Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of Magnetic Resonance Imaging–Based Neuroimaging Studies

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ABSTRACT

Objective: To evaluate the impact of therapeutic oral doses of stimulants on the brains of ADHD subjects as measured by magnetic resonance imaging (MRI)–based neuroimaging studies (morphometric, functional, spectroscopy).

Data Sources: We searched PubMed and ScienceDirect through the end of calendar year 2011 using the keywords (1) *psychostimulants* or *methylphenidate* or *amphetamine,* and (2) *neuroimaging* or *MRI* or *fMRI,* and (3) *ADHD* or *ADD* or *attention-deficit/hyperactivity disorder* or *attention deficit hyperactivity disorder.*

Study Selection: We included only English language articles with new data from case-control or placebo controlled studies that examined attention-deficit/hyperactivity disorder (ADHD) subjects on and off psychostimulants (as well as 5 relevant review articles).

Data Extraction: We combined details of study design and medication effects in each imaging modality.

Results: We found 29 published studies that met our criteria. These included 6 structural MRI, 20 functional MRI studies, and 3 spectroscopy studies. Methods varied widely in terms of design, analytic technique, and regions of the brain investigated. Despite heterogeneity in methods, however, results were consistent. With only a few exceptions, the data on the effect of therapeutic oral doses of stimulant medication suggest attenuation of structural and functional alterations found in unmedicated ADHD subjects relative to findings in controls.

Conclusions: Despite the inherent limitations and heterogeneity of the extant MRI literature, our review suggests that therapeutic oral doses of stimulants decrease alterations in brain structure and function in subjects with ADHD relative to unmedicated subjects and controls. These medication-associated brain effects parallel, and may underlie, the well-established clinical benefits.

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurobiological disorder estimated to affect up to 10% of children and 5% of adults worldwide.[1,2] Across the lifecycle, it is associated with high levels of morbidity and disability and exerts an enormous toll in all areas of functioning, including academic, occupational, and interpersonal.[3] Neurobiological evidence supports a brain basis for ADHD, with alterations in widespread neural regions.[4–7]

Stimulants (methylphenidate and amphetamine compounds) are the mainstay of treatment for ADHD because of their robust clinical efficacy.[8,9,10] The therapeutic effects of stimulants are most likely mediated by increases in activity of dopamine and norepinephrine in fronto-striatal circuitry, with downstream effects throughout the brain.[11]

Although animal studies suggested that stimulants may have detrimental effects on the rodent brain, these studies have generally used very large doses—up to 50 mg/kg—administered parenterally (intraperitoneally), whereas therapeutic doses range from 0.5 to 2.0 mg/kg/d and are administered orally in humans.[12,13] Moreover, since animal studies often rely on "normal" wild-type rodents not affected by ADHD-related brain alterations, it is impossible to assess whether medication-related plasticity in these animals is neurotoxic or neuroprotective and whether the observed effects would be the same on an abnormally developing human brain. As a consequence, the relevance of these animal studies to humans taking therapeutic doses has been challenged.[13–15]

Structural magnetic resonance imaging (MRI) and functional MRI (fMRI) respectively allow examination of detailed anatomy and dynamic functional processes in the brain. Because MRI does not involve exposure to ionizing radiation, it can be used both as a technique to examine the effects in children and also as a repeated measure to investigate baseline and posttreatment effects. Because of these strengths, a number of studies have investigated the effects of stimulants on the ADHD brain.

Yet, to the best of our knowledge, there have been only 2 integrative, quantitative meta-analytic reviews[16,17] examining the extant MRI literature on the effects of stimulants on the brain. Moreover, these reviews limited their analysis to (mostly) voxel-based morphometry studies, and only 1 included adults.[17] More specifically, these 2 previous quantitative analyses examined the effect of the proportion of medicated subjects in ADHD groups on gray matter volumes largely measured by voxel-based morphometry.[16,17] Nakao et al[16] reported that stimulant medication is associated with "normalization" of basal ganglia abnormalities in ADHD. Similar results were reported by Frodl et al,[17] who showed that stimulant treatment was associated with fewer ADHD-associated brain abnormalities (basal

Clinical Points

- Stimulant treatment for attention-deficit/hyperactivity disorder (ADHD) is known to be efficacious, but concerns about effects on the developing brain remain.
- Our review of structural and functional neuroimaging studies finds no evidence that stimulant treatment negatively impacts brain development or function. In contrast, these studies suggest that stimulant treatment attenuates the brain abnormalities that have been associated with ADHD.

ganglia in children and anterior cingulate cortex [ACC] in adults) compared with controls. However, since these studies were limited to morphometric studies and did not include either fMRI, including functional connectivity and perfusion studies, or spectroscopy, additional work on the subject is needed. As stimulant medications are widely and chronically prescribed in children, adolescents, and adults with ADHD, a better understanding of the effects of therapeutic oral doses of stimulants on brain structure and function in individuals with ADHD of all ages is an area of high clinical, scientific, and public health relevance.

The main aim of this qualitative review, therefore, was to summarize the findings from the extant morphometric, functional, and spectroscopic MRI literature to assess the current state of knowledge of the effect of stimulants on brain structure, function, and biochemistry in child and adult subjects with ADHD. Our overall question was whether stimulants improve (attenuate), worsen, or have no effect on brain structure and function in ADHD subjects. We operationalized improvement and worsening through examination of the imaging values for the medicated and unmedicated groups in relation to the non-ADHD control group or in relation to each other in a crossover design (ie, testing the same subjects both on and off medication). If, in relation to the control group, the medicated group had values that tended to be closer to the control group than were the values for the unmedicated group, we argue that this result suggests a relative improvement or an attenuation of abnormality in brain structure or function. If, on the other hand, the medicated group had values that were more different than the unmedicated group in relation to the control group, we argue that this result would suggest a worsening effect. If the medicated and unmedicated groups were the same relative to the controls, we argue that this result would suggest no effect. Thus, our conceptual framework was to examine the results of each published study in regards to treatment effects resulting in worsening, neutrality, or improvement in neural structure and function relative to controls. To the best of our knowledge, this is the first examination of effects of stimulants on both brain structure and brain function and the only review to integrate findings from articles that used either placebo- or case-control designs.

DATA SOURCES

A systematic search strategy was used to identify relevant studies. First, we carried out PubMed and ScienceDirect searches of articles through the end of calendar year 2011 using a union of the following keywords: (1) *psychostimulants* or *methylphenidate* or *amphetamine*, and (2) *neuroimaging* or *MRI* or *fMRI*, and (3) *ADHD* or *ADD* or *attention-deficit/hyperactivity disorder* or *attention deficit hyperactivity disorder.*

STUDY SELECTION AND DATA EXTRACTION

These searches yielded a combined 116 studies. From these, we reviewed titles and abstracts and pared down those reports in the English language that were published as articles or letters in peer-reviewed journals and that contained new data (resulting in 49 articles). We manually reviewed the reference list of all these 49 articles as well as the 5 relevant review articles we found. In order to limit the scope of our review, we included only those studies that utilized MRI-based measurements and included subjects with ADHD. We therefore excluded articles that used non-MRI methods (eg, positron emission tomography, electrophysiology) or studies with animal subjects, which resulted in a remaining 33 articles.

To ensure quality and interpretability of results, we included only case-control or placebo-controlled studies. For case-control studies, we required that a non-ADHD control group was used. This resulted in the exclusion of 3 additional studies.[18–20] From the 30 articles that remained, we included the 29 studies that reported quantitative comparisons between ADHD subjects on and off psychostimulant medications (1 study described results only qualitatively[21]). The resulting 29 articles included 6 structural MRI studies,[22–27] 20 fMRI studies,[28–46] and 3 magnetic resonance spectroscopy studies.[49–51] We combined details of study design and medication effects in each imaging modality. Below, we review the methods and findings of these 29 published studies.

RESULTS

Effect of Psychostimulants on Brain Structure in ADHD

In Table 1, the methods, principal findings, and summary of medication effects from the 6 structural MRI studies are listed. These are summarized below.

Summary of methods used in structural neuroimaging studies.

Sample characteristics. All available structural studies included child and/or adolescent subjects (ages range from 4 to 20 years) of both sexes. The ADHD group sample sizes for the studies varied widely, with groups as small as 12 to as large as 103.

Diagnosis and comorbidity. All ADHD subjects included in the 6 structural MRI studies met criteria for *DSM-IV* combined type, as assessed with structured interviews or with review of clinic records. Exclusion criteria for all studies included Tourette's and any Axis I disorders, with varying additional exclusions, such as oppositional defiance disorder, learning disabilities, or both. Medication-related exclusions also varied across studies, with some studies excluding medicated ADHD subjects if they were concurrently taking other psychiatric medications, while many publications did not report any exclusion relating to medication.

Table 1. Effect of Psychostimulants on Brain Structure in Children and Adolescents With ADHD

Study	Subjects, n	Sex	Age, Range (mean), y	Design	Measure	Regions of Interest	Principal Findings	Summary of Medication Effects
Bledsoe et al,[27] 2009	18 ADHD-RX 13 ADHD-TN 15 HC	Male/female	(11)	Cross-sectional, case-control Naturalistic dosing with "stimulants" for >1 y	Area	Total cerebellar vermis, anterior cerebellar vermis, posterior superior cerebellar vermis, posterior inferior cerebellar vermis	(1) HC, ADHD-RX > ADHD-TN for posterior inferior cerebellar vermis	Treatment associated with normalization of posterior inferior cerebellar vermis; no other regions of interest were smaller in ADHD-TN
Castellanos et al,[26] 2002	103 ADHD-RX 49 ADHD-TN 139 HC	Male/female	4–19 (10)	Cross-sectional, case-control Naturalistic dosing with "stimulants"	Volume	Total cerebral volume; total, frontal, parietal, temporal, and occipital gray matter; total, frontal, parietal, temporal, and occipital white matter; caudate, cerebellum	(1) HC > ADHD-TN, ADHD-RX for gray matter volumes, caudate, cerebellum, total cerebral volume (2) HC, ADHD-RX > ADHD-TN for all white matter volumes	Treatment associated with white matter normalization, but no effect in total cerebral volume or in gray matter volumes, including cerebellum and caudate
Semrud-Clikeman et al,[24] 2006	16 ADHD-RX 14 ADHD-TN 21 HC	Male/female	9–15 (13)	Cross-sectional, case-control Naturalistic dosing with "stimulants" for >1 y ADHD-RX: washed out, but no length mentioned	Volume	Caudate, ACC	(1) HC > ADHD-RX, ADHD-TN for left and right caudate (2) HC, ADHD-RX > ADHD-TN for right ACC (3) HC > ADHD-TN for left ACC (trend)	Treatment associated with right ACC normalization, but no effect in caudate
Schnoebelen et al,[23] 2010	12 ADHD-RX 13 ADHD-TN 15 HC	Male/female	9–16 (13)	Cross-sectional, case-control Naturalistic dosing with "stimulants" for >1 y ADHD-RX: washed out, but no length mentioned	Volume	Overall corpus callosum, 5 subregions including genu, splenium	(1) No significant group differences for overall corpus callosum or subregions (2) HC > ADHD-TN in splenium	Treatment history associated with subtle attenuation of reduced splenium volume reported previously
Shaw et al,[22] 2009	19 ADHD-RXnc 24 ADHD-RX 294 HC (template)	Male/female	9–20 (T1: 13; T2: 16)	Case-control, longitudinal Naturalistic dosing Scans ~4 y apart	Cortical thickness	Vertices across the whole cortex	(1) HC, ADHD-RXnc > ADHD-RX for rate of cortical thinning in left middle frontal gyrus/inferior frontal gyrus, right precentral gyrus, and right parietal/occipital regions	Treatment associated with normalized rate of change in thickness across several cortical regions
Sobel et al,[25] 2010	31 ADHD-RX 16 ADHD-TN 57 HC	Male/female	7–18 (12)	Cross-sectional, case-control Naturalistic dosing with "stimulants," mean duration = 43.3 mo ADHD-RX: no washout for scan	(1) Volume (2) Surface morphology	Caudate, putamen, globus pallidus	(1) HC > ADHD-ALL in putamen (2) No diagnosis or medical effect on conventional volumes in caudate/globus pallidus (3) HC > ADHD-RX > ADHD-TN for surface deformations in caudate, putamen, globus pallidus	Treatment associated with attenuation of basal ganglia surface deformations

Abbreviations: ACC = anterior cingulate cortex; ADHD=attention-deficit/hyperactivity disorder; ADHD-ALL = all ADHD subjects, irrespective of medication status; ADHD-RX = ADHD subjects treated with a stimulant medication; ADHD-RXnc = ADHD subjects not currently treated with psychostimulants; ADHD-TN = stimulant-naive ADHD subjects; HC = healthy control subjects.

Design. All structural MRI studies compared matched groups of ADHD subjects with and without a history of medication to a non-ADHD, unmedicated control group. All medicated groups had been treated with a mix of different types and doses of psychostimulants. All studies had a case-control design, and none contained a placebo group. Five of 6 studies were cross-sectional, whereas the remaining study[22] imaged ADHD children at 2 time points (~ 4 years apart), and compared brain measures in groups stratified by medication status at follow-up, regardless of status at baseline. In terms of medication status at the actual time of scan, 2 studies[23,24] washed out medicated subjects before the scan but did not mention the length of washout, 1 study[25] did not wash out subjects for the scan, and the remaining 3 studies[22,26,27] did not mention if medicated subjects were washed out for the scan.

Neuroimaging methods. Neuroimaging was executed on 1.5T or 3T scanners. Analytic methods varied, with some studies using manual segmentation routines and some using fully automated analyses. Three structural MRI studies[23,24,26] looked at volumes of specific regions of interest; 1 study[25] looked at volume and surface deformations of regions of interest, 1 study[27] looked at the surface area of regions of interest, and 1 study[22] looked at cortical thickness across the entire cortex. The regions of interest measured across the studies were quite varied. Only the caudate was specifically investigated in more than 1 study.[24–26]

Summary of results in structural neuroimaging studies. Alterations in brain structure were found in unmedicated ADHD versus control groups in all 6 structural MRI studies. Additionally, in all studies, medication was associated with attenuation of abnormalities in at least a portion of the regions assessed. Castellanos et al[26] and Semrud-Clikeman et al[24] were unable to find any association of medication to ADHD-related *global* volume reductions in the caudate. Likewise, Sobel et al[25] were unable to find medication-related differences in overall caudate volume (similar to null findings of Castellanos et al[26] and Semrud-Clikeman et al[24]), but did find significant *regional* caudate volume reductions in the treatment-naive group (measured as surface deformations), which were attenuated in the treated group. Similarly, in the cerebellum, Castellanos et al[26] found no association of medication with ADHD-related total cerebellar volume reductions, whereas Bledsoe et al,[27] when investigating local subregions of the cerebellum, found that chronic stimulant treatment was associated with attenuation of reduced posterior inferior vermis volumes.

For the many regions of interest that were measured in only 1 study, several showed medication-associated attenuations, including attenuation in ADHD-related volume reduction across white matter in all lobes of the brain,[26] in the ACC,[24] and in the splenium of the corpus callosum.[23] Stimulant treatment was also associated with rate of change of the cortical thickness in right motor strip, left middle/inferior frontal gyrus, and in a right parietal-occipital region similar to controls.[22]

Many null effects of medication status were found across studies, such that no statistical differences were found between volumes in ADHD-naive and ADHD-medicated groups in regions of interest. These regions included large lobular gray matter measurements across the brain,[26] global caudate volume,[24,26] overall cerebellar gray matter volume,[26] overall basal ganglia volumes,[25] and overall corpus callosum volume.[23] Notably, when corpus callosum, caudate, cerebellar, striatal, and frontal gray volumes had local volume rather than global volume measures,[23,25,27] or were subjected to vertex-by-vertex cortical thickness analyses,[22] all regions showed medication-associated attenuations. Across all structural MRI studies and all regions measured, medication was never associated with worsening of brain findings relative to controls.

Effect of Psychostimulants on Brain Function in ADHD

We found 20 published studies examining the effects of stimulants on brain function in ADHD. In Table 2, the methods, principal findings, and summary of medication effects are listed. These are summarized below.

Summary of methods used in functional neuroimaging studies. The 20 functional MRI articles varied widely in all aspects of methods, including sample characteristics, design, and analytic approach.

Sample characteristics. Fifteen of 20 articles included child and/or adolescent subjects, whereas the remaining 5 included adult subjects or youth and parent dyads. Thirteen of the 20 studies included only male subjects, whereas the remaining 7 included mixed male and female samples. The ADHD group sample sizes were modest for the functional studies, with a range of 9–19 subjects per group.

Diagnosis and comorbidity. The ADHD subjects were diagnosed on the basis of structured interviews, semi-structured interviews, or clinician assessment. Some samples included only subjects with the combined type, while others included all types. Exclusion criteria for comorbidities varied across the studies, with several studies making no mention of comorbidity exclusion, while others excluded subjects with a varying number of other *DSM-IV* diagnoses. Medication-related exclusions also varied across studies, with some excluding medicated ADHD subjects if they were concurrently taking other psychiatric medications, while others did not report any exclusion criteria relating to medication.

Design. Design varied across the fMRI studies. Notably, all but one employed either a placebo-controlled or case-control crossover design or a cross-sectional design. Only Bush et al[28] included subjects randomly assigned to either drug or placebo groups. This report, however, lacked a control group. For the studies that included a medication intervention (ie, not the cross-sectional studies), designs were used that included naturalistic dosing versus treatment after a washout period, or intervention trials ranging from a challenge dose to a 1-year trial. Medication history of subjects upon trial entry varied, however, with only the studies from Rubia et al[29–32] and Konrad et al[33] requiring that subjects be treatment naive at entry.

Table 2. Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Children + adolescents								
Anderson et al,[34] 2002	10 ADHD-RX,PL 6 HC	Male	(10)	Double-blind, crossover, placebo-controlled, and case-control No information on medical history prior to trial Methylphenidate-IR (1.5 mg/kg BID) or placebo for 1 wk Methylphenidate/placebo dose 1–3 h prior to scan Scans 1 wk apart, in counterbalanced order	T2 relaxation time (negatively related to perfusion) during resting state	Cerebellar hemispheres, cerebellar vermis	(1) ADHD-RX > ADHD-PL in cerebellar vermis in hyperactive subjects (2) ADHD-PL > ADHD-RX in cerebellar vermis in nonhyperactive subjects	Treatment decreased vermal perfusion in hyperactive subjects, but increased perfusion in nonhyperactive subjects
Kobel et al,[39] 2009	14 ADHD-RX,OFF 12 HC	Male	9–13 (11)	Crossover, case-control Naturalistic dosing (methylphenidate-IR or methylphenidate-OROS) for >3 mo For treatment scan, medication given 1.5 h prior to scan For off of treatment scan, washout > 24 h Scans >2 wk apart, in counterbalanced order	BOLD activity during n-back working memory task	Whole brain	(1) HC > ADHD-ALL in left frontal cortex, left and right parietal lobe, and right cerebellum (2) No differences between ADHD-RX and ADHD-OFF	No treatment effects detected
Konrad et al,[33] 2007[a]	9 ADHD-TN,RX 11 HC (baseline scan), HC (follow-up scan)	Male	8–12 (11)	Crossover, case-control All subjects treatment naive at start of trial Methylphenidate-IR (mean daily dose = 0.8 mg/kg) for 1 yr ADHD-TN: 1-wk washout Scans 1 y apart	BOLD activity during Attentional Network Test (includes alerting, reorienting, and executive control contrasts)	Whole brain	Reorienting (1) HC showed greater increase in temporo-parietal junction from baseline to follow-up scans than ADHD increase from treatment naive to treatment (2) ADHD showed greater increase in insula and putamen from treatment naive to treatment than HC from baseline to follow-up scans (3) ADHD-TN (at time 2) > ADHD-RX in insula and putamen Executive control (4) HC showed greater increase in ACC from baseline to follow-up scans than ADHD increase from treatment naive to treatment (5) ADHD-RX > ADHD-TN (at time 2) in ACC (trend)	Treatment may attenuate compensatory overactivity in insula and putamen during reorienting and in ACC during executive control, but showed no significant effect on temporo-parietal junction hypoactivity during reorienting

(continued)

Table 2 (continued). Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Children + adolescents								
Peterson et al,[37] 2009	16 ADHD-RX,OFF 20 HC	Male/female	7–18 (13)	Crossover, case-control ADHD subjects good treatment responders at start of trial Naturalistic dosing (methylphenidate, dextroamphetamine, or dextroamphetamine/amphetamine) For treatment scan, medication given 45–60 min previous to scan For off of treatment scan, washout > 72 h Scans 7–63 days apart (mean = 25), in counterbalanced order	(1) Suppression of BOLD signal during Stroop color-word task (2) Granger causality modeling of inferior frontal gyrus/ventral ACC interaction	Whole brain for activation, ventral ACC and left LPFC for connectivity	(1) HC, ADHD-RX > ADHD-OFF in ventral ACC suppression (2) ADHD-RX > ADHD-OFF in PCC suppression (3) HC > ADHD-RX > ADHD-OFF in left LPFC (trend) (4) HC, ADHD-RX > ADHD-OFF for influence of ventral ACC on LPFC activity	Treatment improved suppression of default-mode activity in the ventral ACC and posterior cingulate cortex, attenuated lateral prefrontal cortex underactivity, and increased connectivity between default areas and lateral prefrontal cortex to levels comparable with controls
Pliszka et al,[45] 2006	9 ADHD-RX 8 ADHD-TN 15 HC	Male/female	9–15 (13)	Cross-sectional, case-control Naturalistic dosing of methylphenidate or amphetamine for 1–9 y ADHD-RX: washout, length not mentioned	BOLD activity during Stop signal	Right dlPFC, ACC, and ventrolateral PFC defined by task-related activity	Successful vs unsuccessful inhibition (1) ADHD-ALL > HC in right dlPFC, right and left ventrolateral PFC (2) ADHD-TN > ADHD-RX, HC in ACC	Treatment associated with attenuation of overactivity in ACC, but no effect in LPFC
Posner et al,[38] 2011	15 ADHD-RX,OFF 15 HC	Male/female	11–16 (13)	Crossover, case-control For treatment scan, naturalistic dosing For off of treatment scan, washout > 48 h Scans in counterbalanced order	BOLD activity during emotional Stroop	Whole brain	Positively valenced distraction[b] (1) ADHD-OFF > HC in left mePFC (2) No significant differences between ADHD-RX and HC in left mePFC Negatively valenced distraction[b] (3) ADHD-OFF > ADHD-RX, HC in left and right mePFC deactivation	Treatment normalized alterations in medial prefrontal cortex across different emotionally valenced task conditions
Posner et al,[41] 2011	15 ADHD-RX,OFF 15 HC	Male/female	11–16 (13)	Crossover, case-control For treatment scan, naturalistic dosing For off of treatment scan, washout > 48 h Scans in counterbalanced order	BOLD activity and effective connectivity during subliminal presentation of fearful faces	Whole brain for activations, LPFC-amygdala for dynamic causal modeling	(1) ADHD-OFF > HC in right amygdala and in bilateral amygdala-LPFC connectivity (2) No significant differences between ADHD-RX and HC in right amygdala or in bilateral amygdala-LPFC connectivity	Treatment normalized amygdala overactivity and overconnectivity of amygdala with LPFC while subliminally viewing fearful faces

(continued)

Table 2 (continued). Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Children + adolescents								
Prehn-Kristensen et al,[48] 2011	12 ADHD-RX,OFF 12 HC	Male[c]	11–17 (13)	Crossover, case-control For treatment scan, naturalistic dosing of methylphenidate (mean daily dose = 0.8 mg/kg) For off of treatment scan, washout > 48 h Scans > 1 wk apart, in counterbalanced order	BOLD activity during delayed matching to sample with face distractor	Whole brain	(1) HC > ADHD-OFF in fronto-cingulate, temporo-parieto-occipital regions, and in caudate (2) HC > ADHD-RX in caudate and temporo-occipital regions (but clusters were reduced compared to HC > ADHD-OFF contrast) (3) ADHD-RX > HC in right insula	Treatment normalized underactivity in fronto-cingulate and parietal regions, and attenuated effect in caudate and temporo/occipital lobe regions during a distracted working memory task
Rubia et al,[29] 2009	12 ADHD-RX,PL 12 HC	Male	10–16 (13)	Double-blind, crossover, placebo-controlled, and case-control All subjects treatment naive at start of trial Methylphenidate-IR (0.3 mg/kg)/placebo 1 h previous to scan Scans 1 wk apart, in counterbalanced order	BOLD activity during time discrimination	Whole brain	(1) HC > ADHD-PL in right + left OFC/IFC/mePFC/ACC/caudate, right cerebellum (2) ADHD-PL > HC in left MFG/STG/occipital lobe/cerebellum (3) ADHD-RX > ADHD-PL in left OFC/IFG/insula, right mePFC, left ACC, right cerebellum (4) ADHD-PL > ADHD-RX for right IFG/mePFC/insula, right superior frontal gyrus, right medial temporal lobe, right hippocampus, right putamen/globus pallidus (5) HC vs ADHD-RX, no differences at lenient threshold	Treatment normalized all group activation differences observed in placebo condition during time discrimination task
Rubia et al,[30] 2009	13 ADHD-RX,PL 13 HC	Male	10–16 (13)	Double-blind, crossover, case-control All subjects treatment naive at start of trial Methylphenidate-IR (0.3 mg/kg)/placebo 1 h previous to scan Scans 1 wk apart, in counterbalanced order	BOLD activity and connectivity during rewarded Continuous Performance Test	Defined by task-related activity	Vigilant attention contrast *Activation:* (1) HC > ADHD-PL in right IFC/ventromedial OFC/hippocampus, left basal ganglia, left and right insula/parahippocampal gyrus/cerebellum (2) HC, ADHD-RX > ADHD-PL in left and right IPL/STG, right superior parietal (3) ADHD-RX > HC in right dlPFC, inferior cerebellar vermis (regions negative correlation w/commission errors) *Connectivity:* (4) HC, ADHD-RX > ADHD-PL in intercorrelation between: (a) Left/right inferior frontal cortex and striatum, thalamus, cerebellum (b) Cerebellum and IPL, striatum, cingulate (c) Thalamus and PCC Reward contrast (5) HC > ADHD-PL, ADHD-RX in right cerebellum (6) HC, ADHD-RX > ADHD-PL in left cerebellum (7) ADHD-PL > ADHD-RX, HC in left OFC, left and right STG *No connectivity analysis during reward contrast*	During vigilant attention, treatment increased compensatory activity and improved inhibition and normalized underactivity in parieto-temporal regions and underconnectivity in fronto-striatal-cerebellar circuits. During reward contrast, treatment attenuated altered levels of activity in orbitofrontal and cerebellar regions

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Table 2 (continued). Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Children + adolescents								
Rubia et al,[31] 2011	12 ADHD-RX,PL 13 HC	Male	10–15 (13)	Double-blind, crossover, placebo-controlled, and case-control All subjects treatment naive at start of trial Methylphenidate-IR (0.3 mg/kg)/placebo 1 h before scan Scans 1 wk apart, in counterbalanced order	BOLD activity during Simon oddball task	Whole brain	(1) ADHD-RX > ADHD-PL in left cerebellum/fusiform/MTG/inferior temporal gyrus and right IFC/premotor/STG/IPL (2) HC > ADHD-PL in right IFG/IPL/supplementary motor area/ACC/PCC/superior parietal lobule and left vmPFC/basal ganglia/thalamus/STG/MTG/occipital lobe (3) HC > ADHD-RX in left supplementary motor area/ACC/precuneus/MTG/occipital lobe/STG/IPL	Treatment had region-specific normalization effects in inferior and ventromedial fronto-striatal regions during interference inhibition
Rubia et al,[32] 2011	12 ADHD-RX,PL 13 HC	Male	10–15 (13)	Double-blind, crossover, placebo-controlled, and case-control All subjects treatment naive at start of trial Methylphenidate-IR (0.3 mg/kg)/placebo 1 h before scan Scans 1 wk apart, in counterbalanced order	BOLD activity during Stop task	Whole brain	Unsuccessful inhibition contrast (1) ADHD-RX > ADHD-PL in left MFG, right IPL/precuneus/occipital lobe and bilateral IFC/insula/putamen/caudate (2) HC > ADHD-PL in left IFC/PCC/precuneus, right premotor cortex/IPL/ITL/cerebellum, and bilateral dmPFC/pre–supplementary motor area/superior parietal lobule/occipital lobe/pulvinar (3) No significant differences between ADHD-RX and HC Successful inhibition contrast (4) No significant differences between medication conditions (5) HC > ADHD-PL in left IFC, right medial temporal lobe/occipital lobe/lingual gyrus/IPL/precuneus/PCC/cerebellum and bilateral insula/ACC/pulvinar/presupplementary motor area (6) No significant differences between ADHD-RX and HC	Treatment normalized activation during error processing, and during both error processing and successful inhibitions, no differences could be detected between medicated ADHD subjects and HC
Shafritz et al,[43] 2004	19 ADHD-RX,PL 14 HC[d]	Male/female	14–17 (15)	Double-blind, crossover, placebo-controlled, and case-control Mixed medical history prior to trial Methylphenidate-IR (15–25 mg) dose For treatment scan, methylphenidate 1.5 h prior to scan For placebo scan, washout for at least 72 h Scans 1 wk apart, in counterbalanced order	(1) BOLD activity during divided attention (2) BOLD activity during selective attention	Whole brain	Divided attention (1) HC > ADHD-PL in MTG (2) HC, ADHD-RX > ADHD-PL in dorsal striatum (3) ADHD-RX > ADHD-PL in MTG	Treatment normalized underactivity in dorsal striatum but not MTG; effects were specific to divided but not selective attention

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Table 2 (continued). Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Children + adolescents								
Teicher et al,[35] 2000	11 ADHD-RX,PL 6 HC	Male	(10)	Double-blind, crossover, placebo-controlled, and case-control No information on medical history prior to trial Methylphenidate-IR (1.5 mg/kg BID) or placebo for 1 wk Scans 1 wk apart, in counterbalanced order Methylphenidate/placebo dose 1–3 h previous to scan	T2 relaxation time (negatively related to perfusion) during resting state	Thalamus, caudate, putamen	(1) ADHD-PL > HC in putamen (2) ADHD-PL > ADHD-RX in putamen in hyperactive subjects (3) ADHD-RX > ADHD-PL in putamen in nonhyperactive subjects	Treatment attenuated hyperperfusion in hyperactive ADHD subjects and hypoperfusion in nonhyperactive ADHD subjects
Vaidya et al,[42] 1998	10 ADHD-RX,OFF 6 HC-RX, HC-OFF	Male	8–13 (10)	Crossover, case-control ADHD: naturalistic methylphenidate dose (range, 7.5–30 mg) HC: 10-mg challenge dose of methylphenidate For treatment scan, methylphenidate 1–2 h previous to scan For ADHD-OFF scan, > 36-h washout Scans > 1 wk apart, in counterbalanced order	(1) BOLD extent during stimulus-controlled Go/No-Go (2) BOLD extent during response-controlled Go/No-Go	Striatum, frontal lobes (including ACC)	Stimulus-controlled Go/No-Go In striatum: (1) HC-OFF > HC-RX (2) ADHD-RX > HC-RX (3) HC-OFF > ADHD-RX > ADHD-OFF In frontal lobes: (4) HC-RX > HC-OFF (5) ADHD-RX > ADHD-OFF	Treatment associated with increased frontal activation in controls and ADHD subjects; interaction in striatum, where treatment attenuated striatal underactivity in ADHD, and decreased activity in controls during stimulus-controlled task. No significant effects in response-controlled Go/No-Go
Adults								
Bush et al,[28] 2008	10 ADHD-TN,RX 11 ADHD-TN,PL	Male/ female	18–51 (32)	Double-blind, randomized, placebo-controlled 3 of 21 treatment-naive subjects had previous unsuccessful trial with methylphenidate Methylphenidate-OROS (titrated from 36 mg to optimal response) for 6 wk Scans 6 wk apart	BOLD signal change and spatial variability during Multi-Source Interference Task	Defined by task-related activity	(1) ADHD-RX > ADHD-PL in change from baseline in left and right dorsal anterior midcingulate cortex/insula (2) ADHD-RX > ADHD-PL in ACC, right dlPFC, left and right superior parietal (3) ADHD-RX responders (N = 7) > ADHD-RX nonresponders (N = 4), placebo (N = 11) in dorsal anterior midcingulate cortex	Treatment associated with increased activation in cingulo-fronto-parietal network, dorsal anterior midcingulate cortex effects greater in treatment responders

(continued)

Table 2 (continued). Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Adults								
O'Gorman et al,[36] 2008	9 ADHD-RX,OFF 11 HC	Male	20–48 (30)	Crossover, case-control Naturalistic dosing (includes methylphenidate-OROS, methylphenidate-IR, and dextroamphetamine) >1 mo For treatment scan, IR given 1 h previous to scan, sustained release given 5 h previous to scan For off of treatment scan, washout >1 wk Scans in counterbalanced order	Resting-state perfusion measured by continuous arterial spin labeling	Whole brain	(1) ADHD-OFF > HC in left caudate, IFG, cingulate, precuneus, MFG, postcentral gyrus (2) ADHD-OFF > ADHD-RX in left IFG, parahippocampal gyrus, postcentral gyrus, supramarginal gyrus (3) ADHD-OFF > ADHD-RX, HC in left caudate (4) ADHD-RX > HC for right precentral gyrus, cingulate, IPL	Treatment associated with attenuation of regional hyperperfusion in frontal and parietal regions, and normalization of hyperperfusion in caudate
Schlochtermeier et al,[44] 2011	10 ADHD-RXnc 10 ADHD-TN 10 HC	Male		Case-control, cross-sectional ADHD-RXnc were medicated in childhood, and medication-free for >1 y	BOLD signal during neutral and negative pictures, some with emotional valence cued	Amygdala, ACC, ventral striatum	Unexpected positive vs neutral pictures (1) HC > ADHD-TN in bilateral ventral striatum and sACC (2) ADHD-RXnc > ADHD-TN in left ventral striatum Unexpected negative vs neutral pictures (3) HC > ADHD-TN in right ventral striatum and sACC (4) ADHD-RXnc > ADHD-TN in bilateral ventral striatum Expected vs unexpected negative pictures (5) HC > ADHD-TN in sACC	Treatment in childhood associated with normalization of underactivity in sACC and ventral striatum in response to emotional stimuli
Stoy et al,[40] 2011	12 ADHD-RXnc[e] 11 ADHD-TN[f] 12 HC	Male	(28)	Case-control, cross-sectional ADHD-RXnc were medicated in childhood, and medication-free for >1 y	BOLD signal during Monetary Incentive Delay Task	Ventral striatum during reward anticipation and OFC during reward outcome, exploratory whole-brain analysis	(1) No group effects for ventral striatum or OFC regions of interest Gain anticipation (2) HC > ADHD-TN in left IFG (3) HC > ADHD-RXnc in right IFG Loss anticipation (4) HC > ADHD-RXnc in right MFG (5) No significant difference between treatment groups Gain outcome (6) No effects of group Loss outcome (7) HC, ADHD-RXnc > ADHD-TN in insula (8) HC > ADHD-TN in right precentral gyrus	Effect of ADHD not significant in regions of interest, but treatment had lateralization effect in inferior frontal gyrus during anticipation of a reward, and normalization of insula but not precentral gyrus hypoactivity during negative feedback

(continued)

Table 2 (continued). Effects of Psychostimulants on Brain Function in ADHD

Study	Subjects, N	Sex	Age, Range (mean), y	Design	Measure/Task	Regions of Interest	Principal Findings	Summary of Medication Effects
Other								
Epstein et al,[46] 2007[g]	13 ADHD-RX,PL (youth) 15 ADHD-RX,PL (parent)	Male/female	Youth: (17) Parent: (49)	Double-blind, crossover, placebo-controlled, and case-control Mixed medical history prior to trial Methylphenidate-IR (0.3 mg/kg) or placebo Treatment or placebo dose given 60–120 min previous to scan Scans 1 d apart, in counterbalanced order	BOLD activity during Go/No-Go	Striatum, prefrontal cortex, post parietal lobe gyri, cerebellum	From accompanying study (1) HC-YOUTH > ADHD YOUTH-PL in bilateral MFG/caudate, right IFG/IPL/ACC (2) HC-PARENT > ADHD PARENT-PL in bilateral IFG, left caudate (3) ADHD PARENT-PL > HC-PARENT in left IPL, ACC From medication study (4) ADHD YOUTH-RX > ADHD YOUTH-PL for left MFG, left IFG, right IPL, ACC, right caudate, and left cerebellum (5) ADHD PARENT-RX > ADHD PARENT-PL for left caudate (6) ADHD PARENT-PL > ADHD PARENT-RX for right IPL and left MFG	Methylphenidate associated with increased fronto-striatal and cerebellar activation in youth; adults on methylphenidate showed similar increases in activation for striatum and cerebellum, but not prefrontal cortex

[a]All comparisons including ADHD-TN (follow-up scan) were from an exploratory fixed-effects analysis of 5 subjects who refused medication during trial: these analyses compared ADHD-TN (at baseline and follow-up scans) and HC (at baseline and follow-up scans, N = 11).
[b]Analyses of group × valence interaction control for the effects of cognitive distraction.
[c]Per personal electronic communication with A. Prehn-Kristensen, PhD, in April 2013.
[d]Shafritz et al[44] also included a group of reading disordered subjects without ADHD, but those results are not presented.
[e]Five of 12 currently fulfilled ADHD diagnosis; others were remitted.
[f]Five of 11 currently fulfilled ADHD diagnosis; others were remitted.
[g]Epstein et al[47] contained 2 studies in one publication. Methods reported are from the medication study, whereas placebo versus HC results are from accompanying study that analyzed the subset of dyads that were randomly assigned to get placebo first (N = 9 dyads) and a matched group of 9 HC dyads.
Abbreviations: ACC = anterior cingulate cortex; ADHD = attention-deficit/hyperactivity disorder; ADHD-ALL = all ADHD subjects, irrespective of medication status; ADHD-OFF = subjects treated with stimulant medication but washed out for scan; ADHD-PL = placebo-treated ADHD subjects; ADHD-RX = ADHD subjects treated with a stimulant medication; ADHD-RXnc = ADHD subjects not currently treated with psychostimulants; ADHD-RX,OFF = one scan performed when ADHD subject was on psychostimulant, one performed after subject was washed out; ADHD-RX,PL = one scan performed when ADHD subject was on psychostimulant, one performed when on placebo; ADHD-TN = psychostimulant-naive ADHD subjects; ADHD-TN,PL = one scan performed when subjects were treatment naive, one performed when on placebo; ADHD-TN,RX = one scan performed when subjects were treatment naive, one performed when on stimulants; BID = twice a day; BOLD = blood oxygenation level-dependent; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsal medial prefrontal cortex; HC = healthy control subjects; HC-RX = one scan performed when control subject was on psychostimulant; HC-RX = one scan performed when control subject was medication free; IFC = inferior frontal cortex; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; IR = immediate release; ITL = inferior temporal lobe; mePFC = medial prefrontal cortex; MFG = middle frontal gyrus; MRI = magnetic resonance imaging; MTG = middle temporal gyrus; OFC = orbitofrontal cortex; OROS = osmotic release oral system; PCC = posterior cingulate cortex; PFC = prefrontal cortex; sACC = subgenual anterior cingulate cortex; STG = superior temporal gyrus; vmPFC = ventral medial prefrontal cortex.

Neuroimaging methods. Neuroimaging was executed on 1.5T, 2T, or 3T scanners. Of the 20 publications, 17 investigated neural response during a cognitive task (and 3 additional studies of connectivity between regions); however, the cognitive tasks used were different in each article despite testing overlapping processes such as attention and interference control (eg, attentional network task [ANT], continuous performance test, multisource interference task[47]), cognitive control (eg, the Stroop color-word task, Simon oddball task), working memory (eg, n-back task, delayed matching to sample), emotional processes (eg, emotional Stroop), and inhibition (eg, stop signal task, Go/No-Go). The remaining studies derived measures of local blood perfusion during a resting state by using T2-relaxometry[34,35] or continuous arterial spin labeling.[36]

Regions of interest investigated across the studies were also varied: some studies examined activity across the whole brain, some examined regions of interest functionally defined by regions active during task, and some examined regions of interest defined independently of the data based on a priori hypotheses. For the connectivity analyses, coupling was examined either between 2 a priori regions of interest[37,38] or across 11 regions that were activated during the task.[30] Two[34,35] of the 3 resting state perfusion studies each analyzed an a priori region of interest (cerebellum and basal ganglia), and the remaining perfusion study[36] examined the whole brain.

Summary of results in functional neuroimaging studies.

Effect of stimulants on task-elicited activation. Alterations in functional activation were found in all studies comparing ADHD to control subjects, and, in all but one of these studies,[39] stimulant medication was associated with attenuation of control versus ADHD activation differences in at least a portion of the regions found to be altered. Three brain regions were almost universally included in analyses because they have been found previously to be involved in ADHD or were activated by the specific task assessed. These regions were the striatum (including caudate and putamen), ACC, and prefrontal cortex (PFC).

Of the 15 task-based studies investigating medication effects on activity in the striatum versus a control comparison group (Pliszka et al[45] used only frontal regions of interest, Bush et al[28] had no control group), 6 studies found no ADHD-related abnormalities in striatal activation while performing executive,[32,37,39] reward,[40] or emotional tasks.[38,41] Of the 9 studies that did show alterations in striatal activity in the medication-naive versus control groups, all found that medication attenuated ADHD-related striatum dysfunction.

The ACC was examined in all 16 task-based fMRI studies with control comparison groups. Six of these studies found no ADHD-related abnormalities in ACC activation while performing executive/attentional[30,39,42,43] or emotion-eliciting[38,41] tasks. Of the 10 studies that did show alterations in ACC activity in the medication-naive versus control groups, all but two[32,44] found that medication attenuated abnormal ACC function.

The PFC was examined in 15 of the 16 task-based fMRI studies with control comparisons. Three of these studies found no ADHD-related alterations in PFC activation while performing executive/attentional[33,43] or emotion-eliciting[38] tasks. Of the 12 studies that did show alterations in PFC activity in medication-naive versus control groups, results were somewhat mixed. Two studies[39,45] showed no medication effect on ADHD-related activity alterations during executive/attentional tasks, whereas 9 studies[29–32,37,38,40,46,48] showed that medication attenuated dysfunction in regions of the PFC. In 4 studies,[30,40,42,46] medication was associated with greater differences than medication-free control subjects in regions of the PFC.

Non–fronto-striatal regions were not consistently examined across the task-based fMRI studies, although 11 of the 16 task-based studies with control comparison groups did examine whole brain effects. Results followed the general pattern that when unmedicated ADHD subjects showed an abnormality, medication was associated either with no effect in a particular region or with attenuation of this abnormality. For instance, temporal lobe regions were measured in 12 studies, 7 of which showed abnormalities in activation in the unmedicated ADHD group. Four of these 7 showed that medication attenuated temporal lobe dysfunction,[29,30,32,48] whereas 3 of the 7 showed a lack of effect of the medication on activity.[31,33,43] Patterns of results were similar across parietal lobe, occipital lobe, insula, cerebellum, and subcortical regions (see Table 2 for details).

Across all studies and all regions of the brain (aside from PFC, ACC, and striatum), only 4 regions indicated that medication in ADHD subjects was associated with greater differences than control subjects. These were greater PFC activation in medicated ADHD subjects versus non-ADHD control subjects during executive/attentional[30,42,46] and reward[40] tasks, greater inferior parietal lobule activation during a Go/No-Go task,[46] greater activity in the cerebellar vermis during rewarded continuous performance test,[30] and greater insula activity during a distracted working memory task. No differences were found in these regions in the unmedicated ADHD subjects versus controls.

Effect of medication on functional connectivity. Functional connectivity was investigated along with task-related activity in 3 studies. Rubia et al[30] showed that during a vigilant attention task, hypoconnectivity found between multiple brain regions in the ADHD treatment–naive group was attenuated after a challenge dose of methylphenidate. Peterson et al[37] showed that, during a Stroop task, hypoconnectivity between ventral ACC and lateral PFC found after a washout period was attenuated when youth with ADHD were taking their naturalistic dose. Finally, Posner et al[38] found that decreased connectivity between amygdala and lateral PFC after a washout was attenuated in ADHD when subjects were taking their naturalistic dose.

Effect of psychostimulants on resting-state perfusion. Anderson et al[34] and Teicher et al[35] reported effects of a placebo-controlled trial of methylphenidate (for 1 week) on perfusion values in the cerebellum and basal ganglia,

Table 3. Effects of Psychostimulants on Brain Metabolites in ADHD

Study	Subjects, n	Sex	Age, Range (mean), y	Design	Measure	Region of Interest	Principal Findings	Summary of Medication Effects
Carrey et al,[49] 2003	14 ADHD 9 Historical controls	Male/female	7–13	Pretreatment vs posttreatment; average 13 wk of treatment with stimulants or nonstimulants	Glutaminergic tone, choline and NAA	Prefrontal cortex and striatum	Decreased glutaminergic tone in the striatum with treatment approximating findings in controls	Treatment associated with attenuation of glutaminergic tone
Kronenberg et al,[51] 2008	7 ADHD No controls	Male/female	>18	Pretreatment vs posttreatment; 5–6 wk of treatment with methylphenidate	Choline and NAA	ACC	Decreased choline compounds; increased NAA levels in ACC	Absence of controls precludes conclusions
Hammerness et al,[50] 2012	10 ADHD 12 HC	Male/female	12–18	Pretreatment vs posttreatment; 6–8 wk of OROS methylphenidate treatment	Glutaminergic tone	ACC	Decreased glutaminergic tone in the ACC with treatment approximating findings in controls (trend)	Treatment associated with attenuation of glutaminergic tone

Abbreviations: ACC = anterior cingulate cortex, ADHD = attention-deficit/hyperactivity disorder, HC = healthy control subjects, NAA = *N*-acetylaspartate, OROS = osmotic-release oral system.

respectively. Both studies found an interaction effect between baseline levels of hyperactivity in ADHD children and changes in perfusion in the respective region of interest. Together, these articles suggest that methylphenidate has an effect on brain perfusion in a region-specific manner and that these effects were mediated by baseline values of hyperactivity. In the third perfusion study, O'Gorman et al[36] showed that stimulants attenuated hyperperfusion in frontal and parietal regions and attenuated hyperperfusion in the caudate. No information was given on baseline measures of hyperactivity in O'Gorman et al.[36]

Effect of Psychostimulants on Brain Biochemistry in ADHD (magnetic resonance spectroscopy studies)

In Table 3, the methods, principal findings, and summary of medication effects on brain biochemistry in ADHD are listed. These are summarized below.

Of the 3 identified magnetic resonance spectroscopy studies, 2 were conducted in pediatric samples[49,50] and 1 in an adult sample.[51] The studies excluded comorbidity (Carrey et al[49] allowed oppositional defiance disorder and learning disabilities). They ranged in size from 7 to 14 (ADHD) subjects. All compared the same subjects before and after treatment, but 1 study (adult) had no controls and the other 2 studies (pediatric) compared ADHD subjects before and after treatment to historical controls. Of the studies with controls, 1 reported stimulant- (and nonstimulant-) associated attenuation of glutaminergic tone in the striatum[49] and the other[50] stimulant-associated attenuation of glutaminergic tone in the ACC.

DISCUSSION

Despite great variability in study methods in terms of design, neuroimaging technique, and regions of interest studied, results of this qualitative review of the extant MRI literature on ADHD were strikingly consistent and suggest that treatment of ADHD with therapeutic oral doses of stimulants is associated with findings in persons with ADHD that are more similar to non-ADHD controls than were findings of unmedicated ADHD individuals. This conclusion is supported by the consistent direction of all structural and connectivity findings, and nearly all functional activation findings: brain measures in medicated groups of persons with ADHD were closer to control measures than were unmedicated ADHD groups. These qualitative results confirm and extend the findings of 2 recent meta-analyses[16,17] of the voxel-based morphometry MRI literature.

While the 2 previous meta-analytic studies[16,17] provided useful information summarizing the main anatomic regions affected in subjects with ADHD and the impact of medication on these regions, their analyses were largely limited to voxel-based morphometry studies and did not include fMRI, functional connectivity, and perfusion studies in both children and adults with ADHD.[34–36]

The structural MRI studies we reviewed here were quite consistent in design: all included only children and adolescents, all ADHD subjects were of the combined type, and all but 1 study compared volumes at 1 time point between a group of naturalistically medicated ADHD subjects, a group of treatment-naive ADHD subjects, and a non-ADHD control group. Likewise, results of the structural studies were also consistent in many ways. First, when any medication-associated effect was present, it was always in the direction of attenuation of ADHD-control differences. Second, studies that examined local volumes (specifically in frontal, striatal, cerebellar, and corpus callosum regions) were more successful at finding medication effects than the studies that examined volume averaged over larger regions. Together, the structural findings suggest that chronic naturalistic

stimulant treatment is likely to be associated with attenuation of ADHD-related brain structure abnormalities, but in a targeted manner, affecting specific small regions of the brain. Although there was a range of findings across the structural studies, the more consistent findings in frontal, striatal, cerebellar, and corpus callosum regions suggest that these regions are most relevant. Consistent with our conclusion, the recent meta-analysis of voxel-based morphometry studies in ADHD, a meta-regression showed that percentage of ADHD subjects with a medication history included in each study group was associated with attenuation of volume reductions in the right basal ganglia.[16]

The fMRI studies we reviewed were also quite varied in terms of methods. For instance, some studies included only youth, some included only adults, and 1 included both adults and youth. Studies also varied on diagnostic methods, ADHD subtype inclusion, comorbidity inclusion, medication history, sex of subjects, and length of the treatment trial. The regions most frequently examined in the functional studies, given their known role as targets for stimulants and involvement in ADHD pathology, were striatum, ACC, and PFC. As regards to stimulant-associated attenuation effects, the most consistent findings were for striatum and ACC.

Results were somewhat more mixed in the PFC. In fact, regional effects in 4 studies[30,40,42,46] showed that stimulant treatment was associated with greater activity relative to controls in a parietal, a cerebellar, and an insula region. Notably, all of these findings were from fMRI studies that measured brain response to performance on a specific task. No such effects were found in any analyses of functional connectivity. Although the reasons for these findings are not entirely clear, one explanation for greater activity in medicated ADHD subjects may be that the activations were compensatory and associated with improved task performance, functioning in place of deficient regions that were not targeted by the medication. In fact, Rubia et al[30] examined the relationship of activity in hypoactive regions to behavior on a rewarded continuous performance test and found that greater activity in both of these frontal and cerebellar regions was significantly correlated with reduced error rates. In the remaining studies that found less regional activity, no correlation between the regions and behavior was conducted, but, in the studies with relevant task performance data, the medicated group showed significantly better scores than the unmedicated group.[42,46,48] Finally, none of these regions were found to be altered in the comparisons between unmedicated versus control groups. Therefore, it cannot be concluded that medication effects on these regions are increasing ADHD-related alterations, only that some detectable change in activity is associated with medication that may not be associated with ADHD itself.

Our results have several clinical implications. For parents, patients, and clinicians who have been concerned that the use of stimulants could harm the developing brain, our data indicate that these concerns are unfounded and that treatment with stimulants should be considered if appropriate for the clinical presentation of the patient. Our results also raise the possibility that brain changes associated with stimulant treatment might account for stimulant-associated improvements in neurocognition and other areas. Of particular interest is the possibility that, given the wide range of brain areas affected, stimulants could improve several neurocognitive functions. Because such effects have not been consistently observed in short-term treatment studies, this idea requires future, long-term studies that assess changes in both brain and clinical parameters over time during treatment.

Although the available 29 MRI studies we identified in the extant literature generally suggest attenuation of ADHD versus control differences in the ADHD brain with stimulant treatment, even across vastly varied methods, there are several limitations to these studies that temper our ability to form firmer conclusions. For example, none of the structural studies included medication intervention as a variable wherein causation could be inferred. All of the structural studies were naturalistic in that groups of subjects were recruited based on their medication status. It is therefore possible that the medicated group may have had qualities or characteristics different from the unmedicated group that led them to pursue treatment.[52] Another issue is that fMRI studies can only inform about brain physiology, and only in association with a given task. Also, in the functional studies, only 1 study was a randomized control trial in which groups of subjects were blindly assigned to either medication or placebo, but, unfortunately, this study lacked a control group, and so it has limited interpretability in terms of the direction of the results and whether they represent improvement or worsening of function.[28] Further, group sample sizes were quite modest by today's standards. Additional limitations include the fact that studies were not uniform for presence of psychiatric comorbidities, medication status, the use of automated versus manual segmentation routines, or the length of time that subjects were receiving medications or were washed out from medications.

In addition, both structural and functional studies varied in terms of the presence and length of a washout period. For example, some examined the effects of chronic stimulant treatment after washing out subjects for varying lengths of time, and, therefore, short-term withdrawal effects may have been present in some of these studies. Many studies included previously medicated subjects in their "unmedicated" groups, which may have confounded the results due to the possibility of long-term effects of stimulants. In order to examine the effect of stimulants on the natural course of the disorder, and to answer the important question of long-term brain effects of previous medication, future studies should image treatment-naive subjects at multiple time points, including baseline, during acute treatment, and after a substantial period of discontinuation.

In addition, we cannot rule out the possibility that stimulants do not attenuate brain structure and function but produce changes different from what is seen in healthy subjects that nonetheless improve function. Forty percent of the fMRI studies did not find differences between ADHD subjects and controls in striatal activation that could be due

to the task used, or to the large variability in altered striatal activation in ADHD subjects and controls (as suggested by Nakao et al[16]). As already mentioned, because previously treated subjects were included in some studies, uncertainty remains as to whether the differences between ADHD subjects and control findings reflect pathophysiology related to ADHD or its treatment, thereby limiting the ability to interpret movement toward what is seen in controls under those circumstances. Finally, adequate controls should be in place both for sex and comorbidity effects, each of which could mediate the expression of ADHD in the brain.[53,54] Only a blocked design, randomized control trial with these factors in place will more definitively identify acute and chronic effects of therapeutic intervention.

Despite the limitations and heterogeneity of the available MRI studies, our qualitative review supports the notion that therapeutic oral doses of stimulants are associated with attenuation of abnormalities in brain structure, function, and biochemistry in subjects with ADHD. We suggest that these are medication-associated brain changes that most likely underlie the well-established clinical benefits of these medications.

Drug names: methylphenidate (Focalin, Daytrana, and others).
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Potential conflicts of interest: **Dr Spencer** receives research support from royalties and licensing fees on copyrighted ADHD scales through Massachusetts General Hospital (MGH) corporate-sponsored research and licensing and has a US patent application pending (provisional number 61/233,686) through MGH corporate licensing on a method to prevent stimulant abuse. In the past 2 years, he has been an advisor or on an advisory board of Alcobra, Ironshore, US Department of Defense, and National Institute of Mental Health (NIMH); and has received research support from Shire, Cephalon, Eli Lilly, Janssen, McNeil, Novartis, and US Department of Defense. In previous years, he has received research support from, has been a speaker or advisor to, or has been on speakers bureaus or advisory boards of Shire, Eli Lilly, GlaxoSmithKline, Janssen, McNeil, Novartis, Cephalon, Pfizer, and NIMH. **Dr Valera** has received honoraria for talk at MGH Psychiatry Academy for a tuition-funded CME course and for related consulting, and she receives funds from NIMH grant R01 HD067744. **Dr Biederman** is currently receiving research support from ElMindA, Janssen, McNeil, and Shire. In 2012, he received an honorarium from the MGH Psychiatry Academy and The Children's Hospital of Southwest Florida/Lee Memorial Health System for tuition-funded continuing medical education (CME) courses. In 2011, he gave a single unpaid talk for Juste Pharmaceutical Spain, received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course, and received honoraria for presenting at an international scientific conference on ADHD; received an honorarium from Cambridge University Press for a chapter publication; received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Eli Lilly, Shire, and AstraZeneca to the Department of Psychiatry at MGH. In 2010, he received a speaker's fee from a single talk given at Fundación Dr Manuel Camelo AC in Monterrey, Mexico; provided single consultations for Shionogi Pharma and Cipher Pharmaceuticals, for which honoraria were paid to the Department of Psychiatry at the MGH; and received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course. In previous years, he has received research support, consultation, or speakers fees from Abbott, Alza, AstraZeneca, Boston University, Bristol-Myers Squibb, Celltech, Cephalon, Eli Lilly, Esai, Fundacion Areces (Spain), Forest, Glaxo, Gliatech, Hastings Center, Janssen, McNeil, Medice (Germany), Merck, MMC Pediatric, NARSAD, National Institute on Drug Abuse, New River, National Institute of Child Health and Human Development, NIMH, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Phase V Communications, Physicians Academy, Prechter Foundation, Quantia Communications, Reed Exhibitions, Shire, Spanish Child Psychiatry Association, Stanley Foundation, UCB Pharma, Veritas, and Wyeth. **Drs Brown**, **Seidman**, **Makris**, **Faraone**, and **Ms Lomedico** report no conflicts of interest.
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