REVIEW

Areas of the Brain Modulated by Single-Dose Methylphenidate Treatment in Youth with ADHD During Task-Based fMRI: A Systematic Review

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Objective: Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder affecting 5% of children. Methylphenidate (MPH) is a common medication for ADHD. Studies examining MPH's effect on pediatric ADHD patients' brain function using functional magnetic resonance imaging (fMRI) have not been compiled. The goals of this systematic review were to determine (1) which areas of the brain in pediatric ADHD patients are modulated by a single dose of MPH, (2) whether areas modulated by MPH differ by task type performed during fMRI data acquisition, and (3) whether changes in brain activation due to MPH relate to clinical improvements in ADHD-related symptoms.

Methods: We searched the electronic databases PubMed and PsycINFO (1967–2011) using the following terms: ADHD AND (methylphenidate OR MPH OR ritalin) AND (neuroimaging OR MRI OR fMRI OR BOLD OR event related), and identified 200 abstracts, 9 of which were reviewed based on predefined criteria.

Results: In ADHD patients the middle and inferior frontal gyri, basal ganglia, and cerebellum were most often affected by MPH. The middle and inferior frontal gyri were frequently affected by MPH during inhibitory control tasks. Correlation between brain regions and clinical improvement was not possible due to the lack of symptom improvement measures within the included studies.

Conclusions: Throughout nine task-based fMRI studies investigating MPH's effect on the brains of pediatric patients with ADHD, MPH resulted in increased activation within frontal lobes, basal ganglia, and cerebellum. In most cases, this increase "normalized" activation of at least some brain areas to that seen in typically developing children.

Keywords: ADHD, fMRI, methylphenidate, neuroimaging, pediatric

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder characterized by age-inappropriate frequency or severity of inattentive or hyperactive-impulsive behavior(s).[1] Its prevalence is estimated at 3% to 7% for American children and adolescents, and is about 5% for children worldwide.[1,2] There is now convincing evidence that in a significant number of cases, ADHD persists into late adolescence and adulthood and that children with ADHD suffer worse social and psychiatric outcomes than normally developing peers.[3–5]

A common and effective pharmacological intervention currently in use for ADHD is oral methylphenidate (MPH).[6] Although MPH has been shown to significantly improve the behavioral symptoms associated with ADHD, both the mechanism behind its therapeutic effect and its direct effects on brain function are unknown.[7] The use of positron emission tomography (PET) imaging in healthy subjects and patients with ADHD has revealed a relationship between MPH and dopamine (DA) transmission; MPH was found to inhibit DA reuptake in the striatum and thus to increase extracellular concentrations of DA in that area.[8–11] This finding has led to the concept that the clinical manifestations of ADHD may result from aberrant DA signaling; MPH treatment for ADHD attempts to restore the appropriate DA balance in the brain. Further research has shown that MPH also blocks the norepinephrine transporter and increases the concentration of norepinephrine in the prefrontal cortex.[12,13] The ionizing radiation associated with PET, however, renders it unsuitable for research in children, and since electrocencephalography and magnetoencephalography

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both yield relatively poor spatial resolution, MRI is the preferred imaging modality for children; it is noninvasive and yields high spatial resolution.

Functional MRI (fMRI) is a noninvasive imaging technique that uses changes in the blood-oxygen-level-dependent (BOLD) signal to discover subjects' brain "activation."[14] In task-based fMRI, patients perform a specific task while lying in an MRI system, in order to determine which areas of their brains are activated by the given task. The change in brain activation is deduced from the change in the regional BOLD signal between the task of interest and the "resting" state or "baseline" task. The differences in activation patterns between two cohorts (e.g., patients with ADHD and typically developing subjects) can then be contrasted.

Task-based fMRI has already been used extensively to characterize the differences between the activated brain areas of unmedicated patients with ADHD versus typically developing children.[15–24] The majority of these studies found a reduction in the activation of areas within the frontal lobes in patients with ADHD, suggesting dysregulation of circuits involving the prefrontal cortices as a hallmark of this disorder.[25,26] This atypical activation pattern was especially apparent when ADHD patients were asked to perform an inhibitory control task.[25] Other brain areas, including the basal ganglia, cerebellum, and portions of the parietal and temporal lobes, have also all been found to be hypofunctional in ADHD.[24,25,27]

Although many studies have sought to understand the neural underpinnings of ADHD, relatively few have addressed how its treatment with MPH works. To date, available neuroimaging data from task-based fMRI studies that examined the changes in brain activation experienced by children with ADHD when they were treated with MPH have not been synthesized. The goal of this systematic review is to compile the results of studies that used task-based fMRI to determine how MPH affects the neurocircuitry of pediatric patients with ADHD. We are particularly interested in determining which brain areas of ADHD patients show changes in neuronal activity after a single dose of MPH. In that context, we examine (1) which areas of the brain are modulated by MPH, (2) whether the areas responding to MPH are different based on the type of task being performed in the fMRI, and (3) whether the changes in brain activation due to MPH correlate with clinical measures of improvement in ADHD-related symptoms. This information will advance knowledge of MPH's effect on the brains of ADHD patients.

METHODS

Journal articles for this systematic review were identified using the electronic databases PubMed and PsycINFO (1967 to 2011). The databases were searched using the following search terms: ADHD AND (methylphenidate OR MPH OR ritalin) AND (neuroimaging OR MRI OR fMRI OR BOLD OR event related). A manual review of relevant authors and journals, including the bibliographies from identified articles, was also performed.

Included studies met all of the following criteria: (1) publication in a peer-reviewed journal, (2) fMRI analysis (i.e., BOLD signal investigation) was conducted on data from children (under 18 years of age) with ADHD, (3) participants were scanned before and after a single dose of MPH medication, and these scans were directly compared as part of the neuroimaging analysis, and (4) the participants performed the same task in MRI during both on- and off-MPH sessions. Articles were excluded if they were reviews or case reports, if they were not in English, if they focused primarily on ADHD in the setting of other comorbid diseases, or if the studies were on animals or focused exclusively on adult ADHD patients. Studies that were identified by manual search or from bibliographies were subject to the same inclusion and exclusion criteria.

Data for our review were extracted from the original articles' texts, tables, and figures. Information was gathered on study design, participants' characteristics, ADHD diagnosis, timing and dosage of MPH, functional task type and improvement on task performance, neuroimaging methods, BOLD signal changes in response to MPH, and clinical improvement of ADHD symptoms.

RESULTS

The original literature search produced a total of 200 abstracts, 9 of which were ultimately included for review (Figure 1). These abstracts were identified by searching PubMed and PsychINFO (1967 to 2011); 147 represented studies done with children under 18 and were written in English. Of these 147 abstracts, 19 additional articles were excluded as case reports or reviews, leaving 128 studies to be manually reviewed. One hundred and sixteen studies did not meet all inclusion criteria; most studies were excluded because they did not use a design with on- and off-MPH medication sessions. Of the 12 eligible studies thus identified, 3 more were excluded because they did not directly compare the imaging results of ADHD subjects on and off MPH. The final number of studies included for review was 9.

General Characteristics of Included Studies

Most of the included studies were performed in either the United States or the United Kingdom (Table 1). The majority of participants were adolescent boys, averaging in age from 10.3 to 17.3 years. All studies included an age-matched, healthy control group for comparison. The majority of included studies focused on the combined subtype of ADHD—which was exclusively studied in five articles and was the most common subtype in two of the other articles. Only one child with the hyperactive subtype was studied across all articles. Most of the studies did not exclude comorbid oppositional defiant disorder or conduct disorder

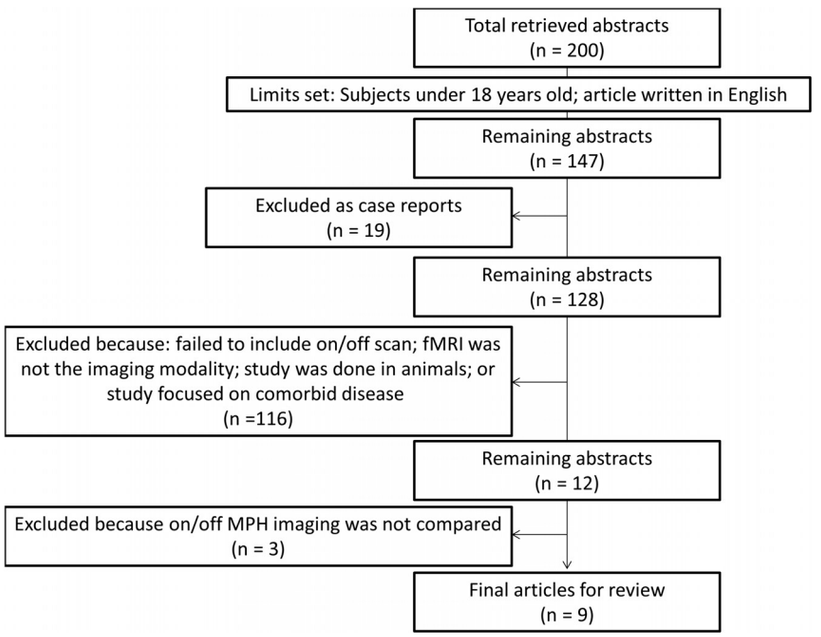

Figure 1. Study selection process. MPH, methylphenidate.

in their ADHD cases. In four studies either all or the majority of all youth with ADHD were not stimulant-medication naive, whereas in the remaining five studies only stimulant-naive subjects were included. The MPH dose for the on-MPH scan sessions ranged from 10 to 40 mg per patient; five articles reported a dose of 0.3 mg/kg but did not report the overall average amount of MPH given to subjects. All on-MPH scan sessions were performed 1 to 2.5 hours after dosing with MPH. In non-naive subjects, MPH medication was withdrawn 10 to 72 hours before the off-MPH scan session. In all studies the order of the on- and off-MPH scans was counterbalanced across subjects. Although each study used its own unique task, these tasks can be broadly separated into four categories: (1) tasks designed to assess inhibitory control (the ability to stop a prepotent response), (2) tasks designed to assess selective attention (the ability to focus in the presence of distracters), (3) tasks designed to assess working memory (the ability to mentally maintain and access important information), and (4) tasks designed to assess time perception (the ability to determine how long a cue has been present). Given that ADHD symptoms can manifest in difficulties sustaining attention (e.g., in selective attention, working memory, and time-perception tasks) and exercising inhibitory control (e.g., in inhibitory control tasks), these types of tasks are appropriate and relatively commonly applied in studying ADHD. Five studies measured inhibitory control; two focused on selective attention; one assessed working memory; and one investigated time perception.

Imaging Methods

The majority of studies had MRI systems with field strength of 1.5 T; one study used a 2 T system and one study used a 3 T system (Table 2). TR and TE times ranged from 720 to 3000 msecs and 32 to 60 msecs, respectively. The flip angle in the majority of studies was 90°. One study did not report the flip angle, and the remaining two studies had a flip angle of 69° and 60°. The field of view was not reported for five of the studies; for the remaining four studies it ranged from 20 cm × 20 cm to 36 cm × 36 cm. The number of image slices taken ranged from 7 to 36; the thickness of the slices varied from 3.2 mm to 8 mm; and gaps between the slices ranged from 0.6 mm to 4 mm. Each group of investigators used different software to analyze its imaging results. Generally, imaging analysis was first done on data from individual subjects separately. The within-task contrasts were determined by statistically comparing the BOLD signal measured during the "active" portion of the task with the BOLD signal measured during the "baseline" task or "resting" state ($p < 0.0005$ to $p < 0.05$), and this within-task comparison was done for each subject once while he or she was on MPH and once while off MPH. These on- and off-MPH within-task contrasts were then grouped with respect to medication status, to be compared across two groups (subjects on MPH vs. subjects off MPH). The significant differences in brain activations due to modulation by MPH were reported ($p < 0.01$ to $p < 0.05$). These second-level comparisons between ADHD patients' brain responses during on- versus off-MPH scan sessions are explained in this review as the effects of MPH on brain activation.

Brain Regions Affected by MPH—All Included Studies

While performing the tasks used in the included studies (inhibitory control, selective attention, working memory, or

Table 1

General Characteristics of Included Studies

Study	Location	Patients: M (n) F (n)	Patients' ages (years)	Controls: M (n) F (n)	Controls' ages (years)	ADHD combination subtype (n/% of patients)	Patients' comorbid disorders	Patients MPH naive?	Dose of MPH	Time between dose and on scan[a]	Time between d/c MPH and off scan[a]	Task	What did task assess?
Vaidya et al. (1998)[28]	USA	M: 10	10.5 ± 1.4	M: 6	9.3 ± 1.5	8 (80)	None	No	16.3 mg	2.0–2.5 hours	36 hours	Go/No-Go Tasks	Inhibitory control
Shafritz et al. (2004)[29]	USA	M: 11 F: 4	15.1 ± 0.3	M: 7 F: 7	16.6 ± 0.8	15 (100)	CD & ODD not excluded	No	0.3–0.42 mg/kg	~ 1.25 hours	72 hours	Visual and auditory tasks	Selective attention
Zang et al. (2005)[30]	China	M: 9	13.0 ± 1.6	M: 9	12.8 ± 1.1	3 (33)	7 ODD 1 DD	Yes	10 mg	1.5 hours	NA	"Stroop-like" task	Inhibitory control
Epstein et al. (2007)[31]	USA	M: 9 F: 4	17.3 ± 1.2	M: 7 F: 2	17.4 ± 1.1	5 (42)	None	No	0.3 mg/kg	1–2 hours	~10 hours	Go/No-Go Task	Inhibitory control
Kobel et al. (2008)[32]	Switzerland	M: 14	10.4 ± 1.3	M: 12	10.9 ± 1.6	9 (64)	3 ODD/CD 2 GAD 2 ODD/CD/ GAD	No	10–20 mg MPH, 36–40 mg ER-MPH	1.5 hours	24 hours	N-Back Tasks	Working memory
Rubia et al. (2009)[33]	UK	M: 13	12.5 ± 1.3	M: 13	13.1 ± 1.7	13 (100)	1 CD/ODD	Yes	0.3 mg/kg	1 hour	NA	Rewarded Continuous Performance Task	Selective attention
Rubia et al. (2009)[34]	UK	M: 12	13 ± 1	M: 12	13 ± 1	12 (100)	1 CD	Yes	0.3 mg/kg	1 hour	NA	Time Discrimination Task	Time perception
Rubia et al. (2011)[35]	UK	M: 12	13 ± 1	M: 13	13 ± 1	12 (100)	1 CD/ODD	Yes	0.3 mg/kg	1 hour	NA	Visual Tracking Stop Task	Inhibitory control
Rubia et al. (2011)[36]	UK	M: 12	13 ± 1	M: 13	13 ± 1	12 (100)	1 CD/ODD	Yes	0.3 mg/kg	1 hour	NA	Simon Task	Inhibitory control

CD, conduct disorder; d/c, discontinued; DD, dysthymic disorder; F, female; GAD, generalized anxiety disorder; M, male; MPH, methylphenidate; NA, not applicable; ODD, oppositional defiant disorder.

[a] All scans performed in a counterbalanced fashion.

Table 2

Image Acquisition Parameters and Methods of Image Analysis

Study	Magnet field strength (Tesla)	TR (ms)	TE (ms)	Field of view (cm)	Flip angle	Number of slices × slice thickness, skip	Software package used for analysis	Within-task contrast	Task contrast threshold value	On vs. off MPH scan session contrast threshold value	Whole brain or ROI analysis?
Vaidya et al. (1998)[28]	1.5 T	720	40	36 × 36	69°	8 × 6 mm, 1.0–1.5 mm	AIR 2.0	No-Go vs. Go parts of task	$p < .025$, one-tailed	$p < .05$	ROI
Shafritz et al. (2004)[29]	1.5 T	1500	60	20 × 20	60°	14 × 7 mm, NR	SPM 99	Active task vs. resting task	$p < .005$	$p < .01$	Whole brain
Zang et al. (2005)[30]	2 T	1000	60	NR	90°	7 × 8 mm, 4 mm	AFNI	Active task vs. resting task	$p < .0005$ plus a 7-contiguous-voxel cluster at $p < .03$	Unable to determine	Whole brain followed by ROI
Epstein et al. (2007)[31]	1.5 T	2500	40	24 × 24	90°	33 × 3.2 mm, 1 mm	Brain Voyager QX	Correct No-Go vs. correct Go parts of task	$p < .05$ plus a 5-contiguous-voxel cluster	$t > 2.46$	Whole brain followed by ROI
Kobel et al. (2008)[32]	3 T	2500	32	24 × 24	NR	36 × 3 mm, 0.6 mm	SPM5	Active task vs. resting task	$p < .05$ plus a 10- contiguous- voxel cluster	$p < .05$	Whole brain
Rubia et al. (2009)[33]	1.5 T	3000	40	NR	90°	16 × 7 mm, 0.7 mm	XBAM	Correct target vs. non-target parts of task; correct rewarded target vs. correct unrewarded target parts of task	$p < .05$ plus a cluster at $p < .01$	$p < .05$ plus a variably sized voxel cluster at $p < .03$	Whole brain
Rubia et al. (2009)[34]	1.5 T	3000	40	NR	90°	16 × 7 mm, 0.7 mm	NR	Time discrimination vs. temporal order judgment task	Unable to determine	$p < .05$ plus a cluster at $p < .01$	Whole brain
Rubia et al. (2011)[35]	1.5 T	1800	40	NR	90°	16 × 7 mm, 0.7 mm	XBAM	No-Go vs. Go parts of task	Unable to determine	$p < .05$ plus a cluster at $p < .05$	Whole brain
Rubia et al. (2011)[36]	1.5 T	1800	40	NR	90°	17 × 7 mm, 0.7 mm	XBAM	Correct incongruent vs. congruent parts of task; correct "oddball" vs. congruent parts of task	$p < .05$	$p < .05$ plus a cluster at $p < .05$	Whole brain

MPH, methylphenidate; NR, not reported; ROI, region of interest.

Table 3

Brain Regions ofADHDPatients Showing a Significant Increase in Activity After MPHAdministration (on Versus off MPH)[a]

	Frontal lobe(s)						Parietal lobe(s)		Temporal lobe(s)		Occipital lobe(s)		
Study	Superior frontal cortex	Middle frontal cortex	Inferior frontal cortex	Orbital frontal cortex	Anterior cingulate cortex	Medial frontal cortex	Inferior parietal lobule	Posterior cingulate cortex	Superior, middle, inferior temporal	Insular cortex	Precuneus, cuneus, or fusiform	Basal ganglia	Cerebellum
Vaidya et al. (1998)[28]	p = .02	p = .02	p = .02	p = .02	IND	IND	IND	IND	IND	IND	IND	p = .01	IND
Shafritz et al. (2004)[29]	p > .01	p > .01	p > .01	p > .01	p > .01	p > .01	p > .01	p > .01	p > .01	p > .01	p > .01	p < .01	p > .01
Zang et al. (2005)[30]	No difference[b]	Increase seen[b]	No difference	No difference	No difference	IND	IND	IND	IND	Increase seen	IND	No difference	Increase seen
Epstein et al. (2007)[31]	IND	p < .05	p < .05	p < .05	p < .05	IND	p < .05	IND	IND	IND	IND	p < .05	p < .05
Kobel et al. (2008)[32]	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05	p > .05
Rubia et al. (2009)[33]	p > .05	p > .05	p < .05	p < .05	p < .05	p < .05	p > .05	p < .05	p > .05	p > .05	p < .05	p < .05	p < .05
Rubia et al. (2009)[34]	p > .05	p > .05	p < .05	p < .05	p < .05	p < .05	p > .05	p > .05	p > .05	p < .05	p > .05	p > .05	p < .05
Rubia et al. (2011)[35]	p > .05	p < .05	p < .05	p > .05	p > .05	p < .05	p < .05	p > .05	p > .05	p < .05	p < .05	p < .05	p > .05
Rubia et al. (2011)[36]	p > .05	p > .05	p < .05	p > .05	p > .05	p > .05	p < .05	p > .05	p < .05	p > .05	p > .05	p > .05	p < .05
Total[c]	1/9	4/9	6/9	4/9	3/9	3/9	3/9	1/9	1/9	3/9	2/9	5/9	5/9

IND, indeterminate (these regions of interest were not investigated by the article in question); MPH, methylphenidate.

[a] p values less than the threshold value for group comparison indicate that a significant increase in activity was seen when ADHD patients were given MPH.

[b] No difference/Increase seen: one article did not report p values for group comparisons but did report activation increases in response to MPH qualitatively.

[c] Fractions represent the proportion of studies that found an activation increase in that brain region after MPH administration out of the total studies included in this review.

time-perception tasks), patients with ADHD activated the following brain areas: portions of the frontal lobes (including the superior, middle, inferior, and orbital frontal cortices and the anterior cingulate gyrus), parietal lobes (including the inferior parietal lobule and posterior cingulate gyrus), temporal lobes (including the superior, middle, and inferior temporal and insular cortices), occipital lobes (including the precuneus, cuneus, and fusiform gyrus), basal ganglia (including the caudate and putamen), cerebellum, thalamus, and hippocampus. The majority of included studies found significant differences in activation between the on- and off-MPH medication scan sessions in patients with ADHD (8/9 studies). These differences were within the frontal lobe(s) (7/9 studies), parietal lobes (4/9), temporal lobes (4/9), occipital lobes (2/9), basal ganglia (5/9), and cerebellum (5/9) (Table 3).

In addition, several reviewed studies compared the brain activation of ADHD patients after MPH administration with the brain activation of typically developing youth. These comparisons were made in order to determine if MPH "normalized" ADHD patients' brain function to the levels seen in typical youth. Of the nine included studies, six found that MPH increased ADHD youths' brain activation up to the levels seen in typically developing youth, in at least some areas of the brain.[28–33] Normalized areas included the frontal lobes (3/6 studies), parietal lobes (3/6), temporal lobes (2/6), occipital lobes (1/6), basal ganglia (4/6), and cerebellum (1/6).

Table 4
Regional Brain Activation by Task and by Previous Drug Use[a]

Task	Number of studies	Frontal lobe(s)						Parietal lobe(s)		Temporal lobe(s)		Occipital lobe(s)	Basal ganglia	Cerebellum
		Superior frontal cortex	Middle frontal cortex	Inferior frontal cortex	Orbital frontal cortex	Anterior cingulate cortex	Medial frontal cortex	Inferior parietal lobule	Posterior cingulate cortex	Superior, middle, inferior temporal	Insular cortex	Precuneus, cuneus, or fusiform		
Inhibitory control	5	1/5	4/5	4/5	2/5	1/5	1/5	3/5	0/5	1/5	2/5	1/5	3/5	3/5
Selective attention	2	0/2	0/2	1/2	1/2	1/2	1/2	0/2	1/2	0/2	0/2	1/2	2/2	1/2
Working memory	1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Time discrimination	1	0/1	0/1	1/1	1/1	1/1	1/1	0/1	0/1	0/1	1/1	0/1	0/1	1/1
Previous drug use														
Naive	5	0/5	2/5	4/5	2/5	2/5	3/5	2/5	1/5	1/5	3/5	2/5	2/5	4/5
Not naive	4	1/4	2/4	2/4	2/4	2/4	0/5	1/4	0/4	0/4	0/4	0/4	3/4	1/4

[a] Each row refers to a task type or previous medication status, and each column refers to a brain region. Each cell represents the proportion of studies that found increased activity in response to MPH within the area of the brain indicated in the column header, as against the total number of studies that fell into the category described by the row header.

Brain Regions Affected by MPH—Inhibitory Control Task

Five of the included studies assessed inhibitory control; that is, the ability to stop a prepotent response. Examples of tasks that assess inhibitory control are the Go/No-Go Task,[20,34] Stroop Task,[35] Stop Task,[32] and Simon Task[33] (Table 1). In these studies, ADHD patients responded to tasks by activating portions of the following areas: frontal, parietal, temporal, and occipital lobes, basal ganglia, cerebellum, and hippocampus. Of these areas, patients treated with MPH had greater activation in the frontal lobes (5/5 studies), parietal lobes (3/5), temporal lobes (3/5), occipital lobes (1/5), basal ganglia (3/5), and cerebellum (3/5) than when they were untreated (Table 4). In three of these five studies, MPH at least partially normalized ADHD patients' brain activation to the levels seen in healthy youth. These areas included the frontal lobes (2/3 studies), parietal lobes (2/3), temporal lobes (1/3), occipital lobes (1/3), basal ganglia (2/3), and cerebellum (1/3).

Brain Regions Affected by MPH—Selective Attention Task

Two of the included studies assessed selective attention—that is, the ability to focus in the presence of distracters. Examples of tasks that assess selective attention are visual and auditory attention tasks[28] and rewarded continuous performance tasks[30] (Table 1). In these studies, ADHD patients responded to tasks by activating portions of the

folowing areas: frontal, parietal, temporal, and occipital lobes, basal ganglia, cerebellum, and thalamus. Of these areas, patients treated with MPH had greater activation in the frontal lobes (1/2 studies), parietal lobes (1/2), occipital lobes (1/2), basal ganglia (2/2), and cerebellum (1/2) compared to when they were untreated (Table 4). Neither of these studies found an increase in activation within the temporal lobe in response to MPH. In both of these studies, MPH at least partially normalized ADHD patients' brain activation to the levels seen in healthy youth, including the parietal lobes (1/2 studies), temporal lobes (1/2), basal ganglia (1/2), and cerebellum (1/2).

Areas of the Brain Affected by MPH—Working Memory Task

One of the included studies assessed working memory—that is, the ability to mentally maintain and access important information. An example of a task that assesses working memory is the N-Back Task (Table 1).[36] In this study, patients with ADHD responded to the task by activating portions of the following areas: frontal, parietal, and occipital lobes. This single study found no increase in any of these areas when comparing patients with ADHD for on- versus off-MPH conditions (Table 4). This study did not find that MPH normalized ADHD patients' brain activation to the levels seen in healthy youth.

Areas of the Brain Affected by MPH—Time-Perception Task

One of the included studies assessed time perception—that is, the ability to determine how long a cue has been present. An example of a task that assesses time perception is the Time Discrimination Task (Table 1).[31] In this study, patients with ADHD responded to the task by activating portions of the following areas: frontal lobe, basal ganglia, and insula. The study found an increase in all three of these areas when comparing ADHD patients for on- versus off-MPH conditions (Table 4). Brain activation in all of these areas was normalized to the levels seen in healthy youth in response to MPH.

Clinical Improvement with MPH

None of the included studies reported measures of the symptom severity experienced by ADHD patients for on- and off-MPH conditions. It was therefore not possible to establish a link between changes in brain activation and indices of symptom improvement. Out of the nine studies included in this review, however, two found that, when compared to the condition without MPH, MPH improved task performance while elevating the activation in areas of the frontal lobes and basal ganglia.[29,34] In both of these studies, task performance of ADHD patients during the MPH condition was not directly compared to the task performance of typically developing youth; it is therefore difficult to know if MPH helped ADHD youth perform tasks as quickly and accurately as their typically developing peers in these studies. Of the remaining seven studies, six found an increase in brain activation but no concurrent improvement in task performance in response to MPH,[28,30–33,35] and one study found that MPH improved task performance but did not change brain activation.[36]

Imaging Trends by MPH Medication Naiveté

Of the nine included studies, five were conducted in MPH-naive subjects with ADHD.[30–33,35] These five studies found an increase in activation in response to first-time MPH in the frontal lobes (5/5 studies), parietal lobes (3/5), temporal lobes (4/5), occipital lobes (2/5), basal ganglia (2/5), and cerebellum (4/5) (Table 4). The remaining four studies were conducted in patients with ADHD who had previously been treated with stimulant medication.[28,29,34,36] Of these four studies, one did not find a change in activation between patients with ADHD on- and off-MPH scan sessions,[36] whereas the remaining three studies reported that the frontal (2/4 studies) and parietal (1/4) lobes , basal ganglia (3/4), and cerebellum (1/4) were activated more during the on-MPH session.[28,29,34] None of these studies found an increase in activation in response to MPH in the occipital or temporal lobes.

DISCUSSION

The purpose of this systematic review was to determine which areas of the brain are modulated by MPH medication in pediatric ADHD patients during task performance, whether these affected brain areas differ by task, and whether any of these brain areas can be linked to improvement in the clinical symptoms of ADHD.

The results of our review suggest that when patients with ADHD are given a single dose of MPH, an increase in activation primarily occurs within the frontal lobes (especially in the inferior and middle frontal gyri), the basal ganglia, and the cerebellum. Abnormalities in these regions have all been implicated in patients with ADHD. Structurally, the prefrontal cortex (which includes portions of the inferior and middle frontal gyri), the caudate (part of the basal ganglia), and the cerebellum have consistently been found to have a smaller volume in patients with ADHD than in typically developing children.[37] Functionally, when assessing unmedicated brain activation of patients with ADHD during task performance, less activation has been found in the frontal lobes,[15,17–22,24] striatum,[15,16,18,20] and cerebellum[24,38] in comparison to brain activation of healthy control subjects. The MPH-responsive areas of the brain in youth with ADHD discussed within this review therefore reflect areas that, both structurally and functionally, have previously been reported as abnormal in ADHD. Of the nine studies included in this review, six found that MPH at least partially normalized the activation of the brains of patients with ADHD to the levels seen in typically developing comparison subjects while performing a task.[28–33] The areas most frequently normalized were those in the basal ganglia (4 studies),[28,29,31,33] followed by the frontal

lobes[31–33] and parietal lobes[30,32,33] (both found in 3 studies). Taken together, these findings indicate that MPH may help to return the brain functioning of patients with ADHD to the normal levels seen in typically developing children when performing a cognitive task.

The second goal of our systematic review was to determine if brain areas affected by MPH differed by task. When the reviewed studies were grouped by task, we found that the middle and inferior frontal gyri were the brain areas most often affected by MPH during inhibitory control task performance.[29,32–35] Similarly, the one study that used the time-discrimination task found that MPH increased activation in the frontal lobes, specifically within the inferior, orbital, and medial frontal cortices and the anterior cingulate cortex.[31] These findings differed from MPH's effects during selective attention task performance, when the basal ganglia were most often activated.[28,30] Since only two studies used this task, it is difficult to say whether these results represent the true frequency with which this area is affected. The single study that used a working memory task did not find any increase in brain activation in response to MPH, but further studies using this task may find a different result.[36]

In healthy participants, the performance of inhibitory control tasks has been found to preferentially activate the dorsolateral prefrontal cortex (including the middle frontal gyrus), inferior frontal gyrus, anterior cingulate, and parietal cortex.[39] For youth with ADHD, MPH increased activation within each of these areas in at least one of the studies using an inhibitory control task; the middle and inferior frontal cortex activation was increased in almost all of these studies (4/5 studies for each). It is therefore possible that in ADHD, MPH influences the activation within the middle and inferior frontal gyri while performing an inhibitory control task. Given these neuroimaging findings, one might expect that children with ADHD would perform better on inhibitory control tasks after they receive MPH than they do without MPH; however, this prediction was not borne out by our investigation. Only two of the five studies that used an inhibitory control task reported that MPH improved ADHD patients' performance on the task (i.e., errors decreased, variability in reaction time decreased, or target discrimination increased). Although it is possible that this improvement on the task was the result of MPH medication, such an improvement could also be due to practice. In one of these two studies, patients with ADHD went through two imaging sessions, whereas healthy participants were scanned only once; it is thus possible that the ADHD patients' improved on the task because they performed it more than once. In the other of these two studies, both ADHD patients and healthy participants were given MPH and imaged twice, and both improved on task performance. It is therefore difficult to determine whether or not this improvement was due to practice or medication. Furthermore, neither of these two studies reported that MPH normalized the activation within ADHD patients' frontal lobes to the levels seen in typically developing children; in one of these two studies, medicated ADHD patients' brain activations were not directly compared to the typically developing control group, and in the other, normalizations of brain activation within the basal ganglia were found. It is therefore possible that MPH's effects on areas of the frontal lobe are insufficient to improve inhibitory control task performance or that the power of the studies was insufficient to capture improved task performance.

Similar to the inhibitory control task, the time-discrimination task has been found to preferentially activate the dorsolateral prefrontal cortex, inferior frontal gyrus, and cerebellum during performance by healthy adults.[40] In the single included study that used this type of task, activation in the inferior, orbital, and medial frontal gyrus, anterior cingulate gyrus, and cerebellum was increased by MPH administration during task performance in patients with ADHD. MPH normalized all these areas of ADHD patients' brains to the activation levels seen in typically developing children, but patients with ADHD did not commit significantly fewer errors on the task when they were treated with MPH. This finding may indicate that MPH does not have a powerful enough effect to improve time-discrimination task performance. It is also possible, however, that the number of patients with ADHD included in this single study (12 boys) was too small to capture a statistically significant difference in task performance.

In contrast to inhibitory control and time-discrimination tasks—which selectively activate areas mostly in the frontal lobe—selective attention tasks, including visual and auditory attention tasks and continuous performance tasks, have been found to activate a wide range of brain regions, including portions of the frontal, parietal, temporal, and occipital lobes, the cerebellum, and the basal ganglia.[41,42] Although at least one of the two selective attention studies included in this review found that MPH increased brain activation in the frontal, parietal, and occipital lobes, as well as the basal ganglia and cerebellum, neither of these studies found increased activation in the temporal lobes.[28,30] Therefore, MPH may not work in this region during performance of a selective attention task. Both of the included studies reported increased activation in the basal ganglia in response to MPH, but only one study showed normalization to healthy control levels in this area.[28] Neither of these studies found that MPH improved how well patients with ADHD performed on the task, which again may be an issue of insufficient power.

Finally, this review included a single study that assessed working memory; that study found no increase in brain activation in response to MPH. With only a single study to consider, no definite conclusions about the nature of MPH's effects during working memory task performance can be made.

The last goal of this review was to determine if brain regions affected by MPH could be related to improvement

in clinical ADHD symptoms. We found that none of the included studies reported measurements of the severity of ADHD symptoms before and after MPH medication administration. We were therefore unable to compare brain regions of interest between studies that found clinical improvement and those that did not. Previous work has shown, however, that MPH ameliorates the symptoms of ADHD. The landmark Collaborative Multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder revealed that medication management with MPH effectively reduced inattentive and hyperactive symptoms of ADHD.[43] In that study, participants received individually titrated doses of MPH, starting (on average) at about 12 mg. The doses of MPH reported in this review are comparable to that amount (the lowest dose in the reviewed studies was 10 mg). We therefore speculate that had ADHD symptoms been recorded as part of the reviewed studies, improvement in these symptoms was possible.

Though it was not an explicit goal of this review, we also examined the effect of previous medication status on brain activation in response to MPH. When the included studies were grouped based on whether or not ADHD participants had received stimulant medication prior to the reported study, it became evident that there was a difference in MPH-induced brain activation patterns between the stimulant-naive and non-naive groups. In response to MPH, studies that used stimulant-naive participants reported an increase in activation—in the inferior frontal cortex, parietal lobes, temporal lobes, occipital lobes, and cerebellum—more often than studies that used non-naive participants. This result may indicate that these areas of the brain are more responsive to initial MPH treatment but, over time, become less sensitive to the medication's effects. Alternatively, chronic treatment with MPH may increase baseline activation of these areas such that the difference between on- and off-MPH treatment scan sessions is no longer evident. This possibility is supported by a SPECT study that found chronic MPH treatment improved cerebral blood flow to frontal and temporal lobes in patients with ADHD; these changes were still detectable two months after discontinuation of MPH.[44] It is therefore possible that after a period of treatment with MPH, tonic blood flow to brain areas affected by MPH is increased. This permanently increased blood flow would then translate to increased blood oxygenation levels in these areas, resulting in readings of higher brain activation at baseline—that is, the pre-MPH (single dose) imaging session. However, results from the only study that has assessed the chronic effects of MPH in pediatric patients with ADHD using fMRI analysis do not corroborate these findings: following one year of MPH treatment, boys with ADHD did not show increased neural activity during the performance of tasks designed to assess executive (inhibitory) control and selective attention compared to the pretreatment imaging session.[45]

This review has focused exclusively on pediatric neuroimaging, but there is considerable interest in the effects of MPH on adult ADHD patients' brain activity, given that ADHD persists into adulthood in 15%–65% of childhood cases, depending on diagnostic criteria.[3] In one of the studies included in this review, MPH's effects were reported on both child and adult groups of child-parent dyads diagnosed with ADHD.[34] That study used an inhibitory control task and found that although areas of the frontal lobes, striatum, and cerebellum showed increased activity in the children in response to MPH, only the striatum (specifically, the caudate) showed increased activation in the adults. By contrast, a study that examined the activation of the dorsal anterior midcingulate cortex (part of the frontal lobe) in adults while performing an inhibitory control task (the multisource interference task) found that after six weeks of treatment with MPH, activation in this area increased, in comparison to the placebo-treated group.[46] The study also found that MPH treatment increased activation in the dorsolateral prefrontal and premotor cortex (portions of the superior, middle, and inferior frontal gyri), parietal cortex, striatum (specifically, the caudate), cerebellum, and thalamus, compared to placebo. With only two studies to consider, it is difficult to state whether adults with ADHD exhibit similar brain activation responses to MPH as children with ADHD. However, both of these studies with adult participants agree that MPH increases the brain activation during inhibitory control task performance within the striatum, specifically within the caudate.

The major limitation of this systematic review is the small number of studies it included. To date, only nine studies have examined how a single-dose of MPH affects the brain response during task performance in youth with ADHD. These nine studies employed only four types of task, which limits the applicability of this review to other types of tasks. Another limitation of this systematic review is that four of our included studies[30–33] were published by the same first author; insofar as those studies included overlapping patient populations, they would not represent independent contributions to this review. In addition, this review has reported the general anatomical brain areas associated patterns rather than Brodmann areas or Talairach coordinates. Although all included papers described the anatomical locations of BOLD signal changes, only some reported Brodmann areas or Talairach coordinates, making it difficult to universally compare these more specific regions of interest. Finally, many of the included studies were not specific about the multiple comparison corrections applied in their analyses—which may affect the validity of the findings.

The results of this systematic review point to several areas of future research. As none of the included studies examined the relationship between ADHD symptom improvement and BOLD brain activation in response to MPH, this component would be an important one to include in future

studies. Another avenue for future research may lie in investigating MPH's effect on functional connectivity, either during task performance or the resting state. The current studies reveal the effects of MPH on functional brain activation, whereas a connectivity analysis would lead to a better understanding regarding the underlying neural networks. The nine studies included in this review focused mostly on the MPH-induced functional activation differences in the brains of youth with ADHD. One of these studies, however, also examined the changes in brain functional connectivity during selective attention task performance. That study found that MPH normalized all intercorrelation differences between children with ADHD and healthy control children, providing more insight into the possible effects of MPH administration on brain networks. Future studies that examine these functional connectivity responses to MPH may help expand understanding of this drug's effects.

In conclusion, children with ADHD showed changes in brain activation due to a single dose of MPH, especially within the frontal lobes, basal ganglia, and cerebellum. MPH appears to more frequently affect regions of the frontal lobes during inhibitory control tasks compared to those assessing selective attention. By contrast, during selective attention tasks, MPH results in an increase in activation in a wider range of areas, including parts of the parietal and occipital lobes, as well as the cerebellum and basal ganglia. These regions correspond to those that exhibit typical activation patterns during task performance by typically developing participants and may provide evidence that MPH facilitates the return of brain function in ADHD patients to, or close to, a typically functioning state. As it stands, the existing literature supports the notion that MPH helps normalize brain activation, specifically within the frontal lobes, basal ganglia, and cerebellum, but whether or not the activation of these areas correlates with ADHD symptom improvement has yet to be demonstrated.

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