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Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of MRI-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 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 that were case or placebo-controlled and examined ADHD subjects on and off psychostimulants (as well as 5 relevant review papers).

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.

Keywords

Stimulants; ADHD; Brain; MRI

Introduction

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]

The stimulants (methylphenidate [MPH] and amphetamine [AMP] compounds) are the mainstay of treatment for ADHD because of their robust clinical efficacy. [8, 9, 10] The therapeutic effects of stimulants are 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 [IP]), whereas therapeutic doses range from 0.5–2.0 mg/kg/day and are administered orally in humans. [12, 13] Moreover, since animal studies

often rely on “normal” wild type rodents not affected with ADHD-related brain alterations, it is impossible to assess if medication-related plasticity in these animals is neurotoxic or neuroprotective, and if 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 to examine the effects in children, and also as a repeated measure to investigate baseline and post-treatment 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 two integrative quantitative meta-analytic reviews examining the extant MRI literature on the effects of stimulants on the brain. Moreover, these reviews limited their analysis to (mostly) voxel based morphometry (VBM) studies, and only one included adults. More specifically, these two previous quantitative analysis examined the effect of the proportion of medicated subjects in ADHD groups on gray matter volumes largely measured by VBM. [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 ganglia in children and anterior cingulated cortex [ACC] in adults) compared with controls. However, since these studies were limited to morphometric studies and did not include either functional MRI, 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 cross-over design (i.e., 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 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 would suggests a worsening effect. If the medicated and unmedicated groups were the same relative to the controls, we argue that this 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 function, and the only review to integrate findings from papers that used either placebo- or case-control designs.

METHODS

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”. These searches yielded a combined 116 studies. From these, we reviewed titles and abstracts and pared down those reports in the English language published as articles or letters in peer-reviewed journals, and that contained new data (resulting N = 49). We manually reviewed the reference list of all these 49 articles as well as the 5 relevant review papers 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 papers that used non-MR methods (e.g., PET, Electrophysiology), or studies with animal subjects, which resulted in a remaining 33 papers.

To ensure quality and interpretability of results, we only included studies that were case- and/or placebo-controlled. 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 papers 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 papers included 6 structural MRI studies, 20 functional MRI studies and 3 MRS studies. 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 4–20) of both sexes. 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 six structural 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 (ODD) and/or Learning Disabilities (LD). 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.

Design: All structural 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 were case-controlled, none contained a placebo group. Five of six studies were cross-sectional, whereas the remaining study [22] imaged ADHD children at two 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, two studies washed out medicated subjects before the scan but didn't mention the length of washout, [23, 24] one study did not washout subjects for the scan, [25] and the remaining 3 did not mention if medicated subjects were washed out for the scan. [22, 26, 27]

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 studies looked at volumes of specific regions of interest (ROIs; [23, 24, 26] one study looked at volume and surface deformations of ROIs, [25] one study looked at the surface area of ROIs, [27] and one study looked at cortical thickness across the entire cortex. [22] The ROIs measured across the studies were quite varied. Only the caudate was specifically investigated in more than one study. [24–26]

Summary of results in structural neuroimaging studies—Alterations in brain structure were found in unmedicated ADHD vs. 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 Pliszka 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 Pliszka et al. [24]), but did find significant *regional* caudate volume reductions in the treatment naïve group (measured as surface deformations), which were attenuated in the treated group. Similarly, in the cerebellum, Castellanos et al. 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 ROIs that were measured in only one 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 (CC; [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, where no statistical differences were found between volumes in ADHD-naïve and ADHD-medicated groups in ROIs. 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 CC volume. [23] Notably, when CC, 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 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 Stimulants 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 papers varied widely in all aspects of methods, including sample characteristics, design, and analytic approach.

Sample Characteristics: Fifteen of twenty papers included child and/or adolescent subjects, whereas the remaining five 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. ADHD group sample sizes were modest for the functional studies, with a range of 5–19 subjects per group.

Diagnosis and Comorbidity: ADHD subjects were diagnosed based on structured interviews, semi-structured interviews, or on 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 placebo- or case-controlled crossover, or cross-sectional designs. 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 (i.e. not the cross-sectional studies), designs were used that included naturalistic dosing vs. after a washout period, or intervention trials ranging from a challenge dose to a one-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 naïve at entry.

Neuroimaging Methods: Neuroimaging was executed on 1.5T, 2T, or 3T scanners. Of the twenty 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 paper despite testing overlapping processes such as attention and interference control (e.g., attentional network task [ANT], continuous performance task [CPT], multi-source interference task [34]), cognitive control (e.g., the Stroop color-word task, Simon Oddball), working memory (e.g., n-back task, delayed matching to sample), and emotional processes (e.g., emotional Stroop), and inhibition (e.g., stop signal task, go/no-go). The remaining studies derived measures of local blood perfusion during a resting state by using T2-relaxometry, [35, 36] or continuous arterial spin labeling (CASL). [37]

ROIs investigated across the studies were also varied: some studies examined activity across the whole brain, some examined ROIs functionally defined by regions active during task, and some examined ROIs defined independently of the data based on *a priori* hypotheses. For the connectivity analyses, coupling was examined either between two *a priori* regions of interest, [38, 39] or across 11 regions that were activated during the task. [30] Two of the three resting state perfusion studies each analyzed an *a priori* ROI (cerebellum and basal ganglia) [35, 36] and the remaining perfusion study examined the whole brain. [37]

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, [40] stimulant medication was associated with attenuation of control vs. 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've 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 vs. a control comparison group (Plizka et al. used only frontal ROIs, Bush et al. had no control group), 6 studies found no ADHD-related abnormalities in striatal activation while performing executive, [32, 38, 40] reward, [41] or emotional tasks. [39, 42] Of the 9 studies that did show alterations in striatal activity in the medication-naïve vs. 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, 40, 43, 44] or emotion-eliciting [39, 42] tasks. Of the 10 studies that did show alterations in ACC activity in the medication-naïve vs. control groups, all but two [32, 45] 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, 44] or emotion-eliciting [39] tasks. Of the 12 studies that did show alterations in PFC activity in medication-naïve vs. control groups, results were somewhat mixed. Two studies showed no medication effect on ADHD-related activity alterations during executive/attentional tasks, [40, 46] whereas 9 studies showed that medication attenuated dysfunction in regions of the PFC. [29–32, 38, 39, 41, 47, 48] In 4 studies, medication was associated with greater differences from medication-free control subjects in regions of the PFC. [30, 41, 43, 47]

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, 44] 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), in only four regions was medication associated with greater differences from control subjects. These were greater PFC activation in medicated vs. non-ADHD control subjects during executive/attentional [30, 43, 47] and reward [41] tasks, greater inferior parietal lobule activation during a go/no-go task [47], greater activity in the cerebellar vermis during rewarded CPT, [30] and greater insula activity during a distracted working memory task. No differences were found in these regions in the unmedicated ADHD subjects vs. controls.

Effect of medication on functional connectivity: Functional connectivity was investigated along with task-related activity in three studies. Rubia et al. [30] showed that during a vigilant attention task, hypoconnectivity found between multiple brain regions in the ADHD treatment naïve group was attenuated after a challenge dose of MPH. Peterson et al. [38] 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 on their naturalistic dose. Finally, Posner et al. [39] found that decreased connectivity between amygdala and lateral PFC after a washout was attenuated in ADHD when subjects were on their naturalistic dose.

Effect of psychostimulants on resting-state perfusion: Anderson et al. [35] and Teicher et al. [36] reported effects of a placebo-controlled trial of MPH (for 1 week) on perfusion values in the cerebellum and basal ganglia, respectively. Both studies found an interaction effect between baseline levels of hyperactivity in ADHD children and changes in perfusion in the respective ROI. Together, these papers suggest that MPH 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. [37] 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 the O'Gorman et al. [37] paper.

Effect of Psychostimulants on Brain Biochemistry in ADHD (MRS 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 three identified Magnetic Resonance Spectroscopy (MRS) studies, two were conducted in pediatric samples [49, 50] and one was an adult sample. [51] The studies excluded comorbidity (Carrey et al. [49] allowed ODD and LD). They ranged in size from 7 to 14 (ADHD subjects). All compared the same subjects before and after treatment but one (adult) had no controls and the other two (pediatric) compared to historical controls. Of the studies with controls, one reported stimulant (and non stimulant) 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 two recent meta–analyses of the VBM MRI literature.

While the two previous meta-analytic studies [16, 17] provided useful information summarizing the main anatomical regions affected in subjects with ADHD and the impact of medication on these regions, their analyses were largely limited to VBM studies and did not include functional MRI, functional connectivity and perfusion studies in both children and adults with ADHD. [35–37]

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 one study compared volumes at one time point between a group of naturalistically medicated ADHD subjects, a group of treatment naïve 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, suggests that these regions are most relevant. Consistent with our conclusion, the recent meta-analysis of VBM 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 functional MRI studies we reviewed were also quite varied in terms of methods. For instance, some studies included only youth, some included only adults, and one 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 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, 41, 43, 47] 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 CPT and found that greater activity in both of these frontal and cerebellar regions were 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. [43, 47, 48] Finally, none of these regions were found to be altered in the comparisons between unmedicated vs. 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 vs. 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 functional MRI 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 if 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 vs. 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 naïve 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 normals 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 reflects pathophysiology related to ADHD or its treatment thereby limiting the ability to interpret movement towards what is seen in controls under those circumstances. Finally, adequate controls should be in place both for sex and comorbidity effects which each 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 definitely 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 likely underlie the well-established clinical benefits of these medications.

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CLINICAL POINTS

1. Stimulant treatment for ADHD is known to be efficacious but concerns about effects on the developing brain remain.
2. 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.

Table 1

Effect of psychostimulants on brain structure in ADHD

Reference	Subjects N	Sex	Age Range (mean)	Design	Measure	ROIs	Principal Findings		Summary of Medication Effects
Children + Adolescents									
Bledsoe et al., 2009[27]	18 ADHD-RX 13 ADHD-TN 15 HC	M/F	(11)	• Cross-sectional, Case-controlled • Naturalistic dosing with "stimulants" for > 1yr	area	Total Verm, Ant Verm, Post Sup Verm, Post InfVerm	**1**	HC, ADHD-RX > ADHD-TN for Post InfVerm	RX associated with normalization of Post InfVerm, no other ROIs were smaller in ADHD-TN
Castellanos et al., 2002[26]	103 ADHD-RX 49 ADHD-TN 139 HC	M/F	4–19 (10)	• Cross-sectional, Case-controlled • Naturalistic dosing with "stimulants"	volume	TCV, TGM, TWM, FGM, PGM, TeGM, OGM, FWM, PWM, TeWM, OWM, Cau, Cblm	**1** **2**	HC >ADHD-TN, ADHD-RX for GM volumes, Cau, Cblm, TCV HC, ADHD-RX > ADHD-TN for all WM volumes	RX associated with WM normalization, but no effect in TCV, or in GM volumes including Cblm and Cau
Pliszka et al., 2006[24]	16 ADHD-RX 14 ADHD-TN 21 HC	M/F	9–15 (13)	• Cross-sectional, Case-controlled • Naturalistic dosing with "stimulants" for > 1yr • ADHD-RX: Washed out, but no length mentioned	volume	Cau, ACC	**1** **2** **3**	HC > ADHD-RX, ADHD-TN for L and R Cau HC, ADHD-RX > ADHD-TN for R ACC HC > ADHD-TN for L ACC (trend)	RX associated with right ACC normalization, but no effect in Cau
Schnoebelen et al., 2010[23]	12 ADHD-RX 13 ADHD-TN 15 HC	M/F	9–16 (13)	• Cross-sectional, Case-controlled • Naturalistic dosing with "stimulants" for > 1 yr • ADHD-RX: washed out, but no length mentioned	volume	Overall CC, 5 subregions including Genu, Splenium	**1** **2**	No sig group diffs for overall CC or subregions HC > ADHD-TN in splenium	RX history associated with subtle attenuation of reduced splenium volume reported previously

Reference	Subjects N	Sex	Age Range (mean)	Design	Measure	ROIs	Principal Findings	Summary of Medication Effects
Shaw et al., 2009[22]	19 ADHD-RXnc 24 ADHD-RX 294 HC (template)	M/F	9–20 (T1: 13 T2: 16)	• Case-controlled, Longitudinal • Naturalistic dosing • Scans ~4 yrs apart	cortical thickness	vertices across the whole cortex	**1** HC, ADHD-RXnc> ADHD-RX for rate of cortical thinning in L MFG/IFG, R PreCG, and R Par/Occip regions	RX associated with normalized rate of change in thickness across several cortical regions
Sobel et al., 2010[25]	31 ADHD-RX 16 ADHD-TN 57 HC	M/F	7–18 (12)	• Cross-sectional, Case-controlled • Naturalistic dosing with “stimulants”, mean duration = 43.3 mos • ADHD-RX: No washout for scan	**1** volume **2** surface morphology	Cau, Put, GP	**1** HC > ADHD-ALL in Put **2** No diagnosis or med effect on conventional volumes in Caud/GP **3** HC > ADHD-RX > ADHD-TN for surface deformations in Caud, Put, GP	RX associated with attenuation of BG surface deformations

ABBREVIATIONS: ACC: Anterior cingulate cortex; ADHD-RX: ADHD subjects treated with a stimulant medication; ADHD-RXnc: ADHD subjects not currently treated with psychostimulants; ADHD-TN: Stimulant naïve ADHD subjects; Ant: Anterior; BG: Basal ganglia; Cau: Caudate; Cblm: Cerebellum; CC: Corpus Callosum; FGM: Frontal gray matter; FWM: Frontal white matter; GM: Gray matter; GP: Globus Pallidus; HC: Healthy control subjects; IFG: Inferior frontal gyrus; Inf: Inferior; MFG: Middle frontal gyrus; Occ: Occipital; OGM: Occipital gray matter; OWM: Occipital white matter; Par: Parietal; PGM: Parietal gray matter; Post: Posterior; PreCG: PrecentralGyrus; Put: Putamen; PWM: Parietal white matter; R: right; ROI: Region of interest; RX: Treatment; Sup: Superior; TCV: Total cerebral volume; TeGM: Temporal gray matter; TeWM: Temporal white matter; TGM: Total gray matter; TWM: Total white matter; TX: Treatment; Verm: Cerebellar Vermis; WM: White matter.

Table 2

Effect of psychostimulants on brain function in ADHD

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
Children + Adolescents								
Anderson et al., 2002	10 ADHD-RX,PL 6 HC	M	(10)	• Double-blind, Crossover, Placebo-, and Case-controlled • No info on med Hx prior to trial • MPH-IR (1.5 mg/kg BID) or PL for 1 wk • MPH/PL dose 1–3 hr prior to scan • Scans 1 wk apart, in counterbalanced order	T2 relaxation time (negatively related to perfusion) during resting state	Cblm Hem, Verm	**1** ADHD-RX > ADHD-PL in Verm in hyperactive subjects **2** ADHD-PL > ADHD-RX in Verm in non-hyper subjects	RX decreased vermal perfusion in hyperactive subjects, but increased perfusion in non-hyperactive subjects
Kobel et al., 2009	14 ADHD-RX, OFF 12 HC	M	9–13 (11)	• Crossover, Case-controlled • Naturalistic dosing (MPH-IR or MPH-OROS) for > 3 mos • For RX scan, med given 1.5 hr prior to scan • For OFF scan, washout > 24hr • Scans > 2 wks apart, in counterbalanced order	BOLD activity during n-back working memory task	whole brain	**1** HC > ADHD-ALL in L FC, L & R Par, and R Cblm **2** No diffs between ADHD-RX and ADHD-OFF	No RX effects detected
Konrad et al., 2007[b]	9 ADHD-TN, RX 11 HC (b/l), HC (f/u)	M	8–12 (11)	• Crossover, Case-controlled • All subjects TN at start of trial	BOLD activity during ANT (includes alerting, reorienting, and executive control contrasts)	whole brain	<u>REORIENTING (a)</u> **(1)** HC showed greater increase in TPJ from b/l to f/u than	RX may attenuate compensatory over-activity in insula and Put during reorienting

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
							ADHD increase from TN to RX **(2)** ADHD showed greater increase in Ins and Put from TN to RX than HC from b/l to f/u **(3)** ADHD-TN (at time 2) > ADHD-RX in Ins and Put EXECUTIVE CONTROL **(4)** HC showed greater increase in ACC from b/l to f/u than ADHD increase from TN to RX **(5)** ADHD-RX > ADHD-TN (at time 2) in ACC (trend)	and in ACC during executive control, but showed no significant effect on TPJ hypoactivity during reorienting
				• MPH-IR (mean daily dose: 0.8 mg/kg) for 1 yr • ADHD-TN: 1 wk washout • Scans 1 yr apart				
Peterson et al., 2009	16 ADHD-RX,OFF 20 HC	M/F	7–18 (13)	• Crossover, Case-controlled • ADHD subjects good RX responders at start of trial • Naturalistic dosing (MPH, D-AMP, or D-AMP/AMP) • For RX scan, med given 45–60 min previous to scan • For OFF scan, washout > 72 hr • Scans 7–63 days apart (mean 25 days), in counterbalanced order	**1** Suppression of BOLD signal during Stroop color word **2** Granger causality modelling of IFG/vACC interaction	whole brain for activation, vACC and L LPFC for connectivity	**1** HC, ADHD-RX > ADHD-OFF in vACC suppression **2** ADHD-RX > ADHD-OFF in PCC suppression **3** HC > ADHD-RX > ADHD-OFF in L LPFC (trend) **4** HC, ADHD-RX > ADHD-OFF for influence of vACC on LPFC activity	RX improved suppression of default-mode activity in the vACC and PCC, attentuated lateral PFC under-activity, and increase increased connectivity between default-areas and lateral PFC to levels comparable with controls

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
Pliszka et al., 2006	9 ADHD-RX 8 ADHD-TN 15 HC	M/F	9–15 (13)	• Cross-sectional, Case-controlled • Naturalistic dosing of MPH or AMP for 1–9 yrs • ADHD-RX: washout, length not mentioned	BOLD activity during Smiddle signal	R DLPFC, ACC, VLPFC defined by task-related activity	SUCCESSFUL VS. UNSUCCESSFUL INHIBITION **1** ADHD-ALL > HC in R DLPFC, R & L VLPFC **2** ADHD-TN > ADHD-RX, HC in ACC	RX associated with attenuation of over-activity in ACC, but no effect in lateral PFC
Posner et al., 2011a	15 ADHD-RX, OFF 15 HC	M/F	11–16 (13)	• Crossover, Case-controlled • For RX scan, naturalistic dosing • For OFF scan, washout > 48 hr • Scans in counterbalanced order	BOLD activity during emotional Stroop	whole brain	POSITIVELY-VALENCED DISTRACTION[c] **(1)** ADHD-OFF > HC in L mPFC **(2)** No significant differences between ADHD-RX and HC in L mePFC NEGATIVELY-VALENCED DISTRACTION[c] **(3)** ADHD-OFF > ADHD-RX, HC in L & R mePFC deactivation	RX normalized alterations in mePFC across different emotionally valenced task conditions
Posner et al., 2011b	15 ADHD-RX, OFF 15 HC	M/F	11–16 (13)	• Crossover, Case-controlled • For RX scan, naturalistic dosing • For OFF scan, washout > 48 hr • Scans in counterbalanced order	BOLD activity and effective connectivity during subliminal presentation of fearful faces	whole brain for activations, LPFC-Amyg for DCM	**1** ADHD-OFF > HC in R Amyg and in bilateral Amyg-LPFC connectivity **2** No significant differences between ADHD-RX and HC in R Amyg or in bilateral Amyg-LPFC connectivity	RX normalized Amyg over-activity and over-connectivity of Amyg with LPFC while subliminally viewing fearful faces
Prehn-Kristensen et al., 2011	12 ADHD-RX, OFF 12 HC	M[d]	11–17 (13)	• Crossover, Case-controlled • For RX scan, naturalistic dosing of MPH	BOLD activity during delayed matching to sample with face distractor	whole brain	**1** HC > ADHD-OFF in fronto-cingulate, tempero-parieto-occipital regions, and in caudate	RX normalized underactivity in fronto-cingulate and parietal regions, and attenuated effect

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
				(mean daily dose: 0.8 mg/kg) • For OFF scan, washout > 48 hr • Scans > 1 week apart, in counterbalanced order			**2** HC > ADHD-RXin caudate and tempero-occipital regions (but clusters were reduced compared to HC > ADHD-OFF contrast) **3** ADHD-RX> HC in R Ins	in caudate and temp/occip regions during a distracted working memory task
Rubia et al., 2009a	12 ADHD-RX, PL 12 HC	M	10–16 (13)	• Double-blind, Crossover, Placebo-, and Case-controlled • All subjects TN at start of trial • MPH-IR (0.3 mg/kg)/PL 1hr previous to scan • Scans1 week apart, in counterbalanced order	BOLD activity during time discrimination	whole brain	**1** HC > ADHD-PL in R+L OFC/IFC/ mePFC/ACC/ Cau, R Cblm **2** ADHD-PL > HC in L MFG/STG/Occip/ Cblm **3** ADHD-RX > ADHD-PL n L OFC/ IFG/Ins, R mePFC, L ACC, R Cblm **4** ADHD-PL > ADHD-RX for R IFG/mePFC/INS, R SFG, R MTL, R Hippo, R Put/GP **5** HC vs. ADHD-RX, no differences at lenient threshold	RX normalized all group activation differences observed in placebo condition during time discrimination task
Rubia et al., 2009b	13 ADHD-RX, PL 13 HC	M	10–16 (13)	• Double-blind, Crossover, case-controlled • All subjects TN at start of trial • MPH-IR (0.3 mg/kg)/PL 1 hr previous to scan • Scans 1 week apart, in counterbalanced order	BOLD activity and connectivity during rewarded CPT	defined by task-related activity	VIGILANT ATTENTION CONTRAST*Activation:* **(1)** HC > ADHD-PL in R IFC/vmOFC/ Hippo, L BG, L & R Ins/PHG/Cblm **(2)** HC, ADHD-RX > ADHD-PL in L & R IPL/STG, R Sup Par **(3)** ADHD-MPH > HC in R DLPFC, InfVerm (regions negcorr w/ commission errors)	During vigilant attention, RX increased compensatory activity and improved inhibition and normalized under-activity in parieto-temporal regions and under-connectivity in fronto-striatal-cerebellar circuits. During reward contrast,

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
							Connectivity: **(4)** HC, ADHD-RX > ADHD-PL in inter-correlation between: **a.** L/R IFC and Str, Thal, Cblm **b.** Cblm and IPL, Str, Cg **c.** Thal and PCC <u>REWARD CONTRAST</u> **(5)** HC > ADHD-PL, ADHD-RX in R Cblm **(6)** HC, ADHD-RX > ADHD-PL in L Cblm **(7)** ADHD-PL > ADHD-RX, HC in L OFC, L & R STG No connectivity analysis during reward contrast	RX attenuated altered levels of activity in orbitofrontal and cerebellar regions
Rubia et al., 2011a	12 ADHD-RX, PL 13 HC	M	10–15(13)	• Double-blind, Crossover, Placebo-, and Case-controlled • All subjects TN at start of trial • MPH-IR (0.3mg/kg)/PL 1hr before scan • Scans 1 week apart, in	BOLD activity during Simon oddball task	whole brain	**1** ADHD-RX > ADHD-PL in L Cereb/Fusiform/ MTG/ITG & R IFC/ Premotor/STG/IPL **2** HC >ADHD-PL in R IFG/IPL/SMA/ACC/ PCC/ SPL and L vmPFC/BG/Thal/ STG/MTG/Occip **3** HC > ADHD-RX in L SMA/ACC/	RX had region specific normalization effects in inferior and ventromedial fronto-striatal regions during interference inhibition

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
				counterbalanced order			Precun/MTG/ Occip/ STG/IPL	
Rubia et al., 2011b	12 ADHD-RX, PL 13 HC	M	10–15 (13)	• Double-blind, Crossover, Placebo-, and Case-controlled • All subjects TN at start of trial • MPH-IR (0.3mg/kg)/PL 1hr before scan • Scans 1 week apart, in counterbalanced order	BOLD activity during Smiddle task	whole brain	UNSUCCESSFUL INHIBITION CONTRAST **(1)** ADHD-RX > ADHD-PL in L MFG, R IPL/ Precun/Occip& Bilateral IFC/Ins/ Put/Cau **(2)** HC > ADHD-PL in L IFC/PCC/Precun, R PreMC/IPL/ITL/ Cblm, & Bilateral dmPFC/pre-SMA/ SPL/Occip/ Pulvinar **(3)** No significant differences between ADHD-RX and HC SUCCESSFUL INNHIBITON CONTRAST **(4)** No significant differences between medication conditions **(5)** HC > ADHD-PL in L IFC, R MTL/ Occip/Ling/ IPL/ Precun/PCC/ Cereb& Bilateral Ins/ACC/ Pulvinar/ Pre-SMA **(6)** No significant differences between ADHD-RX and HC	RX normalized activation during error processing, and both during error processing and successful inhibitions no differences could be detected between medicated ADHD and healthy controls
Shafritz et al., 2004	19 ADHD-RX, PL 14 HC[a]	M/F	14–17 (15)	• Double-blind, Crossover, Placebo-, and Case-controlled	**1** BOLD activity during divided attention	whole brain	DIVIDED ATTENTION **1** HC > ADHD-PL in MTG	RX normalized under-activity in dorsal striatum but not MTG; effects were

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
				• Mixed med Hx prior to trial • MPH-IR (15–25mg) dose • For RX scan, MPH 1.5 hr prior to scan • For PL scan, washout for at least 72hr • Scans 1 week apart, in counterbalanced order	**2** BOLD activity during selective attention		**2** HC, ADHD-RX > ADHD-PL in dStr **3** ADHD-RX > ADHD-PL in MTG	specific to divided but not selective attention
Teicher et al., 2000	11 ADHD-RX, PL 6 HC	M	(10)	• Double-blind, Crossover, Placebo-, and Case-controlled • No info on med Hx prior to trial • MPH-IR (1.5 mg/kg BID) or PL for 1 wk • Scans 1 wk apart, in counterbalanced order • MPH/PL dose 1–3 hr previous to scan	T2 relaxation time (negatively related to perfusion) during resting state	Thal, Cau, Put	**1** ADHD-PL > HC in Put **2** ADHD-PL > ADHD-RX in Put in Hyperactive subjects **3** ADHD-RX > ADHD-PL in Put in non-hyper subjects	RX attenuated hyper-perfusion in hyperactive ADHD subjects and hypo-perfusion in non-hyperactive ADHD subjects
Vaidya et al., 1998	10 ADHD-RX,OFF 6 HC-RX,OFF	M	8–13 (10)	• Crossover, Case-controlled, • ADHD: Naturalistic MPH dose (range 7.5–30mg) • HC: 10mg challenge dose of MPH	**1** BOLD extent during *stimulus controlled* Go/No-Go **2** BOLD extent during *response-controlled* Go/No-Go	Str, FL (including ACC)	STIMULUS-CONTROLLED GO/NO-GO: In Str: (1) HC-OFF > HC-RX, (2) ADHD-RX > HC-ON, (3) HC-OFF> ADHD-RX> ADHD-OFF In FL: (4) HC-RX> HC-OFF, (5) ADHD-RX> ADHD-OFF	RX associated with increased frontal activation in controls and ADHD subjects; interaction in striatum where RX attenuated striatal under-activity in ADHD, and decreased activity in controls during stimulus-

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
				• For RX scan, MPH 1–2 hr previous to scan • For ADHD-OFF scan, > 36 hr washout • Scans > 1 week apart, in counterbalanced order				controlled task. No significant effects in response-controlled Go/ No-Go
Adults								
Bush et al., 2008	10 ADHD-TN, RX 11 ADHD-TN, PL	M/F	18–51 (32)	• Double-blind, Randomized, Placebo-controlled • 3 of 21 TN had previous unsuccessful trial with MPH • MPH-OROS (titrated from 36mg to optimal response) for 6 weeks • Scans 6 weeks apart	BOLD signal change and spatial variability during Multi-Source Interference Task (MSIT)	defined by task-related activity	**1** ADHD-RX > ADHD-PL in change from baseline in L & R daMCC/Ins **2** ADHD-RX > ADHD-PL in ACC, R DLPFC, L & R Sup Par **3** ADHD-RX RESPONDERS (N=7) > ADHD-RX NONRESPONDERS (N=4), PL (N=11) in daMCC	RX associated with increased activation in CFP network, daMCC effects greater in treatment responders
O'Gorman et al., 2008	9 ADHD-RX, OFF 11 HC	M	20–48 (30)	• Crossover, Case-controlled, • Naturalistic dosing (includes MPH-OROS, MPH-IR, and D-AMP) > 1 mo • For RX scan, IR given 1 hr previous to scan, SR given 5 hr previous to scan	Resting-state perfusion measured by Continuous arterial spin labeling (CASL)	whole brain	**1** ADHD-OFF > HC in L Cau, IFG, CG, Precun, meFG, PoCG **2** ADHD-OFF > ADHD-RX in L IFG, PHG, PoCG, SMG **3** ADHD-OFF > ADHD-RX, HC in L Cau **4** ADHD-RX > HC for R PrCG, Cg, IPL	RX associated with attenuation of regional hyper-perfusion in frontal and parietal regions, and normalization of hyper-perfusion in caudate

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
				• For OFF scan, washout > 1wk • Scans in counterbalanced order				
Schlochtermeier et al., 2011	10 ADHD-RXnc[e] 10 ADHD-TN[f] 10 HC	M		• Case-controlled, Cross-sectional • ADHD-RXnc were medicated in childhood, and free for > 1 yr	BOLD signal during neutral and negative pictures, some with emotional valence cued	Amyg, ACC, VS	UNEXPECTED POSITIVE VS NEUTRAL PICTURES **(1)** HC > ADHD-TN in Bilateral VS and sACC **(2)** ADHD-RXnc> ADHD-TN in L VS UNEXPECTED NEGATIVE VS NEUTRAL PICTURES **(3)** HC > ADHD-TN in R VS and sACC **(4)** ADHD-RXnc> ADHD-TN in Bilateral VS EXPECTED VS UNEXPECTED NEGATVE PICTURES **(5)** HC > ADHD-TN in sACC	RX in childhood associated with normalization of under-activity in sACC and VS in response to emotional stimuli
Stoy et al., 2011	12 ADHD-RXnc[e] 11 ADHD-TN[f] 12 HC	M	(28)	• Case-controlled, Cross-sectional • ADHD-RXnc were medicated in childhood, and free for > 1 yr	BOLD signal during Monetary Incentive Delay Task	ROIs in VS during reward anticipation & OFC during reward outcome, exploratory whole brain analysis	**(1)** No group effects for VS or OFC ROIs GAIN ANTICIPATION **(2)** HC > ADHD-TN in L IFG **(3)** HC > ADHD-RXnc in R IFG LOSS ANTICIPATION **(4)** HC > ADHD-RXnc in R MFG **(5)** No significant difference between treatment groups	Effect of ADHD not significant in ROIs, but RX had lateralization effect in IFG during anticipation of a reward, and normalization of Insula but not PrCGhypoactivity during negative feedback.

	Subjects N	Sex	Age Range (Mean)	Design	Measure/Task	ROIs	Principal Findings	Summary of Medication Effects
							GAIN OUTCOME **(6)** No effects of group LOSS OUTCOME **(7)** HC, ADHD-RXnc> ADHD-TN in Ins **(8)** HC > ADHD-TN in R PreCG	
Other								
Epstein et al., 2007[g]	13 ADHD-RX,PL (youth) 15 ADHD-RX,PL (parent)	M/F	YOUTH: (17) PARENT: (49)	• Double-blind, Crossover, Placebo-, and Case-controlled • Mixed med Hxprior to trial • MPH-IR (0.3 mg/kg) or Placebo • RX or PL Dose given 60–120 min previous to scan • Scans one day apart, in counterbalanced order	BOLD activity during Go/No-Go	Str, PFC, Post Par gyri, Cblm	From accompanying study **(1)** HC-YOUTH > ADHD YOUTH-PL in Bi MFG/Cau, R IFG/IPL/ACC **(2)** HC-PARENT > ADHD PARENT-PL in Bi IFG, L Cau **(3)** ADHD PARENT-PL > HC-PARENT in L IPL, ACC From medication study **(4)** ADHD YOUTH-RX > ADHD YOUTH-PL for L MFG, L IFG, R IPL, ACC, R Cau, and L Cblm **(5)** ADHD PARENTS-RX > ADHD PARENTS-PL for L Cau **(6)** ADHD PARENTS-PL > ADHD PARENTS-RX for R IPL and L MFG	MPH associated with increased fronto-striatal and cerebellar activation in youth; Adults on MPH showed similar increases in activation for striatum and cerebellum, but not PFC

[a] Shafritz et al also included a group of reading disordered subjects without ADHD, but those results not presented

[b] All comparisons including ADHD-TN (f/u) were from an exploratory fixed-effects analysis of 5 subjects who refused medication during trial: these analysis compared ADHD-TN (at b/l and f/u) and HC (at b/l and f/u, N = 11)

[c] Analyses of group × valence interaction control for the effects of cognitive distraction

[d] Per personal electronic communication with A. Prehn-Kristensen, PhD in April 2013

[e] Only 5 of 12 currently fulfilled ADHD diagnosis, others were remitted

[f] Only 5 of 11 currently fulfilled ADHD diagnosis, others were remitted

[g] Epstein et al 2007 contained 2 studies in one publication. Methods reported are from the medication study, whereas PL vs. HC results are from accompanying study which analyzed the subset of dyads that were randomly assigned to get PL first (N = 9 dyads), and a matched group of 9 HC dyads.

ABBREVIATIONS: =: No detectible difference between groups; ACC: Anterior cingulate cortex; 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,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-RX: ADHD subjects treated with a stimulant medication; ADHD-TN,RX: one scan performed when subjects were treatment naïve, one performed when on stimulants; ADHD-TN: Psychostimulant naïve ADHD subjects; ADHD-TN,PL: one scan performed when subjects were treatment naïve, one performed when on placebo; AMP: Amphetamine; Amyg: Amygdala; ANT: Attentional Network Test; b/l: Baseline scan; BG: Basal ganglia; BID: two time per day (bis in die);BOLD: Blood oxygenation level dependant; Cau: Caudate; Cblm: Cerebellum; Cblm Hem: Cerebellar Hemispheres; CG: Cingulate; CFP: Cingulo-fronto-parietal; Control-OFF: Refers to Control subjects who are not on stimulant medication at the time of MRI scan; Control-ON: Refers to Control subjects who are on stimulant medication at the time of MRI scan; CPT: Continuous Performance Test; D-AMP: Dextroamphetamine; daMCC: Dorsal anterior midcingulate cortex; D-Amp: Dextroamphetamine; DCM: Dynamic Causal Modeling; DLPFC: Dorsolateral prefrontal cortex; dStr: Dorsal striatum; FC: Frontal cortex; FL: Frontal lobes; f/u: Follow-up scan; GP: Globus pallidus; HC: Healthy control subjects; HC-ON,OFF: one scan performed when control subject was on psychostimulant, one performed med free; Hippo: Hippocampus; Hx: History; IFC: Inferior frontal cortex; IFG: Inferior frontal gyrus; Inf: Inferior; Ins: Insula; IPL: Inferior parietal lobule; ITG: Inferior temporal gyrus; Ling: Lingual gyrus; LPFC: Lateral Prefrontal Cortex; meFG: Medial frontal gyrus; MFG: Middle frontal gyrus; mePFC: Medial prefrontal cortex; MPH: Methylphenidate; MPH-IR: Methylphenidate immediate release; MPH-OROS: Methylphenidate Osmotic-release oral system; MTG: Middle Temporal Gyrus; MTL: Medial temporal lobe; Occip: Occipital lobe; OFC: Orbitofrontal cortex; Par: Parietal lobe; PCC: Posterior Cingulate Cortex; PFC: Prefrontal Cortex; PHG: Parahippocampalgyrus; PoCG: PostcentralGyrus; PreCG: Precentralgyrus; Precun: precuneus; PreMC: Premotor cortex;Put: Putamen; ROI: Region of interest; sACC: subgenual anterior cingulate cortex; SFG: Superior frontal gyrus ; SMA: Supplementary motor area; SPL: Superor parietal lobule; STG: Superior Temporal Gyrus;Str: Striatum; Thal: Thalamus; TPJ: Tempero-parietal junction; Verm: Cerebellar Vermis; VLPFC: Ventrolateral prefrontal cortex; vACC: Ventral Anterior Cingulate Cortex; vmOFC: VentromedialOrbitofrontal Cortex; VS: Ventral striatum;

Table 3

Effect of psychostimulants on brain metabolites in ADHD

Reference	Subjects N	Sex	Age Range (mean)	Design	Measure	ROIs	Principal Findings	Summary of Medication Effects
Carrey et al. 2003[49]	14 ADHD 9 Historical controls	M/F	7–13	Pre vs Post avg 13 weeks of tx with stimulants or non stimulants	Glutamine rgic tone, choline and NAA	PFC and Striatum	Decreased glutaminergic tone in the striatum with treatment approximating findings in controls	Rx associated with attenuation of glutaminergic tone
Kronenberg et al., 2008[51]	7 ADHD No controls	M/F	>18	Pre vs Post 5–6 weeks of tx with MPH	Choline and NAA	ACC	Decreased choline compounds; increased NAA levels in ACC	Absence of controls precludes conclusions
Hammernes s et al., 2012[50]	10 ADHD 12 HC	M/F	12–18	Pre vs. Post 6–8 weeks of OROS MPH Tx	Glutamine rgic tone	ACC	Decreased glutaminergic tone in the ACC with treatment approximating findings in controls (Trend)	Rx associated with attenuation of glutaminergic tone

ABBREVIATIONS: ACC: Anterior cingulate cortex; PFC: PreFrontal Cortex; ROI: Region of interest; RX: Treatment; M: male; F: female; NAA: N-acetyl-aspartate; MRS: Magnetic Resonance Spectroscopy.