Neural Activation During Cognitive Emotion Regulation in Previously Depressed Compared to Healthy Children: Evidence of Specific Alterations

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Objective: Impairments in cognitive emotion regulation (CER) have been linked to functional neural abnormalities and the pathogenesis of major depressive disorder (MDD). Few functional magnetic resonance imaging (fMRI) studies have investigated the neural underpinnings of CER in samples with depression. As CER develops in childhood, understanding dysfunctional CER-related alterations in brain function during this period could advance knowledge of the developmental psychopathology of MDD.

Method: This study tested whether neural activity in brain regions known to support cognitive reappraisal differed between healthy 7- to 15-year-old children and same-age peers with a history of MDD (MDD-ever). A total of 64 children participated in this event-related fMRI study, which used a developmentally appropriate and validated fMRI reappraisal task. Children were instructed to passively view sad or neutral images and to decrease negative emotions using cognitive reappraisal.

Results: MDD-ever and healthy children showed similar patterns of cortical activation during reappraisal, but with a significant difference found in 1 key CER region, the left inferior frontal gyrus (IFG). In addition, individual differences in CER were associated with left IFG activity during reappraisal.

Conclusion: Alterations in the neurocircuitry of reappraisal are evident in children with a depression history compared to healthy controls. The finding that MDD-ever children showed reappraisal-related neural responses in many regions similar to healthy controls has clinical implications. Findings suggest that identification of alterations in reappraisal in children with remitted depression, for whom much, although not all, of the neural circuitry remains intact, may be an important window of opportunity for intervention.

Key Words: childhood depression, emotion regulation, cognitive reappraisal, fMRI, MDD

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Dysfunctional cognitive emotion regulation (CER) strategies have been linked to functional neural abnormalities as well as risk, course, and outcomes associated with major depressive disorder (MDD) in adults.[1-2] One CER strategy that has received the bulk of empirical focus is cognitive reappraisal.[3-4] By reinterpreting (i.e., reappraising) the affective meaning of emotion-eliciting situations, one may regulate and modify one's emotional responses to a distressing event. Neuroimaging studies examining patterns of neural activation during the use of reappraisal in healthy adults and those with depression are consistent with decades of cognitive-behavioral research on mechanisms (i.e., cognitive vulnerabilities for depression) and treatment (e.g., cognitive-behavioral therapy [CBT]) that implicate impaired CER processes in the etiology and course of MDD.[5] Related to these deficits, individuals at risk for MDD are more likely to process everyday life events as being negative, resulting in more experiences of negative mood, emotion, and affect.[6] When these cognitive vulnerabilities are paired with an inability to use adaptive CER strategies such as reappraisal, risk for MDD increases.[7] There are known associations between the infrequent and/or inefficient use of cognitive reappraisal tactics in relation to the development and course of MDD.[8] Nonetheless, functional magnetic resonance imaging (fMRI) studies investigating the neural underpinnings of reappraisal in children at risk for, currently diagnosed with, or in a remitted phase of depression are absent from the translational developmental neuroscience literature.

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Developmental Course of Emotion Regulation in the Context of Developing MDD

Developmentally informed research has established that depressotypic emotion regulation (ER) strategies are evident early in children's development.[9] Although ER strategies continue to evolve across the lifespan, strong correlations exist between cognitive-based ER strategies that develop and are practiced in late childhood and behavioral patterns of CER strategy used in later life.[10-17] That is, extant findings indicate that late childhood is a critical developmental period for acquiring adaptive CER strategies to self-regulate affective arousal.[18]

From a developmental affective neuroscience perspective, cortical (especially the prefrontal cortex [PFC]) brain regions that support the development of complex thought processes necessary for CER undergo significant changes in function as well as structure starting in early adolescence. In addition to normative neurodevelopment that occurs in adolescence, this is also the age at which individuals are most likely to be diagnosed with MDD. The dynamic interplay between pubertal changes, cognitive transitions, heightened social awareness, and maturing brain regions that support the use of CER may contribute aberrant trajectories of adolescent emotion development, which in turn may increase the risk of MDD episodes. Given that adolescence is a period of high risk for MDD, understanding dysfunction in CER processes and related alterations in brain function before and during this developmental period could have important implications for advancing our knowledge of risk and occurrence of MDD in adolescents. Using a previously validated approach,[19] the current study tested whether neural response in brain regions known to support the reappraisal of negative stimuli in adults differed between typically developing children aged 7 to 15 years and those with 1 or more past episodes of MDD.

Neural Circuitry of Cognitive Reappraisal in Healthy Adults

fMRI research conducted in healthy adults has informed our understanding of the source brain regions that provide the neural underpinning for implementing reappraisals as well as the target neural systems that are acted upon during reappraisal. Although fMRI studies of reappraisal have varied along a number of experimentally significant dimensions (distancing versus reappraising, stimuli valence, and regulatory direction; increase versus decrease emotion response), when results are taken as a whole, findings indicate that the implementation of reappraisal to modulate emotion responsivity is supported by many of the same frontoparietal and cognitive control regions that regulate memory, attention, and numerous other thought processes. The most commonly observed regions involved in implementing reappraisals (i.e., source regions) include but are not limited to the following: dorsolateral (dlPFC) and the inferior parietal cortex, when combined this is also known as the frontoparietal network. In the context of reappraisal, this network is thought to direct attention to reappraisal-relevant stimulus features, to hold in mind appraisal goals, and to manipulate information during the construction of new appraisals.[20] In addition, the dorsal anterior cingulate cortex (dACC) and posterior dorsomedial prefrontal cortex (dmPFC) regions, which, in the context of reappraisal, are thought to support the monitoring and tracking of the effectiveness of reappraisals;[21] and the ventrolateral PFC (vlPFC), which is thought to support goal-appropriate selection of a new reappraisal of the initial stimuli.[22] The left vlPFC is thought to be of particular importance in reappraisal paradigms that focus on reinterpretation tactics. The left vlPFC may be used to deliberately select semantic elements needed to construct a new stimulus-appropriate reappraisal and is involved in inner-speech processes.

These cortical regions and networks provide the neural substrates for using cognitive reappraisal effectively. Supporting evidence for the importance of these cortical brain regions has been found in several studies that indicate that increased neural activation in cortical brain regions while engaged in reappraisal correlates with effective modulation of self-reported emotional experience as well as other effectively modulated measures such as behavioral and physiological correlates of emotion responsivity. Given that reappraisal is associated with modulation of emotion experience, it should also modulate subcortical/limbic regions involved in the generation of emotion. Although results have been mixed, likely due to variation in methodological approach, the consensus remains that reappraisal modulates activity in subcortical structures associated with emotion generation.[23-24] Specifically, findings from healthy adults have shown that using reappraisal to down-regulate negative emotions after presentation of negative stimuli is associated with decreased neural activation in the amygdala,[4] ventral striatum, and, to a lesser extent, the ventromedial prefrontal cortex (vmPFC). These findings in healthy adults suggest that individuals who have difficulties with reappraisal, such as adults with depression, should show reduced activity in cortical regions, especially the vlPFC. Based on observations in healthy adults, it is also expected that adults with depression will show increased activation in emotion generation regions such as the amygdala, which may result from reduced modulation by cortical regions.

Reappraisal in Healthy Children

To date, few fMRI studies have examined neural activation during reappraisal in children and adolescent samples.[19,25-28] Results indicate that childhood development is associated with both linear and quadratic (inverted U-shaped) increases in activity in dorsal and lateral PFC regions. For instance, researchers have found a linear association between participants' age (i.e., 10–23) and reappraisal ability at both the neural and behavioral levels.[26] Specifically, activation in a portion of the left inferior frontal gyrus (IFG: also known as vlPFC) demonstrated a positive linear association with age. Increasing age was also associated with increased ratings of reappraisal successes during the fMRI task, which were both related to increased activation of the left IFG during reappraisal. The IFG may be especially relevant, given recent findings demonstrating that this region becomes more effective at supporting reappraisal with age. Although the strength of neural activation may differ between children and adults, findings suggest that children will show activation patterns in cortical and subcortical regions similar to those seen in healthy adults.

Although developmental affective neuroscience research specific to CER processes is in its infancy, 2 highlights have emerged from the existing literature. First, neurodevelopment within brain regions that support one's ability to regulate emotion are highly similar to what has been observed in studies of "cold" cognitive tasks. Second, improved capacities and efficacy of using CER strategies