Archival Report

Biological Psychiatry

Altered Intrinsic Functional Brain Architecture in Children at Familial Risk of Major Depression

Xiaoqian J. Chai, Dina Hirshfeld-Becker, Joseph Biederman, Mai Uchida, Oliver Doehrmann, Julia A. Leonard, John Salvatore, Tara Kenworthy, Ariel Brown, Elana Kagan, Carlo de los Angeles, John D.E. Gabrieli, and Susan Whitfield-Gabrieli

ABSTRACT

BACKGROUND: Neuroimaging studies of patients with major depression have revealed abnormal intrinsic functional connectivity measured during the resting state in multiple distributed networks. However, it is unclear whether these findings reflect the state of major depression or reflect trait neurobiological underpinnings of risk for major depression.

METHODS: We compared resting-state functional connectivity, measured with functional magnetic resonance imaging, between unaffected children of parents who had documented histories of major depression (at-risk, $n = 27$; 8–14 years of age) and age-matched children of parents with no lifetime history of depression (control subjects, $n = 16$).

RESULTS: At-risk children exhibited hyperconnectivity between the default mode network and subgenual anterior cingulate cortex/orbital frontal cortex, and the magnitude of connectivity positively correlated with individual symptom scores. At-risk children also exhibited 1) hypoconnectivity within the cognitive control network, which also lacked the typical anticorrelation with the default mode network; 2) hypoconnectivity between left dorsolateral prefrontal cortex and subgenual anterior cingulate cortex; and 3) hyperconnectivity between the right amygdala and right inferior frontal gyrus, a key region for top-down modulation of emotion. Classification between at-risk children and control subjects based on resting-state connectivity yielded high accuracy with high sensitivity and specificity that was superior to clinical rating scales.

CONCLUSIONS: Children at familial risk for depression exhibited atypical functional connectivity in the default mode, cognitive control, and affective networks. Such task-independent functional brain measures of risk for depression in children could be used to promote early intervention to reduce the likelihood of developing depression.

Keywords: Chidren, Default mode network, Depression, Familial risk, Resting-state fMRI, Subgenual ACC

http://dx.doi.org/10.1016/j.biopsych.2015.12.003

Neuroimaging in patients with major depression (major depressive disorder [MDD]) has revealed abnormal activation patterns in multiple brain networks, including the default mode network (DMN) and cognitive control and affective networks. The DMN, anchored in the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), is suppressed in healthy adults during tasks that demand external attention but does not show the typical pattern of task-induced deactivation in adults and adolescents with MDD (1–3). The cognitive control network, including the dorsolateral prefrontal cortex (DLPFC), which is typically activated during cognitively demanding tasks, has shown decreased activation in adults with MDD (4,5). The affective network includes the amygdala and other limbic region structures (6,7) and, most saliently for MDD, the subgenual anterior cingulate cortex (sgACC), which is considered a core region in the functional and structural pathophysiology of MDD (8–10). The affective network exhibits abnormal activation patterns during emotion processing in adults with MDD (11–13). These abnormal activations in distributed networks may account for corticolimbic dysregulation in MDD (8,14).

Mirroring these brain activation abnormalities, patients of different ages with MDD have shown abnormal intrinsic functional connectivity of the brain measured via resting-state functional magnetic resonance imaging (rs-fMRI) (15). First, increased resting-state connectivity within the DMN and between the DMN and sgACC has been reported in adults (16,17) and adolescents (18) with MDD. Hyperconnectivity of sgACC correlated with duration of current depressive episodes in adults (16) and with emotional dysregulation in pediatric depression (19). These results support the possibility that DMN-sgACC hyperconnectivity might underlie depressive rumination (20). Second, several studies reported decreased resting-state connectivity within the cognitive control network in adult patients with MDD (21–23). In line with this evidence, MDD has been conceptualized as an imbalance between the DMN and the cognitive control network (24–26). Third, atypical connectivity between the amygdala and cortical structures has

ISSN: 0006-3223

been found in adults (27,28) and children (29) with MDD and is thought to reflect deficits in emotion regulation.

Despite evidence of abnormal functional connectivity across distributed brain networks in patients with MDD, it is unclear whether these differences reflect the state of current depression versus neurobiological traits that predispose individuals to be at risk for MDD. One approach to distinguishing between current state and predisposing traits is the study of unaffected individuals at heightened risk for MDD, such as unaffected children at familial risk for MDD by virtue of having a parent with MDD. Such familial history increases the risk of MDD in offspring by threefold to fivefold (30) and increases the risk of a broader spectrum of mood and anxiety disorders (31). Understanding whether rs-fMRI findings represent trait or state markers of MDD in the young can lead to the identification of informative neural biomarkers of risk for mood and anxiety disorders and help develop early intervention strategies to mitigate this risk. Resting-state fMRI also possesses significant translational strengths in its short duration of scanning and the lack of task performance demands that can complicate interpretation of activations.

In the present study, we examined rs-fMRI in unaffected children at familial risk for MDD and other mood and anxiety disorders by virtue of being offspring of parents with MDD (at-risk group) and compared them with age-matched children who were offspring of parents with no lifetime history of any mood disorder (control group). Two previous studies examining at-risk children and adolescents found decreased connectivity between the amygdala and frontal-parietal network in unaffected children of depressed mothers and in children with early-onset depression (29) and decreased connectivity within the frontal-parietal cognitive control network in unaffected adolescent girls with parental depression (32).

Based on previous functional connectivity results in patients with MDD, we focused on functional connectivity differences between at-risk and control children in the DMN, the cognitive control network, and the affective network, using a seed-based functional connectivity approach. We examined connectivity differences from the two midline anchor regions of the DMN (mPFC and PCC), which are associated with self-referential processing (33) and self-focused rumination in MDD (20,34), and from seed regions in left and right DLPFC and amygdala. We tested 1) whether unaffected at-risk children exhibit patterns of abnormal functional connectivity similar to those reported in patients with MDD, and 2) whether connectivity of DMN-sgACC is related to symptom scores in at-risk children. To further test whether resting-state connectivity can be a useful neural biomarker for risk for MDD, we built classification models based on resting-state data to discriminate at-risk versus control children.

METHODS AND MATERIALS

Participants

We initially recruited 38 offspring, 8 to 14 years of age, of parents with a lifetime history of MDD (at-risk group) and 30 age-matched offspring of parents with no lifetime mood disorder (control group). The study was approved by the Institutional Review Boards at Massachusetts General Hospital and at Massachusetts Institute of Technology. Parents provided written informed consent for their and their child's participation, and youths provided written assent. Exclusion criteria included the presence of acute psychosis or suicidality in a parent or a child, the presence at any point in the life span 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.

The final sample included in the analyses consisted of 27 at-risk and 16 control participants with no prior history of depression or current clinical-range symptom scores. Participants who did not complete the scan, had excessive head movement during the scan, or had a history of depression or clinical-range symptom scores were excluded. See Supplement for details.

Diagnostic Assessment

At enrollment for the present study, each child and both parents in each family were assessed for current and lifetime mood disorders (MDD, bipolar disorder, and dysthymia), using structured clinical interviews in which the mother was the informant. Interviews about parents used the depression, mania, dysthymia, and psychosis modules from the Structured Interview for DSM-IV (35) and those about the child used the depression, mania, dysthymia, and psychosis modules from the Schedule of Affective Disorders and Schizophrenia for School-Aged Children–Epidemiological Version for DSM-IV (36).

Other Assessments

Cognitive Function. To compare cognitive function between groups, we used the Kaufman Brief Intelligence Test-2, a 20-minute screen for verbal and nonverbal cognitive functioning (37).

Current Symptoms, Parent Report. To assess current behavioral and emotional symptoms in the children, we asked mothers to complete the Child Behavior Checklist (CBCL) (38) (see Supplement for details) about all children. The CBCL includes a total problems score, as well as scores reflecting internalizing (affective and anxiety) and externalizing symptoms (attentional problems and disruptive behavior). T-scores of 70 and above have been shown to discriminate clinical-range from nonclinical-range children (38).

Current Symptoms, Self-Report. To assess current depressive symptoms by self-report, we administered the Child Depression Inventory (CDI) (39) to all children. See Supplement for details of the CDI.

Participant Demographics

Children in the at-risk and control groups did not differ significantly in age, gender distribution, or IQ ($ps > .3$) (Table 1). The at-risk group had marginally higher CBCL total ($p = .05$), internalizing ($p = .096$), and anxiety ($p = .08$) scores but did not differ significantly in CBCL external problem scores ($p = .34$). None of the children had clinical-range CBCL scores (>70). CDI total scores did not differ significantly