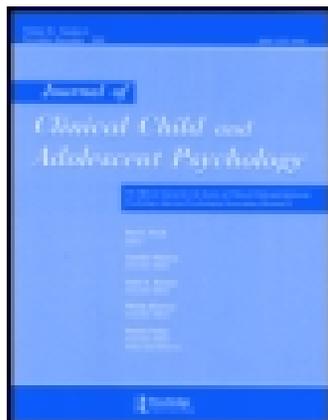


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Neural Aspects of Inhibition Following Emotional Primes in Depressed Adolescents

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Adults diagnosed with major depressive disorder (MDD) have been found to be characterized by selective attention to negative material and by impairments in their ability to disengage from, or inhibit the processing of, negative stimuli. Altered functioning in the frontal executive control network has been posited to underlie these deficits in cognitive functioning. We know little, however, about the neural underpinnings of inhibitory difficulties in depressed adolescents. We used functional magnetic resonance imaging in 18 adolescents diagnosed with MDD and 15 age- and gender-matched healthy controls (CTLs) while they performed a modified affective Go/No-Go task that was designed to measure inhibitory control in the presence of an emotional distractor. Participants were presented with either a happy or a sad face, followed by a go or a no-go target to which they either made or inhibited a motor response. A group (MDD, CTL) by valence (happy, sad) by condition (go, no-go) analysis of variance indicated that MDD adolescents showed attenuated BOLD response in the right dorsolateral prefrontal cortex (DLPFC) and in the occipital cortex bilaterally, to no-go targets that followed a sad, but not a happy, face. Adolescents diagnosed with MDD showed anomalous recruitment of prefrontal control regions during inhibition trials, suggesting depression-associated disruption in neural underpinnings of the inhibition of emotional distractors. Given that the DLPFC is associated with the maintenance of goal-relevant information, it is likely that sad faces differentially capture attention in adolescents with MDD and interfere with task demands requiring inhibition.

Individuals with major depressive disorder (MDD) consistently exhibit negative biases across a range of cognitive functioning, including attention, interpretation, and memory. These biases are posited to be directly involved in initiating or sustaining a depressive episode (Joormann & Gotlib, 2010; Joormann, Yoon, & Zetsche, 2007), and as such have been used as targets of treatment

for depression since Beck developed cognitive therapy in the 1960s (Beck, 1976). The mechanisms underlying these biases, however, are not well understood. One mechanism that may contribute to the selective attention to negatively valenced stimuli in depressed individuals is an impaired ability to inhibit the processing of negative material (Joormann, 2004; Joormann et al., 2007). Researchers have shown that depressed individuals exhibit increased interference from negative stimuli on the emotional Stroop task (Gotlib & McCann, 1984), have difficulty inhibiting the processing of negative stimuli on the negative affective priming task (Goeleven, Raedt,

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Baert, & Koster, 2006; Joormann & Gotlib, 2010), and are quicker to respond to sad targets in an affective Go/No-Go (GNG) task (Erickson et al., 2005; Murphy et al., 1999). Collectively, these findings suggest that the emotional nature of the stimuli used in these tasks—typically emotionally salient negative words or faces—disrupts inhibitory functioning in depressed individuals. That is, depressed individuals have difficulty disengaging from the processing of mood-congruent stimuli. This impairment in disengagement, a form of inhibitory dysfunction, is posited to lead to sustained attention to negative stimuli and to the high levels of rumination characteristic of MDD (Gotlib & Joormann, 2010).

Researchers have now begun to examine the neural correlates of impairments in the ability of depressed individuals to inhibit the processing of mood-congruent material. A number of studies have scanned depressed adults as they complete paradigms involving controlled processing of negatively valenced emotional materials. These tasks include the negative affective priming task (Eugène, Joormann, Cooney, Atlas, & Gotlib, 2010), the emotional Stroop task (Wagner et al., 2006), and the emotional GNG task (Elliott, Rubinsztein, Sahakian, & Dolan, 2002). The results of these studies suggest a neural model of inhibitory deficits in depression. Specifically, investigations have found depressed individuals to exhibit anomalous activation, compared to their nondepressed peers, in cognitive control regions, including the rostral anterior cingulate cortex, medial prefrontal cortex, inferior frontal gyrus, and the right dorsolateral prefrontal cortex (DLPFC; e.g., Eugène et al., 2010; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007; Wang et al., 2008). Thus, altered function in frontal executive control networks may underlie the pronounced behavioral deficits in inhibiting negatively valenced stimuli that have been documented in depressed individuals. Of importance, these neural regions are involved not only in inhibitory control but also in the regulation and reappraisal of negative emotion (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004), further supporting the formulation that deficits in the ability to inhibit negative emotionally salient material underlie the onset and maintenance of MDD (Joormann, 2010).

Much of our understanding of inhibitory deficits in MDD comes from studies of chronically depressed adults. It is not clear, however, whether these same patterns are present in younger individuals who are early in the course of the disorder. This question is particularly important given that the neural networks subserving inhibitory function and cognitive control continue to develop throughout adolescence (Casey et al., 1997; Eigsti et al., 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004). In particular, researchers have documented distinct behavioral and neural changes

throughout adolescence in individuals' ability to inhibit the processing of negative stimuli (Cohen-Gilbert & Thomas, 2013; Somerville, Hare, & Casey, 2011; Tottenham, Hare, & Casey, 2011). More specifically, behavioral studies have shown that younger adolescents experience greater interference from emotional distractors and exhibit greater difficulty inhibiting the processing of this material than do adults. Similar patterns have been reported in neuroimaging studies: compared with adults, adolescents show increased activation in subcortical, limbic regions and attenuated prefrontal activation during the processing of emotional distractors (Hare et al., 2008). These findings suggest that during adolescence there is relatively immature top-down control over more mature bottom-up emotional processing. It is unclear, however, how this imbalance is manifested in adolescents with depression.

Conducting neuroimaging investigations in depressed adolescents that use negatively valenced material in the context of a cognitive control task is critical to furthering our understanding of the interaction between a negative mood state and cognitive functioning in the developing brain. The GNG task is an ideal paradigm to use in such studies. This task requires participants to respond to a selected go target, presented more than 75% of the time, and to override the prepotent tendency to make a motor response when presented with the less frequent no-go target (Casey et al., 1997). Indeed, depressed and nondepressed adolescents differ behaviorally in their performance on an emotional version of the GNG task. For instance, Kyte, Goodyer, and Sahakian (2005) found that depressed adolescents showed enhanced attention to emotional stimuli, exhibiting fewer errors of commission when presented with no-go sad words. Similarly, Ladouceur et al. (2006) found that depressed adolescents were significantly faster at responding to sad face go trials than were both healthy controls and adolescents with anxiety, despite the absence of group differences in accuracy. In both studies, depressed adolescents failed to inhibit their responses to negative emotional stimuli. In a similar affective GNG task, Han et al. (2012) found that higher symptom severity in depressed adolescents was correlated with faster reaction time to affective targets, including happy, fearful, angry, and sad faces. The neural mechanisms that underlie this aberrant behavioral performance in depressed adolescents remain largely unknown. Elucidating these mechanisms can clarify whether negative attentional biases are due to dysfunctional inhibition of emotionally charged stimuli in the context of a protracted development of neural regions involved in attentional and inhibitory processes. Such findings may further help to explain why the onset of depression occurs most commonly during adolescence (Kessler, Avenevoli, & Ries Merikangas, 2001).

To date, only one study has examined the neural correlates of performance on a GNG task in depressed adolescents. In this study, which used affectively neutral stimuli, Pan et al. (2011) assessed the neural correlates of inhibitory control in adolescents who had attempted suicide, depressed adolescents with no history of attempted suicide, and healthy adolescent controls. Results of their investigation revealed that, compared to their nondepressed counterparts, nonsuicidal depressed adolescents had increased activation of the insula and the anterior cingulate cortex during both go- and no-go trials. Of importance, however, because this study used non-valenced stimuli, it is not clear how depressed and non-depressed teens differ in neural activation during the inhibition of emotionally salient material. Further, Pan et al. used a block design that did not permit them to separate accurate and inaccurate trials or, equally important, to conduct separate analyses of the go and no-go trials, which is critical to an assessment of inhibitory functioning.

No study has yet examined neural aspects of inhibitory processing during an emotional GNG task in adolescents who are experiencing a major depressive episode. Thus, in the present study, we used an emotion-modified GNG task to examine, in a sample of currently depressed adolescents, the neural correlates of difficulties in the inhibition of negatively valenced emotional material that have been documented in previous studies. In this modified GNG task, an emotional face (sad or happy) is presented before the go or no-go target (a circle or a square). By presenting the emotional stimuli prior to the go or no-go target stimulus, we could vary the presentation of the emotional stimulus and examine whether prolonged exposure to affective stimuli differentially influenced subsequent response inhibition within the same trial.

Based on previous findings of impaired inhibition of emotional content in depressed adolescents and adults (e.g., Kyte et al., 2005; Ladouceur et al., 2006), we predicted that depressed adolescents in the present study, compared with their nondepressed peers, will make more errors of commission in response to no-go targets that are preceded by a sad emotional face, reflecting impaired inhibitory processing due to the interference of negative stimuli. Similarly, based on previous findings of a mood-congruent attentional bias in depressed adolescents and adults (e.g., Gotlib, Krasnoperova, Yue, & Joormann, 2004; Williams, Watts, MacLeod, & Mathews, 1997), we also predicted that depressed adolescents will exhibit longer response latencies to go trials that are preceded by a sad facial expression. Finally, in terms of neural functioning, we predicted that depressed adolescents would be characterized by anomalous activation of prefrontal cortex during inhibition trials.

METHODS

Participants

Eighteen depressed (MDD; 15 female) and 15 healthy control (CTL; 10 female) adolescents, ages 12–17 years, participated in the study.¹ Participants in the depressed group met *Diagnostic and Statistical Manual* (4th ed., text rev.; American Psychological Association, 2000) criteria for MDD as their primary diagnosis. Depressed adolescents were recruited through the Pediatric Mood Disorders Clinic of an American academic department of psychiatry and from the local community; healthy controls were recruited from the surrounding community. Exclusion criteria for all participants included (a) nonfluent English speakers; (b) contraindications to scan (e.g., metal implants, braces, etc.); (c) history of major neurological disorder or illness; (d) a diagnosis of Bipolar I disorder, attention deficit hyperactive disorder, psychotic disorders or current alcohol/drug dependence; and (e) intellectual delay or learning difficulties. For the healthy controls, exclusion criteria also included any past or current Axis I disorder. All participants were offered hourly compensation for their participation in the study.

Procedure

Clinical assessment. All study participants completed both a parental consent and child assent to participate in the study. At the first laboratory session, adolescents and one parent were administered the Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997), a semistructured clinical interview used to confirm diagnosis in the MDD group and to rule out the possibility of Bipolar I disorder, ADHD, and/or drug or alcohol dependency in all participants. The Kiddie Schedule for Affective Disorders and Schizophrenia was also used to assess exclusionary criteria of a current or lifetime Axis I disorder in the control participants. These interviews were conducted by raters with established symptom and diagnostic reliability ($\kappa > 0.9$). Final diagnostic decisions were made by a board-certified child and adolescent psychiatrist (M.S.). In addition, all participants completed the Children's Depression Inventory (CDI; Kovacs, 1985), a self-report measure of depressive symptoms, Tanner staging (Marshall & Tanner, 1969, 1970) to assess self-report of pubertal status, and completed demographic questionnaires.

¹We originally recruited nine additional participants (four MDD and five CTL), but they were excluded from analysis due to motion artifacts, failure to record behavioral responses, or poor and outlying behavioral performance, resulting in a sample size for analysis of 18 MDD and 15 CTL participants.

Neuroimaging. Participants who met eligibility criteria returned for a second visit to complete a functional Magnetic Resonance Imaging (fMRI) scan. All scans were conducted on a 3 Tesla GE whole-body scanner (GE Healthcare Systems, Milwaukee, WI). Foam padding was used to minimize head movement. Twenty-nine axial slices were taken with 4-mm slice thickness. High-resolution T2-weighted fast spin-echo structural images (Repetition Time [TR]=3,000 ms, Echo Time [TE]=68 ms, ETL=12, Field of View [FOV]=22 cm, 192×256) were acquired for anatomical reference. A T2*-sensitive gradient echo spiral in/out pulse sequence was used for functional imaging (TR = 2,000 ms, TE = 30 ms, flip angle = 80° , FOV = 22 cm). An automated high-order shimming procedure, based on spiral acquisitions, was used to reduce B_0 inhomogeneity. Additional high-resolution images were acquired with an axial 3D FSPGR sequence for T1 contrast (140 slices, 1.3 mm thickness, TR = 6.0 ms, TE = 1.2 ms, TI = 500 ms, flip angle = 11° , FOV = 24 cm, 192×256).

Task. We used a modified affective GNG task to examine the neural correlates of inhibitory control (Figure 1). This task required participants to make a button press when they saw the visual go target (a blue circle) and to inhibit this response when they saw the infrequently presented no-go target (a blue square). The blue circle and blue square were not counterbalanced within or across participants, given that we did not expect that target shape would affect behavioral performance. The go target was presented 75% of the time, thereby creating a prepotent response tendency that must be inhibited in the presence of the no-go target.

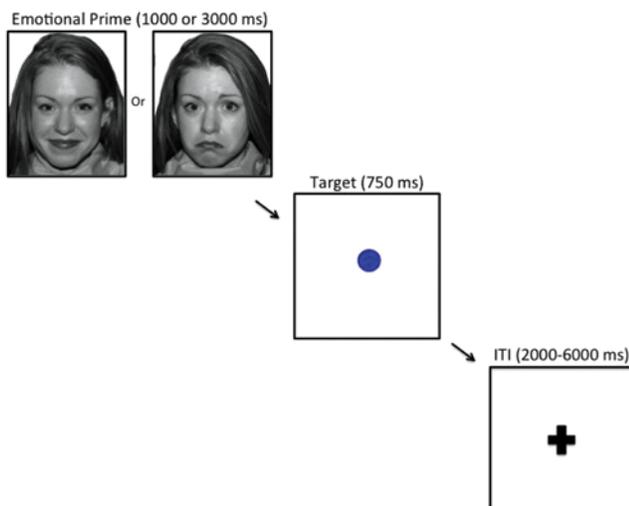


FIGURE 1 Experimental design. Participants are presented with a picture of a happy or sad face (prime), followed by a go or no-go target that indicates whether the participant should make a button response or inhibit a response. Intertrial intervals (ITIs) in the form of a variable-duration fixation cross separate each face-target trial.

To be able to assess whether inhibitory function was influenced by the presence of antecedent emotional stimuli, we modified the traditional GNG task by presenting either a happy or sad face picture (prime) immediately prior to the go or no-go target. The emotional face prime was presented for 1,000 ms (50% of the trials) or 3,000 ms (50% of the trials); to increase power, these two durations were collapsed for the behavioral and neural analyses. The go or no-go target that followed the emotional face prime for each trial was presented for 750 ms. Participants were instructed to make a response to the go target as quickly and accurately as possible and to not respond to the no-go target. Go responses were recorded by pressing a button on an MR-compatible button box in the scanner. All face and target pairs were interspersed with a fixation cross, which was pseudo-randomized to maximize the hemodynamic response function, and lasted 2,000, 4,000, or 6,000 ms. The order of presentation of the face-target pairs was counterbalanced across participants to minimize any possible order effects.

The novel design of this GNG task avoided important confounds not previously addressed in the literature. Specifically, in previous iterations of the emotional GNG task, emotional stimuli (typically faces) have served as response targets (e.g., Hare, Tottenham, Davidson, Glover, & Casey, 2005). This use of emotional stimuli as response targets implicitly requires that participants label the emotion in order to perform the task correctly. Of importance, however, such labeling has the potential to reduce the salience of the emotional expression (Hariri, Bookheimer, & Mazziotta, 2000; Lieberman, Hariri, Jarcho, Eisenberger, & Bookheimer, 2005), which may in turn decrease the interference experienced in this paradigm by depressed adolescents. Similarly, our task design allowed for the examination of the effect of prolonged emotional stimuli on inhibitory function. Our lab and others have shown that attention biases in depression are most strongly observed when emotional stimuli are presented for 1,000 ms or longer (Gotlib et al., 2004; Joormann & Gotlib, 2007). Thus, using the emotional stimuli prior to the target rather than as the target itself (presented for 750 ms) allowed us to present the emotional stimuli for longer durations in order to examine the effect of emotional stimuli on response inhibition.

The task was presented using E-Prime software Version 2.0. A total of 240 trials were divided across two emotion conditions (happy, sad) and two response conditions (go and no-go). The happy and sad emotional expressions were facial displays from the NimStim picture set (<http://www.macbrain.org/resources.htm>). Ten actors (five female, five male) were displayed showing happy or sad emotional expressions. We presented happy faces rather than neutral faces to the participants because previous researchers have found that neutral

faces can be interpreted as negative by children and adolescents (e.g., Tottenham, Phuong, Flannery, Gabard-Durnam, & Goff, 2013).

Imaging data analysis. Analyses were performed in FSL Version 4.1.6 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl), using FEAT (FMRI Expert Analysis Tool). The first four volumes of each participant's functional scan were discarded to allow for stabilization of longitudinal magnetization. The remaining images were preprocessed using a series of steps. Preprocessing included motion correction to the mean image using MCFLIRT (Motion Correction FMRIB's Linear Image Registration; Jenkinson, Bannister, Brady, & Smith, 2002), spatial smoothing (Gaussian kernel FWHM = 5 mm), and high-pass temporal filtering ($t > 0.01$ Hz; Woolrich, Ripley, Brady, & Smith, 2001). Functional data were linearly registered to a common stereotaxic space by first registering to the in-plane T2 image (6° of freedom) then to the MNI152 T1 2 mm brain (12° of freedom) (Jenkinson & Smith, 2001).

Statistical analysis was conducted using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL. A general linear model analysis was performed for each participant, including regressors for each face/target combination (happy/go, happy/no-go, sad/go, sad/no-go) that the participants correctly responded to, as well as two separate regressors for incorrect trials (go incorrect and no-go incorrect), for a total of six regressors. Motion correction parameters were included as covariates of noninterest. All four runs were combined in a fixed effects analysis for each participant, then combined in a higher level mixed effects model to investigate within and between-group differences. Higher level group analyses were conducted using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects State) Stage 1 and 2 (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Within-group Z statistical images for each condition were thresholded at $Z > 2.0$, corrected for multiple comparisons ($p < .05$).

RESULTS

Participant Characteristics

Demographic and clinical characteristics of the MDD and CTL participants are presented in Table 1. The two groups of participants did not differ in age, $t(31) = 0.59$; gender distribution, $\chi^2(1) = 1.24$; or pubertal stage, $t(30) = 0.85$, all $ps > .05$. As expected, adolescents in the MDD group had significantly higher CDI scores than did adolescents in the CTL group, $t(31) = 9.03$, $p < .01$. Eight of the 18 depressed participants had a comorbid

TABLE 1
Demographic Information and Clinical Characteristics

	CTL ^a	MDD ^b
Gender (% Female)	67	83
<i>M</i> Age	15.32 (1.49)	15.61 (1.51)
Tanner Stage	4.25 (0.58)	4.42 (0.52)
CDI Score	4.33 (3.64)	26.67 (8.04)
Comorbid Anxiety (<i>n</i>)	0	8
Psychotropic Medication Use (<i>n</i>)	0	7

Note: Standard deviations are presented in parentheses. CTL = control participants; MDD = depressed participants; CDI = Children's Depression Inventory.

^a*n* = 15.

^b*n* = 18.

anxiety disorder. Seven of the depressed participants were also taking psychotropic medication for depression at the time of the scan. Of importance, medicated and unmedicated depressed adolescents did not differ on any measure of behavioral response or BOLD signal; therefore, we did not include medication status as a covariate in our analyses.

Behavioral Data

Latency of go responses. Latencies of correct responses to go trials in the scanner were analyzed using a two-way (group [MDD, CTL] repeated over valence [happy, sad]) analysis of variance (ANOVA). Mean latencies are presented by group and valence in Table 2. The ANOVA did not yield a significant main effect of group, $F(1, 31) = 0.10$, $p = .76$, $\eta^2 = .003$, or a significant interaction of group and valence, $F(1, 31) = 1.84$, $p = .19$, $\eta^2 = .06$. There was, however, a main effect of valence, $F(1, 31) = 8.84$, $p < .01$, $\eta^2 = .22$, across both groups; participants were significantly faster to respond to targets following happy faces than following sad faces.

TABLE 2
Behavioral Performance on the Modified Affective Go/No-Go Task

	CTL ^a		MDD ^b	
	Happy	Sad	Happy	Sad
<i>M</i> Reaction Time (ms)	444.7 (41.8)	456.6 (39.8)	452.5 (33.1)	456.9 (39.3)
Go Accuracy (% Correct)	96.5 (5.2)	94.7 (5.9)	92.1 (7.2)	90.9 (7.2)
No-Go Accuracy (% Correct)	88.3 (12.2)	88.0 (10.1)	86.9 (10.7)	88.2 (10.5)

Note: Standard deviations are presented in parentheses. CTL = control participants; MDD = depressed participants.

^a*n* = 15.

^b*n* = 18.

Accuracy of go responses and no-go inhibitions. Percentage of correct responses to go and no-go targets for the MDD and CTL participants for the happy and sad conditions are also presented in Table 2. Two-way (group [MDD, CTL] repeated over valence [happy, sad]) ANOVAs conducted on the percentage of correct go responses did not yield a significant main effect of group, $F(1, 31) = 3.31, p = .08, \eta^2 = .10$, or a significant interaction of group and valence, $F(1, 31) = 0.25, p = .62, \eta^2 = .08$. There was, however, a significant main effect of valence, $F(1, 31) = 6.89, p = .01, \eta^2 = .18$: across both groups, participants were more accurate for go targets following happy faces than for go targets following sad faces. The ANOVA conducted on the percentage of correct inhibitions in the no-go condition did not yield significant main effects of group, $F(1, 31) = 0.03, p = .87, \eta^2 = .001$, or valence, $F(1, 31) = 0.12, p = .74, \eta^2 = .004$, or a significant interaction of group and valence, $F(1, 31) = 0.35, p = .56, \eta^2 = .01$.

Imaging Data

A Group (MDD, CTL) \times Valence (happy, sad) \times Condition (go, no-go) ANOVA was conducted using whole-brain data to isolate regions involved in cognitive control and to examine whether activation in these regions was modulated by group status and by the valence of emotional stimuli. This voxel-wise ANOVA yielded significant three-way interaction effects in two brain regions: a frontal cluster encompassing both the right inferior frontal gyrus and DLPFC (x, y, z coordinates of peak voxel: 60, 2, 26; centralized subpeak: 46, 42, 24; Brodmann's Area 6/9; Figure 2) and a cluster encompassing the occipital cortex (x, y, z coordinates

of peak voxel: 10, -66, 8; Brodmann's Area 18; Figure 3).

Given our focus in this study on inhibitory functioning, we conducted, within clusters arising from the three-way interaction of group, valence, and condition, follow-up analyses of no-go trials. Specifically, we examined Group \times Valence interactions. These analyses yielded a main effect of valence in the occipital cortex, $F(1, 31) = 6.43, p = .02, \eta^2 = .17$: both groups showed higher levels of activation in this region when inhibiting a no-go target that followed a sad face than when inhibiting a no-go target that followed a happy face. There was no comparable effect in the DLPFC, and no main effect of group in either region of interest.

The analyses also yielded a significant interaction of group and valence in the DLPFC, $F(1, 31) = 2.04, p = .01, \eta^2 = .06$. Decomposition of multifactor effects indicated that these interactions were due to differences between the MDD and CTL adolescents in neural activation during response inhibition to targets that varied as a function of valence. Specifically, whereas CTL adolescents showed similar levels of activation in the DLPFC while inhibiting a response following the presentation of happy and sad faces, $t(14) = 0.87, p > .05$, depressed adolescents showed less activation in the DLPFC while they were inhibiting a response to a no-go target that followed a sad face than to a no-go target that followed a happy face, $t(17) = 3.2, p < .01$.

Similar findings for the interaction of group and valence were obtained for no-go trials in the occipital cortex, $F(1, 31) = 6.15, p = .02, \eta^2 = .17$. Whereas CTL adolescents showed equivalent levels of activation in the occipital cortex while inhibiting responses to targets following the presentation of happy and sad faces,

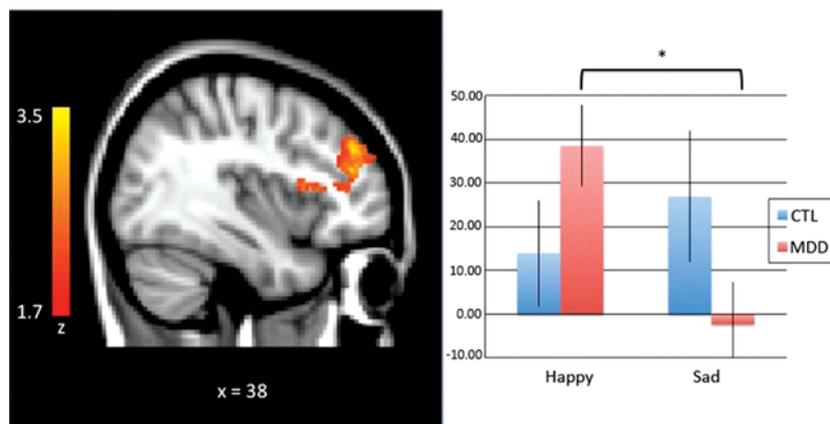


FIGURE 2 A Group (MDD, CTL) \times Valence (happy, sad) \times Condition (go, no-go) analysis of variance revealed decreased dorsolateral prefrontal cortex activation during sad face no-go target trials relative to happy face no-go target trials in the major depressive disorder (MDD) group; the control (CTL) group showed no such modulation based on emotion type. Activation maps (left) are thresholded at a $Z > 2.0$ 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 BOLD signal response were extracted from this functionally defined region of interest and plotted in the bar graph (right).

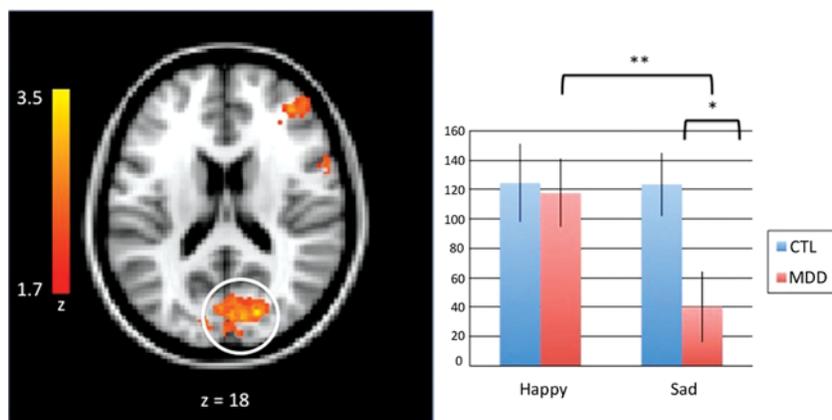


FIGURE 3 A Group (MDD, CTL) \times Valence (happy, sad) \times Condition (go, no-go) analysis of variance revealed decreased BOLD signal in the occipital cortex in response to sad face no-go target trials in the major depressive disorder major depressive disorder (MDD) group. Activation maps (left) are thresholded at a $Z > 2.0$ 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 BOLD signal response were extracted from this functionally defined region of interest in the occipital cortex (circled) and plotted in the bar graph (right). CTL = control.

$t(14) = 0.04$, $p > .05$, depressed adolescents showed less activation in this region during no-go targets that followed a sad face compared to no-go targets that followed a happy face, $t(17) = 3.38$, $p < .01$. In addition, depressed adolescents had significantly lower levels of activation in the occipital cortex than did CTL adolescents during no-go targets that followed the presentation of a sad face, $t(31) = 2.52$, $p < .05$; the two groups did not differ in levels of activation in the occipital cortex during inhibition of responses to targets that followed a happy face, $t(14) = 0.04$, $p > .05$.

DISCUSSION

The present study was designed to examine difficulties in response inhibition in the presence of emotional distractors in depressed adolescents. In this context, we assessed behavioral and neural aspects of inhibition following the presentation of happy and sad faces in carefully diagnosed depressed adolescents and in age- and gender-matched healthy controls. Depressed and nondepressed adolescents did not differ in their behavioral performance on the task. When we compared depressed and nondepressed adolescents' neural activation during no-go targets, however, we documented a mood-congruent distraction effect in the DLPFC. CTL participants showed equivalent levels of BOLD response to no-go targets that followed happy and sad faces; in contrast, depressed adolescents exhibited significantly less DLPFC activation when they were inhibiting a response following the presentation of a sad face than following the presentation of a happy face. We found a similar pattern of BOLD response in the occipital cortex. Specifically, the MDD adolescents exhibited less

activation in the occipital cortex than did the CTL adolescents in response to no-go targets that followed the presentation of a sad face; in contrast, the two groups did not differ in activation in this region in response to no-go targets that followed the presentation of a happy face. Thus, the depressed adolescents showed anomalous neural responses related to inhibitory functioning on trials involving the presentation of sad faces.

Previous experiments using the more traditional emotional GNG task, which involve making or inhibiting a response to an emotional target, have found mood-congruent behavioral facilitation effects in depressed adolescents (Erickson et al., 2005; Kyte et al., 2005; Ladouceur et al., 2006). Similar to Han et al.'s (2012) findings, however, we did not find this enhanced attention to negative stimuli in our behavioral data. In fact, several groups of investigators have failed to replicate behavioral results in the scanner, likely due to minor, but important, changes to task designs that are necessary to accommodate scanning environments (e.g., Rubia, Smith, Brammer, Toone, & Taylor, 2005; Seidman et al., 2006; Smith, Taylor, Brammer, Toone, & Rubia, 2006). We did, however, find differential neural activation in MDD adolescents in regions that are involved in executive function and inhibition, suggesting that neural underpinnings of task performance are more sensitive to group differences than are behavioral outcomes (Halari et al., 2009).

Differential recruitment of the DLPFC by the depressed and nondepressed adolescents in this study indicates that disrupted DLPFC functioning may contribute to the pathogenesis of MDD in both adolescents and adults. Our results add to existing literatures implicating a role for DLPFC dysfunction in depression. Investigators have previously reported dampened resting-state DLPFC responses in depressed adolescents

(Halari et al., 2009; Koenigs & Grafman, 2009), decreased DLPFC activation during cognitive information processing in depressed adults (Siegle et al., 2007), and increased DLPFC activation with greater symptom remission in depressed adults (Koenigs & Grafman, 2009). The DLPFC is a key node in the executive network of the brain and is posited to be specifically involved in guiding and maintaining attention toward task-relevant goals in the face of interference (Banich, 2009; Miller & Cohen, 2001; Munakata et al., 2011). Whether attenuated activation in the DLPFC in depressed adolescents is due to increased limbic activation to mood-congruent faces in the sad no-go trials, as has been proposed (Mayberg, 1997; Monk et al., 2008), is not clear because the design of our task prohibited the separation of the emotion and cognitive trial epochs. Nevertheless, the current study provides preliminary evidence in support of the possibility that the processing of mood-congruent sad faces interferes with subsequent cognitive control in depressed adolescents. Given findings indicating that depressed individuals experience difficulty disengaging from negative stimuli (Gotlib & Joormann, 2010), we suggest that in the current study, sad faces were especially salient for depressed adolescents and, as a result of increased processing of salient material, the depressed adolescents were less able than their nondepressed peers to effectively recruit the DLPFC during performance of the response inhibition epoch of each trial. Particularly relevant to the role of the DLPFC in the pathogenesis of MDD is its involvement in the regulation and reappraisal of negative emotions (Ochsner et al., 2002; Ochsner et al., 2004). Thus, dysfunction in this neural region may contribute to the deficits in emotion regulation that have been posited to characterize individuals with MDD (Joormann, 2010).

We also found depression-related differences in activation in the occipital cortex: Compared to the CTL adolescents, depressed adolescents showed a greater decrease in activation of this region during no-go trials that were preceded by a sad face. It is noteworthy that activation in this cluster extends from the striate cortex, which is associated with basic visual processing (Somers, Dale, Seiffert, & Tootell, 1999), and into the extrastriate cortices, which are associated with modulating basic visual processing (Haxby, Hoffman, & Gobbini, 2000). Although we did not predict this finding, ours is not the first study to report inhibition-related activation in the occipital cortex. For example, in a study of neural correlates of inhibition during a GNG task with a relatively large sample, Steele et al. (2013) suggested that activation in the occipital cortex, particularly within the cuneus/precuneus, during no-go conditions is due to decreased recruitment of the default mode network rather than to an inhibition-related increase in this region. In this context, therefore, to the extent that the

processing of a no-go target that follows a sad face is likely to be cognitively demanding, depressed adolescents may decrease their recruitment of task-irrelevant regions (e.g., extrastriate cortex) more so than do their nondepressed counterparts, a pattern that may reflect increased effort or attention to the task. Because we did not predict depression-related differences in neural recruitment of the occipital cortex, it is important in future research to replicate these findings and to delineate the role of the occipital cortex in the interaction of depression status, attention, and the processing of mood-congruent information.

We should note three limitations of this study. First, to distinguish neural response to go versus no-go targets, we used a rapid event-related design. Inherent in all event-related designs, however, is a randomized intertrial interval. Using an intertrial interval in the context of the current GNG task (ranging 2,000–6,000 ms) may have interfered with participants' initiation of a prepotent motor response by making it easier to inhibit a motor response following a no-go target. This decrease in task difficulty due to adaptation of the task to the scanner environment is supported by near-ceiling behavioral accuracy levels for both groups, which may be responsible for the lack of group differences in the behavioral measures in this study.

Second, nearly half of the depressed adolescents in this study were taking one or more psychotropic medications to treat their depression; the effects of these pharmacologic agents on brain function are largely unknown. Of importance, however, although the medicated adolescents obtained higher scores on the CDI than did their unmedicated counterparts (M medicated = 29.43 [7.79]; M unmedicated = 13.04 [11.86]), $t(31) = 3.81$, $p < .01$, these two groups of depressed adolescents did not differ on any dependent measure in this study, including response times, errors of omission/commission, and neural activation. Moreover, most of the adolescents who were taking psychotropic medication had limited lifetime exposure (M = only 5.2 months). Nevertheless, it will be important for future research to examine how different types of medications may alter hemodynamic response functions in depressed individuals in response to the demands of inhibition tasks.

Finally, we should note that we had only 33 participants in this study. Therefore, it will be important in future research to replicate these results and to continue to elucidate the effect of depression severity on inhibitory function in the presence of affective stimuli.

In conclusion, the present findings are important in documenting the role of impairment in DLPFC activation during inhibitory functioning in adolescents diagnosed with MDD. Future studies should extend this work to examine the extent to which affective material interferes with cognitive control processes in depressed

adolescents. Moreover, it will be important to examine prospectively how disruptions in these control processes may contribute to the onset and maintenance of depression and to recovery from this disorder. Findings from such research will have important implications for the development and evaluation of new interventions for MDD.

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