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Neuroimaging can help identify biomarkers of early onset bipolar disorder

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Bipolar Disorder (BP) in youth is now recognized as a significant public health problem that is often associated with impaired family and peer relationships, poor academic performance, high rates of chronic mood symptoms and mixed episodes, psychosis, disruptive behavior disorders, anxiety disorders, substance use disorders, high rates of medical problems, elevated rates of hospitalization, and suicide attempts and completions (1-3). It takes on average about 10 years to identify and begin treatment of BP, and patients with undiagnosed bipolar disorder may also have higher behavioral health costs than those with diagnosed bipolar disorder (4,5). Failure to differentiate BP depression from other conditions that share similar symptoms such as the depression of major depressive disorder (MDD) in youth or attention deficit hyperactivity (ADHD) has significant clinical consequences.Given the high rates of morbidity and mortality and chronic course of the condition, early diagnosis and treatment in bipolar youth is a key factor for not only mood stabilization, but also to enable youth to follow a normative developmental path and prevent an unrecoverable loss in psychosocial development and education (2).

Recent advances in neuroimaging techniques, such as functional MRI (fMRI), have made it possible to study in vivo brain activity of children in a safe (e.g., no risk of radiation) and detailed (e.g., better temporal and spatial resolution compared to SPECT and PET) manner (6). fMRI can help improve understanding of pathophysiological processes by identifying abnormalities in neural systems implicated in core symptoms of BP. There is growing evidence from functional neuroimaging studies that abnormal function in prefrontal and subcortical systems plays an important role in emotion regulation processes (7) and has been linked, respectively, with impaired cognitive control processes and mood instability that are commonly found in BP youth and adults (8,9).

Similar to most studies in adults, structural neuroimaging findings in BP youth indicate abnormalities in subcortical (10-12) and cortical (13,14) regions implicated in emotion processing, cognitive control, and emotion regulation. Subcortical regions (e.g., amygdala) and orbitofrontal cortex OFC are involved in emotion processing and implicated in both adult and youth BP (9,15,16). In contrast to the findings of enlarged, normal, or smaller amygdala in adult BP (17-19), a recent meta-analysis in BP youth (20) reported a consistent finding of smaller amygdala volumes in BP youth relative to healthy controls, indicating the need to study BP youth to better understand developmental and core neural abnormalities in BP. Moreover, some neuroimaging findings in adults indicate different subcortical findings in early onset or first episode BP such as an age-dependent reduction in amygdala gray matter (GM) volume (21) and reduced amygdala GM volume in first episode BP (22). On the other hand, adults with BP had reduced volume and GM density in a variety of different prefrontal cortical (PFC) regions implicated in cognitive control and emotion regulation processes (23-27). Similarly, youth with BP had abnormally decreased GM volume in the dorsolateral PFC (14).

Findings from functional neuroimaging studies in BP adults and youth support the structural findings indicating abnormalities in subcortical and cortical neural systems involved in emotion processing, cognitive control, and emotion regulation (8,9,28). Despite the few reports of no increase or reduced activity in subcortical regions to fearful faces (29) and during affect generation (30), respectively, a majority of the studies of emotion processing in euthymic BP adults, relative to healthy contols, have reported greater subcortical limbic activity (including amygdala, ventral striatum and medial temporal cortex/hippocampus) to emotional facial expressions (19,31,32) and to verbal emotional stimuli (33). Similarly, findings in euthymic BP youth, compared to healthy controls, showed increased amygdala and striatal activity to passive viewing of happy and angry faces (34), increased striatal activity to positive emotional scenes (35), increased striatal and anterior cingulated cortex activity when encoding happy faces, and increased amygdala activity to negative emotional words (36), during an incidental versus directed emotion processing condition (37), and during a non-emotional cognitive control task such as the Stroop color-word task (38). It is possible that patterns of neural activity to emotional stimuli may be different to positive versus

negative stimuli (39), thus future longitudinal studies in large samples are necessary to identify neurodevelopmental trajectories of emotion processing in BP.

Studies in BP youth have reported significant deficits in response flexibility and facial expression recognition (40), abnormally elevated perception of threat from neutral faces (associated with increased subcortical activity (41)), abnormally increased attention to threat faces (42), and misperception of faces as being angry (43). Studies that employ emotion regulation tasks that simultaneously recruit both emotion processing and cognitive control processes are needed to elucidate the functional abnormalities in neural systems underlying voluntary emotion regulation in BP youth.

Understanding connectivity as in neural network rather than individual neural abnormalitiesis required to identify core neural abnormalities in BP. Similar to the studies in adults, few studies have reported significant impairment of connectivity between subcortical and cortical neural systems in euthymic BP youth (44,45). These findings support the previously reported functional abnormalities in these neural systems that are implicated in emotion processing and may underlie the pathophysiology of BP in youth (41,46,47). However, no study has investigated the direction of connectivity between subcortical and cortical regions in BP youth. Moreover, only one study has so far studied connectivity of neural regions in BP youth during a resting state (48), which is a very important method to understand baseline neural activity in contrast to task-dependent fMRI measures, and suggested an altered task-independent fronto-temporal circuit.

Imaging studies have mainly focused on using neuroimaging for differential diagnosis (6) and have already started to identify different patterns of neural activity that may help differentiate BP youth from those with ADHD and severe mood dysregulation (49-52). On the other hand, considering our limitations in using clinical data to guide treatment decisions, neuroimaging can also be a very important tool to identify neural activity associated with treatment response. Similarlya few studies in BP youth have started to identify the neural regions (e.g., amygdala, ventrolateral prefrontal cortex, anterior prefrontal cortex) that may help predict treatment response (35,39,53).

Accumulating studies in early onset BP are in accord withthe vision of the National Institute of Medicine (54) to identify biomarkers of psychiatric illnesses and treatment response. Recent findings of biomarkers of early onset BP arevery promising in the effort to achieve this goal; however, we still have a lot to learn and are in need of longitudinal studies that will employ converging imaging techniques (e.g., MRI for size of neural structures, fMRI for task related activity and resting state analysis, Diffuse Tensor Imaging (DTI) for hard wiring of the neural network, Magnetic Resonance Spectroscopy (MRS) for neural metabolism) when studying BP and differential diagnosis, treatment response, and high-risk populations.

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