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

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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

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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