ORIGINAL ARTICLE

Common and Unique Therapeutic Mechanisms of Stimulant and Nonstimulant Treatments for Attention-Deficit/Hyperactivity Disorder

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Context: Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent and impairing psychiatric disorder that affects both children and adults. There are Food and Drug Administration–approved stimulant and nonstimulant medications for treating ADHD; however, little is known about the mechanisms by which these different treatments exert their therapeutic effects.

Objective: To contrast changes in brain activation related to symptomatic improvement with use of the stimulant methylphenidate hydrochloride vs the nonstimulant atomoxetine hydrochloride.

Design: Functional magnetic resonance imaging before and after 6 to 8 weeks of treatment with methylphenidate (n = 18) or atomoxetine (n = 18) using a parallel-groups design.

Setting: Specialized ADHD clinical research program at Mount Sinai School of Medicine, New York, New York.

Participants: Thirty-six youth with ADHD (mean [SD] age, 11.2 [2.7] years; 27 boys) recruited from randomized clinical trials.

Main Outcome Measures: Changes in brain activation during a go/no-go test of response inhibition and investigator-completed ratings on the ADHD Rating Scale-IV-Parent Version.

Results: Treatment with methylphenidate vs atomoxetine was associated with comparable improvements in both response inhibition on the go/no-go test and mean (SD) improvements in ratings of ADHD symptoms (55% [30%] vs 57% [25%]). Improvement in ADHD symptoms was associated with common reductions in bilateral motor cortex activation for both treatments. Symptomatic improvement was also differentially related to gains in task-related activation for atomoxetine and reductions in activation for methylphenidate in the right inferior frontal gyrus, left anterior cingulate/supplementary motor area, and bilateral posterior cingulate cortex. These findings were not attributable to baseline differences in activation.

Conclusions: Treatment with methylphenidate and atomoxetine produces symptomatic improvement via both common and divergent neurophysiologic actions in frontoparietal regions that have been implicated in the pathophysiology of ADHD. These results represent a first step in delineating the neurobiological basis of differential response to stimulant and nonstimulant medications for ADHD.

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a highly prevalent and impairing psychiatric disorder that affects both children and adults and accounts for an outsized portion of psychotropic medication use in youth.[1] Yet, the mechanisms by which Food and Drug Administration–approved stimulant and nonstimulant medications for ADHD exert their therapeutic effects are poorly understood, and there are almost no data to guide treatment selection. The psychostimulant methylphenidate hydrochloride, a mainstay of ADHD treatment, is an indirect catecholamine agonist that blocks both dopamine transporter (DAT) and norepinephrine transporter (NET),[2] whereas atomoxetine hydrochloride, the first approved nonstimulant ADHD treatment, is a selective NET inhibitor that has little affinity for DAT.[3] The partially overlapping pharmacologic profiles of these medications suggest both similarities and differences in their therapeutic mechanisms of action, consistent with reports that many children with ADHD respond to both treatments but that approximately one-third respond preferentially to one or the other.[4]

The acute pharmacologic actions of single challenge doses of methylphenidate and atomoxetine provide preliminary evidence about the results of comparative treatment efficacy studies.[4] Positive responses to both medications may reflect similar acute actions on inhibitory and executive functions of the prefrontal cortex[5-11] and, possibly, the anterior cingulate cortex.[7,8] Ato-

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moxetine and methylphenidate act at promiscuous NETs that clear both dopamine and norepinephrine in prefrontal regions that lack DAT.[12-14] Methylphenidate may also act via the abundant DAT expressed in striatum to enhance inhibitory functions[6-8,15] and through the moderate levels of DAT in posterior cingulate cortex to suppress task-independent activity that has been linked to distractibility.[11,15-18] In contrast, atomoxetine has little effect on neuronal activity in striatum,[12] where there is sparse expression of NET,[19] and the possible effects of atomoxetine on the few NETs present in posterior cingulate cortex are poorly understood.[11,19] The additional therapeutic actions of methylphenidate could account for the larger-effect size reported for stimulants than for atomoxetine.[4] However, there are likely important neuropharmacologic differences between single-challenge doses of medication and treatment administered over a more extended period. The relevance of the acute effects of single-challenge doses to the symptomatic improvement produced by ADHD medications over the course of treatment is not clear, particularly for atomoxetine, which takes several weeks to exert its clinical effects.[20,21]

Little is known about how ongoing treatment of ADHD affects neural activity, and, more important, how the neurophysiologic changes produced by treatment relate to clinical improvement. Several weeks of methylphenidate treatment for ADHD was found to downregulate striatal DAT,[22] reduce striatal and prefrontal resting perfusion,[23,24] and enhance inhibitory-related activation in the prefrontal cortex and anterior cingulate cortex,[25] although only the last finding was tenuously linked to clinical improvement.[25] Similar information is not available for atomoxetine.

The lack of data linking pharmacologic actions to therapeutic improvement represents a missed opportunity to better understand how medications work, an essential step in developing targeted approaches to treatment. Therefore, we used event-related functional magnetic resonance imaging (MRI) to compare the relationship between symptomatic improvement and changes in brain activation during response inhibition produced by 6 to 8 weeks of treatment with methylphenidate vs atomoxetine in youth with ADHD. Based on findings from single-dose challenge studies,[5-10,12,13] we initially hypothesized that symptomatic improvement would be related to gains in neural activation during response inhibition in the prefrontal cortex and anterior cingulate cortex for both medications but that improvement would be associated with increased striatal activation for methylphenidate only. Findings from more recent studies[11,16-18] suggest that methylphenidate, and possibly atomoxetine, could also decrease activation (ie, task-related interference) in the posterior cingulate cortex.

METHODS

PARTICIPANTS

This study was approved by the institutional review board of Mount Sinai School of Medicine, New York, New York. Written informed consent was obtained from the parents of all the participants. Verbal assent from all the participants was certified by a witness unaffiliated with the study. Youth and their parents were financially compensated for participation. Participants were recruited from 2 industry-sponsored trials (n=4) and from a National Institutes of Health–funded treatment study (n=32) conducted between 2004 and 2011. Thirty-six youth (27 boys and 9 girls) with a mean (SD) age of 11.2 (2.7) years (age range, 7-17 years) completed the study procedures and were included in the present analyses. Consent was additionally obtained from 16 youth who did not complete the procedures, 3 for excessive motion or anxiety during baseline MRI and 13 because they dropped out of the study before completing posttreatment MRI (**Figure 1**). Seven of the latter 13 children were never randomized to treatment, and 3 children each discontinued treatment with atomoxetine and methylphenidate owing to either nonresponse or adverse events. These youth did not differ in age, sex, subtype, severity, or comorbidity from the 36 study completers.

Participants all met the *DSM-IV* criteria for ADHD, any subtype, on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version[26] and were rated at least 1.5 SD above age and sex norms on the ADHD Rating Scale-IV-Parent Version (ADHD-RS-IV).[27] The exclusion criteria were poor response or tolerability to an adequate trial of either methylphenidate or atomoxetine; a substance abuse history or a positive urine screening test result; participation in a treatment study in the past 30 days; a past or present primary diagnosis of mood, anxiety, or psychotic disorder; head injury; and any medical condition that could affect brain function. Twenty-three participants were medication naive. Of the remaining 13 participants, 5 had taken a stimulant medication at some point before the study but not at study enrollment. Eight participants were taking a stimulant medication when they enrolled in the study, and they completed a 2-week washout before the baseline visit. None of the participants were receiving nonstimulant medications when they enrolled in the study.

STUDY DESIGN

Thirty-six participants were randomly assigned to treatment with osmotically released methylphenidate hydrochloride (Concerta; McNeil-PPC Inc) (n=18) or atomoxetine hydrochloride (Strattera; Eli Lilly & Co) (n=18) as part of the double-blind clinical trials in which they were enrolled. The mean (SD) length of treatment was 52 (16) days for methylphenidate and 54 (17) days for atomoxetine (t_{34}=0.78; P=.75). Medication was titrated to a standard of optimal response and tolerability using sequential dose-escalating procedures, with an absolute dose schedule for methylphenidate and a weight-adjusted schedule for atomoxetine, as per standard clinical practice. Methylphenidate hydrochloride administration was initiated at 18 mg/d and was titrated upward in 18-mg/d increments to a maximum daily dose of 72 mg. Atomoxetine hydrochloride therapy was started at a daily dose of 0.5 or 0.8 mg/kg (depending on the trial) and was titrated to 1.8 mg/kg using either a flexible (n=4) or a stepped (n=32) dose-optimizing approach, with a maximum total daily dose of 120 mg. The mean (SE) daily dose at posttreatment MRI was 54.0 (3.6) mg for methylphenidate hydrochloride and 1.4 (0.1) mg/kg for atomoxetine hydrochloride. Posttreatment MRIs and assessments were conducted once participants had achieved a stable response at the optimal dose (the highest dose tolerated in relation to room for clinical improvement and tolerability). Posttreatment MRIs were conducted a mean (SD) of 5.3 (2.4) hours after the administration of methylphenidate and 5.0 (2.2) hours after atomoxetine administration (t_{34}=0.45; P=.66), within the window of activity for both treatments.[28,29] Youth treated with methylphenidate vs atomoxetine did not differ on any characteristics at baseline (**Table 1**).

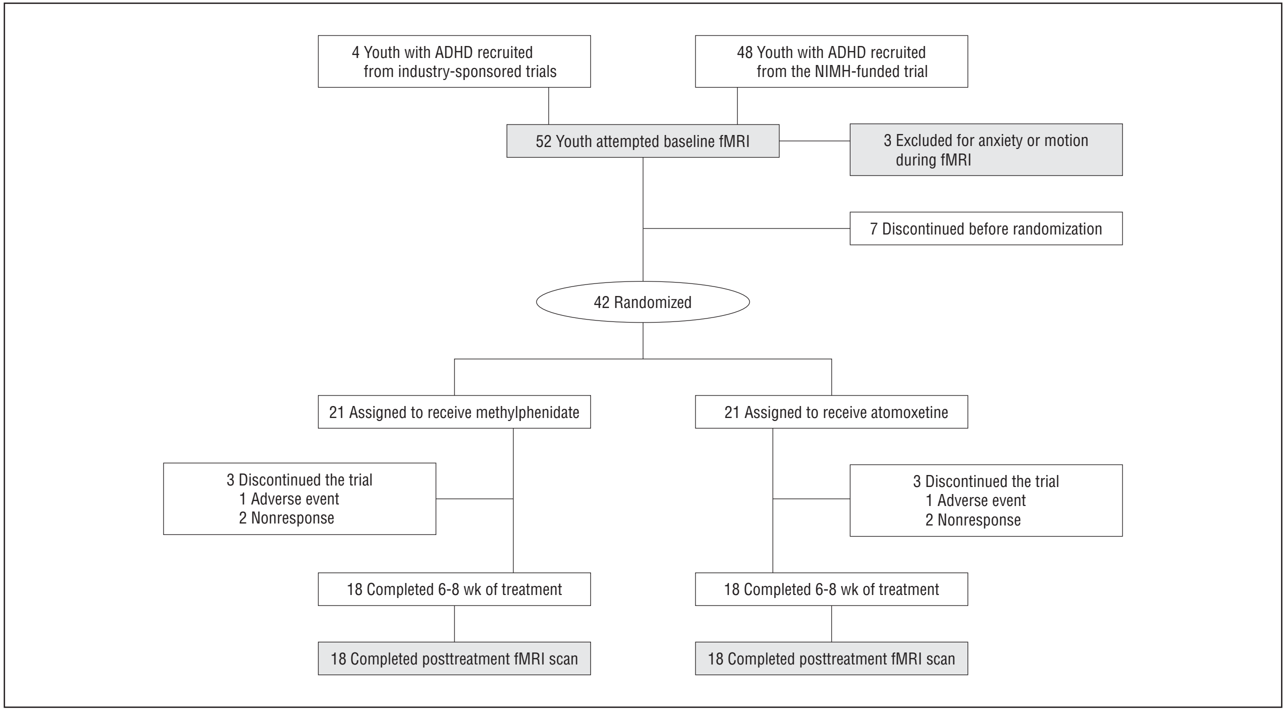

Figure 1. Flow diagram of participant progress through the study. Shading denotes procedures performed as part of the present study. ADHD indicates attention-deficit/hyperactivity disorder; fMRI, functional magnetic resonance imaging; and NIMH, National Institute of Mental Health.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Sample

Characteristic	Methylphenidate Hydrochloride Group (n = 18)	Atomoxetine Hydrochloride Group (n = 18)	Statistic	*P* Value
Sex, No. (%)				
Male	15 (83)	15 (83)		
Female	3 (17)	3 (17)	$\chi^2<0.001$	>.99
Age, mean (SD), y	11.0 (2.4)	11.4 (3.0)	$t_{34} = 0.39$	.70
ADHD subtype, No. (%)				
Combined	10 (56)	10 (56)		
Hyperactive	1 (6)	1 (6)	$\chi^2<0.001$	>.99
Inattentive	7 (39)	7 (39)		
Comorbid ODD	8 (44)	7 (39)	$\chi^2 = 0.11$	.74
ADHD-RS-IV total score, mean (SD)	38.0 (10.1)	34.8 (10.6)	$t_{34} = 0.68$	.37
Previous stimulant treatment for ADHD, No. (%)	8 (44)	5 (28)	$\chi^2 = 1.08$	.30
Required washout, No. (%)	5 (28)	3 (17)	$\chi^2 = 0.64$	.42

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale-IV-Parent Version; ODD, oppositional defiant disorder.

OUTCOME ASSESSMENTS

ADHD Symptoms

The ADHD-RS-IV total score served as the measure of clinical response. The ADHD-RS-IV is a validated scale with 18 items that correspond to each of the behavioral descriptors of ADHD in the *DSM-IV*.[27,30] The frequency/severity of each item in the past week was scored from 0 (never or rarely) to 3 (very often) after an interview with the parent(s) (and adolescent for youth aged ≥13 years). Percentage change in the ADHD-RS-IV total score was calculated by dividing the difference of the baseline and posttreatment scores by the baseline score, and multiplying by 100.

Response Inhibition

Participants performed an established go/no-go task[31-33] during functional MRIs. The task measured the ability to inhibit responses to rare nontargets (no-go trials) in the context of responding to frequent targets (go trials). The task consisted of 6 runs that each lasted 4 minutes. Each run began with 10 seconds of fixation and contained 57 trials (43 go trials [75%] and 14 no-go trials [25%]). Stimuli were presented for 500 milliseconds, with an interstimulus interval of 3500 milliseconds. Promotional images from the *Spiderman* movie were used as stimuli. Participants were instructed to respond as quickly and accurately as possible with the right hand using a fiberoptic button system. The percentage of correctly

Table 2. Motion and Task Performance During MRI and Clinical Outcome[a]

Variable	Methylphenidate Hydrochloride Group Baseline	Methylphenidate Hydrochloride Group Post-Tx	Atomoxetine Hydrochloride Group Baseline	Atomoxetine Hydrochloride Group Post-Tx	$F_{1,34}$ Main Effect of Time	$F_{1,34}$ Main Effect of Group	$F_{1,34}$ Time × Group Interaction
Performance							
Correct inhibitions, %	76 (14)	80 (17)	73 (14)	78 (15)	5.77[b]	0.28	0.28
Correct responses, %	94 (5)	94 (5)	96 (6)	96 (6)	1.60	0.51	0.84
RT, milliseconds	490 (100)	452 (89)	499 (107)	483 (122)	8.88[c]	0.34	1.39
RTSD, milliseconds	155 (74)	119 (50)	168 (114)	138 (61)	8.25[c]	0.43	0.06
Motion							
Translational, mm	0.4 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	1.27	0.07	0.58
Rotational, mm	1.7 (0.3)	1.4 (0.2)	1.4 (0.3)	1.3 (0.2)	1.01	0.50	0.20
Usable functional runs, No.	5.1 (0.3)	5.3 (0.2)	5.3 (0.3)	5.1 (0.2)	0.16	0.01	2.51
Clinical outcome							
ADHD-RS-IV total score	38 (10)	17 (12)	35 (11)	14 (8)	102.33[d]	1.04	0.04

Abbreviations: ADHD, attention-deficit hyperactivty disorder; ADHD-RS-IV, ADHD Rating Scale-IV-Parent Version; MRI, magnetic resonance imaging; post-Tx, posttreatment; RT, reaction time; RTSD, RT standard deviation.

[a] Data are given as mean (SD). Performance, motion, and clinical outcome were tested with separate 2 (time: baseline vs post-Tx) × 2 (group: methylphenidate vs atomoxetine) repeated-measures analyses of variance.

[b] $P = .02$.

[c] $P < .01$.

[d] $P < .001$.

inhibited responses on no-go trials served as the measure of response inhibition.

Brain Activation

Brain activation during response inhibition was measured using event-related functional MRI. Participants underwent MRI twice using the same 3.0-T head-dedicated MRI machine (Siemens Allegra; Siemens Medical Systems). Six series of 120 functional T2*-weighted images depicting the blood oxygenation level–dependent signal were acquired in the axial plane using gradient-echo echo-planar imaging (repetition time, 2 seconds; echo time, 40 milliseconds; section thickness, 3 mm; gap, 1 mm; resolution, 3.28 mm^2; and 28 sections). A high-resolution T2-weighted anatomic volume of the brain was acquired at the same 28 section locations using a turbo spin-echo pulse sequence (section thickness, 4 mm with no gap; and in-plane resolution, 0.41 mm^2).

BEHAVIORAL ANALYSES

The effects of treatment on response inhibition and ADHD symptoms were analyzed using separate 2-way repeated-measures analyses of variance, in which the percentage of correct inhibitions and the ADHD-RS-IV total score served as dependent measures. Medication (methylphenidate vs atomoxetine) served as the between-group factor and time (baseline vs posttreatment) as the within-group factor. Additional analyses of variance tested the percentage of correct responses, reaction time (RT), and the standard deviation of RT on go trials.

The relationship of age to symptomatic improvement for methylphenidate vs atomoxetine treatment was examined using stepwise linear regression, in which the ADHD-RS-IV change score served as the dependent measure. Age was entered as a continuous variable in the first step of the regression. The second step consisted of the dichotomous medication variable, which was entered as a prelude to testing the interaction (ie, product) of the dichotomous medication variable with the age variable in the third step. The age and medication variables were centered on zero. The *F* tests of the change in R^2 for the first and third steps of the regression were used to test for the association of age with improvement in the entire sample and for differences in this association between treatment groups, respectively. Behavioral results are reported at a 2-tailed significance level of $P < .05$.

FUNCTIONAL MRI DATA ANALYSES

Preprocessing

Functional images were processed using statistical parametric mapping software (SPM8; Wellcome Trust Center for Neuroimaging). Each participant's baseline and posttreatment functional time series were separately motion corrected, and functional series with more than 1 voxel (4 mm) of motion were discarded. The methylphenidate and atomoxetine groups did not differ in mean (SD) translational movement, rotational displacement, or number of functional series included in the analysis (**Table 2**). The remaining baseline and posttreatment functional time series were coregistered to their respective high-resolution T2-weighted images (section thickness, 4 mm; 28 sections) and then to each other. The functional images were subsequently spatially normalized to a standard template (Montreal Neurological Institute) using normalization parameters estimated from the baseline high-resolution T2-weighted image and were then resampled using a sinc interpolation, resulting in a voxel size of 2×2×2 mm. Coregistered and spatially normalized functional images were checked manually by 2 of us (K.P.S. and J.F.). Finally, the functional images were smoothed using an 8×8×16-mm full-width at half maximum gaussian kernel.

First-level analyses used a within-subjects design to contrast activation in baseline vs posttreatment MRIs for each participant. A general linear model was conducted to determine the relationship between observed event-related blood oxygenation level–dependent signals and 4 regressors that represented expected neural responses to correct and incorrect no-go and go events.[34] Six motion parameters were entered as covariates of no interest.[35] The neural effect of response inhibition and the impact of treatment on this activation were modeled by applying appropriate linear contrasts to parameter estimates for correct

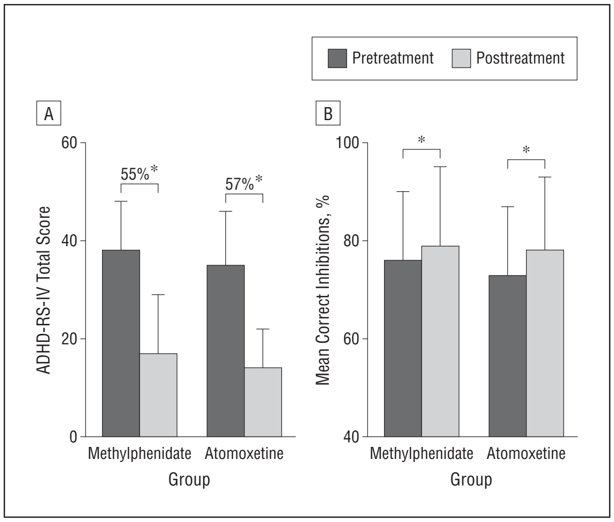

Figure 2. Treatment improved ratings of attention-deficit/hyperactivity disorder (ADHD) symptoms and response inhibition on the go/no-go task. A, Treatment significantly reduced ratings on the total score of the ADHD Rating Scale-IV-Parent Version (ADHD-RS-IV) ($F_{1,34}$=102.33, $P<.001$). The mean percentage improvement in the ADHD-RS-IV ratings was 55% for the methylphenidate group and 57% for the atomoxetine group. B, Treatment also increased the percentage of successful inhibitions on no-go trials of the go/no-go task ($F_{1,34}$=5.77, P=.02). There were no differences between the 2 medications in the improvement of symptom ratings and inhibitory function over treatment. Error bars indicate 1 SD. Asterisks indicate significant time effects (baseline vs posttreatment). Methylphenidate and atomoxetine both given in hydrochloride form.

no-go events minus correct go events in the baseline MRI and in the posttreatment minus baseline MRIs, respectively, resulting in 2 contrast maps per participant.

Group-Level Analyses

Second-level random-effects group analyses of the functional imaging data were conducted using SPM8 software. Preliminary *t* tests were performed to define baseline activation related to response inhibition in the whole sample and to test for group differences in baseline activation. The hypotheses relating activation changes and symptomatic improvement were tested using a multiple linear regression model that partially parceled out practice effects. The posttreatment minus baseline contrast maps of all the participants were entered into a general linear model with 3 regressors: (1) the centered ADHD-RS-IV change score, (2) the centered medication type, and (3) an interaction predictor, which was the product of the dichotomous medication type variable with the ADHD-RS-IV change score. The ADHD-RS-IV change score regressor identified activation changes that were associated with symptomatic change across the whole sample and that were, thus, similarly related to improvement irrespective of medication type. The medication type regressor functioned as a between-group contrast to test for differential changes in activation that were independent of clinical improvement. Finally, the interaction predictor identified activation changes that were differentially related to symptomatic improvement for methylphenidate and atomoxetine (ie, divergent regression slopes). Of note, the medication type regressor and interaction predictor both involved between-group contrasts that subtract out activation changes shared by the 2 groups of youth with ADHD, including practice, expectation, and other nonspecific factors.

The resultant voxelwise statistical maps were thresholded for significance using a cluster size algorithm that protects against false-positive results.[36] The height (intensity) threshold of each activated voxel was set at $P<.005$, and the extent (cluster) threshold was fixed at $\kappa>100$ voxels. A Monte Carlo simulation (procedure described by Slotnick and Schacter[37]) that accounted for image resolution and smoothing parameters established that a cluster extent of 100 contiguous resampled voxels (2 mm^3) corrected for multiple voxel comparisons at $P<.01$. To illustrate significant findings, parameter estimates for hemodynamic signal change were extracted from volumes of interest that were defined as 8-mm-radius spheres centered at the peaks of maximal activation.

RESULTS

CLINICAL AND BEHAVIORAL IMPROVEMENT

Treatment with methylphenidate vs atomoxetine was associated with comparable improvements in both ADHD symptoms and response inhibition on the go/no-go task (**Figure 2**). Separate repeated-measures analysis of variance revealed significant main effects of time for both the ADHD-RS-IV total score ($F_{1,34}$=102.33, $P<.001$) and the percentage of correct inhibitions on no-go trials ($F_{1,34}$=5.77, P=.02). Treatment also increased the speed and reduced the variability of responses on go trials, with significant main effects of time for RT ($F_{1,34}$=8.88, $P<.001$) and standard deviation of RT ($F_{1,34}$=8.25, $P<.001$). However, no significant main effects of medication or time × medication interactions for any of the performance measures were noted (Table 2).

Mean (SD) ADHD-RS-IV change scores did not differ for methylphenidate vs atomoxetine (55% [30%] vs 57% [23%], t_{34}=0.52, P=.88). Stepwise linear regression found no association of symptomatic improvement with age in either the whole sample or the separate medication groups. Specifically, only a small proportion of the variance was accounted for by the ADHD-RS-IV change score entered in step 1 (R^2=0.001, $F_{1,34}$=0.02, P=.88) and the medication variable entered in step 2 ($R^2<0.001$, $F_{1,33}$=0.003, P=.96). Most important, the age × medication interaction predictor entered in step 3 did not account for a significant proportion of additional variance in symptomatic improvement (R^2=0.003, $F_{1,32}$=0.10, P=.76).

BASELINE NEURAL ACTIVATION

Successful response inhibition at baseline activated a frontoparietal network that included the bilateral inferior frontal gyrus, right middle frontal gyri, bilateral anterior cingulate cortex, inferior parietal lobule, and caudate nucleus and deactivated the right precuneus ($P<.005$) (eTable 1 and eFigure; http://www.archgenpsychiatry.com). Baseline activation in the left superior parietal and paracentral lobules was greater in youth treated with methylphenidate than in those treated with atomoxetine ($P<.005$) (eTable 2).

NEURAL CORRELATES
OF SYMPTOMATIC IMPROVEMENT

Multiple linear regression revealed that clinical improvement was associated with both common and unique changes in neural activation for atomoxetine and methylpheni-

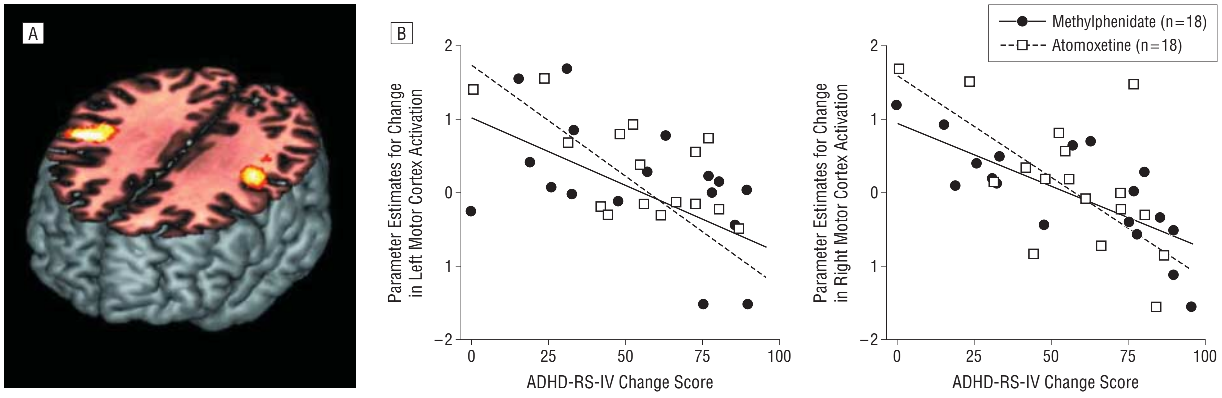

Figure 3. Common therapeutic action of methylphenidate hydrochloride and atomoxetine hydrochloride treatments for attention-deficit/hyperactivity disorder (ADHD). A, Symptomatic improvements with methylphenidate and atomoxetine use were associated with reductions in bilateral motor cortex activation in youth with ADHD (n=18 each). Results are displayed at $P < .005$ uncorrected, with a cluster threshold of greater than 100 contiguous voxels. B, Parameter estimates for left and right motor cortex signal change during treatment are plotted against percentage improvement in ratings on the ADHD Rating Scale-IV-Parent Version (ADHD-RS-IV change score). Parameter estimates were extracted from 8-mm-radius spheres centered at the peaks of maximal activation. Noncentered ADHD-RS-IV change scores are plotted for clarity. Regression lines in each scatterplot correspond to the lines of best fit.

Table 3. Brain Regions Showing Common and Differential Changes in Neural Activation Related to Symptomatic Improvement for the Methylphenidate (n = 18) and Atomoxetine (n = 18) Groups

Brain Region	Brodmann Area	Voxel Coordinates[a] x	y	z	Volume[b]	$F_{1,32}$	*P* Value	Relation to ADHD-RS-IV[c]
Common changes								
Right primary motor cortex	4	42	−18	36	615	27.60	<.001	↓MPH, ↓ATX
Left primary motor cortex	4	−42	−18	32	325	20.81	<.001	↓MPH, ↓ATX
Differential changes								
Right inferior frontal gyrus	45	36	18	24	517	20.25	<.001	↓MPH, ↑ATX
Left anterior cingulate cortex	32	−12	30	26	1428[d]	28.89	<.001	↓MPH, ↑ATX
Left supplementary motor area	6	−20	6	52		28.83	<.001	
Bilateral posterior cingulate cortex	31	10	−46	46	565	20.21	<.001	↓MPH, ↑ATX

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale-IV-Parent Version; ATX, atomoxetine hydrochloride; MPH, methylphenidate hydrochloride.

[a] Coordinates of peak activation based on the Montreal Neurological Institute stereotactic coordinate system.

[b] Number of voxels. One voxel = 8 mm^3.

[c] Arrows denote the direction of the relationship between activation and ADHD-RS-IV change score for the MPH and ATX groups: ↑, positive; ↓, negative.

[d] One cluster with 2 separate peaks.

date treatment (**Figure 3** and **Table 3**). The ADHD-RS-IV change score regressor identified corresponding regions of the right and left motor cortices in which decreases in activation were associated with symptomatic improvement irrespective of the treatment ($P < .005$). Greater symptomatic improvement was seen in youth who showed larger reductions in the magnitude of activation in the motor cortex during treatment (Figure 3B). This relationship between activation and improvement was independent of medication type. In contrast, the medication type regressor detected no differential changes in activation that were independent of clinical improvement.

The interaction term identified several frontoparietal regions that showed differential changes in activation related to clinical improvement with the use of methylphenidate vs atomoxetine (**Figure 4** and Table 3). Symptomatic improvement was related to gains in the magnitude of activation in the right inferior frontal gyrus, left anterior cingulate cortex/supplementary motor area, and bilateral posterior cingulate cortex with atomoxetine treatment and reductions in activation in these same regions with methylphenidate treatment ($P < .005$ for all) (Figure 4B). There was no evidence that changes in striatal activation were associated with improvement in either the whole sample or the 2 treatment groups separately, even when a small volume correction was used to account for the small size of striatal structures.

COMMENT

These findings provide the first evidence, to our knowledge, of distinct frontoparietal therapeutic mechanisms of action for stimulant and nonstimulant treatments in youth with ADHD. Comparable improvements in response inhibition and ADHD symptoms were seen after 6 to 8 weeks of daily treatment with methylphenidate vs atomoxetine. Symptomatic improvement was divergently associated with gains in task-related activation for atomoxetine and reductions in activation for methylphenidate in the right infe-

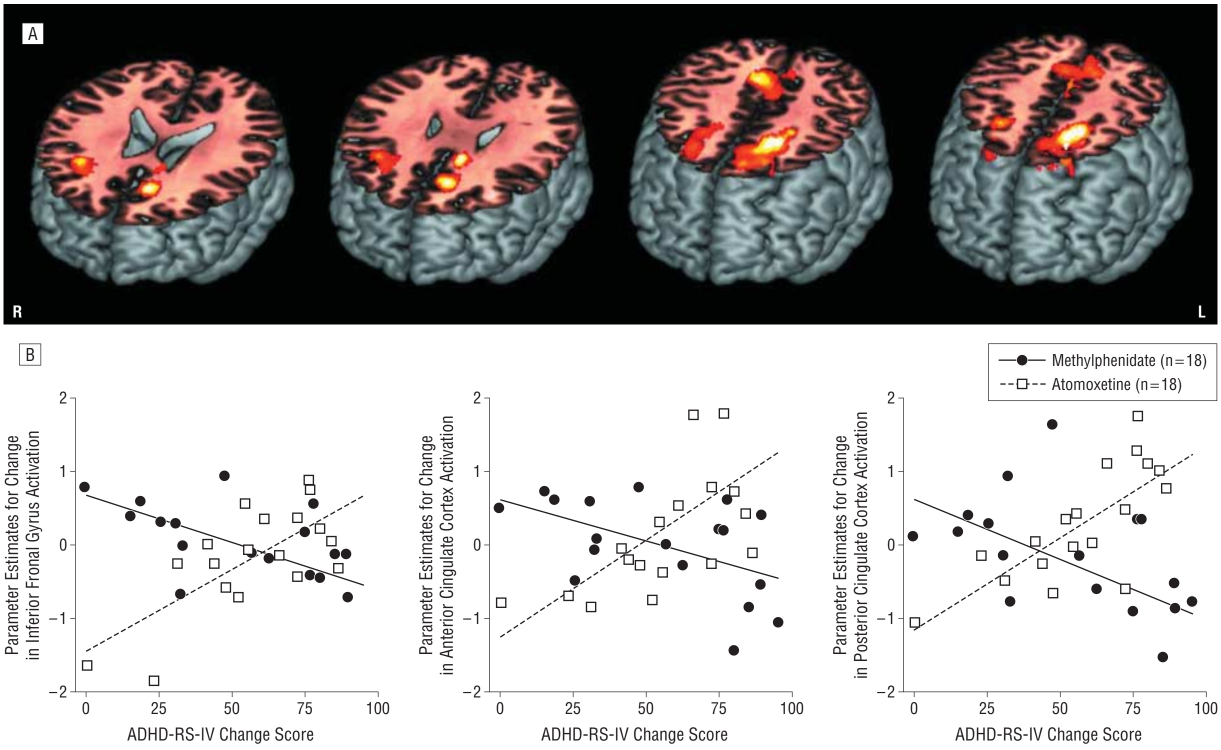

Figure 4. Unique therapeutic actions of methylphenidate and atomoxetine treatments for attention-deficit/hyperactivity disorder (ADHD). A, Symptom improvement was differentially related to gains in activation for the atomoxetine hydrochloride group and reductions in activation for the methylphenidate hydrochloride group in the right inferior frontal gyrus, left anterior cingulate/supplementary motor area, and bilateral posterior cingulate cortex in youth with ADHD (n=18 each). Results are displayed at $P < .005$ uncorrected, with a cluster threshold at greater than 100 contiguous voxels. L indicates left; and R, right. B, Parameter estimates for signal change during treatment in the right inferior frontal gyrus, left anterior cingulate cortex/supplementary motor area, and bilateral posterior cingulate cortex are plotted against percentage improvement in ratings on the ADHD Rating Scale-IV-Parent Version (ADHD-RS-IV change score). Parameter estimates were extracted from 8-mm-radius spheres centered at the peaks of maximal activation. Noncentered ADHD-RS-IV change scores are plotted for clarity. Regression lines in each scatterplot correspond to the lines of best fit.

rior frontal gyrus, left anterior cingulate/supplementary motor area, and bilateral posterior cingulate cortex. These results confirm the importance of medial and lateral prefrontal inhibitory mechanisms to the therapeutic actions of both methylphenidate and atomoxetine but also indicate that different processes in these regions underlie response to the 2 treatments. Results also suggest a unique contribution of posterior cingulate cortex deactivation to the therapeutic actions of methylphenidate that may reflect the suppression of task-independent activity linked to distractibility. These frontoparietal mechanisms have been implicated in the pathophysiology of ADHD and potentially represent the neurophysiologic basis of differential response to ADHD treatments reported in the literature.[4] In contrast, the comparable improvement-related reductions seen in motor cortex activation with methylphenidate and atomoxetine treatment may represent a common therapeutic mechanism that could account for the observation that many individuals respond to multiple ADHD medications.[4]

The common therapeutic actions of methylphenidate and atomoxetine on motor cortex activation may reflect direct pharmacologic actions at catecholamine transporters. Moderate levels of both DAT and NET are expressed in the motor cortex[15,19] and may provide the substrate for single-challenge doses of atomoxetine and methylphenidate to produce comparable changes in the intracortical facilitation and inhibition of motor activity.[38] Several weeks of methylphenidate treatment has been found to normalize deficient motor cortex inhibition in children with ADHD, with an increase in inhibition correlated with clinical improvement.[39] The therapeutic reductions in motor cortex activation in the present study may, therefore, reflect attenuation in the prepotency of the inhibited responses. At the same time, the lack of a between-group contrast for the ADHD-RS-IV change score regressor in the present study, plus the absence of placebo control conditions in previous studies of motor cortex,[38,39] makes it impossible to conclusively ascribe this attenuation in motor prepotency to the therapeutic actions of the 2 medications, as opposed to practice, expectation, and other nonspecific factors shared by youth treated with methylphenidate and those treated with atomoxetine. The potential for this motor cortex mechanism to serve as a therapeutic target for a broad range of future interventions merits further investigation in placebo-controlled studies.

The divergent therapeutic effects of methylphenidate and atomoxetine on inferior frontal activation indicate that clinical improvement is not solely attributable to the direct pharmacologic actions of medication. Challenge doses of both methylphenidate and atomoxetine block the same promiscuous NET and produce comparable increases in extracellular catecholamine levels in the prefrontal cortex,[12-14] which indirectly modulates event-related prefrontal activation,[5,7,8,11] likely via dopamine D1 receptors and α_2-adrenoceptors.[9] However, long-term administration of atomoxetine but not methylphenidate was found to attenuate the prefrontal noradrenergic response to challenge.[40] The divergent inferior frontal actions of the treatments would, therefore, seem to reflect differences in functional adaptations of NET, α_2-adrenoceptors, and/or downstream signal mechanisms (eg, cyclic adenosine monophosphate). These results suggest that improvement of ADHD symptoms involves more than acute catecholamine transporter and/or receptor actions.

The present findings, nevertheless, suggest that inferior frontal and anterior cingulate mechanisms serve an important role in the therapeutic actions of atomoxetine. The inferior frontal gyrus, particularly in the right hemisphere, is purported to be a neural effector for response inhibition[41,42] and to exert inhibitory control over the primary motor, supplementary motor, and premotor cortices.[43,44] Gains in this inferior frontal activation may have contributed to the improvements in response inhibition seen in this and other studies with atomoxetine therapy.[10,45,46] The anterior cingulate cortex forms a separate network that has been implicated in the top-down control of volitional behavior,[47] including the implementation of these task sets in downstream sensorimotor processors,[48] and has been shown to interact with inferior frontal gyrus during go/no-go tasks.[49] These anterior cingulate and inferior frontal mechanisms have been implicated in the inhibitory and executive deficits that are central to the pathophysiology of ADHD.[50,51] The present results suggest that the beneficial actions of atomoxetine involve a gain in inhibitory effort and top-down control of attention,[52] with a coincident amelioration of the frequently reported prefrontal hypoactivation.[50,51] The improvement-related reductions in prefrontal activation for methylphenidate would seem paradoxical and may reflect the indirect actions of the medication in interconnected brain regions (eg, the posterior cingulate cortex[53]).

The divergent therapeutic effects of the 2 treatments on posterior cingulate activation conversely provide clues regarding the mechanisms of action for methylphenidate. Moderate levels of DAT expression in the posterior cingulate offer the pharmacologic substrate for methylphenidate to directly enhance deactivation and, thereby, produce clinical improvement.[15] This enhanced posterior cingulate deactivation is consistent with findings from single-dose challenge studies of methylphenidate[11,18] and potentially represents the neurobiological basis for suppression of distracting mental processes with treatment.[16,54] The reductions in posterior cingulate interference may have improved neural efficiency and, thereby, diminished the need for prefrontal inhibitory effort,[55] which could have accounted for the improvement-related decreases in inferior frontal and anterior cingulate activation for methylphenidate. In contrast, the sparse density of NET sites for atomoxetine to directly affect posterior cingulate activation suggests that the observed gain in activation may reflect the downstream effects of excitatory inferior frontal and anterior cingulate actions of treatment.[56]

The lack of evidence in this study implicating striatum in the therapeutic actions of methylphenidate treatment is surprising given the robust acute effects that stimulants have on striatal dopamine function. Single therapeutic doses of methylphenidate produce robust increases in extracellular dopamine levels,[57,58] which potentiate corticostriatal inputs,[59] and have been found to enhance striatal activation in children with ADHD.[6-8] However, repeated surges in extracellular dopamine over weeks of daily methylphenidate treatment have been shown to trigger adaptive downregulations in neuronal activity,[60,61] dopamine synthesis,[62] and DAT binding,[22] all of which could have blunted further stimulant-induced dopamine release[40] and may account for the lack of effect for methylphenidate treatment on striatal activation in this and the few other available treatment studies.[24,25] Nevertheless, it is possible that the actions of methylphenidate in striatum may have contributed to clinical improvement by influencing activation in other critical regions (eg, the posterior cingulate cortex[63]).

The divergent effects of atomoxetine and methylphenidate treatment in association with clinical improvement highlight the importance of adopting a network-based framework to understand medication-related changes in regional activation. Clinical improvement involved changes in activation in the same direction (ie, increases for atomoxetine and decreases for methylphenidate) in the inferior frontal gyrus/anterior cingulate cortex and posterior cingulate cortex, regions that generally operate in opposition to each other during optimal behavioral performance.[53] For atomoxetine, these changes suggest that the therapeutic increases in prefrontal activation engendered homeostatic gains in posterior cingulate activity. Conversely, the therapeutic deactivation of posterior cingulate cortex by methylphenidate may have reduced the need for prefrontal inhibitory activation. The comparable changes in frontal and parietal activation associated with clinical improvement for each treatment may have addressed the functional disconnection of anterior and posterior cingulate cortices that has been reported in patients with ADHD.[64] Yet, these improvement-related changes in activation were accompanied by improvements in response consistency (ie, standard deviation of RT) that are more commonly seen when frontal and parietal regions are activated in opposition to each other.[65]

The unique focus of this study on the differential effects of stimulant and nonstimulant treatments for ADHD, together with an innovative analytic approach that incorporated clinical improvement and changes in brain activity, provides a window into the possible neurophysiologic mechanisms of differential response. To summarize, effective treatment with methylphenidate and atomoxetine produces a variety of direct, indirect, and downstream effects on neural activation during response inhibition via a common mechanism in motor cortex and distinct mechanisms in frontoparietal regions. These findings provide a neurobiological basis for understanding selective response to the 2 classes of medication, which represents an important first step in matching treatments to individual patients.

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