

Amygdala Response to Emotional Faces: A Neural Marker of Risk for Bipolar Disorder?

Cecile D. Ladouceur, Ph.D.

Bipolar disorder (BD) is a serious and recurrent neuropsychiatric illness that affects 2% to 5% of the population.¹ Evidence from adoption, twin, high-risk, and family studies indicate that BD is highly heritable. Yet, to date, the single strongest predictive factor of the risk for developing BD is high family loading for the disorder. Although there have been some advances in the identification of early signs of BD, developmental differences in the presentation of the disorder in youth (e.g., symptoms of inattention, irritability, impulsivity, etc.) can often be misinterpreted for the onset of other forms of psychopathology (e.g., ADHD, ODD) and lead to inappropriate or less efficient treatment. Consequently, identification of early biomarkers of BD in at-risk youth through the use of neuroimaging techniques could improve earlier detection in young persons likely to develop the disorder and could inform early preventive strategies. More importantly, grounding such research studies within a developmental affective neuroscience framework is crucial to enhance our ability to elucidate specific mechanisms that may contribute to the trajectories toward BD and other affective disorders, such as anxiety and depression.

In the current issue of the *Journal*, two articles provide preliminary evidence for the importance of investigating the functioning of neural systems that support processing of emotionally salient and socially relevant information (i.e., emotional faces) as potential neural markers of risk for mood disorders, including BD. Olavsky and colleagues² provide compelling findings demonstrating that the use of neuroimaging techniques, along with a paradigm that involves viewing emotional faces, may be a useful strategy to elucidate potential neural markers of risk for BD in children and adolescents having a first-degree relative with the disorder. The article by Liu and colleagues³

complements these findings by demonstrating that changes in endocrinological responses to social stress may influence the functioning of neural systems implicated in processing emotional faces in adolescents at high risk for psychopathology (i.e., anxiety and mood disorders, substance use). Although this latter study did not focus specifically on risk for BD, it offers compelling evidence for the importance of investigating changes in neural systems implicated in processing socially relevant emotional information during adolescence—a sensitive developmental window for the onset of mood disorders.

BD has been ranked as one of the top 10 leading causes of disability in the world.⁴ The emergence of BD in children and adolescents is of particular concern because it may have a more severe presentation and course, including high rates of hospitalizations, psychosis, suicidal behaviors, substance abuse, as well as behavioral, academic, social, family, and legal problems.⁵ Given the impact of BD on the development of children and adolescents and the serious negative consequences on functioning into adulthood, it is crucial that we develop new strategies to detect early signs of the illness—ideally before cognitive, emotional, or behavioral manifestations of the illness emerge and contribute to poor functioning. Therefore, the search for candidate endophenotypes of BD⁶ is an area that merits further investigation.

One avenue of research that has emerged in recent years is the focus on the functioning of neural systems implicated in emotion processing and regulation.^{7,8} Although the majority of this work has been performed in adults, there is an increasing number of studies in youth with BD demonstrating that deficits in the functioning of neural systems supporting emotion processing and regulation may contribute to the pathophysiology of BD.⁸ Recent research

advances have begun to document structural alterations in both the subcortical and cortical regions in youth at familial risk for BD,⁹ yet few studies have reported altered functioning of neural regions implicated in emotion processing and regulation. The article by Olsavsky and colleagues² contributes in filling this gap. In a well-designed study, Olsavsky and colleagues² report preliminary neuroimaging findings suggesting that right amygdala hyperactivity while rating subjective fear in response to viewing fearful faces may constitute a candidate endophenotype for BD. The study included a large sample of youth (N = 101), ranging in age from 8 to 18 years, of whom 32 were diagnosed with BD-I, 13 were unaffected youth at familial risk for BD (with a sibling or parent diagnosed with BD), and 56 were healthy comparison individuals with no history of psychiatric illness and no first-degree relatives with an anxiety or mood disorder. The novel findings from this study make an important contribution to the literature on risk for BD in many ways. For instance, Olsavsky and colleagues² demonstrate, for the first time, that unaffected youth at familial risk for BD exhibit a pattern of heightened amygdala response to emotionally salient stimuli (e.g., fearful faces) similar to that of youth diagnosed with BD, carefully matched on age, gender, and IQ, suggesting that such amygdala hyperactivation to fearful faces could be considered as a candidate endophenotype for BD. As the authors acknowledge, the extent to which such a finding represents a specific biomarker of BD has yet to be determined, given that amygdala hyperactivation to fearful faces has also been reported in a number of studies in pediatric anxiety and mood disorders. Thus, future work is needed to investigate the predictive value of amygdala hyperactivation to fearful faces for future onset of BD within the realm of longitudinal follow-up designs. Given the evidence that the rate of mood disorders, including BD, increases dramatically during adolescence, one potential avenue could be focusing specifically on factors that influence developmental changes in the structural and functional connectivity of frontolimbic systems implicated in emotion processing and regulation during adolescence.

Recognizing that the field is still growing in this particular area, the article by Liu and colleagues offers potential clues with regard to some of the developmental changes that may

be worth investigating in at-risk youth. Liu and colleagues³ recruited a group of adolescents (age 14-17 years) at high risk for affective and substance use disorders by virtue of being from disadvantaged families (i.e., poverty, exposure to high levels of stress).³ Salivary cortisol measures, indexing stress reactivity, were acquired during a social stress test and later related to functional neuroimaging data associated with emotion face processing. Results revealed that greater reactivity to stress was associated with reduced responses in frontolimbic regions (i.e., hippocampus and rostral prefrontal cortex) while viewing fearful faces. These preliminary findings highlight the importance of examining the interaction between particular neurobiological systems that undergo important changes during adolescence. Indeed, these findings suggest that alterations in the normal development of these systems in the context of individual risk (e.g., temperament, genetic predisposition) and psychosocial factors (e.g., family conflict, stressful life events, poor parent socialization of emotion regulation skills) might contribute to increased risk for affective disorders. Although we assume that the relationships between these sets of factors are bidirectional, longitudinal research studies are needed to investigate the nature of these relationships, as well as mediating and moderating factors that may contribute to developmental trajectories.

One of these factors could be puberty-related reactivity in subcortical regions to emotionally salient information (e.g., emotional faces). Findings from animal studies indicate that pubertal maturation is associated with changes in processing threat and socially relevant cues as well as stress responsiveness.^{10, 11} Moreover, an emerging body of work is beginning to document puberty-specific neurodevelopmental changes in adolescence,^{12,13} including changes in face processing¹⁴ and emotional information processing.¹⁵ Interestingly, recent findings in adults demonstrate that levels of endogenous testosterone modulate prefrontal-amygdala connectivity, supporting the control of social behavior.¹⁶ Together these findings highlight the importance of investigating the contribution of specific developmental factors such as puberty within our models of risk for future onset of affective disorders. Although many studies, including the one by Liu and colleagues, have included measures of pubertal status, the research designs were not intended to

specifically test hypotheses regarding puberty-related effects. Therefore, it will be important that future research studies consider incorporating methodological designs that can disentangle the effects of age versus puberty on the functioning of neural systems of emotion processing and regulation in adolescence. By enhancing our understanding of the development of these neural systems in at-risk youth, such as identifying heightened periods of plasticity, we may be able to uncover important clues regarding optimal ways to tailor early intervention strategies that will positively impact individual developmental trajectories. &

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Dr. Ladouceur is with the University of Pittsburgh School of Medicine, Pittsburgh, PA.

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Correspondence to Cecile D. Ladouceur, Ph.D., Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA, 15213; e-mail: ladouceurcd@upmc.edu

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