Neural Markers in Pediatric Bipolar Disorder and Familial Risk for Bipolar Disorder

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Objective: Bipolar disorder (BD) is highly heritable. Neuroimaging studies comparing unaffected youth at high familial risk for BD (i.e., those with a first-degree relative with the disorder; termed "high-risk" [HR]) to "low-risk" (LR) youth (i.e., those without a first-degree relative with BD) and to patients with BD may help identify potential brain-based markers associated with risk (i.e., regions where HR+BD≠LR), resilience (HR≠BD+LR), or illness (BD≠HR+LR).

Method: During functional magnetic resonance imaging (fMRI), 99 youths (i.e., adolescents and young adults) aged 9.8 to 24.8 years (36 BD, 22 HR, 41 LR) performed a task probing face emotion labeling, previously shown to be impaired behaviorally in youth with BD and HR youth.

Results: We found three patterns of results. Candidate risk endophenotypes (i.e., where BD and HR shared deficits) included dysfunction in higher-order face processing regions (e.g., middle temporal gyrus, dorsolateral prefrontal cortex). Candidate resilience markers and disorder sequelae (where HR and BD, respectively, show unique alterations relative to the other two groups) included different patterns of neural responses across other regions mediating face processing (e.g., fusiform), executive function (e.g., inferior frontal gyrus), and social cognition (e.g., default network, superior temporal sulcus, temporoparietal junction).

Conclusion: If replicated in longitudinal studies and with additional populations, neural patterns suggesting risk endophenotypes could be used to identify individuals at risk for BD who may benefit from prevention measures. Moreover, information about risk and resilience markers could be used to develop novel treatments that recruit neural markers of resilience and attenuate neural patterns associated with risk.

Clinical trial registration information—Studies of Brain Function and Course of Illness in Pediatric Bipolar Disorder and Child and Adolescent Bipolar Disorder Brain Imaging and Treatment Study; http://clinicaltrials.gov/; NCT00025935 and NCT00006177.

Key words: bipolar, brain, adolescence, risk, endophenotype

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Bipolar disorder (BD), 1 of the 10 leading causes of disability (per The Global Burden of Disease, 2004 update of the World Health Organization), is highly heritable, with estimates ranging from 59% to 85%.[1,2] Neuroimaging studies comparing youth at high familial risk for BD (i.e., those with a first-degree relative with the disorder; "high-risk" [HR]) to "low-risk" (LR) youth (i.e., those without a first-degree relative with BD) and to youth with BD can help to identify potential brain-based markers associated with risk, resilience, or illness (Figure 1).

Previous work has defined risk endophenotypes as biomarkers that are associated with illness, are familial, are state independent, and are found more commonly in unaffected family members of patients than in the general population.[3] Brain-based measures found in HR youth and youth with BD, but not in LR youth, may reflect neural markers of risk for BD (potential risk endophenotypes, HR+BD≠LR).[4] Comparison among BD, HR, and LR groups can also identify potential biomarkers for resilience to BD.[5] Specifically, regions where HR youth show differences in brain activity, relative to BD and LR youth, may reflect potential compensatory, protective, or resilience markers (HR≠BD+LR). Finally, regions where youth with BD show dysfunction relative to HR and LR youth may reflect potential illness-related "scars" (disorder sequelae, BD≠HR+LR). Of note, in cross-sectional designs such as this, it is only possible to identify associations, not causality. Therefore we cannot conclude that these brain profiles definitively lead to risk or resilience or result from disorder, but only that they are associated with these outcomes. Identifying causality requires longitudinal studies with the ability to rule out all alternative explanations. Thus, these potential associations should be interpreted tentatively.

We used a face emotion labeling paradigm to investigate neural mechanisms in these populations, because both HR youth and youth with BD make more errors labeling emotions on faces,[6,7] particularly ambiguous faces.[8] A recent meta-analysis suggests that during face processing, pediatric BD is marked by alterations in both emotion processing

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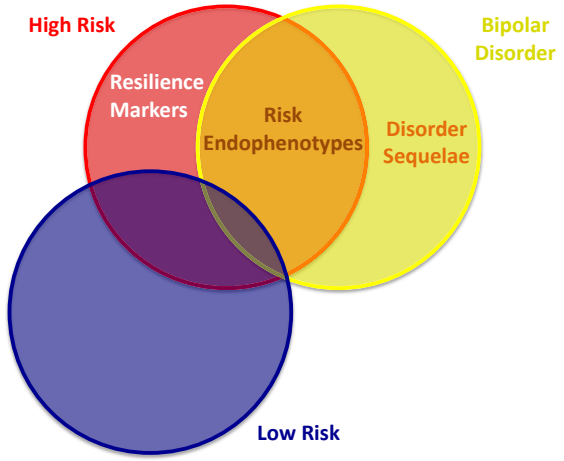
FIGURE 1 Identifying neural markers associated with risk, resilience, or disorder sequelae. Note: Having all three of these groups (high- and low-risk youths and those with bipolar disorder [BD]) is necessary to disentangle these markers. Brain activation patterns (a) shared by high-risk (HR) and BD (but not low-risk [LR]) youths (HR+BD≠LR) may indicate potential risk endophenotypes; (b) unique to high-risk youths (HR≠BD+LR) may indicate potential resilience markers; (c) and unique to youths with BD (BD≠HR+LR) may indicate potential disorder sequelae.



(i.e., limbic, dorsolateral prefrontal cortex) and visual perception (i.e., occipital) regions.[9] The few face processing studies in HR youth also demonstrate alterations in limbic, dorsolateral prefrontal cortex, and occipital function.[10-15] However, with few exceptions,[10,14] and in two additional studies not using face stimuli,[16,17] studies have not included both HR youth and youth with BD, possibly because of the difficulties involved in recruiting such samples. As discussed above, such direct comparisons are important to disentangle risk factors for, versus consequences of, BD.

Moreover, although previous studies in HR or BD populations used paradigms in which participants rated aspects of face stimuli, no study yet has used a task that involved face emotion labeling per se to identify risk and resilience markers and disorder sequelae in BD. Such a study would be important because behavioral deficits in facial emotion labeling have been documented in both youth with BD and HR youth. Recently, we used a face emotion labeling paradigm in an overlapping sample of youth with BD or disruptive mood dysregulation disorder (DMDD) to test whether the neural mechanisms of irritability, a symptom dimension common to both disorders, differ in BD versus DMDD.[18] Although the goal of that paper[18] was to differentiate bipolar versus DMDD (two disorders often conflated with one another), the current study investigates risk, resilience, and sequelae in youth with BD or at familial risk for the illness.

Thus, here we address gaps in the literature by identifying shared and unique neural alterations in BD and HR youth, relative to LR youth, during face emotion labeling. We compare HR and LR youth and youth with BD to identify potential risk and resilience endophenotypes as well as disorder sequelae. We are interested in identifying regions that fit into one of three patterns: patterns of potential risk endophenotypes (HR+BD≠LR); resilience markers (HR≠BD+LR); and disorder sequelae (BD≠HR+LR). Of note, these group difference patterns represent a heuristic that can lead to identifying potential risk and resilience endophenotypes and disorder sequelae but should be interpreted tentatively. Overall, we expect to find these patterns (i.e., HR+BD≠LR; HR≠BD+LR; and BD≠HR+LR) in limbic, dorsolateral prefrontal, and occipital regions, consistent with prior studies. However, as this study, unlike most prior studies, directly compares HR youth and youth with BD, we will be better equipped to separate patterns relating to potential risk vs. resilience markers and risk endophenotypes versus disorder sequelae.

METHOD

Participants

Data from 99 individuals (i.e., older children, adolescents, and young adults) aged 9.8 to 24.8 years were included (36 BD, 22 HR, 41 LR). Thirteen additional participants were excluded due to poor data quality, and 10 pairs and 1 trio within the dataset were biologically related (see Supplement 1, Methods, available online). BD was diagnosed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[19] in youths less than 18 years of age or the Structured Clinical Interview for *DSM* Disorders (SCID)[20] in youths more than 18 years of age. Inclusion in the HR group required a first-degree relative with BD. Exclusion criteria consisted of any bipolar spectrum disorder, pervasive developmental disorder, or schizophrenia; other disorders were included to avoid recruiting a particularly resilient group. LR youth were free of all psychopathology and did not have any first-degree relatives with BD. Exclusion criteria for all groups included orthodontic braces, other magnetic resonance imaging (MRI) contraindications, history of neurological or other significant medical disorders, and IQ < 80. Participants with BD and HR participants were recruited from across the United States and LR participants from the Washington, DC metropolitan area via advertisements and received monetary compensation. Participants more than 18 years of age and parents of minor participants gave written informed consent after receiving complete description of the study; minors gave written assent. Procedures were approved by the institutional review board of the National Institute of Mental Health (NIMH)/National Institutes of Health (NIH). Data from 22 of 41 LR youths and 24 of 36 youths with BD included in the current report have been previously published.[18,21] No imaging data in the 22 HR youths have been published.

Face Emotion Labeling Task

Participants performed a jittered, event-related task during functional MRI (fMRI) acquisition in which they labeled the emotion on angry, fearful, and happy faces morphed with neutral faces to create 0% (i.e., neutral), 50%, 75%, and 100% intensity faces presented for 4,000 milliseconds total (2,000 milliseconds of face only, 2,000 milliseconds of face with options to label the emotion on the face). Before each face presentation, a fixation cross appeared for a variable amount of time (mean = 1,800 milliseconds, range = 500–7,000 milliseconds). Across four 8.5-minute runs, there were 28 trials per emotion intensity condition (e.g., angry 50%, angry 75%, etc.), except for neutral faces (i.e., 0% intensity of each angry, fearful, and happy),