A Neural Substrate for Behavioral Inhibition in the Risk for Major Depressive Disorder

Julie Frost Bellgowan, MS, Peter Molfese, PhD, Michael Marx, PhD, Moriah Thomason, PhD, Daniel Glen, BS, Jessica Santiago, MEd, Ian H. Gotlib, PhD, Wayne C. Drevets, MD, J. Paul Hamilton, PhD

Objective: Behavioral inhibition (BI) is an early developing trait associated with cautiousness and development of clinical depression and anxiety. Little is known about the neural basis of BI and its predictive importance concerning risk for internalizing disorders. We looked at functional connectivity of the default-mode network (DMN) and salience network (SN), given their respective roles in self-relational and threat processing, in the risk for internalizing disorders, with an emphasis on determining the functional significance of these networks for BI.

Method: We used functional magnetic resonance imaging to scan, during the resting state, children and adolescents 8 to 17 years of age who were either at high familial risk (HR; n = 16) or low familial risk (LR; n = 18) for developing clinical depression and/or anxiety. Whole-brain DMN and SN functional connectivity were estimated for each participant and compared across groups. We also compared the LR and HR groups on levels of BI and anxiety, and incorporated these data into follow-up neurobehavioral correlation analyses.

Results: The HR group, relative to the LR group, showed significantly decreased DMN connectivity with the ventral striatum and bilateral sensorimotor cortices. Within the HR group, trait BI increased as DMN connectivity with the ventral striatum and sensorimotor cortex decreased. The HR and LR groups did not differ with respect to SN connectivity.

Conclusion: Our findings show, in the risk for internalizing disorders, a negative functional relation between brain regions supporting self-relational processes and reward prediction. These findings represent a potential neural substrate for behavioral inhibition in the risk for clinical depression and anxiety.

Key Words: depression risk, default-mode, ventral striatum, behavioral inhibition, fMRI

J Am Acad Child Adolesc Psychiatry 2015;54(10):841–848.

Major depressive disorder (MDD) is among the leading causes of disability worldwide.[1,2] Given the substantial contribution of MDD to the global burden of disease, a great deal of research has focused on the etiology and pathophysiology of depression, and has implicated neural, genetic, and environmental factors.[3-6] To better understand trajectories toward MDD on a developmental time-scale, significant attention has been devoted to studying the children without depression of adults with clinical depression.[7-12] In this context, prospective longitudinal work has shown that the children of parents with depression are 3 times more likely to develop a depressive or bipolar disorder than are children without a parent with depression.[13] Moreover, having a familial history of depression opens the door to a broader spectrum of risk for psychopathology, with children of parents with depression at significantly elevated risk for developing substance use and anxiety disorders.[13] Therefore, although these children are most at risk for developing a mood disorder among other Axis I disorders,[13] they are best understood in terms of pluripotency for internalizing and substance use disorders more generally.

The recognized importance of identifying risk factors for depression and anxiety has motivated a new generation of research comparing samples at high to low familial risk on a variety of biological dimensions. Neural investigations of children who have never been depressed who have family members with depression have typically used established experimental paradigms from affective neuroscience to identify neural functional abnormalities in young persons at elevated risk for MDD. These studies have found that adolescents and young adults most at risk exhibit neural responses to emotionally valenced stimuli similar to those that characterize adults with mood and/or anxiety disorders.[14,15] Specifically, researchers have observed, in the risk for MDD, increased response of limbic prefrontal cortical networks and decreased response of dorsal prefrontal cortical networks under conditions of negative affective challenge. For example, a recent study incorporating sad mood induction found greater activation of the amygdala in the risk for MDD[11]; another study of neural response to sad film clips found increased activation of the insula and right caudate nucleus[9] in youth at high versus low risk for depression. Similarly, a recent study of neural response during fearful-face processing found greater amygdala and

Supplemental material cited in this article is available online.

nucleus accumbens activation to fearful faces in children and teens at risk for MDD.[7] Highlighting a failure of dorsal prefrontal cortical response under negative affective conditions in the risk for depression, another fear-processing study reported decreased response to fearful faces in the dorsolateral prefrontal cortex (DLPFC) in high- versus low-risk groups.[10] Similarly, researchers examining the neural correlates of regulation of an induced sad mood reported decreased activation in DLPFC in high-risk participants.[11]

The extant research examining the functional neural substrates of familial risk for MDD shows a pattern of neural response in children at elevated risk for depression that is common with that observed in adults with depression[15] and anxiety.[14] In furthering our understanding of neural-level foundations of familial risk for developing internalizing disorders, however, it is important that we incorporate knowledge of the intermediate behavioral phenotypes in the trajectory from familial risk for depression to the spectrum of internalizing disorders for which the children of parents with depression are at risk. Specifically, we propose that although it is important to consider the neural correspondence between risk for depression and MDD and clinical anxiety, it is critical that we address the more proximate objective of identifying links between neural function and emotional traits that are expressed abnormally in children at high risk—traits that could be crucial in the transition from mental health to mental illness. Given that higher levels of anxiety—as broadly construed—in children have been shown in longitudinal investigations to predict higher rates of clinically significant depression[16] and anxiety,[17] it is reasonable to investigate the neural underpinnings of anxious behaviors as a phenotypic link between the risk for depression and expression of MDD and/or clinical anxiety. Therefore, we examined, in the present investigation, the neural correlates of behavioral inhibition (BI) in the context of familial risk for mood and anxiety disorders. BI is a temperamental characteristic linked to fear-associated behaviors such as shyness and cautiousness[18]; moreover, BI has been observed reliably in infancy[19,20] and shown to be stable across childhood.[21] Elevated BI has been observed in children of parents with MDD[18] and is a risk factor for the development of clinical anxiety,[22] which in turn is a risk factor for depression.[23,24] Moreover, elevated BI directly predicts subsequent development of depression[25]; furthermore, heightened expression of this trait persists into and beyond the first episode of MDD.[26]

We examined BI in the familial risk for mood and anxiety disorders from the perspective of resting-state functional magnetic resonance imaging (fMRI) investigations of the brain's intrinsic functional connectivity. Such investigations have consistently found correlated activity among distinct brain networks in a task-free context.[27] To date, researchers have identified at least 7 networks that show distinct functions and patterns of interrelated activity.[28] In the present investigation, we compared youth at high versus low familial risk for internalizing disorders with respect to connectivity of 2 of the most reliably observed intrinsic networks: the default-mode network (DMN) and the salience network (SN). The DMN, comprising the ventromedial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobe, is a postulated neural substrate for encoding and elaborating on information from an egocentric reference frame.[29,30] Consistent with this formulation, functional abnormalities in the DMN have been found to be correlated with levels of self-relational, ruminative thinking in MDD.[31,32] The SN, which comprises the amygdala and fronto-insular and dorsal anterior cingulate cortices, is hypothesized to subserve processing of personally and biologically relevant stimuli.[33] Furthermore, meta-analyses of functional neuroimaging data have shown this network to play a significant role in depression[17] and anxiety.[14]

Given that conceptualizations of self-relational cognition (e.g., introversion, shyness) and biological relevance (e.g., threat sensitivity, caution) in BI map well onto the postulated functions of the DMN and SN, respectively, we hypothesized that, in addition to documenting greater BI in youth at familial risk for depression and/or anxiety, we would observe significant differences between high- and low-risk groups in DMN and SN connectivity in limbic and

FIGURE 1 Flow chart depicting sequence of recruitment, screening, and assessment of participants. Note: FIGS = Family Interview for Genetic Studies; K-SADS = Kiddie Schedule of Affective Disorders and Schizophrenia.