrine in noradrenergically innervated structures (Kuczenski and Segal, 2001). Therefore, the observed effect of MPH may reflect MPH effects on cerebellar noradrenergic systems, although we cannot rule out contributions owing to effects of MPH on serotonergic systems. The dopaminergic innervation of the human cerebellar vermis is variably described as being sparse to rich (see Melchitzsky and Lewis, 2000), although Volkow *et al* (2001) have shown using PET and [^{11}C]raclopride that MPH does not appear to increase cerebellar dopamine levels. Therefore, it is uncertain whether the effects of MPH on rCBF in the cerebellar vermis are related to effects on dopaminergic systems. These data are consistent with the hypothesis (Arnsten, 2000; Biederman and Spencer, 1999) that ADHD may be because of dysregulation of the noradrenergic system.

MPH-related changes also include a decrease in the rCBF in brain areas related to motor preparation and action including the precentral gyrus and caudate nucleus. Hyperactivity of these regions could be associated with the excessive motoric activity and poor response inhibition characteristic of ADHD. Decreasing brain activity in these regions may enable individuals with ADHD to engage putative brain regions involved in higher-order functions (ie language) to organize behavior without competition from goal-inappropriate behavioral hyperactivity. The effect of psychostimulants on caudate activity is relatively consistent among previous studies (Matochik *et al*, 1993; Teicher *et al*, 2000; Vaidya *et al*, 1998) showing that right caudate activity is increased by MPH administration. Our study suggests that the baseline activity in the left caudate may be relatively increased in ADHD subjects.

Our findings suggest that those ADHD subjects with higher off-medication activity of the midbrain, posterior cerebellum, and middle frontal gyrus will be less likely to respond to MPH on indices measured by current ADHD rating scales. Measures of [18F]fluorodopa (FDOPA) activity in children with ADHD suggest baseline dysfunction of the midbrain with abnormal dopamine synthesis or storage of FDOPA activity in the midbrain (Ernst *et al*, 1999). This neural response to MPH administration may reflect a neural correlate of treatment nonresponse. It is also plausible that those subjects who are naturally compensating for their deficits by increasing brain activity in these regions already will benefit less from the medication because the compensatory activity has already maximized the amount of activity that is possible in those regions. In essence, a ceiling effect is met and the MPH cannot increase the activity any higher in those regions. Indeed, we have other data (JS, unpublished) that show ADHD adults have a higher baseline rate of brain activity in similar regions that we found to correlate with the least amount of change with MPH during performance of a working memory task. The potential presence of 'compensatory' activity requires further exploration in other ADHD samples. The lack of significant positive correlations between rCBF and changes in symptoms with MPH may reflect a lack of power from this sample size.

The findings of this small study require replication in a larger study sample. This study should also be replicated in children, who are the bulk of the recipients of MPH prescriptions, using less invasive techniques, such as functional magnetic resonance imaging. Future studies will be strengthened by the use of a reversal, double-blind crossover study in which the effects of MPH on rCBF can be discriminated from changes that may be because of alterations in the symptoms related to the chronic dosing condition. This study suggests one method that may be useful in identifying subject characteristics' corresponding to responsivity to MPH. Another potential technique for assessing responsivity to stimulants could include both responders and nonresponders to a medication and correlations between brain activity and measures of the degree of responsivity.

A primary goal of this study was to identify rCBF response to MPH at rest to aid the interpretation of future studies that use cognitive paradigms to test the substrates of ADHD in response to medication. Our findings provide a guide to interpret data for future ADHD pharmacological studies of MPH. A further goal of the study was to evaluate the use of functional imaging in predicting response to MPH. The results from this study suggest that functional imaging has potential as a tool for identifying individuals' response to pharmacological treatment.

ACKNOWLEDGMENTS

The study was supported in part by the National Institute of Mental Health (K08 MH01053 & RO3 MH55550) and the William K Warren Foundation. We thank Delecia Votaw, BS, CNMT, Michael White, BS, CNMT, and Margie Jones, BS, CNMT of the Emory Center for PET, the participants and their spouses, friends, and family members for completion of rating scales. We also thank Tim Ely and Caroline Zink for technical assistance and Henry H

Holcomb, MD, Deb Medoff, PhD, and Carol Tamminga, MD for their insightful discussions and support.

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