Hyperactivation in Cognitive Control and Visual Attention Brain Regions During Emotional Interference in Adolescent Depression

Natalie L. Colich, Tiffany C. Ho, Lara C. Foland-Ross, Caitlin Eggleston, Sarah J. Ordaz, Manpreet K. Singh, and Ian H. Gotlib

ABSTRACT

BACKGROUND: Individuals with major depressive disorder (MDD) are characterized by biases in attention to negative emotional material. While there is evidence that anomalous functioning in frontocingulate regions may underlie these biases, we know little about the neural correlates of negative emotional biases in depressed adolescents.

METHODS: Eighteen adolescents diagnosed with MDD and 21 matched healthy control adolescents underwent functional magnetic resonance imaging while performing an emotional distractor task. In each trial participants were presented with task-relevant house pairs and task-irrelevant face pairs. Participants indicated whether the house pairs were identical while ignoring the face pairs, which were fearful, sad, or neutral.

RESULTS: Despite equivalent behavioral performance (response time and accuracy) between groups, adolescents with MDD exhibited greater activation in frontocingulate regions, including the dorsal anterior cingulate cortex and inferior frontal gyrus/middle frontal gyrus, and occipitoparietal regions, including the lateral occipital cortex and superior parietal lobule, when ignoring fearful versus neutral faces. Response times to these trial conditions also correlated negatively with activation in inferior frontal gyrus/middle frontal gyrus and lateral occipital cortex, suggesting that these regions are recruited to effectively ignore emotional distractors. Groups did not differ when ignoring sad versus neutral faces or fearful versus sad faces.

CONCLUSIONS: Adolescents with MDD recruit both cognitive control and visual attention regions to a greater degree than do control adolescents, reflecting greater cognitive demand when downregulating threat-related stimuli.

Keywords: Adolescence, Anterior cingulate cortex, Depression, Executive function, Occipital cortex, Selective attention

http://dx.doi.org/10.1016/j.bpsc.2016.09.001

Major depressive disorder (MDD) is the leading cause of disability among adolescents (1). Moreover, adolescent-onset MDD is highly recurrent: 40% of depressed adolescents have a subsequent episode of depression within 3 years, and 50% experience recurrent episodes throughout adulthood (2–4). These high relapse rates highlight the inadequacy of current treatments for adolescent depression, arguably due in part to our lack of knowledge about brain function in adolescent MDD (5,6). Thus, it is critical that we examine neural mechanisms that underlie depression in adolescence and develop treatments based on models of adolescent, rather than adult, MDD.

Investigators have posited that biases in attention to and memory for negative stimuli contribute to the onset of depression (7,8). Attentional biases may be due to the increased salience of negative stimuli for depressed individuals, or to difficulties in inhibiting the processing of, or disengaging from, negative information (8). Consistent with these formulations, depressed adolescents have been found to exhibit specific impairments in performing cognitive tasks in an emotional context. For example, depressed adolescents attend more to negative stimuli than to neutral or positive stimuli on a dot-probe task (9), and show greater interference when required to ignore negative information in an emotional n-back task (10). These behavioral studies indicate that depressed adolescents not only have difficulty disengaging from relevant negative information, but also are impaired in their ability to attend to nonemotional material in the presence of negatively valenced distractor, or task-irrelevant, stimuli.

The neural correlates underlying biased processing of emotional information, and in particular negative information, in the context of performing cognitive tasks in adolescent MDD are not well understood. Studies that have assessed depressed adults as they complete cognitive tasks with emotional stimuli indicate that anomalous recruitment of frontocingulate cognitive control regions, including the dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and dorsal anterior cingulate cortex (dACC), may underlie...
difficulties in the processing of emotionally salient stimuli (11). For example, Fales et al. (12) found that, compared with nondepressed control participants, depressed adults showed greater amygdala activity while attending to task-relevant neutral stimuli and ignoring negative distractors (fearful faces) than when ignoring neutral distractors (neutral faces). Moreover, only the nondepressed adults showed the predicted pattern of increased DLPFC recruitment when ignoring fearful faces. Similarly, when ignoring emotional distractors during an emotional oddball task, depressed adults showed attenuated recruitment of bilateral IFG, superior frontal gyrus, and middle frontal gyrus (MFG) relative to nondepressed control participants (13). Together, these findings support a neural model of adult depression in which greater activation of frontocingulate cognitive control regions (e.g., DLPFC, IFG, dACC) is needed to suppress hyperactive emotion generative regions (e.g., amygdala) to appropriately process cognitively demanding conflicting stimuli and to reallocate attention (14,15). However, this model has not been tested systematically in adolescent depression.

Although several researchers have examined the neural correlates of either emotion processing or cognitive inhibition in adolescent MDD (16–19), few investigators have assessed the interaction of these two processes in depressed adolescents. Given that the PFC and ACC regions continue to mature both structurally and functionally during adolescence (20,21), understanding their functioning in the context of the cognitive processing of emotional stimuli in adolescents is critical to our understanding of the development of early-onset MDD. To date, only one functional magnetic resonance imaging (fMRI) study has directly assessed cognitive inhibition during emotional processing in depressed adolescents (22). In that study, adolescents performed a go/no-go task with negatively and positively valenced primes (sad and happy faces, respectively) that were presented prior to the presentation of the go and no-go targets. Interestingly, compared with healthy control participants, depressed adolescents, despite equivalent task performance, showed reduced DLPFC and occipital cortex activation only to no-go targets that followed sad faces. Thus, while these findings indicate that DLPFC hypoactivation may underlie failed suppression of mood-congruent stimuli, it is not clear whether this result generalizes to other forms of negative stimuli. In particular, fearful faces, as a proxy for threat, have been shown to elicit negative emotional processing biases (23) and have also been used to probe amygdala hyperactivation in both depressed adolescents (24–26) and depressed adults (12,27). It is unclear whether the documented difficulties of depressed adolescents in inhibiting negative stimuli are due to heightened attention to sad stimuli, to threat-related stimuli, or to both types of stimuli. In examining this question, therefore, it is important to use a task that includes both mood-congruent (sad) and threat-related (fearful) emotional stimuli separately to elucidate the stimulus-specific nature of negative emotional biases in adolescent MDD and to test neural cognitive-emotion models of adult MDD, most of which have been formulated on the basis of findings with fearful face stimuli, in adolescents.

The present study was designed both to extend to adolescent depression previous findings obtained with depressed adults, suggesting that frontocingulate dysfunction underlies difficulties disengaging from negative emotional stimuli, and to elucidate the involvement of mood-congruent (sad) and threat-related (fearful) stimuli in this processing bias. Specifically, we examined the neural correlates of attention to task-relevant neutral stimuli in the presence of salient but irrelevant negative emotional (sad and fearful) and neutral distractors in depressed and nondepressed adolescents. We hypothesized that depressed adolescents would show greater interference when presented with sad and fearful face distractors than would healthy control adolescents, indexed by longer response latencies or decreased accuracy. We hypothesized further that adolescents with MDD would exhibit hypoactivation in frontocingulate regions known to be involved in cognitive control and conflict processing (e.g., DLPFC, IFG, dACC), and hyperactivation in brain regions implicated in negative emotion reactivity (e.g., amygdala) during successful inhibition of negative (sad and fearful face) distractors.

**METHODS AND MATERIALS**

**Participants**

Forty-six adolescents (ages 12–17 years) were recruited to participate in this study. Seven participants (3 MDD and 4 control [CTL] adolescents) were excluded from the analysis due to motion artifacts (1 MDD), failure to record behavioral responses (3 CTL adolescents), and poor behavioral performance (overall accuracy <50%; 2 MDD, 1 CTL adolescent). Thus, we report results from 39 participants (18 diagnosed with MDD [16 female participants]) and 21 CTL adolescents (16 female participants). The seven excluded participants did not differ from the 39 included participants with respect to age or symptom severity, as assessed by scores on the Children’s Depression Inventory (CDI) (28) (ps > .23). Nine of the CTL participants and 13 of the MDD participants also completed an additional fMRI task, as described in Colich et al. (22). The order of fMRI tasks was counterbalanced across all participants. MDD participants met DSM-IV (29) criteria for MDD and had CDI scores above the clinical threshold of 12 (30). Participants were recruited from the local community via media advertisements; depressed adolescents were also recruited through the Pediatric Mood Disorders Clinic at Stanford University. Participants were compensated for their participation. Exclusion criteria for all participants included 1) contraindications to scan (e.g., metal implants, braces); 2) history of major neurological disorder; and 3) any primary diagnosis other than MDD, including diagnoses of bipolar disorder, schizophrenia, or attention-deficit/hyperactivity disorder. For CTL adolescents, exclusion criteria also included any past or current Axis I disorder. MDD participants who were taking psychotropic medications were instructed to continue their normal medication regimen throughout their participation in this study. This study was approved by Stanford University’s Institutional Review Board, and informed written consent and assent was obtained from parent and child.

**Clinical Assessment**

At the first laboratory session, adolescents and the accompanying parent were administered the Kiddie Schedule for Affective Disorders and Schizophrenia (31) to confirm diagnosis of MDD in the MDD group and to rule out any past or
current Axis I disorder in the CTL group. This interview was also used to assess present or lifetime Axis I disorder in all participants. All interviews were conducted by research staff that had established excellent symptom and diagnostic reliability ($k > 0.9$). Final diagnostic decisions were made by a board-certified child and adolescent psychiatrist (MKS). In addition, all adolescents completed the CDI (28), a self-report measure of depressive symptoms; the State Trait Anxiety Inventory (32), a self-report measure of trait anxiety; and the Tanner Staging questionnaire (33,34), a self-report measure of pubertal status.

**Neuroimaging Data Acquisition**
Details concerning data acquisition are presented in the Supplement.

**fMRI Task Design**
We used a modified version of an emotional distractor task (35) that has been used in previous studies of depression and anxiety (12,36). In this modified task, participants saw four images presented around a fixation cross: one pair of images (houses or faces) presented on a vertical plane and the other pair (faces or houses) presented horizontally. Participants were instructed to make judgments only about whether the two houses presented on each trial were identical (they were identical on half of the trials, and were presented on either the horizontal or vertical plane on half of the trials). The face pairs were task distractors and the faces in each pair were neutral, sad, or fearful. Further task design details are presented in the Supplement.

**fMRI Data Analysis**
A whole-brain voxelwise general linear model analysis was conducted for each participant for each run, including regressors for each emotion distractor valence (neutral, sad, fearful) for trials on which the participant responded correctly, and a regressor for the inaccurate trials to remove these trials from the implicit baseline. Within-group and between-group Z statistical images were thresholded at $Z > 2.3$ with a cluster probability of $p < .05$, corrected for whole-brain multiple comparisons using Gaussian random field theory. In contrast to previous studies that have used this task (12,35,36), we assessed only correct trials and conducted whole-brain analyses to be able to identify activation in neural regions that are necessary for the successful inhibition of emotional face distractors. Details concerning data preprocessing and additional data analysis details are presented in the Supplement.

**RESULTS**

**Participant Characteristics**
Demographic and clinical characteristics of the MDD and CTL groups are presented in Table 1. The two groups did not differ in age, gender, pubertal stage, or ethnicity ($p > .1$). As expected, the MDD group had significantly higher CDI and State-Trait Anxiety Inventory scores than did the CTL group ($p < .001$). Half of the MDD participants had a comorbid anxiety disorder, and half were taking psychotropic medications at the time of the scan (seven of the nine individuals with comorbid anxiety were taking psychotropic medications; for details about specific medications and anxiety disorder diagnoses see Supplemental Tables S1 and S2). Importantly, there were no significant differences between the comorbid and noncomorbid, or between the medicated and unmedicated, MDD participants with respect to either the behavioral or the neural data (all $t < 1.768$, all $p > .096$). In the Supplement we present means and SDs for participants with and without medications, and with and without comorbid anxiety diagnoses, and the statistics associated with the $t$-test comparisons between the medication and comorbidity subgroups (Supplemental Tables S3 and S4).

**Behavioral Data**
Results for task accuracy and response time are presented in the Supplement.

**fMRI Data**
In the main text we present only between-group comparisons; we present all within-group comparisons in the Supplement.

Sad Versus Neutral Distractors. To examine group differences in neural regions involved in ignoring task-irrelevant sad versus neutral faces, we conducted a whole-brain analysis of variance (Group [MDD, CTL] repeated over Distractor Valence [sad, neutral]). This voxelwise analysis of variance (ANOVA) yielded no significant clusters.

Fearful Versus Neutral Distractors. To examine group differences in neural regions involved in ignoring task-irrelevant fearful versus neutral faces, we conducted a whole-brain ANOVA (Group [MDD, CTL] repeated over Distractor Valence [fearful, neutral]). This voxelwise ANOVA yielded a significant interaction of group and distractor valence in four large clusters: dACC, right IFG/MFG, left lateral occipital cortex, and right lateral occipital cortex/superior parietal lobule (SPL) (see Table 2 for peak coordinates and statistics). Follow-up $t$ tests were conducted to determine the

<table>
<thead>
<tr>
<th>Table 1. Demographic Information and Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, Years, Mean (SD)</strong></td>
</tr>
<tr>
<td>CTL ($n = 21$)</td>
</tr>
<tr>
<td>14.78 (1.36)</td>
</tr>
<tr>
<td><strong>Sex, Female, $n$</strong></td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td><strong>Tanner Stage, Mean (SD)</strong></td>
</tr>
<tr>
<td>4.1 (0.53)</td>
</tr>
<tr>
<td><strong>Caucasian (%)</strong></td>
</tr>
<tr>
<td>48</td>
</tr>
<tr>
<td><strong>CDI Total, Mean (SD)</strong></td>
</tr>
<tr>
<td>4.00 (6.04)</td>
</tr>
<tr>
<td><strong>STAI-T Total, Mean (SD)</strong></td>
</tr>
<tr>
<td>32.52 (8.30)</td>
</tr>
<tr>
<td><strong>Any Comorbid Anxiety Diagnosis, $n$</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td><strong>Psychotropic Medication Use, $n$</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

CDI, Children’s Depression Inventory; CTL, control participants; MDD, major depressive disorder participants; STAI-T, State-Trait Anxiety Inventory.
Table 2. Cluster Peaks for Significant Group (CTL, MDD) by Distractor Valence (Neutral, Fearful) Interaction

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>MNI Coordinates</th>
<th>Z Value</th>
<th>Voxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Lateral Occipital Cortex/Superior Parietal Lobule</td>
<td>34 -66 28</td>
<td>4.15</td>
<td>2273</td>
</tr>
<tr>
<td>R IFG/MFG</td>
<td>56 10 38</td>
<td>4.15</td>
<td>1786</td>
</tr>
<tr>
<td>L Lateral Occipital Cortex</td>
<td>-22 -66 30</td>
<td>4.44</td>
<td>1723</td>
</tr>
<tr>
<td>Anterior Cingulate Cortex</td>
<td>-10 38 20</td>
<td>3.70</td>
<td>1292</td>
</tr>
</tbody>
</table>

Coordinates represent voxels in each region with the most significant magnitude, identified at Z > 2.3, with a (corrected) cluster-significance threshold of p = .05. Voxel size is 3.4 x 3.4 x 4 mm.

DISCUSSION

This is the first study to use fMRI to directly examine cognitive inhibition in the context of processing both mood-congruent and threat-related stimuli in adolescents with MDD. Although both of these classes of stimuli have been implicated in adult models of MDD, our findings suggest that downregulating threat-related stimuli (i.e., fearful faces) evoked greater neural challenge than did regulating mood-congruent stimuli in brain regions related to cognitive control and visual attention in adolescents with MDD. Despite equivalent behavioral performance (response times and accuracy) between groups, depressed adolescents showed greater activation in frontocingulate cognitive control regions, including the IFG/MFG and dACC, and occipitoparietal regions involved in visual attention, including bilateral lateral occipital cortices and right SPL, when ignoring fearful versus neutral distractors (Figure 1). However, surprisingly, when separating neural activation for fear neutral distractor trials from activation for neutral distractor trials, we found that interaction of group and valence was driven by fear relative to neutral distractors within the MDD group. Further, the only group differences were in the neutral condition, in which CTL adolescents showed greater activation in dACC and right SPL than did the MDD adolescents. Our results build on earlier work concerning the role of frontocingulate dysfunction in cognitive-emotional models of MDD, suggest refinements of these models to include occipitoparietal attention regions, and highlight important directions for future work.

In the present study, depressed adolescents exhibited hyperactivation in the dACC, IFG, and MFG when ignoring fearful relative to neutral distractors compared with healthy CTL adolescents (Figure 1). Whereas dACC activity has been found to be associated with conflict monitoring, attention allocation, and the integration of task-relevant information (37,38), recruitment of IFG/MFG is associated more strongly with cognitive control (20). Our finding of greater recruitment of these regions for depressed adolescents in the presence of fearful relative to neutral distractors suggests that, compared with their nondepressed peers, depressed adolescents experience heightened conflict monitoring and attentional demands when attempting to ignore irrelevant yet salient face distractors, and a greater need for sustained attention to the task-relevant stimuli to achieve equivalent levels of behavioral performance. Moreover, our results are consistent with patterns of increased ACC activation in depressed adults relative to healthy control participants when successfully inhibiting negative word distractors (39), suggesting heightened conflict monitoring in both depressed adults and adolescents. However, there are discrepancies between hyper- and hyporecruitment of cognitive control regions in MDD in studies of both adult and adolescent MDD (19,40). Interestingly, whereas we found hyperactivity in IFG/MFG in MDD participants when they ignored task-irrelevant fearful faces, we previously found hydropactivity in DLPFC in an overlapping sample of MDD adolescents when they were primed with sad and happy faces before performing a less cognitively demanding response inhibition task (22). Together, these findings point to nuanced functional differences among prefrontal regions that may be sensitive to task demands, with hypoactive DLPFC reflecting response inhibition deficits (41) and hyperactive IFG/MFG reflecting the need for more cognitive resources in depressed adolescents.

Featual Versus Sad Distractors. Using a whole-brain 2 (Group [MDD, CTL]) x 2 (Distractor Valence [fear, sad; sad, fear]) ANOVA, we examined group differences in neural regions involved in ignoring task-irrelevant fear versus sad faces. These voxelwise ANOVAs yielded no significant clusters.

Correlation of Neural Activation With Task Performance. There was no significant relation across or within groups between task accuracy and parameter estimates in any significant activation cluster. However, in contrast, analyses of response time yielded similar findings for both fearful and neutral distractor faces: for all participants, greater recruitment of the IFG/MFG and bilateral lateral occipital clusters while ignoring these irrelevant stimuli was associated with a faster response to indicate whether the two houses on each trial were identical (see Table 3). There was no association between response times and parameter estimates for dACC activation for either valence of the task-irrelevant face stimuli.

Correlation of Neural Activation With Depression/Anxiety Symptoms. None of the correlations between levels of neural activation in regions that showed within- or between-groups differences during successful ignoring of fearful versus neutral face distractors and symptoms of depression and anxiety was statistically significant. The results of these analyses are presented in the Supplement.
Figure 1. A group (major depressive disorder [MDD], control adolescents [CTL]) × distractor valence (fearful, neutral) analysis of variance yielded greater activation in four clusters encompassing dorsal anterior cingulate cortex (dACC), left (L) middle frontal gyrus/inferior frontal gyrus (MFG/IFG), left lateral occipital gyrus, and right (R) lateral occipital gyrus/superior parietal lobule (SPL) during successful ignore fearful relative to ignore neutral trials in the MDD group relative to the CTL group. Activation maps (left) are thresholded at $Z > 2.3$ and corrected for multiple comparisons using a cluster-based $p < .05$. Montreal Neurological Institute coordinates are indicated for slice distance (in mm). Parameter estimates (showing the amount of signal change measured in arbitrary units) of blood oxygen level-dependent signal response were extracted from each significant cluster and plotted in the bar graph. We present the parameter estimates for the contrast of ignore fear > ignore neutral for each region of interest to be consistent with previous studies that have used a similar task. We also present the parameter estimates for ignore fear and ignore neutral conditions separately for each region of interest. *$p < .05$, **$p < .01$. 

Hyperactivation in Cognitive and Visual Regions in MDD
Contrary to our predictions, we did not find group differences in the amygdala or other regions involved in emotion generation in either the task-irrelevant sad or fearful conditions, compared with the task-irrelevant neutral condition. The processing of emotional faces activates brain regions at multiple levels of information processing, including not only limbic structures such as the amygdala, but also visual areas related to stimulus processing and attention, including occipital and parietal regions involved early in the processing stream (42–44). In our study, depressed adolescents exhibited heightened recruitment of the lateral occipital cortex and SPL, suggesting that depressed adolescents exhibit greater interference in the presence of threat-related stimuli and, consequently, require greater neural recruitment of these regions to disengage from task-irrelevant stimuli. Importantly, recent work with both adults and adolescents with MDD has highlighted functional abnormalities in regions related to visual processing and attention during emotional face processing. The documentation of direct white matter projections between frontal and occipital regions in humans (49) further indicates that regions and connections may be important to study in MDD. Thus, our results suggest that models of MDD-related cognitive biases for negative material should incorporate not only frontocingulate cognitive control regions, but also their interactions with occipitoparietal visual attention regions.

Our interpretations of greater recruitment in cognitive control and visual attention regions during successful inhibition of salient negative emotional distractors relative to neutral distractors in adolescent MDD are further supported by significant correlations between neural activation in IFG/MFG and bilateral lateral occipital cortices and response times during the neutral and fear conditions. Given the strong negative correlations between activations in these regions and response times, it is likely that these regions facilitate attention to task-relevant stimuli (houses), as opposed to task-irrelevant stimuli (distracting faces). However, importantly, the lack of a significant association between recruitment of dACC and response times during these task conditions suggests a different function of the dACC. In this context, it is possible that dACC recruitment reflects conflict monitoring and the integration of task information, and thus plays a role in allocating resources according to task demands (50).

We found neither behavioral nor neural within- or between-group differences in the sad versus neutral face distractor contrast. However, it is important to note that the stimuli were presented for only 250 ms. Thus, our findings are consistent with previous work demonstrating that biases toward depressogenic stimuli occur only when stimuli are presented for longer durations (typically greater than 1000 ms) (23,51); in contrast, biases toward threat-related stimuli typically occur when stimuli are presented for shorter durations (typically 500 ms or less) (52). Therefore, it is possible that we would have found greater interference for sad distractors in the MDD group if we had used longer durations for stimulus presentation. Of course, altering the task design in this way would have changed the cognitive demands of the task and would likely have resulted in ceiling-level performance for both groups, eliminating significant group differences in neural regions underlying attentional and cognitive control processes.

Similarly, it is important to raise the issue of possible differences in levels of arousal between fear and sad face stimuli. Prior research using the same stimuli suggests that fearful and sad faces are equivalent in terms of valence, but that fearful faces are more arousing than sad faces (63,54). Further, there is evidence that arousal levels influence attention or perception (55). Thus, it is possible that fearful faces evoke higher levels of arousal in the depressed participants and that the differences in neural activation between ignoring fear and ignoring sad distractors relative to neutral distractors are due to differences in arousal level. As a related point, highly arousing positively valenced faces may elicit similar effects as fearful faces, which is consistent with our previous finding of hypoactivation in the DLPFC to sad face relative to happy face primes (22). Unfortunately, we did not obtain valence and arousal ratings from our participants, nor did we include positively valenced faces in this task. Future studies should obtain ratings of valence and arousal for all stimuli to examine whether neutral patterns are attributable to valence or arousal, or to depression-related effects on cognitive control and attention to negatively valenced stimuli.

It is noteworthy that the different patterns of neural activation exhibited by the MDD and CTL participants when ignoring fearful versus neutral distractors are consistent with previous reports of differences in selective attention to threat-related stimuli in adolescents and adults with anxiety and comorbid anxiety/depression, but not in adolescents/adults with pure depression (9,56). Although half of our depressed adolescent participants had a comorbid anxiety disorder, our findings did not differ as a function of this comorbidity (Supplemental Table S3). Furthermore, the rate of comorbid anxiety disorders in our depressed sample is similar to the rate at which adolescent depression presents with comorbid anxiety in the general community (60%) (57,58). Our depressed adolescent sample thus reflects the distribution of anxiety disorders in the population of adolescents with depression typically seen in outpatient clinics, strengthening the generalizability of our results. Nevertheless, it will be important in future research to recruit and assess the neural functioning of separate samples of adolescents with pure and comorbid MDD.

Finally, it is important to note that when examining neural activation for fear and neutral distractor trials separately, group differences were present in the neutral condition in which CTL adolescents showed greater activation in the dACC and right SPL when ignoring neutral distractors than did adolescents with MDD. Several studies have demonstrated that neutral facial expressions are not always processed as neutral (59),

### Table 3. RT-Parameter Estimate Correlations

<table>
<thead>
<tr>
<th></th>
<th>dACC</th>
<th>L Lateral Occipital</th>
<th>R Lateral Occipital</th>
<th>R IFG/MFG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ignore Neutral RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>−.048</td>
<td>−.316^p</td>
<td>−.41^p</td>
<td>−.374^p</td>
</tr>
<tr>
<td>p value</td>
<td>.770</td>
<td>.050</td>
<td>.010</td>
<td>.019</td>
</tr>
<tr>
<td>Ignore Fearful RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>−.195</td>
<td>−.418^p</td>
<td>−.458^p</td>
<td>−.500^p</td>
</tr>
<tr>
<td>p value</td>
<td>.234</td>
<td>.008</td>
<td>.003</td>
<td>.001</td>
</tr>
</tbody>
</table>

dACC, dorsal anterior cingulate cortex; IFG/MFG, inferior frontal gyrus/middle frontal gyrus; L, left; R, right; RT, response time.

^p ≤ .05.

^p ≤ .01.
particularly in children (60–62), but also in clinical populations (63,64). However, these studies involve attending to emotional faces rather than actively avoiding emotional distractors. Thus, it may be that CTL adolescents require greater neural recruitment to inhibit processing of ambiguous neutral faces to accurately perform the task. It will be important in future studies that researchers consider whether neutral faces should be used to represent a neutral control condition.

Although this is the first study to carefully assess different negative stimuli to better understand the neural mechanisms underlying cognitive inhibition of emotional distractors, there are three primary limitations of this investigation. First, our sample size is relatively small, and we were underpowered to examine effects of comorbidity/medication on our findings. Second, half of our MDD participants were taking psychotropic medication. Although we found no significant differences in neural activation between the medicated and unmedicated adolescents (Supplemental Table S4), medication status may nevertheless have contributed to our findings (26,65). Third, given the high accuracy rates on our task, we did not have a sufficient number of error trials for each individual to analyze neural activations to incorrect responses. It is possible that hyper-recruitment of cognitive control regions underlies successful inhibition only of irrelevant stimuli, and that if our models included inaccurate trials, we would have found the opposite pattern. It will be important in future research to include more trials across all conditions to ensure that there will be a sufficient number of error trials to be included in the analyses.

Despite these limitations, this study documents aberrant function in frontocingulate and occipitoparietal regions underlying cognitive processing when depressed adolescents attempt to ignore distracting negative stimuli. These findings suggest heightened conflict monitoring and attentional demands when depressed adolescents successfully inhibit salient negative stimuli. These results are important in refining current neural models of adolescent MDD, including highlighting the role of visual attention regions along with cognitive control regions, and identifying neural processes that may contribute to negative cognitive biases in adolescent MDD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by a National Science Foundation Graduate Fellowship (to LNC); American Foundation for Suicide Prevention Grant No. PDF-1-064-13 (to TCH); National Institute of Mental Health Grant Nos. R01MH101545 (to IHG), F32MH09617 (to LCF-R), K01MH106805 (to SJO), and K23MH085919 and R01MH106581 (to MKS); the National Alliance for Research in Schizophrenia and Affective Disorders Distinguished Investigator Award to IHG and Young Investigator Awards to LCF-R and SJO; the Hope for Depression Research Foundation Award to IHG and Young Investigator Awards to LCF-R and SJO; and the Klingenstein Third Generation Foundation Fellowship Award to SJO.

We thank Maria Lemus for her assistance in scheduling and running the participants. We also thank the adolescents and their families who participated in our study. All authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychology (NLC, TCH, IHG) and Department of Psychiatry and Behavioral Sciences (LCF-R, SJO, MKS), Stanford University, Stanford; and the Department of Psychology (CE), University of California, Berkeley, California.

Address correspondence to Natalie Colich, B.A., Department of Psychology, Stanford University, Stanford, CA 94305; E-mail: ncolich@stanford.edu.

Received May 19, 2016; revised Aug 31, 2016; accepted Sep 6, 2016. Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.bpsc.2016.09.001.

REFERENCES

Hyperactivation in Cognitive and Visual Regions in MDD


