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Functional and structural brain correlates of risk for major depression in children with familial depression

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ABSTRACT

Despite growing evidence for atypical amygdala function and structure in major depression, it remains uncertain as to whether these brain differences reflect the clinical state of depression or neurobiological traits that predispose individuals to major depression. We examined function and structure of the amygdala and associated areas in a group of unaffected children of depressed parents (at-risk group) and a group of children of parents without a history of major depression (control group). Compared to the control group, the at-risk group showed increased activation to fearful relative to neutral facial expressions in the amygdala and multiple cortical regions, and decreased activation to happy relative to neutral facial expressions in the anterior cingulate cortex and supramarginal gyrus. At-risk children also exhibited reduced amygdala volume. The extensive hyperactivation to negative facial expressions and hypoactivation to positive facial expressions in at-risk children are consistent with behavioral evidence that risk for major depression involves a bias to attend to negative information. These functional and structural brain differences between at-risk children and controls suggest that there are trait neurobiological underpinnings of risk for major depression.

1. Introduction

Neuroimaging studies have shown that patients with major depression display differences in the function and structure of brain regions involved in emotion identification and reactivity, including the amygdala, hippocampus, striatum, and orbitofrontal cortex, as well as areas involved in emotional regulation, such as dorsolateral prefrontal cortex and anterior cingulate cortex (Stuhrmann et al., 2011). It is unclear, however, whether these differences reflect the clinical state of major depression or neurobiological traits that predispose individuals to be at risk for major depression. Such neurobiological traits are important to identify because they could serve as neural biomarkers of risk for major depression in children and could improve the identification of a subgroup of children at very high risk for major depression that could be targeted for early intervention. One approach to identifying such neurobiological traits is to examine brain function and structure in children who are not themselves depressed but are at familial risk for major depression by virtue of having a parent with a history of major depression, which increases the risk of major depression by three to five fold (Williamson et al., 2004). Here, we compared brain function and structure between children ages 8–14 with versus without familial risk for major depression.

Perhaps the most consistent functional brain difference in acute adult major depression has been hyperactivation of the amygdala to faces with fearful (Peluso et al., 2009; Sheline et al., 2001; Zhong et al., 2011) or sad (Fu et al., 2004; Surguladze et al., 2005; Suslow et al., 2010; Victor et al., 2010) expressions. In contrast, depressed adults often exhibit hypoactivation for happy facial expressions in variable regions including anterior cingulate cortex, amygdala, and fusiform gyrus (Surguladze et al., 2005; Suslow et al., 2010; Victor et al., 2010), although hyperactivation has also been reported (Gotlib et al., 2005; Keedwell et al., 2005). Increased activation to emotional faces has also been found in adolescents (Roberson-Nay et al., 2006; Yang et al., 2010) and 4–6 year olds (Gaffrey et al., 2013) with major depression.

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One approach to distinguishing the clinical state of major depression from predisposing neurobiological traits has been to examine remitted patients who had major depression but who are not currently depressed, but this approach has yielded mixed findings. A number of studies reported that remitted patients (usually treated with antidepressants) do not exhibit amygdala hyperactivation to negative facial expressions (Fu et al., 2004; Norbury et al., 2010; Sheline et al., 2001; Thomas et al., 2011; Victor et al., 2010), suggesting that amygdala hyperactivation is associated with the state and not the trait of major depression. Other evidence, however, favors the idea that amygdala hyperactivation is associated with trait predisposition to major depression. First, two studies of unmedicated patients with remitted major depression found amygdala hyperactivation to emotional faces that did not differ from patients in acute episodes (Neumeister et al., 2006; Victor et al., 2010). Second, healthy individuals with clinical traits thought to predispose for major depression, such as high neuroticism or pessimistic cognitions, also showed increased amygdala responses to emotional faces (Chan et al., 2009; Zhong et al., 2011). However, the complexity of variable histories of major depression and treatment for major depression may make it difficult to distinguish state versus trait characteristics of major depression in patients with a history of major depression.

Several studies have examined children or adolescents with familial risk for major depression but without depression themselves. One study using this approach focused on the amygdala and nucleus accumbens as regions of interest (ROIs), and found that subjects (10–18 years of age) at familial risk for major depression exhibited amygdala hyperactivation to fearful facial expressions and nucleus accumbens hypoactivation to happy facial expressions relative to subjects without familial risk for major depression (Monk et al., 2008). Another study of older adolescents, however, found no differences in amygdala activation between those with or without family history of major depression (although those at risk adolescents had reduced dorsolateral prefrontal cortex responses to emotional faces) (Mannie et al., 2011).

In addition to functional abnormalities, volumetric abnormality in amygdala structure (volume) has been found in studies of major depression, although the findings have been inconsistent (Frodl et al., 2003; Hastings et al., 2004; MacMaster et al., 2008). A meta-analysis suggested that these inconsistencies may be attributed to differences in medication status (Hamilton et al., 2008). Unmedicated patients tend to have smaller amygdala volumes, whereas medicated patients tend to have larger amygdala volumes compared to controls. However, as with functional differences in depressed patients, it remains unclear whether smaller amygdala volume represents a state or trait correlate of major depression. Resolving the contradictory findings in the neuroimaging literature as to whether functional and structural brain findings reflect state or trait neurobiological underpinnings of major depression has important clinical and scientific implications. If they were to be found to represent neurobiological underpinnings of risk for major depression, they may help identify children at very high risk for major depression who may be targeted for prevention or early intervention to avoid developing a serious illness such as major depression.

In the present study, we compared neuroimaging findings in children at familial risk for major depression who were offspring of parents with well-characterized major depressive disorder (at-risk group) with age-matched children who were offspring of parents who had no lifetime history of any mood disorder (control group). We performed whole-brain voxel-wise fMRI analyses, and focused additional a priori analyses on the amygdala, a limbic area that often had shown differences in neuroimaging studies of major depression. The children, while being scanned, viewed fearful (negative) and happy (positive) facial expressions, and also neutral facial expressions as a baseline. Given the behavioral attention bias towards negative facial expression in at-risk children and bias towards positive facial expression in controls (Gibb et al., 2009; Joormann et al., 2007; Kujawa et al., 2011), we hypothesized that at-risk children would show greater brain responses to negative-valenced emotional faces, and lesser brain responses to happy faces compared to control children.

2. Methods

2.1. Participants

Thirty-eight offspring ages 8–14 years of parents with lifetime history of unipolar depression (at-risk group) and 23 age-matched offspring of parents with no lifetime mood disorder (control group) participated in the study. Eligible participants were right-handed, had normal or corrected-to-normal visual acuity, had average or higher IQ (IQ > 90) and had a working command of the English language. Exclusion criteria included the presence of acute psychosis or suicidality in a parent or a child; the presence at any point in the lifespan of bipolar disorder in the parent, autism in the child, or a lifetime history of a traumatic brain injury or neurological disorder in the child. Children were also excluded if they had conditions incompatible with MRI (e.g., metal implants, braces, electronically, magnetically, or mechanically activated devices such as cochlear implants, or claustrophobia). Children were not excluded on the basis of personal history of major depression but could not have current major depressive disorder or dysthymia.

2.1.1. Recruitment

Participants were recruited from among participants in longitudinal studies of offspring at risk, conducted in the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital, supplemented with participants responding to advertisements to the community. The sample included 43 children from a study of offspring at risk for major depression and/or ADHD or neither disorder (31 at-risk and 12 controls); 3 children from a study of offspring at risk for major depression and/or panic disorder or neither disorder (2 at-risk and 1 control); and 6 control offspring of parents without mood disorders from a study comparing offspring of parents with and without bipolar disorder. Children from each of these studies had been recruited when the children were preschool-age from advertisements to clinical psychiatry departments and to the community calling either for adults who had been treated for depression and who had preschool-age children or for families in which neither parent had been treated for mood disorder (see e.g., Rosenbaum et al., 2000). Both parents in each family had been assessed in the course of these studies using the Structured Interview for DSM-IV (First et al., 1995). The sample was supplemented with 5 additional children at-risk, one of whom was a child from a study of siblings of children with bipolar disorder who was found on parental interview to have a parent with unipolar depression, and 4 of whom answered community advertisements for controls but were found to have a parent with major depression. Four additional control children were enrolled based on advertisements to the community calling for children in the age-range 8–14 whose parents had never been treated for depression.

Each of the prior studies from which we recruited had been approved by the Institutional Review Board at the Massachusetts General Hospital, and the present study was approved by the Institutional Review Boards at the Massachusetts General Hospital and at the Massachusetts Institute of Technology. Parents provided written informed consent for their and their child's participation, and youths provided written assent.

2.1.2. Diagnostic assessment

At enrollment for the present study, each child and both parents in each family were assessed for current and lifetime mood disorders (major depression, bipolar disorder, and dysthymia) in the interval since they had last been interviewed (or, for those recruited anew from the community, across their lifetime), using structured clinical interviews in which the mother was the informant. Interviews about