

# Abnormal Amygdalar Activation and Connectivity in Adolescents With Attention-Deficit/Hyperactivity Disorder

Jonathan Posner, M.D., Bonnie J. Nagel, Ph.D., Tiago V. Maia, Ph.D.,  
Anna Mechling, B.A., Milim Oh, M.A., Zhishun Wang, Ph.D., Bradley S. Peterson, M.D.

**Objective:** Emotional reactivity is one of the most disabling symptoms associated with attention-deficit/hyperactivity disorder (ADHD). We aimed to identify neural substrates associated with emotional reactivity and to assess the effects of stimulants on those substrates. **Method:** We used functional magnetic resonance imaging (fMRI) to assess neural activity in adolescents with ( $n = 15$ ) and without ( $n = 15$ ) ADHD while they performed a task involving the subliminal presentation of fearful faces. Using dynamic causal modeling, we also examined the effective connectivity of two regions associated with emotional reactivity, i.e., the amygdala and the lateral prefrontal cortex (LPFC). The participants with ADHD underwent scanning both on and off stimulant medication in a counterbalanced fashion. **Results:** During the task, we found that activity in the right amygdala was greater in adolescents with ADHD than in control subjects. In addition, in adolescents with ADHD, greater connectivity was detected between the amygdala and LPFC. Stimulants had a normalizing effect on both the activity in the right amygdala and the connectivity between the amygdala and LPFC. **Conclusions:** Our findings demonstrate that in adolescents with ADHD, a neural substrate of fear processing is atypical, as is the connectivity between the amygdala and LPFC. These findings suggest possible neural substrates for the emotional reactivity that is often present in youths with ADHD, and provide putative neural targets for the development of novel therapeutic interventions for this condition. *J. Am. Acad. Child Adolesc. Psychiatry*, 2011;50(8):828–837. **Key Words:** ADHD, amygdala, effective connectivity, fear, stimulant medication

Although attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity,<sup>1</sup> one of the most disabling symptoms of the disorder is the heightened emotional reactivity that is present in so many youths with ADHD.<sup>2,3</sup> Youths with ADHD frequently display poorly regulated outbursts of emotion,<sup>1</sup> and they have rates of mood disorders that are far beyond those that would be expected by chance alone.<sup>4</sup> Despite the clinical significance of emotional reactivity in ADHD, the neurobiological substrates for this aspect of the disorder remain poorly investigated.

In the current study, we investigated emotional processing in youths with ADHD using a task that engages the amygdala through the

subliminal presentation of fearful faces.<sup>5</sup> This task is useful for several reasons. First, the importance of the amygdala in emotional processing has been clearly established.<sup>6</sup> Second, anatomical and functional MRI (fMRI) studies suggest that amygdalar morphology and functioning may be anomalous in youths with ADHD.<sup>7,8</sup> Third, by using subliminal presentations of emotional stimuli, we aimed to diminish the effects of differences in supraliminal attention as a potential confound in comparing control subjects versus youths with ADHD.<sup>9</sup>

We focused our study on amygdalar responses to affective stimuli, and also on the neural connections between the amygdala and the lateral prefrontal cortex (LPFC; Brodmann area 47). We investigated the connectivity of the amygdala and LPFC using dynamic causal modeling (DCM)<sup>10</sup> and chose this circuit because the amygdala and LPFC have well described and abundant reciprocal con-



Supplemental material cited in this article is available online.

nections.<sup>11,12</sup> The LPFC receives affective inputs from the amygdala and integrates this information with other sensory inputs, while at the same time coordinating motor output.<sup>13</sup> Through connections with the amygdala, the LPFC is thought to integrate affective cues, such as potential threats, allowing these cues to guide goal-directed behaviors. Conversely, disturbances of the amygdalar-LPFC circuit produce impulsive behaviors characterized both by a disregard for salient, affective cues and by inattention with enhanced effects of distracting stimuli.<sup>14</sup>

We also examined the effects of stimulant medications on amygdalar functioning and amygdalar-LPFC connectivity. We did this by scanning youths with ADHD both on and off of their normally prescribed stimulant medication. Our a priori hypotheses, based on the heightened emotional reactivity that is often present in youths with ADHD, was that these individuals, during their unmedicated scans, would demonstrate the following: 1) amygdalar hyperactivity relative to that in control subjects, and 2) anomalous amygdalar-LPFC connections.<sup>7,8</sup> We further hypothesized that stimulant medications would attenuate amygdalar hyperactivity and anomalous amygdalar-LPFC connections. Stimulants often have a calming effect on youths with ADHD, and this calming effect often includes a reduction in emotional lability. The neural mechanisms by which stimulants reduce emotional lability are largely unknown; few studies have examined this issue. In animal models, however, single-unit recordings during fear condition-

ing indicate that dopamine attenuates activity in both the amygdala and prefrontal cortex.<sup>15,16</sup> We thus reasoned that by augmenting dopamine transmission, stimulants may attenuate the amygdalar-LPFC circuitry in youths with ADHD.

**METHOD**

The Institutional Review Board of the Oregon Health & Science University (OHSU) approved the study procedures. All child participants provided written, informed assent, and a parent or legal guardian provided informed, written consent.

**Participants**

The participants were 15 youths with ADHD and 15 healthy control subjects. Controls were group-matched to the ADHD participants by age, gender, and ethnicity (Table 1) and screened for psychiatric disorders using the Diagnostic Interview Schedule for Children (DISC) Predictive Scales<sup>17</sup> and excluded for any probable active Axis I disorder. A child psychiatrist interviewed all participants with ADHD and at least one parent; for all of the ADHD participants, child and parent versions of the DISC<sup>18</sup> were completed. ADHD participants were excluded if they had any active Axis I disorder other than ADHD, oppositional defiant disorder, or conduct disorder. ADHD participants were also excluded if they were taking any nonstimulant psychotropic medication. Control subjects were medication free. Additional exclusion criteria for both ADHD participants and controls included (1) age <11 years or >16 years; (2) neurological illness; (3) significant head trauma (loss of consciousness >2 minu-

**TABLE 1** Clinical and Demographic Characteristics of the Study Sample

	ADHD (mean ± SD)	Healthy Controls (mean ± SD)	Test Statistic	p Value
Age (y)	13.5 ± 1.2	13.4 ± 1.2	t = 0.3	.8
Gender	3 Male 2 Female	13 Male 2 Female	χ <sup>2</sup> = 0	1.0
Ethnicity	15 White	14 White 1 Multiple ethnicities	Mann-Whitney U = 105	.3
Hollingshead Index of Social Position	32.4 ± 13.9	31 ± 11.8	t = 0.3	.8
FSIQ	111.4 ± 16	114.1 ± 10	t = 0.5	.6
Pubertal status	2.5 ± 0.8	2.7 ± 0.7	Mann-Whitney U = 98	.5
STAI	45.2 ± 7.3	39.5 ± 7.4	t = 2.1	.04 <sup>a</sup>
CDI	46.4 ± 7.0	39.5 ± 0.9	t = 3.4	.003 <sup>a</sup>

Note: Socioeconomic status was assessed with the Hollingshead Index of Social Position. Pubertal status was assessed with the Puberty Development Scale (PDS). ADHD = attention-deficit/hyperactivity disorder; CDI = Children's Depression Inventory; FSIQ = Full Scale Intelligence Quotient; STAI = Spielberger State Anxiety Inventory.

<sup>a</sup>Indicates a statistically significant difference.

tes); (4) serious medical problems; (5) pregnancy; (6) IQ <80; (7) left-handedness; (8) non-native English speaking; and (8) MRI contraindications.

Parents completed the Conners' Parent Rating Scales<sup>19</sup> and Child Behavior Checklist.<sup>20</sup> The parents of ADHD participants completed these assessments based on their child's unmedicated presentation. ADHD participants completed the Wechsler Abbreviated Scale of Intelligence (WASI)<sup>21</sup>; control subjects completed the short form of the WASI, which consists of the Matrix Reasoning and Vocabulary subtests. All participants were administered the Edinburgh Handedness Inventory,<sup>22</sup> Hollingshead Index of Social Position,<sup>23</sup> Children's Depression Inventory (CDI),<sup>24</sup> Spielberger State Anxiety Inventory (STAI),<sup>25</sup> and Puberty Development Scale (PDS).<sup>26</sup> The ADHD participants were to complete two MRI scans; because ratings on the CDI and STAI could in theory vary between the first and second scan, the ADHD participants completed these measures twice, i.e., once at the time of their first MRI scan and again at their second MRI scan. Scores did not differ significantly at these two time points (CDI:  $p = .36$ ; STAI:  $p = .38$ ); therefore we used only the scores obtained with the first MRI scan. ADHD participants and controls did not differ significantly in regard to age, IQ, socioeconomic status, or pubertal stage (Table 1). ADHD participants had higher levels of depressive and anxiety symptoms (as measured by the CDI and STAI, respectively), and these differences were controlled for in the fMRI analyses. Within the ADHD sample, 13 participants were classified as ADHD, Combined Type, and two were classified as ADHD, Predominantly Inattentive Type. The fMRI analyses covaried for ADHD subtype.

### MRI Scanning Sessions

ADHD participants completed two scanning sessions: one while on their normally prescribed stimulant, and another after abstaining from the stimulant for at least 48 hours (i.e., exceeding at least four half-lives for available stimulant formulations). The order of the scanning sessions was counterbalanced across ADHD participants to control for medication status. Control participants completed a single scanning session.

### fMRI Task

The task used a block design consisting of two block types: 1) neutral faces presented supraliminally, and 2) fearful faces presented subliminally followed by neutral faces presented supraliminally. For simplicity, we will refer to the first block type as "neutral face blocks" and to the second block type as "subliminal fearful face blocks." Each block type had 60 trials. On each trial of the neutral face blocks, participants were shown a face with a neutral facial expression for the full duration of the trial (500 milliseconds). On each trial of the subliminal fearful face blocks, participants

were shown a fearful face for 30 milliseconds; then, for the remainder of the trial (i.e., 470 milliseconds), they were shown the same face but with a neutral expression rather than a fearful one. Prior research indicates that such a brief presentation of a fearful face does not permit supraliminal perception.<sup>5</sup> The experiment consisted of two runs of the task. Each run consisted of four blocks, alternating between neutral face blocks and subliminal fearful face blocks with 15 seconds of fixation at the beginning and end of each run. The total scan time per run was 2 minutes 30 seconds.

The fMRI paradigms were presented with E-Prime (v. 1.0; Psychology Software Tools, Pittsburgh, PA) running on a desktop computer. We back-projected the task stimuli onto a screen that participants viewed via a mirror attached to the MRI head coil. Before beginning the task, participants were instructed to try to remember the faces that would be presented. This was done to ensure that the participants were attending to the task. At the conclusion of the scanning session, participants were shown a random selection of the faces presented during the task and asked to circle those they remembered seeing. The faces used during the task were obtained from the NimStim sample; in the supplemental material, we provide further information about the specific faces selected from the NimStim sample,<sup>27</sup> as well as the instructions for the fMRI task and the post-scanning questionnaire (Supplement 1 and Table S1, available online). The faces were presented as grayscale images at the center of the subject's visual field with a visual angle of approximately 15° vertical and 12° horizontal.

### Image Acquisition

Images were acquired using a 3.0-Tesla Siemens Magnetom Tim Trio scanner with a 12-channel head coil at the OHSU Advanced Imaging Research Center. The scanning protocol started with a high-resolution, whole-brain structural image series collected in the sagittal plane using a T1-weighted MPRAGE sequence (TI = 900 milliseconds, flip angle = 10°, TE = 3.58 milliseconds, TR = 2300 milliseconds, bandwidth = 180 Hz/Px, 256 × 240 matrix, slice thickness = 1 mm). Blood oxygen level-dependent (BOLD) images were collected in an oblique plane (parallel to the AC-PC line) using T2\*-weighted echo-planar imaging (TR = 2,000 milliseconds, TE = 30 milliseconds, flip angle = 90°, FOV = 240 mm, in-plane resolution = 3.8 × 3.8 mm, 33 slices covering the whole brain, slice thickness = 3.8 mm, no skip).

### Data Analysis

*Behavioral Analyses.* The total number of recalled faces was calculated for each participant. To compare medicated and unmedicated ADHD participants, we

used a paired t test; to compare ADHD participants with control subjects, we used independent sample t tests.

**Image Processing.** Images were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience). Images were motion and slice time corrected, coregistered with a high-resolution anatomical scan, normalized into the Montreal Neurological Institute (MNI) space, resampled at 2 mm<sup>3</sup>, and smoothed with a Gaussian kernel of 6 mm<sup>3</sup> FWHM.<sup>28</sup> A 128-second temporal high-pass filter removed low-frequency noise. For each participant, linear models were constructed using regressors indexing the duration of each block type (neutral faces and subliminal fearful faces) convolved with the canonical hemodynamic response function.

To account for head motion during scanning, we calculated the root mean square (RMS) values of the adjustments needed to realign each participant's head position into its original position at the beginning of each scanning run. The RMS values were calculated on the basis on three translational directions and rotations. Only runs with <2 mm RMS of motion were used in the imaging analyses. The head motion for the three groups is presented in the supplemental material accompanying this article (Supplement 1, available online). A non-statistically significant trend suggested greater motion in unmedicated ADHD participants than in controls. To control for this trend, we incorporated into each participant's linear model 6 nuisance regressors reflecting motion parameters in three translational directions and rotations.

**fMRI Activation Analyses.** We used hierarchical linear models and for each participant generated a whole-brain voxelwise contrast image that compared subliminal fearful face blocks with neutral face blocks. The contrast images were then entered in factorial models that incorporated random effects and covaried for 1) depressive and anxiety symptoms, 2) ADHD subtype, and 3) presence of comorbid oppositional defiant disorder (ODD)/conduct disorder (CD). In the supplemental material, we include an additional analysis in which depressive and anxiety symptoms were not included as covariates; there was a nominal difference in the level of statistical significance for the study's main findings (Supplement 1, available online). We treated Group as a between-subject factor when comparing ADHD patients with controls, and as a within-subject factor when comparing medicated and unmedicated ADHD participants. Group × task interactions were planned to isolate brain regions that differed between the groups in their response to subliminal fearful faces compared to neutral faces. We used separate factorial models to compare 1) unmedicated ADHD participants versus controls; 2) medicated ADHD participants versus controls; and 3) medicated versus unmedicated ADHD participants. These analyses could not be reduced into a single model with

three levels for Group (controls, unmedicated ADHD participants, and medicated ADHD participants) because comparing ADHD patients versus controls required a between-subject analysis, whereas a within-subject analysis was necessary to compare ADHD patients in a medicated versus an unmedicated state. In the supplemental material, we include a habituation analysis (Supplement 1, available online). This was conducted to exclude the possibility that differences in activation could be the result of differences in the rates of habituation to the fearful faces between ADHD youth and controls.

We localized regions of activation by attaining in SPM the MNI coordinates of the voxel with the peak signal intensity within each area of activation. We transformed the MNI coordinates into Talairach coordinates using *mni2tal* (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) and then used Talairach daemon (<http://www.talairach.org/daemon.html>) to obtain an anatomical label. The labels were confirmed via visual inspection.

**Dynamic Causal Modeling: Background.** We implemented dynamic causal modeling (DCM) using SPM8. DCM permits the construction and statistical testing of models of interacting brain regions.<sup>10</sup> The constructed models are elaborated based on a balloon model that quantifies how synaptic activity translates into hemodynamic responses; coupling parameters are then estimated based on the observed fMRI signal.<sup>10,29,30</sup> Using bilinear differential equations, DCM explicitly models the activity in a given brain area and how this activity causes changes in the neural dynamics of other brain regions. Given the observed data, the likelihood that the model accurately represents the true neural dynamics is then estimated within a Bayesian framework.<sup>31</sup>

Three coupling parameters are estimated. The first parameter (DCM.A) estimates intrinsic connections between two brain regions. DCM.A estimates the effect that one brain region has upon another, irrespective of the fMRI task (i.e., an intrinsic or "baseline" connection between brain regions). The second parameter (DCM.B) estimates perturbations in the intrinsic connections (that is, DCM.A) between two brain regions that are the result of the fMRI task. DCM.B quantifies the effect that the fMRI task has upon the interregional connections rather than the effects that the task has upon specific brain regions. The third parameter (DCM.C) indexes the effects of the fMRI task on specific brain regions. DCM.C replicates the primary fMRI analyses and is therefore not reported.<sup>29</sup>

Time series data for the amygdala and LPFC were extracted using the Wake Forest PickAtlas (<http://www.fmri.wfubmc.edu/download.htm>). Blood Oxygen Level-Dependent (BOLD) signal changes were averaged across the voxels in each of the four regions of interest (i.e., right and left amygdala, right and left

LPFC). Visual inspection of the functional images ensured that the LPFC was free of signal dropout.

*Dynamic Causal Models: Between-Group Analyses.* For each participant, we calculated 1) the intrinsic connectivity (DCM.A) for top-down (LPFC→amygdala) and bottom-up (amygdala→LPFC) connections; and 2) the effects of the fMRI task on these connections (DCM.B). We compared the intrinsic connectivity between the sample groups using  $2 \times 2 \times 2$  factorial models with diagnostic group as the first factor, connection type as the second factor (levels: 1, top-down; 2, bottom-up), and hemisphere as the third factor (levels: 1, left side; 2, right side). As with the fMRI activation analyses, separate factorial models were used to compare the following: 1) unmedicated ADHD participants versus controls; 2) medicated ADHD participants versus controls; and 3) medicated versus unmedicated ADHD participants.

We used a similar approach to examine group differences in DCM.B (i.e., the effects of the task upon the intrinsic connections). A positive DCM.B, here would suggest that the presentation of fearful faces enhanced the connection. Conversely, a negative DCM.B would suggest that the presentation of fearful faces reduced or inhibited the connection.

*Statistical Thresholds.* For the fMRI activation analyses, we determined our statistical threshold using 10,000 Monte Carlo simulations based on a connectivity radius of 3.0 mm. These simulations determined that the conjoint requirement of a volume of 630 mL with a voxelwise  $p$  value of  $<0.01$  would yield an effective  $p$  value of  $<0.000001$ . After accounting for multiple comparisons, the corrected  $\alpha$  is 0.001, a conservative statistical cutoff that minimizes the risk of Type I errors. We conducted the Monte Carlo simulations with AlphaSim<sup>32</sup> adapted to run on a Matlab platform (<http://restfmri.net/forum>). For the DCM analyses, we used the Bonferroni correction for multiple comparisons.

*Stimulant Effects Analysis.* We used a nonparametric analysis as a post hoc method of examining the hypothesis that stimulants have a normalizing effect on amygdalar activation and amygdalar-LPFC connectivity. We conducted the test by assigning a positive (+) or negative (−) value to each of the analyses of amygdalar activation and amygdala-LPFC connectivity. We assigned an analysis a (+) value if the test indicated that with stimulants, the results for the ADHD participants became more similar to those for controls. Conversely, we assigned an analysis a (−) value if the test indicated that with stimulants, the results for the ADHD participants became less similar to those for controls. A statistically significant result in the positive direction would suggest a nonrandom pattern, consistent with our hypothesis that stimulants have a normalizing effect on amygdalar activation and connectivity.

## RESULTS

### Behavioral Results

The number of recalled faces did not differ significantly across groups. No more than a nominal number of fearful faces were recalled (Tables S2 and S3, available online).

### Imaging Results

All of the imaging results are based on whole brain voxelwise analyses. In Table 2, we present the task-related activations for each group (i.e., unmedicated ADHD participants, medicated ADHD participants, and control subjects), as well as the main effects of the task (i.e., the effects of the task across the three groups) based on the contrast: subliminal fearful face blocks versus neutral face blocks. To test our primary hypothesis that amygdala responses in youths with ADHD would differ from controls, we examined group  $\times$  task interactions. We detected an interaction in the right amygdala that was driven by greater activation in the right amygdala in the unmedicated ADHD participants compared with controls (Figures 1 and 2;  $t = 3.64$ ;  $p = .001$ ). No group  $\times$  task interaction was detected when comparing the medicated ADHD participants and controls (Figure 2), because stimulant medication reduced amygdala activation to a level comparable to the levels detected in controls. No group  $\times$  task interaction was detected when comparing the medicated and unmedicated ADHD participants.

#### Dynamic Causal Modeling: Between-Group Comparisons of Intrinsic Connections

When comparing unmedicated ADHD participants with controls, we found greater connectivity in the unmedicated ADHD participants compared with controls ( $F_{1,27} = 6.5$ ,  $p = .01$ ; Figure 3). These findings demonstrate stronger bidirectional and bilateral amygdala-LPFC connections in the unmedicated ADHD participants compared with controls (Figure 3). We found no significant differences when comparing unmedicated and medicated ADHD participants or when comparing medicated ADHD participants and controls.

#### Dynamic Causal Modeling: Between-Group Comparisons of the Effects of the Task on the Intrinsic Connections

When comparing unmedicated ADHD participants with controls, we found a statistical trend

**TABLE 2** Activations Detected During the Functional Magnetic Resonance Imaging (fMRI) Task Based on the Contrast Between Subliminal Fearful Face Blocks and Neutral Face Blocks

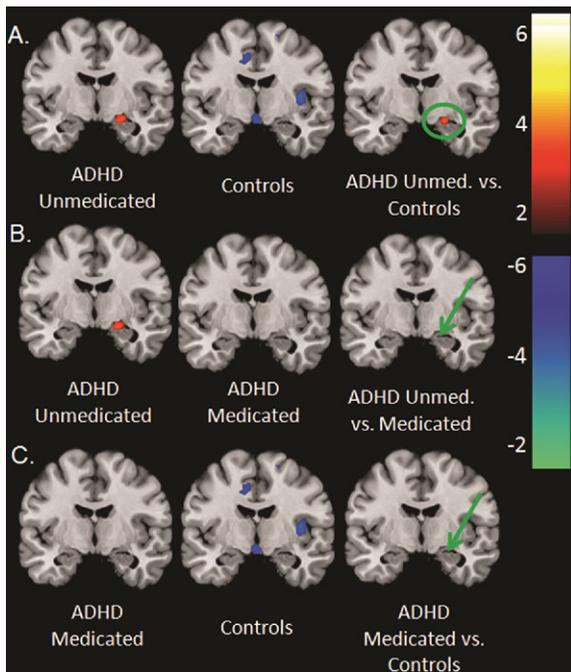
	MNI Coordinate			R/L	Cluster Size	t Value
	x	y	z			
<b>Task main effects</b>						
Activations						
Inferior frontal gyrus	-48	48	0	L	70	2.75
Middle temporal gyrus	52	-38	6	R	666	3.47
Middle temporal gyrus	-62	-52	10	L	128	2.45
Deactivations						
Fusiform gyrus	-30	-38	-16	L	99	-2.56
Insular cortex	42	-22	10	R	172	-2.49
Superior frontal gyrus	28	54	32	R	119	-2.62
Precuneus	-10	-54	40	L	114	-2.28
<b>Within-group analyses</b>						
Unmedicated ADHD youth						
Activations						
Amygdala	22	-12	-10	R	89	4.06
Middle occipital gyrus	32	-64	2	R	70	3.22
<b>Deactivations</b>						
Medicated ADHD youth						
Activations						
Superior occipital gyrus	-22	-90	30	L	282	3.55
Deactivations						
Anterior cingulate cortex	10	38	14	R	265	-3.16
Superior occipital gyrus	22	-98	6	R	73	-3.20
Healthy controls						
Activations						
Superior temporal gyrus	68	-26	0	R	83	4.63
Middle frontal gyrus	-32	18	38	L	542	5.90
Deactivations						
Precentral gyrus	30	-34	60	R	942	-6.57
Cuneus	18	-98	10	R	74	-3.24
Insular cortex	38	-16	6	R	198	-4.12
Parietal cortex	-26	-36	66	L	158	-4.41
Cingulate cortex	-10	-12	46	L	84	-3.50
<b>Group × task interactions</b>						
ADHD unmedicated youth > controls						
Amygdala	20	-10	-10	R	71	3.64
Middle occipital gyrus	30	-62	2	R	78	3.56
Controls > ADHD unmedicated youth						
ADHD medicated youth > controls						
Controls > ADHD medicated youth						
ADHD unmedicated > ADHD medicated youth						
Medicated ADHD > ADHD unmedicated youth						

*Note:* Activations detected during the functional magnetic resonance imaging (fMRI) task based on the contrast between subliminal fearful face blocks and neutral face blocks. The coordinates and t values are reported at the peak voxels in each cluster. All imaging results are based on whole-brain voxelwise analyses. The task main effects indicate activations detected across the three groups. Group × Task interactions indicate between group differences in task-related activation. One voxel = 2 mm<sup>3</sup>. ADHD = attention-deficit/hyperactivity disorder; L = left; MNI = Montreal Neurological Institute brain coordinates; NA = no cluster meets statistical significance; R = right.

suggesting a larger negative DCM.B in the controls compared with the unmedicated ADHD sample ( $F_{1,27} = 3.1, p = .09$ ; Figure 4). A post hoc t test demonstrated a significant dif-

ference in DCM.B for the right-sided connections ( $t = 2.5; p = .01$ ; Figure 4) with a positive DCM.B in the unmedicated ADHD participants (mean = 0.008) and a negative DCM.B for the

**FIGURE 1** Group  $\times$  task interactions. Note: The figure shows coronal slices through the Montreal Neurological Institute (MNI) y-coordinate  $-10$ . Activations are shown in red/orange. Deactivations are shown in blue/purple. Results are based on the contrast: subliminal fearful face blocks versus neutral face blocks. (A) The unmedicated attention-deficit/hyperactivity disorder (ADHD) participants compared with the healthy controls demonstrated greater activation in the amygdala as indicated by the green circle. (B) The unmedicated as compared with the medicated ADHD participants demonstrated greater activation in the right amygdala, but the difference was not statistically significant, as indicated by the green arrow. (C) No differences were detected in amygdalar activation between the medicated ADHD participants and healthy controls, as indicated by the green arrow.



controls (mean =  $-0.005$ ). This suggests that for the controls, the presentation of fearful faces appears to have inhibited the amygdala-LPFC connections bidirectionally on the right side, whereas in the unmedicated ADHD patients the presentation of fearful faces may have increased bidirectional connectivity between the amygdala and LPFC. We found no differences when comparing unmedicated and medicated ADHD participants or when we compared medicated ADHD participants and controls (Figure 4).

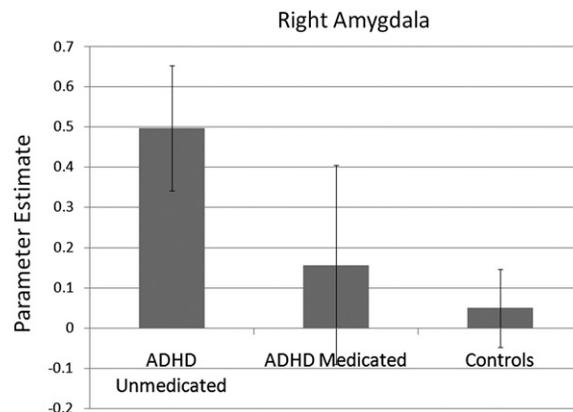
### Stimulant Effects Analysis

We conducted a nonparametric analysis by assigning (+) or (-) values to nine analyses of amygdalar activation and connectivity (Table 3). For example, we found that during the medicated sessions, amygdalar activation for the ADHD youth shifted in the direction of the controls (Figure 2; i.e., the level of amygdalar activation for ADHD subjects in the medicated versus unmedicated scans become more, rather than less, similar to that in controls). We therefore assigned this analysis a (+) value. Of the nine tests conducted, seven yielded findings in which the stimulant medication was associated with a normalizing effect. This was a nonrandom effect (Kolmogorov-Smirnov Test,  $p = .04$ ) and supports the hypothesis that stimulants had a normalizing effect of amygdalar activation and amygdalar-LPFC connectivity.

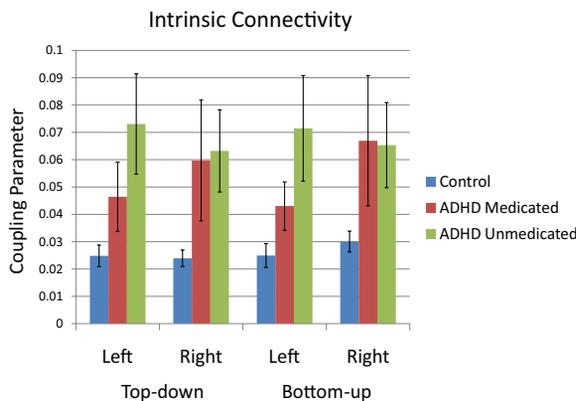
## DISCUSSION

Our study examined the processing of subliminally presented fearful faces in youths with ADHD and the effects of stimulant medications on this processing. We found that in unmedicated youths with ADHD, right amygdalar hyperactivation was associated with the presentation of the fearful faces. This finding overlaps with that of another recent fMRI study in which

**FIGURE 2** Parameter estimates for the activity in the right amygdala (Montreal Neurological Institute brain coordinates:  $x = 20, y = -10, z = -10$ ). Note: Greater activation was detected in the right amygdala in the unmedicated attention-deficit/hyperactivity disorder (ADHD) participants as compared with the controls ( $t = 3.64; p = .001$ ). Conversely, amygdalar activation in the medicated ADHD sample did not differ significantly from that in controls.



**FIGURE 3** Connectivity parameters for the attention-deficit/hyperactivity disorder (ADHD) participants and healthy controls. Note: Baseline connectivity (dynamic causal model matrix A [DCM.A; intrinsic connectivity]) was estimated between the amygdala and lateral prefrontal cortex (LPFC) separately for the left and right hemispheres. Bottom-up (amygdala→LPFC) and top-down (LPFC→amygdala) connection strengths were estimated. Greater connectivity was detected in the unmedicated ADHD participants compared with controls ( $F_{1,27} = 6.5, p = .01$ ). No difference in connectivity was found when comparing unmedicated and medicated ADHD participants or when comparing medicated ADHD participants and controls.

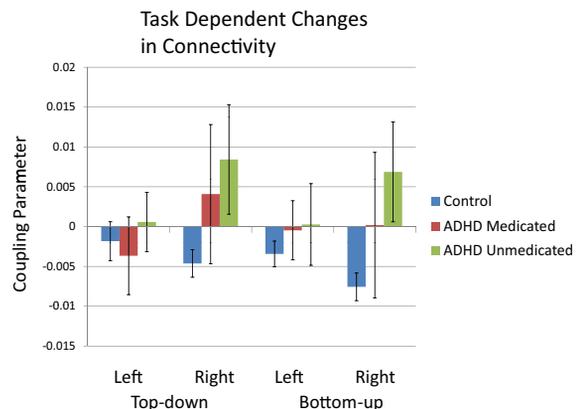


ADHD subjects were asked to provide subjective ratings of fear in response to neutral faces.<sup>8</sup> Although that task design differed from ours in important ways, both studies suggest that fear processing is associated with amygdalar hyperactivation in youths with ADHD. Our study extends these findings by also demonstrating that stimulant medications normalize amygdalar hyperactivation in youths with ADHD. This is consistent with an often-noted clinical response of improved emotional control resulting from the use of stimulant medication.<sup>33</sup> A recent positron emission tomography (PET) study described attenuated release of dopamine in the amygdala of patients with ADHD,<sup>34</sup> a finding that helps explain why dopaminergic agents such as stimulants may help to normalize amygdalar functioning in ADHD patients.

Along with abnormal amygdalar activation, we also found abnormal connectivity between the LPFC and amygdala in unmedicated ADHD participants. Although some studies suggest that the prefrontal cortex (PFC) and in particular, the orbitofrontal cortex, may be involved in the regulation of emotion,<sup>35,36</sup> others suggest a division

within the PFC with the medial portion indexing reward and pleasure, and the more lateral portion indexing loss and negative affect.<sup>11,37</sup> This functional division of the medial and lateral portions of the PFC was supported by a recent meta-analysis of 87 functional neuroimaging studies involving the PFC.<sup>37</sup> The enhanced amygdala-LPFC connectivity in ADHD patients may therefore suggest an over-representation, or amplification, of the negative affect associated with fearful faces. Indeed, intense outbursts of negative emotion, such as frustration, are quite common in youths with ADHD.<sup>38</sup> Similarly, we found that the presentation of fearful faces produced a greater inhibitory effect on the amygdala-LPFC connection in the controls compared with the unmedicated ADHD participants. This difference seemed to be greater in the right amygdala-LPFC connections than on the left, consistent with our main finding of right amygdalar hyperactivation in the unmedicated ADHD sample. Taken together, our findings support the interpretation that anomalous processing of negative stimuli within the amygdala and amygdala-LPFC circuit may underlie the intense, negative emotional reactions often seen in youths with

**FIGURE 4** Connectivity parameters for the attention-deficit/hyperactivity disorder (ADHD) participants and healthy controls. Note: The modulatory effect of the functional magnetic resonance imaging (fMRI) task (DCM.B) on baseline connectivity was estimated between the amygdala and lateral prefrontal cortex (LPFC) separately for the left and right hemisphere. Bottom-up (amygdala→LPFC) and top-down (LPFC→amygdala) connection strengths were estimated. A statistical trend was found suggesting a larger negative DCM.B in the controls as compared with the unmedicated ADHD sample ( $F_{1,27} = 3.1, p = .09$ ). DCM.B = dynamic causal model matrix B (modulatory connectivity).



**TABLE 3** Nonparametric Analysis

Analysis	Value Assigned
Right amygdalar activation	+
DCM.A	
L. amygdala→L. LPFC	+
L. LPFC→L. amygdala	+
R. amygdala→R. LPFC	-
R. LPFC→R. amygdala	+
DCM.B	
L. amygdala→L. LPFC	+
L. LPFC→L. amygdala	-
R. amygdala→R. LPFC	+
R. LPFC→R. amygdala	+

Note: A nonparametric analysis was conducted on the basis of the nine analyses listed in the table. The Kolmogorov-Smirnov test examined the effects of stimulant medication on amygdalar activation and amygdalar-lateral prefrontal cortex (LPFC) connectivity. For each of the tests listed, a (+) value was assigned if the test indicated that in the medicated versus unmedicated scans, the results for the attention-deficit/hyperactivity disorder (ADHD) subjects become more, rather than less, similar to controls. A (-) value was assigned if the test indicated that with stimulants, the results for the ADHD patients shifted away from controls. DCM.A = dynamic causal model, matrix A (intrinsic connectivity); DCM.B = dynamic causal model, matrix B (modulatory connectivity); L = left; R = right.

ADHD. Subsequent investigations with larger sample sizes and more detailed assessments of behavioral responses to negative stimuli should be able to test this interpretation.

Several limitations of this study merit consideration. First, because ADHD participants were scanned twice and the controls only once, the possibility that practice effects account for some of our findings cannot be excluded. This is unlikely, given that the ADHD participants demonstrated amygdalar hyperactivation, and practice effects should produce less amygdalar activation, not more. Second, the ADHD participants began the study on stimulant medications, and it is therefore possible that our results were the product not of ADHD but, rather, of medication exposure itself. This is also unlikely, given our findings that the stimulant medications seem to normalize neural activity. Third, the ADHD participants were not all taking the same stimulant medication. Although stimulant medications overlap considerably in their clinical effects and mechanisms of action, they may nonetheless have different effects on the processing of fearful faces; a larger, follow-up study would be necessary to examine this possibility. Fourth, our sample size was small, and thus a follow-up study

with a larger sample is needed to establish the stability of our findings. Fifth, the threshold between subliminal and supraliminal perception may differ between youths with ADHD and controls. Thus, it is possible that for the youths with ADHD, the presentation of the fearful faces were, at times, supraliminal whereas for the controls, the presentation of the fearful faces remained subliminal. This is unlikely, given that post-scanning questionnaires indicate that the youths with ADHD were no more likely than the controls to recall having seen the fearful faces; but this potential confound cannot be fully excluded. Sixth, dynamic causal modeling is dependent on the construction of a priori models of interacting brain regions. For each model, causality (i.e., neural activity in region A causes change in the neural activity of region B) is mathematically specified and statistically tested; however, as with all cross-sectional research, causal versus correlational links cannot be definitively established.

In conclusion, we have shown increased amygdalar activation in unmedicated youths with ADHD in response to subliminal fearful face processing, as well as the coupling of this increased activation with enhanced connectivity between the amygdala and LPFC. Finally, our study demonstrates that by altering amygdalar activation and amygdalar-LPFC connectivity, stimulant medications can have a normalizing effect on emotional processing. &

Accepted May 20, 2011.

Drs. Posner, Maia, Wang, and Peterson, and Ms. Mechling and Ms. Oh are with the Columbia College of Physicians and Surgeons and the New York State Psychiatric Institute in New York, NY. Dr. Nagel is with Oregon Health and Science University in Portland, OR.

This work was supported by the American Academy of Child and Adolescent Psychiatry, Pilot Research Award (J.P.), Klingenstein Third Generation Foundation (J.P., T.V.M.), National Institute of Mental Health grants K23 MH091249 (J.P.) and K02 MH074677 (B.S.P.), National Institute of Neurological Disorders and Stroke grant K08 NS52147 (B.J.N.), and National Institute on Alcohol Abuse and Alcoholism grant P60 AA010760 (B.J.N.).

Disclosure: Drs. Posner, Nagel, Maia, Wang, and Peterson, and Ms. Mechling, and Ms. Oh report no biomedical financial interests or potential conflicts of interest.

Correspondence to: Dr. Jonathan Posner, College of Physicians and Surgeons and New York State Psychiatric Institute, Unit 74, 1051 Riverside Drive, New York, NY 10032. E-mail: posnerj@childpsych.columbia.edu

0890-8567/\$36.00/©2011 American Academy of Child and Adolescent Psychiatry

DOI: 10.1016/j.jaac.2011.05.010

## REFERENCES

- Barkley R. Attention-Deficit Hyperactivity Disorder: a Handbook for Diagnosis and Treatment. 3rd ed. New York: Guilford Press; 2005.
- Barkley R, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. *J Am Acad Child Adolesc Psychiatry.* 2010;49:503-513.
- Chronis-Tuscano A, Molina BSG, Pelham WE, *et al.* Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2010;67:1044-1051.
- Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am J Psychiatry.* 1991;148:564-577.
- Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci.* 1998;18:411-418.
- LeDoux J. *The Emotional Brain.* New York: Simon & Schuster; 1996.
- Plessen KJ, Bansal R, Zhu H, *et al.* Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2006;63:795-807.
- Brotman M, Rich B, Guyer A, *et al.* Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *Am J Psychiatry.* 2010;167:61-69.
- Pessoa L, Ungerleider LG. Neuroimaging studies of attention and the processing of emotion-laden stimuli. *Prog Brain Res.* 2004;144:171-182.
- Friston K, Harrison L, Penny W. Dynamic causal modelling. *NeuroImage.* 2003;19:1273-1302.
- Kringelbach M. The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Rev Neurosci.* 2005;6:691-702.
- Ongur D, Price J. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex.* 2000;10:206-219.
- Barbas H, Zikopoulos B, Timbie C. Sensory pathways and emotional context for action in primate prefrontal cortex. *Biol Psychiatry.* 2011;69:1133-1139.
- Gehring WJ, Knight RT. Lateral prefrontal damage affects processing selection but not attention switching. *Cogn Brain Res.* 2002;13:267-279.
- Rosenkranz JA, Grace AA. Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *J Neurosci.* 2001;21:4090-4103.
- Rosenkranz JA, Grace AA. Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. *J Neurosci.* 2002;22:324.
- Lucas C, Zhang H, Fisher P, *et al.* The DISC Predictive Scales (DPS): efficiently screening for diagnoses. *J Am Acad Child Adolesc Psychiatry.* 2001;40:443-449.
- Shaffer D, Schwab-Stone M, Fisher P, *et al.* The Diagnostic Interview Schedule for Children—Revised version (DISC-R): I. Preparation, field testing, interrater reliability, and acceptability. *J Am Acad Child Adolesc Psychiatry.* 1993;32:643-650.
- Conners C, Sitarenios G, Parker J, Epstein J. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol.* 1998;26:257-268.
- Achenbach TM, Rescorla LA. *Manual for ASEBA School-Age Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.
- Wechsler D. *Wechsler Abbreviated Scale of Intelligence.* San Antonio, TX: Psychological Corporation; 1999.
- Oldfield R. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* 1971;9:97-113.
- Hollingshead A. *Four Factor Index of Social Status [thesis].* New Haven, CT: Yale University; 1975.
- Kovacs M. *The Children's Depression Inventory (CDI).* Psychopharmacol Bull. 1985;21:995-998.
- Spielberger C, Gorsuch R. *STAI Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press; 1970.
- Petersen A, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: reliability, validity, and initial norms. *J Youth Adolesc.* 1988;17:117-133.
- Tottenham N, Borscheid A, Ellertsen K, Marcus D, Nelson C. Categorization of Facial Expressions in Children and Adults: Establishing a Larger Stimulus Set. *Cognitive Neuroscience Society Annual Meeting, San Francisco, CA, April 2002.*
- Friston KJ, Ashburner CD, Frith JB, Poline JB, Heather RS, Frackowiak RS. Spatial registration and normalization of images. *Hum Brain Mapping.* 1995;3:165-189.
- Mechelli A, Price C, Noppeney U, Friston K. A dynamic causal modeling study on category effects: bottom-up or top-down mediation? *J Cogn Neurosci.* 2003;15:925-934.
- Stephan K, Weiskopf N, Drysdale P, Robinson P, Friston K. Comparing hemodynamic models with DCM. *NeuroImage.* 2007;38:387-401.
- Friston K. Causal modelling and brain connectivity in functional magnetic resonance imaging. *PLoS Biol.* 2009;7:e1000033.
- Cox R. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996;29:162-173.
- Findling R, Ginsberg L, Jain R, Gao J. Effectiveness, safety, and tolerability of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder: an open-label, dose-optimization study. *J Child Adolesc Psychopharmacol.* 2009;19:649-662.
- Volkow N, Wang G, Newcorn J, *et al.* Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch General Psychiatry.* 2007;64:932.
- Almeida J, Versace A, Mechelli A, *et al.* Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol Psychiatry.* 2009;66:451-459.
- Quirk G, Beer J. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Curr Opin Neurobiol.* 2006;16:723-727.
- Kringelbach M, Rolls E. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol.* 2004;72:341-372.
- Barkley R. *ADHD and the Nature of Self-Control.* New York: Guilford Press; 1997.

## SUPPLEMENT 1

### Subject Instructions for the Functional Magnetic Resonance Imaging (fMRI) Task and Post-Scanning Questionnaire

Subjects were given the following instructions for the fMRI task:

*You will be shown several faces. Please look at the faces and try to remember them. After the MRI scan, you will be asked about the faces that you remember seeing.*

After the MRI scan, we asked subjects to identify the faces that they recalled seeing. They were shown a sample of the faces presented (six neutral faces and six fearful faces). They were asked to circle the faces that they recalled seeing. We instructed the subjects to circle the face if they remembered seeing both 1) the person and 2) that person's facial expression.

### Faces Used for the fMRI Task

We selected 15 faces from the NimStim sample to use in the fMRI task. The characteristics of the faces are provided in [Table S1](#), available online.

### Head Motion During Scanning

We calculated the root mean square (RMS) values of the adjustments needed to realign each subject's head position into the position that it was in at the beginning of each scanning run. Only runs with less than 2 mm RMS of motion were used in these analyses. Greater motion was detected in unmedicated ADHD subjects as compared with control subjects; however, after correcting for multiple comparisons, this was not statistically significant. To control for this trend of greater motion in the unmedicated ADHD participants, we incorporated into each subject's linear model six nuisance regressors reflecting motion parameters in three translational directions and rotations. The motion across the three groups was as follows: mean RMS values for controls: 0.37 mm; medicated ADHD subjects: 0.48 mm; and unmedicated ADHD subjects: 0.61 mm; comparison of controls and medicated ADHD subjects:  $p = .24$ ; comparison of controls and unmedicated ADHD subjects:  $p = .05$ ; comparison of medicated versus unmedicated ADHD subjects:  $p = .13$ .

Each of the three groups (unmedicated ADHD participants, medicated ADHD participants, and control subjects) consisted of 15 subjects, with

each subject completing two runs of the fMRI task for total of 30 runs per group. The numbers of runs excluded because of excessive motion, for each group were as follows:

1. unmedicated ADHD participants: three runs excluded (two runs from one subject and one run from a second subject).
2. medicated ADHD participants: one run excluded.
3. and control subjects: four runs excluded (two runs from one subject and two runs from another subject).

Based on the following nonparametric tests, we found no evidence to suggest that the three groups differed in terms of the number of scans excluded because of excessive motion: ADHD unmedicated versus ADHD medicated:

1. related-samples Wilcoxon signed ranks test,  $p = .3$ .
2. ADHD unmedicated participants versus controls: independent-samples Kruskal–Wallis test,  $p = .9$ .
3. and ADHD medicated participants versus controls: independent-samples Kruskal–Wallis test,  $p = .5$ .

### fMRI Activation Analyses—Without Covarying for Depressive and Anxiety Symptoms

We initially conducted group-level analyses by entering contrast images from the subject-level analyses into factorial models that included covariates for depressive and anxiety symptoms. The results indicated that right amygdalar activation was greater in unmedicated ADHD subjects as compared with controls ( $t = 3.64$ ;  $p = .001$ ). We repeated these analyses without covarying for depressive and anxiety symptoms to determine whether these covariates removed important variance from the analysis. The results were only nominally different. Right amygdalar activation remained greater in the unmedicated ADHD subjects as compared with controls, although the  $\alpha$  level changed slightly ( $t = 3.00$ ;  $p = .004$ ). We suspect that including depressive and anxiety symptoms as covariates had little impact on the results because the ADHD subjects and controls differed minimally on anxiety and depression measures.

### Habituation Analysis

Each subject completed two runs of the fMRI task. We reasoned that if habituation were occur-

**TABLE S1** Characteristics of the Faces Used in the Functional Magnetic Resonance Imaging Task

Gender	Race/Ethnicity	Position <sup>a</sup>
Female (n = 8)	White (n = 9)	Mouth open (n = 8)
Male (n = 7)	Asian (n = 2)	Mouth closed (n = 7)
	African American (n = 4)	

Note: <sup>a</sup>The neutral and fearful faces were matched according to the mouth position.

ring, amygdalar activation for the contrast of subliminal fearful face blocks versus neutral face blocks would be greater in run 1 versus run 2. Therefore, we generated for each subject, a contrast image that compared: run 1 versus run 2 based on the contrast of subliminal fearful face blocks versus neutral face blocks. These contrast images were then entered into group level analyses. In this analysis, greater amygdalar activation in run 1 versus run 2 would suggest habituation. Conversely, if amygdalar activation did not differ significantly between run 1 and run 2, habituation would be unlikely. We found no evidence for habituation in the unmedicated ADHD subjects ( $p = .3$ ), medicated ADHD subjects ( $p = .06$ ), or control subjects ( $p = .4$ ).

**TABLE S2** Faces Recalled During the Post-Scanning Questionnaire

Subject Group	Faces Recalled (%) <sup>a</sup>	
	Neutral Faces	Subliminal Fearful Faces
Unmedicated ADHD subjects	71	7
Medicated ADHD subjects	80	7
Healthy controls	83	9

Note: ADHD = attention-deficit/hyperactivity disorder.  
<sup>a</sup>For each group, the number of faces recalled as percentage of the total number of faces presented during the post-scanning questionnaire.

**TABLE S3** Group Comparisons of the Number of Faces Recalled During the Post-Scanning Questionnaire Administration

Comparison	Neutral Faces Recalled		Subliminal Fearful Faces Recalled	
	Test Statistic	<i>p</i> Value	Test Statistic	<i>p</i> Value
Controls vs. unmedicated ADHD subjects	<i>t</i> = 1.7	.1	<i>t</i> = 0.4	.7
Controls vs. medicated ADHD subjects	<i>t</i> = 0.4	.7	<i>t</i> = 0.4	.7
Unmedicated vs. medicated ADHD subjects	Paired <i>t</i> = 1.7	.1	Paired <i>t</i> = 0	1.0

*Note:* No group differences were detected in the number of faces recalled during the post-scanning questionnaire. ADHD = attention-deficit/hyperactivity disorder.