Effects of Stimulants on Brain Function in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis

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Background: Psychostimulant medication, most commonly the catecholamine agonist methylphenidate, is the most effective treatment for attention-deficit/hyperactivity disorder (ADHD). However, relatively little is known on the mechanisms of action. Acute effects on brain function can elucidate underlying neurocognitive effects. We tested methylphenidate effects relative to placebo in functional magnetic resonance imaging (fMRI) during three disorder-relevant tasks in medication-naïve ADHD adolescents. In addition, we conducted a systematic review and meta-analysis of the fMRI findings of acute stimulant effects on ADHD brain function.

Methods: The fMRI study compared 20 adolescents with ADHD under either placebo or methylphenidate in a randomized controlled trial while performing stop, working memory, and time discrimination tasks. The meta-analysis was conducted searching PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus databases. Peak coordinates of clusters of significant effects of stimulant medication relative to placebo or off medication were extracted for each study.

Results: The fMRI analysis showed that methylphenidate significantly enhanced activation in bilateral inferior frontal cortex (IFC)/insula during inhibition and time discrimination but had no effect on working memory networks. The meta-analysis, including 14 fMRI datasets and 212 children with ADHD, showed that stimulants most consistently enhanced right IFC/insula activation, which also remained for a subgroup analysis of methylphenidate effects alone. A more lenient threshold also revealed increased putamen activation.

Conclusions: Psychostimulants most consistently increase right IFC/insula activation, which are key areas of cognitive control and also the most replicated neurocognitive dysfunction in ADHD. These neurocognitive effects may underlie their positive clinical effects.

Key Words: ADHD, fMRI, meta-analysis, methylphenidate, review, stimulants

Attention-deficit/hyperactivity disorder (ADHD) is defined by age-inappropriate inattention, impulsiveness, and hyperactivity (1). Attention-deficit/hyperactivity disorder is associated with inhibition, attention, working memory (WM), and timing deficits (2–5), underpinned by functional magnetic resonance imaging (fMRI) abnormalities in the underlying inferior frontal cortex (IFC) and dorsolateral prefrontal (DLPFC), striatal and parietal regions, and networks (2,3,6,7), which are also structurally abnormal (8–10).

Psychostimulants, such as methylphenidate, followed by dexamphetamines, are first-line pharmacologic treatment for ADHD and reduce symptoms in about 70% of patients (11,12). However, their mechanisms of action are poorly understood. At therapeutic doses, methylphenidate blocks 60% to 70% of striatal dopamine transporters (DAT) (13), which are abnormally low in medication-naïve ADHD patients (14). However, in other regions, such as frontal lobes, methylphenidate blocks 70% to 80% of norepinephrine transporters (15), which reuptake both dopamine and norepinephrine, leading to increased extracellular catecholamine levels (15).

Functional magnetic resonance imaging studies of acute effects of psychostimulants reveal true underlying mechanisms of action without confounds of secondary effects of improved behavior under chronic treatment. Randomized placebo-controlled fMRI studies of acute methylphenidate effects in medication-naïve ADHD boys using whole-brain image analyses found increased activation in predominantly right, but also left, IFC during tasks of sustained attention, inhibition, and time discrimination (TD) (4,16–18); in parietal regions during sustained attention, error monitoring, and interference inhibition (16–18); the cerebellum during attention, TD, and interference inhibition (4,16,18); and striatum during reward and response inhibition (16,18). Studies in chronically medicated ADHD patients found that an acute clinical stimulant dose relative to off medication significantly enhanced bilateral medial frontal activation during an emotional Stroop (19), deactivated cingulate default mode regions during a cognitive Stroop task (20), or had no effect during WM (21). Region of interest (ROI) fMRI studies focusing on frontal and striatal regions found that compared with atomoxetine and placebo, methylphenidate had no effect during WM (22) but significantly enhanced right IFC activation during motor inhibition (23) and during time discrimination together with atomoxetine (24). Functional magnetic resonance imaging studies in chronically medicated ADHD patients using the go/no-go task found that an acute dose of methylphenidate in medication responders compared with off medication enhanced activation in inferior, medial frontal, and anterior cingulate cortex (ACC) and striatum (25,26).

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Given these relatively inconsistent findings, we aimed to provide new analyses and to conduct a systematic review and meta-analysis on the available whole-brain fMRI studies to determine the most prominent and replicable areas modulated by acute psychostimulant treatments. Whole-brain analyses do not restrict the search volume unnecessarily and hence do not bias findings toward a priori hypothesized regions (27). For this purpose, we first re-analyzed with a whole-brain analysis three of our previously published ROI analyses of methylphenidate effects relative to placebo and atomoxetine (22–24), focusing on the contrast of methylphenidate versus placebo only. Second, we performed a voxel-based meta-analysis of whole-brain analysis fMRI studies on the acute effects of methylphenidate/stimulants relative to placebo in medication-naïve ADHD patients or relative to off-medication status in chronically medicated ADHD patients. Based on biochemical mechanisms of action of stimulants on frontal and striatal regions (15,28–30) and findings of enhanced right IFC and basal ganglia activation with acute stimulant medication in ADHD (4,16–18,23–26), we hypothesized that these two regions would be the most prominent and replicable areas that would be modulated by psychostimulants.

Methods and Materials

Whole-Brain Analysis of fMRI Comparison between Methylphenidate and Placebo during Stop, TD, and WM Tasks

Detailed descriptions of participant selection, tasks, and individual fMRI analyses are previously published (22–24) and in Supplement 1.

In brief, right-handed boys with a diagnosis of hyperactive-impulsive/inattentive combined ADHD between 10 and 17 years (19 for stop; 20 for TD and WM tasks), IQ >70, and no comorbidity except conduct disorder in two patients were scanned in a double-blind placebo-controlled design (Table 1) 1.5 hours after oral administration of either methylphenidate (Equasym [Shire Pharmaceuticals, Dublin, United Kingdom], .3 mg/kg, range 5–20 mg), placebo (vitamin C, 50 mg), or atomoxetine (Strattera [Lilly Pharmaceuticals, Indianapolis, Indiana], 1 mg/kg, range 16–66 mg) (not analyzed). Patients were medication-free between scans, which were 7 days apart. Functional magnetic resonance imaging tasks included a tracking stop task that measured successful and failed stop versus baseline go trials, a TD task measuring the ability to discriminate two time intervals that differed by several hundreds of milliseconds contrasted with an order judgment task, and an n-back WM task that contrasted the function of recognizing letters shown 3/2/1 letters back with the ability to detect a target letter ("Is it X?"). Twenty-nine (stop) or 20 (WM/TD) age-matched healthy control subjects were scanned once (Table 1).

Participants were paid £50 for each visit. Written informed consent and assent were obtained and the study was approved by the local ethics committee.

Gradient-echo echo-planar imaging magnetic resonance imaging data were acquired on a GD Sigma 3T Horizon DHx system (General Electric, Milwaukee, Wisconsin) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings' College London (see Supplement 1 for image acquisition details).

Whole-brain fMRI analyses were conducted using XBAM software (http://www.brainmap.co.uk). Individual and group-level analyses are described in detail elsewhere (3,22,24) and in Supplement 1. Briefly, fMRI data were realigned to minimize motion-related artifacts and smoothed using a Gaussian filter (full-width at half maximum 8.82 mm) (31). Time-series analyses of individual subject activation were performed with a wavelet-based re-sampling method (31). We convolved the task epoch of each event of interest for each task (i.e., successful/failed stop–go trials for Stop; 3/2/1-back vs. 0-back for WM; time discrimination versus order judgment for TD), with two Poisson model functions (delays of 4 sec and 8 sec). Individual activation maps were recalculated by testing the goodness-of-fit of this convolution with the blood oxygen level-dependent time series that used the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). This statistic, the sum of squares ratio, was used in further analyses (32). Using rigid body and affine transformation, the individual maps were registered into Talairach standard space (33). A group brain activation map was then produced for each medication and each experimental condition.

Then, repeated measures analyses of variance (ANOVAs) were conducted with drug condition as the repeated variable (methylphenidate, placebo) for the following contrasts: successful stop–go trials; failed stop–go trials; TD–order judgment; WM: a 2*3 factorial repeated measures design was used, with drug and WM load (1-back, 2-back; 3-back, all contrasted with 0-back) as within-subject variables.

Combined voxel/cluster tests were applied coupled with permutation testing to allow for type I error control at the cluster

Table 1. Demographic Data for Healthy Control Subjects and ADHD Patients

Task	Stop Task		Time Discrimination Task		Working Memory Task	
Variables	Control Subjects (29) Mean (SD)	ADHD (19) Mean (SD)	Control Subjects (20) Mean (SD)	ADHD (20) Mean (SD)	Control Subjects (20) Mean (SD)	ADHD (20) Mean (SD)
Age (Years, Months)	13, 9 (2, 6)	13, 1 (1, 7)	13, 8 (2, 5)	13, 0 (1, 7)	13, 8 (2, 5)	13, 0 (1, 7)
IQ	110 (12)	92 (11)	113 (10)	91 (11)	114 (11)	91 (11)
SDQ Total	4 (4)	22 (7)	4 (4)	22 (7)	4 (4)	22 (7)
SDQ Hyperactive/Inattentive	1 (2)	8 (3)	2 (2)	8 (2)	2 (2)	8 (2)
CPRS-R (DSM-IV) Total *t*	44 (5)	79 (11)	44 (5)	78 (11)	44 (5)	78 (11)
CPRS-R Cognitive/Inattention Problems *t*	46 (4)	69 (9)	45 (4)	69 (9)	45 (4)	69 (9)
CPRS-R Hyperactivity *t*	45 (4)	81 (13)	47 (4)	79 (14)	46 (4)	79 (14)
CPRS-R Global Index: Restless Impulsive *t*	46 (5)	78 (11)	44 (3)	76 (12)	44 (3)	76 (12)
CPRS-R ADHD *t*	46 (5)	76 (8)	44 (4)	75 (8)	44 (4)	76 (8)

ADHD, attention-deficit/hyperactivity disorder; CPRS-R, Conners' Parent Rating Scale Revised; SDQ, Strengths and Difficulties Questionnaire; *t*, *t* scores.