

Functional Magnetic Resonance Imaging of Methylphenidate and Placebo in Attention-Deficit/Hyperactivity Disorder During the Multi-Source Interference Task

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Context: Previous studies have reported hypofunction, structural abnormalities, and biochemical abnormalities of the dorsal anterior midcingulate cortex (daMCC) in attention-deficit/hyperactivity disorder (ADHD). Stimulant medications are effective treatments for ADHD, but their neural effects have not been fully characterized.

Objective: To determine whether the methylphenidate hydrochloride osmotic-release oral system (OROS) would increase functional magnetic resonance imaging (fMRI) activation, compared with placebo, in the daMCC and other frontoparietal regions subserving attention during the Multi-Source Interference Task (MSIT).

Design: Randomized, placebo-controlled, 6-week, before-after fMRI study.

Setting: Academic medical center ambulatory clinic.

Patients: Twenty-one adults with ADHD randomized to 6 weeks of treatment with methylphenidate OROS (n = 11) or placebo (n = 10).

Interventions: Patients underwent fMRI twice while performing the MSIT (scan 1 at baseline and scan 2 at 6 weeks).

Main Outcome Measures: Group-averaged, random-effects, repeated-measures, general linear model analyses were used to compare daMCC (and whole-brain) fMRI activation during the MSIT. Individual-based daMCC volume-of-interest confirmatory analyses and behavioral data are also presented.

Results: Performance and baseline fMRI measures in the daMCC and other a priori brain regions did not differ between groups. Group comparisons showed a group \times scan interaction and *t* test confirmation of higher activation in the daMCC at 6 weeks in the methylphenidate OROS group than in the placebo group ($P < 1 \times 10^{-4}$, cluster corrected for multiple comparisons). Individual daMCC volume-of-interest analyses confirmed group-averaged findings and suggested that daMCC activity might be related to clinical response. Methylphenidate OROS also produced higher activation in the dorsolateral prefrontal cortex and the parietal cortex at 6 weeks.

Conclusion: Methylphenidate OROS increased daMCC activation during the MSIT and may act, in part, by normalizing daMCC hypofunction in ADHD.

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ATTENTION-DEFICIT/HYPER-activity disorder (ADHD) is the most common neurobehavioral disorder in children and adolescents, and it frequently persists into adulthood.¹⁻⁶ Stimulants are effective treatments for ADHD,⁷⁻⁹ but their exact mechanism of action has not been established. Given the great morbidity associated with ADHD, including impaired academic, occupational, and social functioning and increased rates of substance abuse, traffic accidents, and persistent neuropsychologic impairments,¹⁰⁻¹⁴ determining the under-

lying neural substrate of ADHD and the neurobiological basis of successful treatments for ADHD is of great importance.

Convergent data from neuroimaging, neuropsychological, genetics, and neurochemical studies¹⁵⁻⁴⁶ have implicated dysfunction of the dorsal anterior midcingulate cortex (daMCC), the dorsolateral prefrontal cortex (DLPFC), and the parietal cortex (together, the cingulo-frontoparietal [CFP] cognitive/attention network), along with the striatum and cerebellum, as contributing to the pathophysiologic mechanism of ADHD. The daMCC findings are particularly consis-

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tent, with many imaging studies reporting daMCC hypofunction,^{15-23,46} structural abnormalities,²⁴⁻²⁶ or biochemical abnormalities.⁴⁷ The daMCC plays key roles in cognition, attention, target detection, motor control (response selection and inhibition), error detection, and feedback-based decision making,⁴⁸⁻⁵³ and daMCC dysfunction is likely to result in the cardinal signs of ADHD. Together, these functional and structural imaging data combine with theoretical constructs to strongly implicate daMCC (and CFP network) abnormalities in the pathophysiologic mechanism of ADHD. Related to understanding the pathophysiologic mechanism of ADHD is determining how medications used to treat the disorder produce their effects. Although imaging studies have provided valuable insights, including implication of the dopaminergic/catecholaminergic systems,⁵⁴⁻⁸⁶ the neural mechanisms by which stimulants exert their therapeutic effects are complex and multifaceted and have not been fully established.

To better assess brain changes related to treatment with the methylphenidate hydrochloride osmotic-release oral system (OROS) (Concerta; McNeil-PPC Inc, Ft Washington, Pennsylvania), we incorporated a variety of study design elements to maximize the ability to detect methylphenidate-related brain effects. First, we used the Multi-Source Interference Task (MSIT), a cognitive activation paradigm specifically designed to be a robust and reliable task for identifying and interrogating the daMCC and the CFP network using functional magnetic resonance imaging (fMRI).^{87,88} The MSIT has demonstrated the ability to activate the daMCC in approximately 95% of the more than 100 individuals who have undergone fMRI to date.⁸⁷ Second, patients underwent fMRI using a high-field-strength 3-T fMRI scanner to boost signal-to-noise characteristics. Third, adults with ADHD were studied because persistence of ADHD increases the likelihood of neurobiological causation.¹⁵ Fourth, because clinical response to methylphenidate does not maximally differentiate from placebo until approximately 4 to 6 weeks,^{7,8} patients underwent fMRI at baseline and again 6 weeks after randomization to receive methylphenidate OROS or placebo (week 6 fMRI was performed approximately 4-6 hours after dosing). Fifth, we optimized sample homogeneity by excluding patients with non-ADHD Axis I diagnoses. Finally, the MSIT allowed us to perform 2 complementary types of analyses: (1) more traditional group-based comparisons (eg, placing all patients into standardized anatomical space⁸⁹ and performing between-group "whole-brain" voxelwise comparisons) and (2) confirmatory individual-based daMCC volume-of-interest (VOI) analyses that allowed us to characterize and reduce interpatient anatomical variability by using the MSIT to functionally localize the daMCC for each patient and then extracting and analyzing the data from within these individualized daMCC VOIs (analogous to methods used by O'Craven et al⁹⁰).

These individual-based daMCC VOI analyses were a key part of the study because they permitted us to address 2 outstanding issues. First, they allowed us to remove anatomical variability, a potentially serious confound for group-averaged analyses, from consideration (ie, as detailed previously,¹⁵ if individual patients with ADHD had "normal"

activation but greater anatomical variability than controls, traditional group-averaged analyses could erroneously make it seem that the ADHD group had lower activity because spatially diverse individual activation sites might not overlap sufficiently to produce a group-averaged activation). In light of this, we performed initial group-averaged analyses and then confirmed these results using the MSIT to perform individual-based VOI analyses that identified daMCC activation for each individual and entered these data into repeated-measures analyses of variance (ANOVAs) to characterize drug effects. Second, we performed spatial variability analyses of the daMCC location in all patients with ADHD and compared the results with those of a similar published daMCC spatial variability analysis of healthy adults.⁸⁸

Specifically, we hypothesized that (1) although baseline comparisons would show no differences between the methylphenidate OROS and placebo groups, 6 weeks of treatment with methylphenidate OROS would produce higher daMCC activation than placebo and (2) individual-level daMCC VOI analyses would support the group-averaged findings.

METHODS

PATIENTS

Written informed consent was obtained per the Massachusetts General Hospital Subcommittee on Human Subjects guidelines. The sample included 21 unmedicated adults with ADHD per *DSM-IV* criteria⁹¹ with childhood onset and persistence of symptoms into adulthood. Additional inclusion criteria were age 18 to 51 years, right-handedness, and IQ greater than 80. Exclusion criteria were the presence of (1) any current Axis I psychiatric diagnosis other than ADHD, as verified by the Structured Clinical Interview for *DSM-IV*⁹²; (2) any clinically significant medical condition; (3) clinically significant abnormal laboratory values; (4) contraindications to MRI (metal objects in body or claustrophobia); (5) seizures or tics; (6) pregnancy or nursing; (7) alcohol or substance abuse (current or in the past 2 years); and (8) a previous adequate trial with methylphenidate.

Patients were ascertained from randomized, double-blind, placebo-controlled clinical studies of methylphenidate preparations.^{7,8} Patients underwent comprehensive assessments, including psychiatric evaluation by a board-certified psychiatrist, structured diagnostic interviews using the Structured Clinical Interview for *DSM-IV* supplemented for childhood disorders by modules (*DSM-IV* ADHD and conduct disorder) from the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version,⁹³ medical history, and laboratory assessments (liver function tests, complete blood cell count, vital signs, and electrocardiography). Cognitive testing (full-scale IQ) was estimated via the Wechsler Adult Intelligence Scale–Revised.⁹⁴

Methylphenidate OROS was titrated to optimal response (maximum daily dose, 1.3 mg/kg; initial dose, 36 mg). During titration, the dosage was increased by 36 mg/d at weekly visits, but only for patients who did not attain an a priori definition of response or improvement.⁷ Adverse effects were minimal, as expected, and did not differ significantly between treatment response groups. Severity and clinical response were assessed using the Adult ADHD Investigator Symptom Report Scale⁹⁵ and the Clinical Global Impression Scale.⁹⁶ Treatment responders were defined as patients showing an Adult ADHD Investigator Symptom Report Scale score reduction greater than

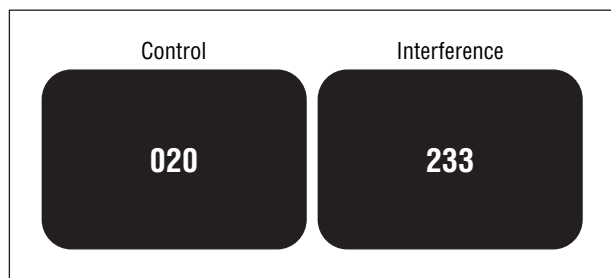


Figure 1. Multi-Source Interference Task trial examples. Per our published protocol,⁸⁷ patients reported, via button press, the identity of the number that differed from the other 2 numbers. During control trials, distractors were zeroes and target numbers were congruent with their button box positions. During interference trials, distractors were drawn from the set of potential target numbers (ie, 1, 2, or 3), and target numbers were never placed congruently with their button box positions. In both examples, the correct answer would be to press button 2. Block-formatted functional series began and ended with 30 seconds of fixation, and the interstimulus interval was 1750 milliseconds. Patients completed a 5-minute practice version just prior to the fMRI session.

30% and a 1- or 2-point improvement in the Clinical Global Impression–Improvement Scale score, per previously published studies.^{7,8} Raters and patients were masked to treatment assignment.

MSIT METHODS AND fMRI PROCEDURES

The MSIT procedures have been detailed elsewhere⁸⁷ and are summarized in **Figure 1**. Patients completed 192 trials during each fMRI (24 trials during each 42-second control [C] or interference [I] block; 96 trials of each type during each fMRI).

Functional MRI was performed in a 3.0-T echoplanar scanner (Allegra; Siemens AG, Munich, Germany) using a head coil.⁵⁰ Patients laid on a padded scanner couch in a darkened room and wore foam earplugs. Foam padding stabilized the head. Stimuli, generated via the MacStim 2.6 program (WhiteAnt Occasional Publishing, West Melbourne, Australia) on a Macintosh Powerbook (Apple Inc, Cupertino, California), were projected onto a screen and viewed via a tilted mirror.

After an initial localizer fMRI, high-resolution MPRAGE (magnetization prepared rapid gradient echo) structural images (1.0 × 1.0 × 1.3 mm; 128 sections; 256 × 256 matrix; echo time, 3.3 milliseconds; repetition time, 30 milliseconds; and flip angle, 40°) were collected for 3-dimensional anatomical localization. Functional MRIs (23 coronal sections, extending posteriorly from $y \approx +60$, 3.125 mm² in-plane resolution × 5 mm thick, skip 0 mm; echo time/repetition time, 30/1500 milliseconds; 264 images per section; flip angle, 90°; field of view, 20 cm²; and 64 × 64 matrix) lasted 6 minutes and 36 seconds.

DATA ANALYSIS

Behavioral Data

Reaction time (RT) and accuracy were analyzed using 2 (group: methylphenidate OROS vs placebo) × 2 (condition: MSIT_{Interference} vs MSIT_{Control}) × 2 (scan: scan 1 [baseline] vs scan 2 [6 weeks]) repeated-measures ANOVAs. We used *t* tests for specific contrasts.

Structural and Functional Neuroimaging Data

Structural and functional images were analyzed using Brain Voyager (Brain Innovation, Maastricht, the Netherlands). Functional data preprocessing included 3-dimensional motion correction, drift correction, and interimage section time correction.

Each patient's functional and high-resolution structural data were coregistered and transformed into Talairach space.

Random-effects general linear model (GLM) analyses were used for between-group comparisons (methylphenidate OROS vs placebo) to enable us to generalize the conclusions to the larger population beyond this sample. The GLM predictors were modeled in a standard manner by convolving with an expected hemodynamic response function. For all contrasts, the a priori focus was on testing the response of the daMCC, defined anatomically using criteria described previously as cingulate cortex anterior to $y=0$ mm, posterior to $y=+30$ mm, and within 15 mm of the midline.^{15,50,88}

Functional MRI analyses were performed as follows. For the main group-averaged contrast (methylphenidate OROS vs placebo, whole brain with a priori daMCC focus), we used a multistep, masked, random-effects, repeated-measures ANOVA GLM analysis. A voxelwise mask representing all voxels showing MSIT_{Interference} > MSIT_{Control} activity for 11 patients treated with methylphenidate OROS during scan 2 ($P < .05$ uncorrected, totaling 2354 mask voxels) was applied to restrict analysis of whole-brain data from all 21 patients to brain areas specifically involved in cognitive task performance. In these masked voxels, a random-effects, repeated-measures ANOVA GLM was calculated to identify brain regions that showed a significant treatment group (methylphenidate OROS vs placebo) × scan (scan 1 [baseline] vs scan 2 [6 weeks]) interaction and a confirmatory *t* test indicating significantly higher scan 2 activation during MSIT_{Interference} trials in the methylphenidate OROS group than in the placebo group. To correct for multiple comparisons, we used a stringent cluster constraint producing a regional false-positive probability of $P < 1 \times 10^{-4}$ (ie, to match previous conservative published α thresholds,¹⁵ for unsmoothed data, we required clustering of ≥ 7 contiguous voxels with $P < .05^{97}$).

Beyond the focused daMCC group analyses, we also report whole-brain findings for any brain region that met the same stringent criteria (interaction plus confirmatory scan 2 *t* test), and for completeness, we provide whole-brain data showing regions with significantly higher scan 2 activation during MSIT_{Interference} trials in the methylphenidate OROS group than in the placebo group (although these post hoc-identified regions should be prospectively confirmed).

Confirmatory individual daMCC VOI analyses were performed using a 3-step modified conjunction process. First, in an initial daMCC search volume (defined anatomically using the previously mentioned criteria), we used a standard MSIT_{Interference} minus MSIT_{Control} contrast to functionally localize the daMCC for each patient (ie, the daMCC was functionally defined as showing significant activation during MSIT_{Interference} above the MSIT_{Control} and fixation baselines). For this initial search volume definition, a regional (daMCC) threshold of $P < 1 \times 10^{-4}$ was used ($P < .05$ per voxel corrected for multiple comparisons with a 7-voxel cluster requirement⁹⁷). To allow for possible increased spatial variability in patients with ADHD, activation in the cingulate cortex that began in but extended beyond the initial daMCC search volume was still considered part of the daMCC. Also, because it was hypothesized that methylphenidate OROS could enhance daMCC activity (possibly resulting in a new or larger regional activation in scan 2), VOI definitions were determined separately for scans 1 and 2. Second, in these functionally defined VOIs, we identified the voxel with the maximal percentage signal change of MSIT_{Interference} above fixation (in the 3 patients with bilateral daMCC activations, the means of the 2 activations were used so that each individual contributed only 1 value). Finally, these percentage fMRI signal change values were compared between groups (methylphenidate OROS vs placebo, and then again after subdividing by clinical treatment response) using repeated-measures ANOVAs.

Table 1. Sample Characteristics^a

Characteristic	Methylphenidate OROS (n=11)	Placebo (n=10)	Test
IQ	113.4 (7.6)	117.7 (11.9)	$P=.33$
Age, y	29.5 (5.9)	34.4 (9.2)	$P=.16$
Sex, F/M, No.	4/7	8/2	$P=.08$
ADHD severity (AISRS) ⁹⁵ score	30.3 (5.2)	32.8 (5.7)	$P=.30$
Dose, mg			
Overall	86.7 (21.8) [54-126]	90.9 (21.2) [54-126]	$F_{1,19}=0.19$; $P=.70$
Responders (methylphenidate OROS, n=7; placebo, n=4)	91.3 (25.2) [54-126]	85.5 (18.7) [54-108]	$F_{3,17}=0.95$; $P=.44$
Failures (methylphenidate OROS, n=4; placebo, n=6)	74.3 (11.3) [63-90]	99.0 (26.5) [72-126]	NA

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Report Scale; NA, not applicable; OROS, osmotic-release oral system.

^aData are given as mean (SD) [range] except where indicated otherwise. Overall, patients were persistently and moderately to severely impaired (of 20 patients with full Structured Clinical Interview for *DSM-IV* data, mean [SD] age at onset was 5.2 [1.4] years, duration of illness was 25.2 [7.6] years, number of past symptoms was 11.6 [4.0], and number of current symptoms was 10.6 [3.7]), and the sample was homogeneous (85% were moderately impaired and 10% were severely impaired). Only 3 of 21 patients had any previous medication treatment for ADHD (none successful); of these, 2 were randomized to receive methylphenidate OROS (1 responded and 1 failed) and 1 to receive placebo (responded). Only 1 of 20 patients polled reported current tobacco use. No significant differences were found in dosing either for methylphenidate OROS vs placebo or when subdivided by treatment response. Regarding sex, a group-averaged whole-brain analysis of variance general linear model at baseline showed no main effect of sex in any cingulo-frontoparietal region of interest (the only region that differed significantly was a small [<25 voxels] region in the left insula), and an unpaired t test showed that the mean (SD) baseline dorsal anterior midcingulate cortex percentage functional magnetic resonance imaging (fMRI) signal did not differ between the 12 women (1.6% [1.2%]) and 9 men (1.1% [0.61%]) ($t_{19}=1.2$; $P=.25$). We took advantage of the robustness of the Multi-Source Interference Task (MSIT) to remove from consideration potential confounds due to spurious relationships that might exist in dorsal anterior midcingulate cortex (daMCC) activation and either performance or demographic characteristics. Specifically, we confirmed that there were no correlations of baseline daMCC percentage fMRI signal change with reaction time (RT), accuracy, IQ, ADHD severity, or sex. No significant correlations or relationships of performance or demographic measures with baseline image 1 daMCC percentage fMRI signal change were found, whether for MSIT_{Interference} RT (Fisher $r=0.18$; $P=.43$), MSIT_{Interference} RT difference score (RT-MSIT_{Interference} minus RT-MSIT_{Control}) ($r=0.20$; $P=.38$), MSIT_{Interference} accuracy ($r=-0.06$; $P=.81$), age ($r=0.11$, $P=.65$), full-scale IQ ($r=0.10$; $P=.68$), baseline AISRS score ($r=0.11$; $P=.65$), or AISRS 6-week change from baseline score ($r=0.14$; $P=.56$).

For completeness (to characterize the ADHD group response), we also performed an overall GLM to identify brain regions activated in the MSIT_{Interference} minus MSIT_{Control} contrast in the full group of 21 patients with ADHD at baseline scan 1. For this single contrast, to reduce interpatient variability and more closely match previous studies, we used a 4-mm full-width at half maximum spatial smoothing filter.

Finally, to quantify the degree to which the locations of individual daMCC activations matched that of the group-averaged data, we performed a spatial variability analysis by calculating mean distances of individuals' daMCC maxima from the group average. Data from these adults with ADHD ($n=21$) were then compared via t test with a published spatial variability analysis of 8 healthy adults from the MSIT validation study.⁸⁸

RESULTS

SAMPLE CHARACTERISTICS AND BEHAVIORAL DATA

The methylphenidate OROS and placebo groups did not differ significantly in IQ, age, sex, baseline ADHD severity, or end-of-trial dosage (**Table 1**). The groups also did not differ with respect to RT or accuracy. A means table for RT and accuracy is provided (**Table 2**).

fMRI RESULTS

Baseline Group Comparison

The methylphenidate OROS and placebo groups did not significantly differ at baseline in any a priori region of interest. In fact, a GLM contrasting methylphenidate OROS MSIT_{Interference} vs placebo MSIT_{Interference} during baseline scan

1 showed that only 1 cortical area differed between groups (the precuneus [area 31]: $x, y, z=13, -51, 34$), and it is not part of the CFP cognitive/attention network.

Group Comparison at 6 Weeks

As predicted, the main group-averaged contrast of interest showed that, compared with placebo, 6 weeks of methylphenidate OROS significantly increased daMCC activation (**Figure 2**). Two separate areas in the daMCC, a third posteriorly adjacent to the daMCC, and a fourth insular region passed a rigorous, multistep, masked, random-effects, repeated-measures ANOVA GLM analysis, showing a significant treatment group (methylphenidate OROS vs placebo) \times scan (scan 1 [baseline] vs scan 2 [6 weeks]) interaction and a confirmatory t test indicating significantly higher scan 2 activation during MSIT_{Interference} trials in the methylphenidate OROS group than in the placebo group (corrected $P < 1 \times 10^{-4}$).

Although not displaying a significant interaction effect, the rest of the CFP cognitive/attention network and other regions typically activated by the MSIT in healthy volunteers and adults with ADHD (the premotor cortex and thalami bilaterally)⁸⁸ showed higher activation in the methylphenidate OROS group than in the placebo group at 6 weeks, even after applying a more stringent cluster constraint (corrected $P < 1 \times 10^{-6}$) (**Figure 3** and **Table 3**).

Single-Patient daMCC VOI Analyses at 6 Weeks

Individual-level daMCC analyses confirmed the group-averaged results. As **Figure 4** shows, there was a sig-

Table 2. MSIT Performance Data^a

Group	Scan 1 (Baseline)		Scan 2 (6 wk)	
	Interference	Control	Interference	Control
Reaction times, ms				
Overall				
Methylphenidate OROS (n=11)	844 (73)	537 (58)	733 (93)	486 (76)
Placebo (n=10)	876 (99)	580 (123)	769 (86)	520 (74)
By treatment response				
Methylphenidate OROS responders (n=7)	835 (91)	537 (38)	729 (113)	490 (84)
Methylphenidate OROS failures (n=4)	860 (31)	536 (90)	741 (58)	480 (72)
Placebo responders (n=6)	892 (101)	597 (156)	779 (81)	527 (87)
Placebo failures (n=4)	853 (107)	555 (62)	753 (102)	510 (60)
Accuracy, %				
Overall				
Methylphenidate OROS	96.6 (3.3)	99.7 (0.7)	98.5 (1.6)	98.9 (2.8)
Placebo	96.0 (4.6)	99.2 (2.0)	98.1 (1.9)	99.5 (0.7)
By treatment response				
Methylphenidate OROS responders	97.0 (3.9)	100.0 (0.0)	98.4 (2.0)	98.4 (3.5)
Methylphenidate OROS failures	95.8 (2.1)	99.2 (1.0)	98.6 (0.5)	99.9 (0.3)
Placebo responders	94.8 (5.7)	98.8 (2.5)	97.4 (2.1)	99.3 (0.8)
Placebo failures	97.9 (0.8)	99.7 (0.5)	99.2 (1.0)	99.7 (0.5)

Abbreviations: MSIT, Multi-Source Interference Task; OROS, osmotic-release oral system.

^aData are given as mean (SD). Two separate 2 (group: methylphenidate OROS vs placebo) × 2 (condition: MSIT_{Interference} vs MSIT_{Control}) × 2 (scan: scan 1 [baseline] vs scan 2 [6 weeks]) repeated-measures analyses of variance showed that the methylphenidate OROS and placebo groups did not differ with respect to reaction time (RT) or accuracy. For RT, there was no main effect of group ($F_{1,19}=1.173$; $P=.29$). Both groups displayed the expected interference effects ($RT_{Interference} > RT_{Control}$, with a significant main effect of condition [$F_{1,19}=384.4$; $P<.001$]). There was a significant main effect of scan ($F_{1,19}=101.1$; $P<.001$), but no condition × group ($P=.87$), scan × group ($P=.83$), or scan × condition × group ($P=.67$) interactions for RT. Similarly, for accuracy, there was no main effect of group ($F_{1,19}=.101$; $P=.75$). Again, there was an expected main effect of condition ($F_{1,19}=23.3$; $P<.001$) but not of scan ($F_{1,19}=1.8$; $P=.19$). There were no condition × group ($P=.60$), scan × group ($P=.60$), or scan × condition × group ($P=.59$) interactions for accuracy. Because functional magnetic resonance imaging data were secondarily analyzed based on treatment response, repeated-measures analyses of variance of performance data were done; these did not show significant treatment group × scan × condition × clinical response (response vs failure) interactions for RT ($F_{3,17}=.015$; $P=.90$) or accuracy ($F_{3,17}=.162$; $P=.92$).

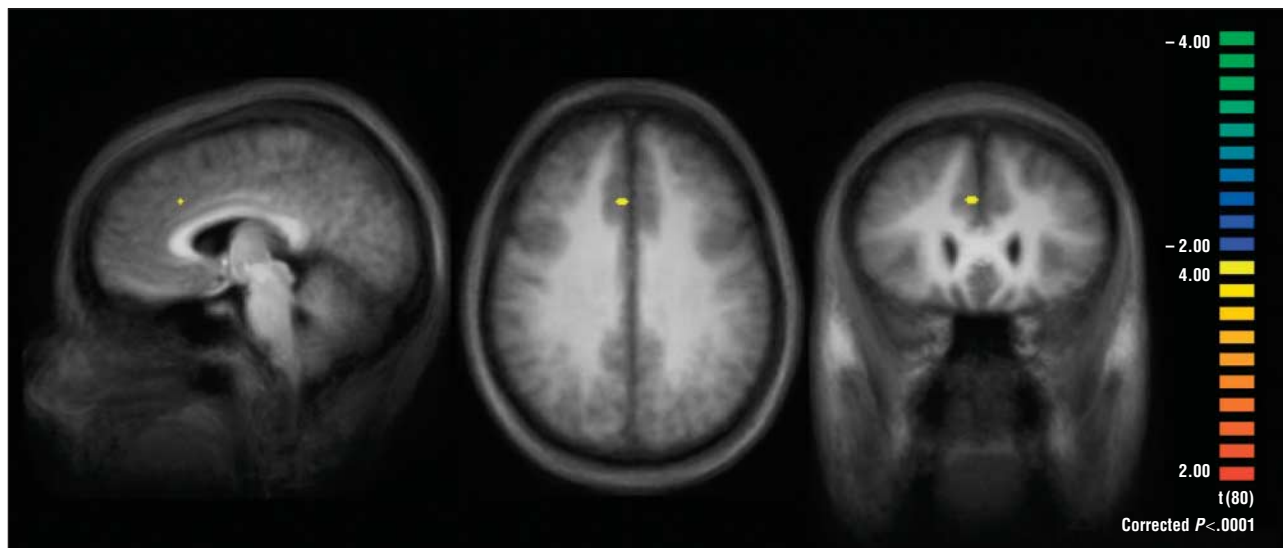


Figure 2. Six weeks of treatment with the methylphenidate osmotic-release oral system (OROS), compared with placebo, produced both a treatment group (methylphenidate OROS vs placebo) × scan (scan 1 [baseline] vs scan 2 [6 weeks]) interaction and significantly increased activation of the dorsal anterior midcingulate cortex (daMCC) bilaterally (x, y, z=5, 23, 31; 22 voxels; x, y, z=-2, 0, 28; 43 voxels), a third region posteriorly adjacent to the daMCC (x, y, z=-6, -4, 43; 7 voxels), and a fourth in the right insula (x, y, z=33, 11, 6; 22 voxels). Corrected regional thresholds (clusterwise) were $P<1 \times 10^{-4}$.

nificant predicted treatment group × scan interaction ($P=.04$), and a *t* test confirmed that the daMCC percentage fMRI signal change was higher in the methylphenidate OROS group at 6 weeks ($P=.02$). Thus, although the methylphenidate OROS and placebo groups did not differ at baseline, the methylphenidate OROS group showed higher daMCC activation at 6 weeks.

Spatial variability analyses revealed that adults with ADHD showed greater variability in the anatomical location of the daMCC than did healthy adults from the MSIT validation study.⁸⁸ As **Figure 5** depicts, healthy individuals displayed a tight spatial correlation between the individual and group data, whereas patients with ADHD displayed significantly greater spatial variability ($P=.04$).

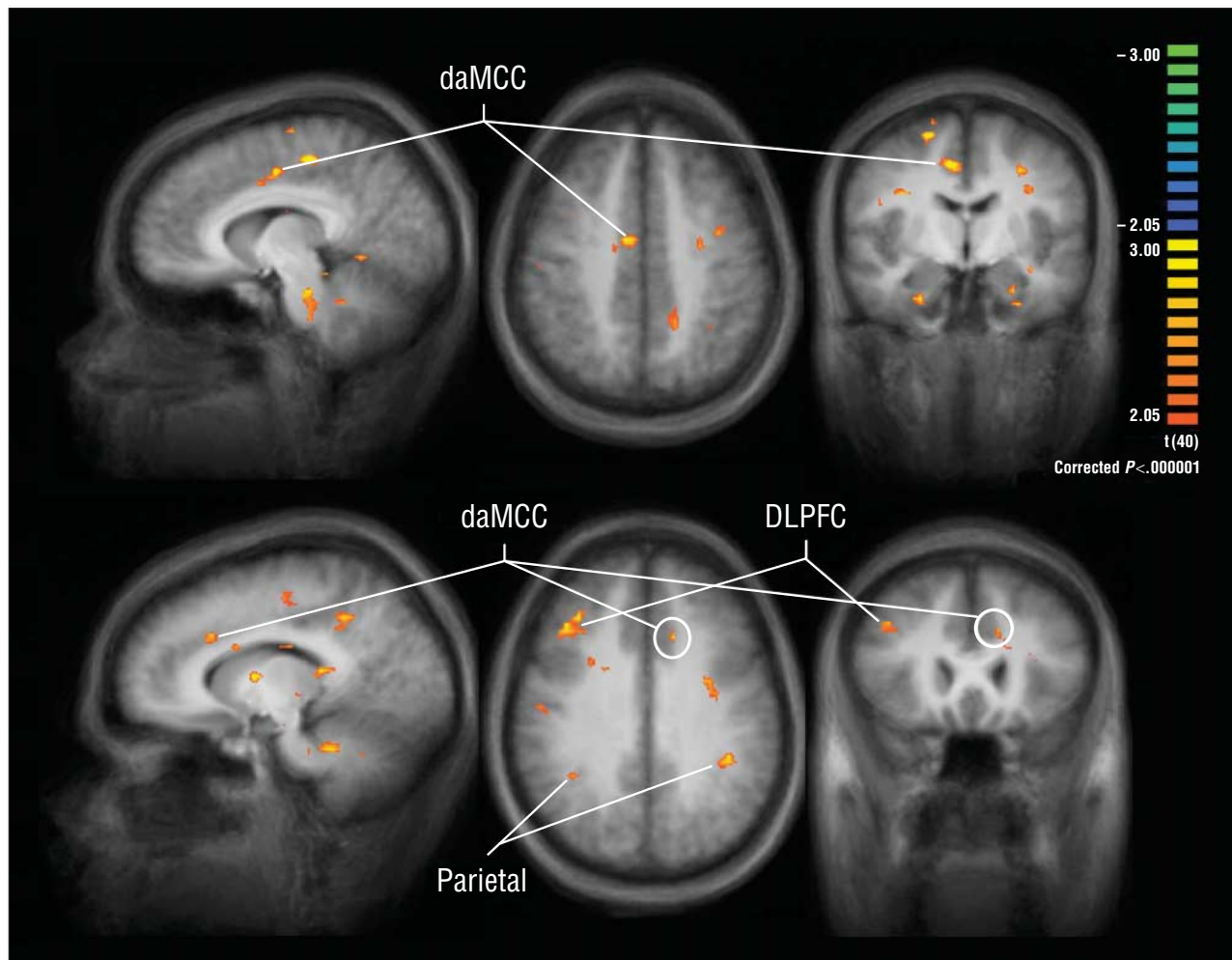


Figure 3. A random-effects general linear model comparison of methylphenidate osmotic-release oral system (OROS) Multi-Source Interference Task (MSIT)_{Interference} minus placebo MSIT_{Interference} activation during image 2 (6 weeks) revealed increased activation of the cingulofrontoparietal network, including the dorsal anterior midcingulate cortex (daMCC) bilaterally, the right-sided dorsolateral prefrontal cortex (DLPFC), and the bilateral superior parietal cortices, in the methylphenidate OROS group (n=11) compared with the placebo group (n=10). The top panels depict sagittal, axial, and coronal sections for the right-sided daMCC (24c/32') from Table 3, and the bottom panels similarly depict the section data for the left-sided daMCC activation from Table 3. Corrected regional thresholds (clusterwise) were $P < 1 \times 10^{-6}$.

Relationship Between daMCC Activation and Treatment Response

Planned group-averaged and single-patient analyses were also performed to identify characteristic brain responses indicative of clinical response to treatment. Although group-averaged data did not show a significant treatment group \times response interaction in any brain region, in the daMCC, an individual patient's VOI-based repeated-measures ANOVA did show a significant treatment group \times response interaction ($F_3 = 3.5$; $P = .04$), and methylphenidate OROS responders predictably showed higher daMCC activation than did methylphenidate OROS failures, placebo responders, and placebo failures (**Figure 6**).

Also, the direction of the daMCC percentage fMRI signal change from baseline to 6 weeks was related to treatment response. In the methylphenidate OROS group, 71% (5 of 7) of the responders showed an increase from baseline in daMCC activity at 6 weeks, whereas only 25% (1 of 4) of the failures showed such an increase (and all 10 placebo users—6 responders and 4 failures—showed

either a decrease or no change in daMCC activation at 6 weeks). The χ^2 analysis showed that these proportions were significantly different ($\chi^2_3 = 10.3$; $P = .02$). The MSIT performance did not differ between groups and thus could not account for the daMCC results.

COMBINED ADHD GROUP MSIT RESPONSE AT BASELINE

For completeness, we also performed an overall GLM to identify brain regions activated in the MSIT_{Interference} minus MSIT_{Control} contrast in the full group of 21 patients with ADHD at baseline. Whereas the group-averaged fMRI data showed that the MSIT activated portions of the CFP network and other brain regions involved in cognition, target detection, response selection, motor planning, and motor output (including the daMCC, premotor cortex, caudate, thalamus, and parietal cortex [**Table 4**]); activation was not observed in the DLPFC. This lack of DLPFC activation supports hypothesized DLPFC hypo-function in ADHD.

Table 3. Brain Regions Showing Higher MSIT Activation in Adult Completers With ADHD of a 6-Week Trial of Methylphenidate OROS vs Placebo^a

Brain Region (Cytoarchitectural Area)	x, y, z	Region Size, Voxels
Left daMCC (24c/32')	-12, 21, 29	53
Right daMCC (24c/32')	9, -7, 43	550
Right DLPFC, middle frontal gyrus (46)	40, 30, 20	102
Right DLPFC, middle frontal gyrus (9)	37, 23, 31	370
Right anterior cingulate cortex (32/24)	14, 39, 13	256
Left inferior frontal gyrus (44)	-43, 12, 16	88
Right premotor cortex (6)	40, 1, 44	61
Left premotor cortex (6)	-28, -8, 40	364
Right hippocampus	25, -7, -26	150
Left hippocampus	-23, -8, -22	112
Left postcentral gyrus (43)	-44, -11, 12	80
Right superior frontal gyrus (6)	18, -11, 61	856
Right precentral gyrus (4)	50, -14, 31	305
Right postcentral gyrus (1)	36, -16, 46	113
Right paracentral lobule (31)	9, -25, 49	605
Right transverse temporal gyrus (41)	41, -22, 9	81
Right thalamus/pulvinar	18, -23, 11	948
Left thalamus/pulvinar	-18, -27, 3	103
Right superior parietal lobule (7)	25, -37, 50	58
Left superior parietal lobule (7)	-30, -50, 41	68
Right caudate	37, -37, 1	291
Left cerebellum	-19, -41, -28	1213
Right cerebellum	14, -41, -28	273
Right inferior parietal lobule (40)	35, -46, 29	99
Left paracentral lobule (31)	-14, -47, 40	449
Left lingual gyrus (19)	-26, -55, 10	625

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; daMCC, dorsal anterior midcingulate cortex; DLPFC, dorsolateral prefrontal cortex; MSIT, Multi-Source Interference Task; OROS, osmotic-release oral system.

^aGroup-averaged activation locations and extents are shown for brain regions that showed higher functional magnetic resonance imaging activation during MSIT^{Interference} trials in the ADHD group that received 6 weeks of methylphenidate OROS (n=11) compared with the group that received placebo (n=10). The activation locations shown are the result of a random-effects general linear model analysis, with a voxelwise threshold of $P < .05$ and to which an additional rigorous 50-contiguous voxel cluster constraint was applied to correct for multiple comparisons (cluster-corrected $P < 1 \times 10^{-6}$). Stereotactic coordinates are presented for local maxima according to the convention of Talairach and Tournoux.⁸⁹ The origin (0, 0, 0) is the anterior commissure at the midsagittal plane, with $x > 0$ corresponding to right of midsagittal, $y > 0$ corresponding to anterior, and $z > 0$ corresponding to superior.

COMMENT

The MSIT was performed during fMRI to examine the responses of the daMCC and other brain regions to 6 weeks of treatment with methylphenidate OROS in adults with ADHD and to compare these responses with placebo. There were 2 principal findings:

1. Both group-averaged and individual daMCC VOI analyses supported the main hypotheses. Both levels of analysis showed that (1) the methylphenidate OROS and placebo groups did not differ at baseline and (2) 6 weeks of treatment with methylphenidate OROS produced higher daMCC activation than placebo. Both levels of analysis displayed significant treatment group \times scan interactions and confirmed higher methylphenidate OROS activation than placebo at 6 weeks. Thus, the individual-

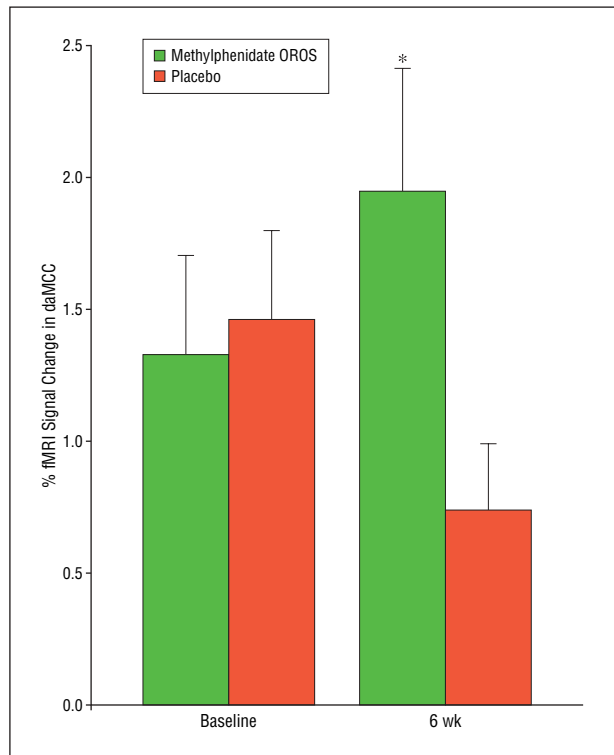


Figure 4. Individual-level dorsal anterior midcingulate cortex (daMCC) analyses confirmed that the methylphenidate osmotic-release oral system (OROS) and placebo groups did not differ at baseline, but the methylphenidate OROS group showed higher daMCC activation at 6 weeks. Specifically, although there was no main effect of treatment group ($F_{1,19}=2.2$; $P=.15$) or scan ($F_{1,19}=0.03$; $P=.87$), there was a significant predicted treatment group \times scan interaction ($F_{1,19}=5.2$; $P=.04$), and a 2-tailed unpaired t test confirmed that at 6 weeks, the mean (SD) daMCC percentage functional magnetic resonance imaging (fMRI) signal change was higher in the methylphenidate OROS group (1.95% [1.4%]) than in the placebo group (0.74% [0.65%]) (mean difference, 1.2%; $t_{19}=2.47$; $P=.02$). Error bars represent SE; asterisk, significant difference during scan 2 at $P < .05$ level.

level daMCC VOI analyses supported the group-averaged findings.

2. The daMCC activation was related to clinical response so that the individual daMCC VOI analyses revealed a significant treatment group \times clinical response interaction, and confirmatory t tests showed that at 6 weeks, methylphenidate OROS responders displayed significantly higher daMCC activation than methylphenidate OROS failures, placebo responders, or placebo failures. In addition, at 6 weeks, methylphenidate OROS responders showed higher daMCC activation than placebo failures in group-averaged and individual daMCC VOI analyses.

There were also 4 secondary findings:

1. At the group level, the fMRI activation levels of the methylphenidate OROS and placebo groups during the MSIT were not significantly different at baseline, but by 6 weeks, the methylphenidate OROS group showed significantly higher activation in the daMCC, DLPFC, and parietal cortex (the CFP cognitive/attention network) and in other brain regions relevant to ADHD (the caudate, premotor cortex, thalamus, and cerebellum).

2. Secondary analyses indicated that the observed methylphenidate OROS effects on the daMCC were not

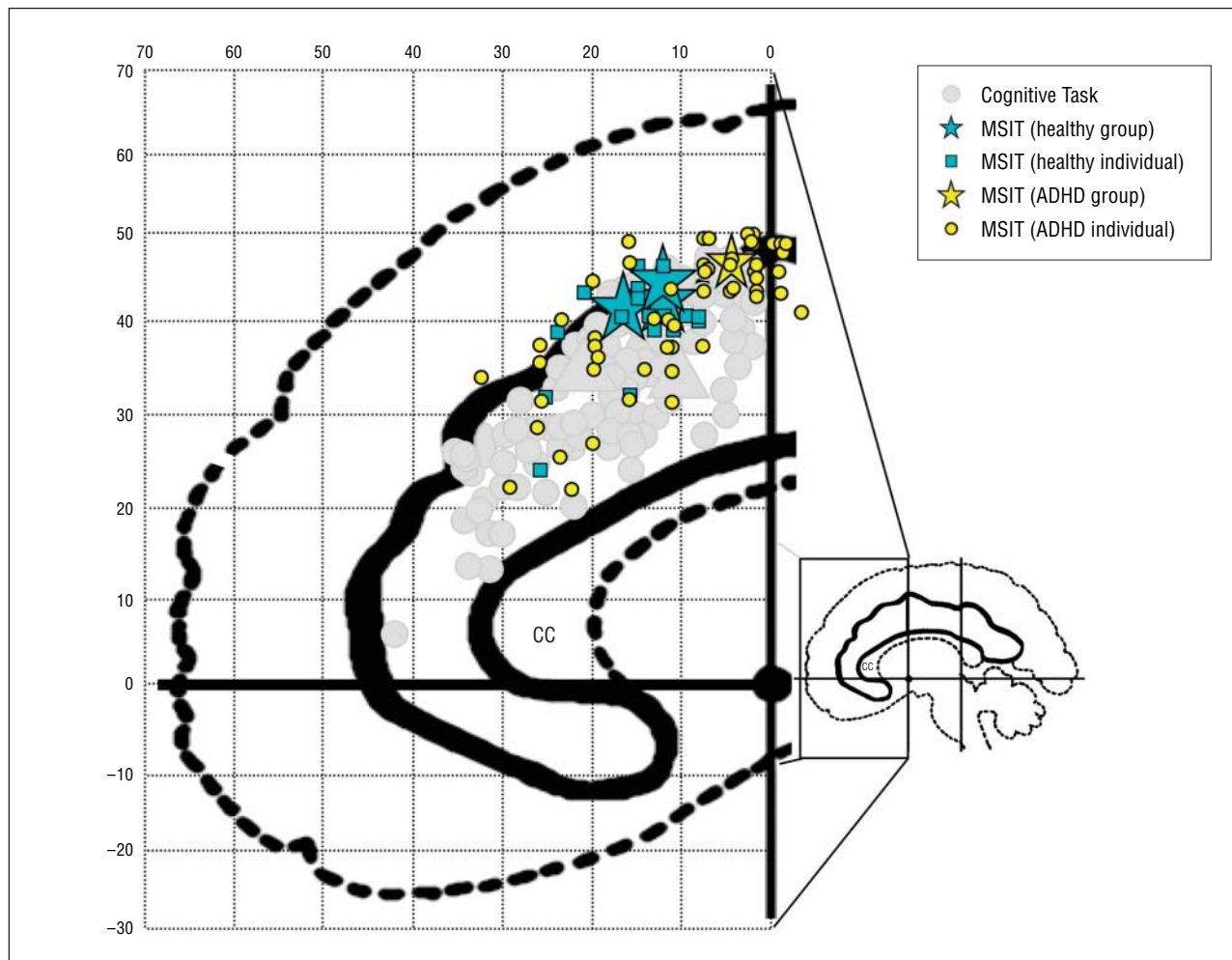


Figure 5. Spatial variability analysis revealed that adults with attention-deficit/hyperactivity disorder (ADHD) ($N=21$) showed greater variability of the anatomical location of the dorsal anterior midcingulate cortex (daMCC) compared with healthy adults ($n=8$) from the Multi-Source Interference Task (MSIT) validation study.⁸⁸ Healthy individuals had a tight spatial correlation between the individual and group-averaged daMCC activation locations (mean [SD] distance of individual daMCC activations from the ipsilateral group-averaged activations was only 8.5 [6.1] mm). In contrast, individual patients with ADHD displayed greater spatial variability (mean distance from the midline group-averaged daMCC activation = 13.2 [8.5] mm; $P=.04$, 2-tailed t test). For reference, daMCC activation sites from cognitive/attention tasks are shown.⁴⁹ CC indicates corpus callosum.

attributable to MSIT task performance, age, IQ, sex, or clinical severity of ADHD.

3. Spatial variability analyses suggest that adults with ADHD show greater variability in the location of the daMCC than healthy adults.

4. The lack of DLPFC activation in 21 adults with ADHD at baseline suggests that the DLPFC may be hypofunctional in ADHD.

As in previous studies by our ADHD imaging group,^{15,24,25} we focused primarily on the daMCC because it plays central roles in cognitive processes that, if disrupted by daMCC hypofunction, could produce the cardinal signs of ADHD: inattention, impulsivity, and hyperactivity. Recent functional imaging and intracranial recording studies in humans and primates⁴⁸⁻⁵⁰ have combined to suggest that the daMCC operates in a feedback-mediated decision-making framework, integrating information about planned operations and expectations with rewards and negative outcomes, shaping decisions, and modulating motor output. Animal studies further suggest that dopamine modulates the daMCC's decision-

making functions,⁹⁸⁻¹⁰² providing a possible link to the present study's methylphenidate OROS findings. Thus, dysfunction of the daMCC could also explain the observed phenomenon of patients with ADHD performing normally on some tasks (when motivated) but showing deficient performance when the task is not deemed salient. Although the exact roles that the daMCC plays in distributed cognitive/attention networks remain to be established, it is increasingly clear that further focused study of the daMCC is important to improving our understanding of the pathophysiologic mechanism of ADHD and other neuropsychiatric disorders.

In this study, the MSIT predictably revealed that beyond the daMCC, methylphenidate OROS also increased activation of other brain regions that have been implicated in attention, motor control, and the pathophysiologic mechanism of ADHD (including the DLPFC, parietal cortex, caudate, premotor cortex, thalamus, and cerebellum). This was expected because these structures subservise cognitive processing in a parallel-distributed manner.^{103,104} The DLPFC is often coacti-

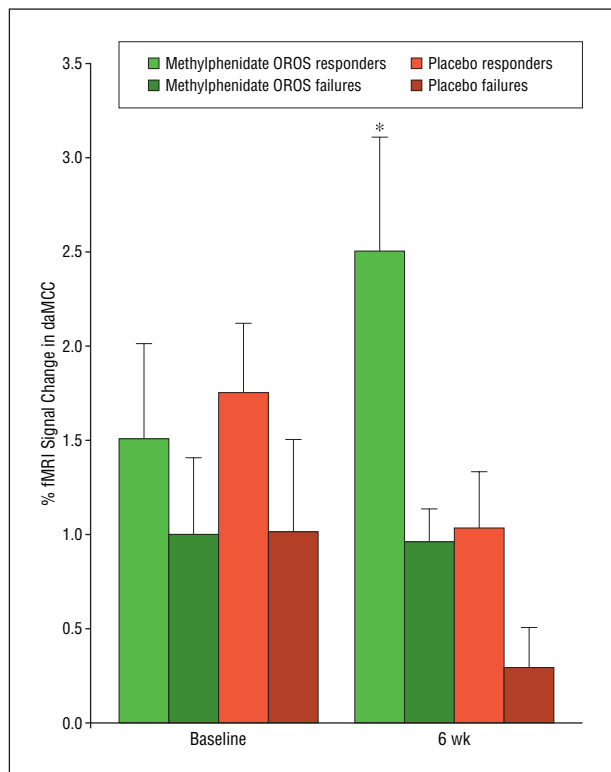


Figure 6. Individual patients' maximal dorsal anterior midcingulate cortex (daMCC) Multi-Source Interference Task (MSIT)_{interference} percentage functional magnetic resonance imaging (fMRI) signal change values were entered into a treatment group (methylphenidate osmotic-release oral system [OROS] vs placebo) \times clinical response (responder vs failure) repeated-measures analysis of variance. These patient-level daMCC analyses revealed that there was a significant treatment group \times clinical response interaction ($F_{3,17}=3.48$; $P=.04$). The asterisk indicates that planned follow-up 2-tailed unpaired t tests confirmed predictions that at scan 2 (6 weeks), mean (SD) daMCC percentage fMRI signal change would be higher in methylphenidate OROS responders (2.51% [1.5%]) than in methylphenidate OROS failures (0.96% [0.26%]; $P=.04$), placebo responders (1.03% [0.66%]; $P=.046$), and placebo failures (0.30% [0.35%]) ($P=.008$). Error bars represent SE.

vated with the daMCC during cognitive tasks,^{105,106} the premotor cortex is responsible for planning and execution of nonautomatic tasks,¹⁰⁷ the parietal cortex has been activated during target detection^{108,109} and Stroop tasks,^{15,106,110-112} and the striatum has been implicated in the pathophysiologic mechanism and treatment effects of ADHD.* Although the precise roles that these various structures play in ADHD and cognition remain to be determined, the data argue strongly that they interact as a distributed network.

Mechanistically, positron emission tomography and single-photon emission computed tomography studies have shown that methylphenidate acts in part by blocking the dopamine transporter, which is responsible for the synaptic reuptake of dopamine and shows higher bioavailability in patients with ADHD than in controls.⁶⁹⁻⁷² However, these imaging modalities have not shown the presumed downstream functional effects of dopamine deficiency by characterizing functional cortical brain responses during cognitive task performance. On the basis of previous studies and the present data, we suggest

*References 16, 18, 27, 35, 54, 62, 69, 78, 113.

Table 4. MSIT Activations and Deactivations in 21 Adults With ADHD at Baseline^a

Brain Region (Cytoarchitectural Area)	x, y, z	Region Size, Voxels
Activations (interference > control trials)		
Right anterior insula	31, 12, 4	1033
Left anterior insula	-32, 9, 8	846
Bilateral dorsal anterior midcingulate cortex (24c'/32')	0, 5, 46	2462
Left premotor cortex (6)	-38, 2, 29	1686
Right premotor cortex (6)	39, -2, 32	734
Right caudate	17, -3, 19	334
Right premotor cortex (6)	28, -8, 54	1129
Left premotor cortex (6)	-25, -11, 51	2378
Right thalamus	12, -14, 10	91
Left thalamus	-13, -18, 12	422
Left inferior parietal lobule (40)	-33, -44, 37	8325
Right inferior parietal lobule (40)	33, -45, 34	5925
Right fusiform gyrus (37)	36, -47, -18	5936
Left fusiform gyrus (37)	-36, -52, -17	4759
Cerebellum, vermis	2, -45, -21	1085
Deactivations (interference < control trials)		
Right middle insula	42, -14, 14	408
Left middle insula	-38, -16, 11	74
Left hippocampus	-25, -34, -12	382
Bilateral posterior cingulate cortex (23)	0, -39, 26	3604
Right superior temporal gyrus (22)	54, -47, 18	102
Left superior temporal gyrus (39)	-48, -54, 23	868

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MSIT, Multi-Source Interference Task.

^aThe group-averaged results shown are the result of a random-effects general linear model analysis, thresholded at $P<.05$ with a 50-contiguous voxel cluster constraint applied to correct for multiple comparisons (corrected $P<1 \times 10^{-4}$). Stereotactic coordinates are presented for local maxima according to the convention of Talairach and Tournoux.⁸⁹ The origin (0, 0, 0) is the anterior commissure at the midsagittal plane, with $x>0$ corresponding to right of midsagittal, $y>0$ corresponding to anterior, and $z>0$ corresponding to superior.

that methylphenidate may initiate its effects by blocking the striatal dopamine transporter and increasing the synaptic availability of dopamine, which in turn may boost "downstream" signal-to-noise postsynaptically in the daMCC and in the CFP network. These actions could improve target detection, filtering of distracting information, error detection, motivation, and reward-based decision-making processes and help regulate motor inhibition (thereby reducing hyperactivity and impulsivity).^{16,48} Although speculative and reductionistic, such a model is neurobiologically plausible, testable, and consistent with the extant literature.

MSIT ADVANTAGES FOR STUDIES OF CLINICAL POPULATIONS AND PHARMACEUTICALS

As discussed elsewhere,^{87,88} the MSIT possesses many of the qualities deemed desirable in a functional neuroimaging test. The present study adds another important advantage because the MSIT has now been shown to display sensitivity to drug effects in specified brain regions of interest. Beyond the intrinsically enhanced robustness of the MSIT, the present study also may have been able to identify brain effects

when some previous studies did not because it incorporated recent technological and procedural advantages that were previously unavailable to maximize the probability of identifying methylphenidate-related brain effects. The present study was performed on a powerful 3-T fMRI magnet system, which affords superior signal-to-noise characteristics, and follow-up imaging was performed at 6 weeks (rather than shortly after the baseline imaging session) because this was recently shown to be a time of maximal clinical response. The data indicate that the MSIT can be a useful task in studies of neuropsychiatric patients and healthy volunteers and in pharmaceutical and other treatment studies.

As shown herein, the MSIT's ability to produce activation in individuals is particularly valuable to patient-based studies and drug studies. Refined localization of brain regions improves the power to detect differences in patient and drug studies. As the individual VOI analyses and spatial variability analysis herein show, use of the MSIT can also help patient studies by permitting elimination of the potential confound of greater anatomical variability in a patient group. The MSIT's ability to concomitantly measure brain activation and behavioral performance permitted us to characterize individual responses and to rule out performance effects as a potential confound for the fMRI data. Although the individual-level study is stressed herein, group-averaged MSIT data can also be used with the advantages of greater power, fewer patients, and higher confidence.

STUDY LIMITATIONS

This study has several limitations. First, although these results are likely to hold true for children and adolescents with ADHD, the specific results described herein are valid only for adults with ADHD and need to be specifically tested in younger patients. Second, although group and individual-level analyses provided evidence that the daMCC response is related to the clinical response, these findings, although predicted, should be viewed as preliminary given the small subsample sizes and potential confounds, and they need to be replicated using larger samples. Third, although the lack of activation of the DLPFC in the full cohort of 21 patients with ADHD suggests that the DLPFC may be dysfunctional in ADHD, the lack of a direct comparison group precludes definitive confirmation of this conclusion (the previous validation study group of healthy adults⁸⁸ cannot be used for comparison because that study used a slightly different version of the MSIT, and those patients were not matched to the present study's sample). Fourth, the study was designed to assess the long-term, not the short-term, effects of methylphenidate OROS; future studies are needed to distinguish any such differential effects. Fifth, this study was not designed to address more complex questions regarding daMCC structure (eg, cytoarchitectural borders and possible effects of the presence or absence of the paracingulate gyrus), distinguishing other regions (eg, delineating borders of the inferior and middle frontal gyri), or comparing results in ADHD with those in other disorders, such as schizophrenia¹¹⁴⁻¹¹⁸—all issues that can be considered in future studies. Sixth, there was a trend toward more women in the placebo group; however, this was only a nonsignificant trend, and neither baseline fMRI activation nor behavioral performance varied by sex. In addition, fMRI hemodynamic responses have not

generally been found to vary by sex (if anything, women may have an accentuated blood oxygenation level-dependent response or cerebral blood flow,¹¹⁹⁻¹²⁵ which would run counter to the observed effects herein in which the placebo group, trending toward more women, showed lower fMRI activity). Moreover, large-scale ADHD studies argue that the clinical response to methylphenidate does not vary with sex,^{7,8} nor does sex moderate the association between ADHD and the phenotypic expression of the disorder (including symptom profile), the prevalence of lifetime or current comorbid psychiatric disorders, or patterns of cognitive and psychosocial functioning.¹²⁶ Finally, the spatial variability analysis should be replicated (slightly different MSIT versions and fMRI parameters were used, and samples were not matched). It was included herein because it makes maximal use of the enriched data sets beyond the main contrast of interest, highlights how individual VOI analyses can be helpful, and graphically illustrates that intergroup differences in anatomical variability are a valid concern to be addressed in future work. Such prospective comparisons between ADHD and control groups using the MSIT will be performed in future studies.

In conclusion, methylphenidate OROS is a highly effective first-line treatment for ADHD. Herein, the MSIT was used during fMRI to characterize the neural effects of methylphenidate OROS compared with placebo in adults with ADHD. The results show that, compared with placebo, methylphenidate OROS increased activation of brain regions that have been implicated in the pathophysiologic mechanism of ADHD, including the daMCC, DLPFC, parietal cortex, premotor cortex, caudate, and cerebellum. Secondary analyses indicate that the MSIT was sensitive to treatment response, showing that methylphenidate OROS responders increased daMCC activation significantly above that of methylphenidate OROS failures, placebo responders, and placebo failures, and also ruled out potential confounds of performance, age, sex, and cognitive abilities on fMRI results. Individual-based daMCC VOI analyses confirmed these group-averaged data results. Analyses of the full ADHD group at baseline suggest that the DLPFC may be dysfunctional in ADHD and that patients with ADHD display greater anatomical variability in the location of the daMCC, facts consistent with previous literature showing structural and functional abnormalities of these brain regions. These data support use of the MSIT and fMRI to identify the neural effects of drugs used to treat ADHD and other neuropsychiatric disorders.

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