Biological Psychiatry: CNNI

# Commentary

# Predicting Mental Health in Adolescence: Frontoinsular Circuitry, Emotion in Daily Life, and Risk for Depression

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Adolescence is a period of marked change in emotional behavior and related neural circuitry. During this unique stage of development, large-scale brain networks undergo dynamic changes, particularly in corticolimbic circuitry that has been implicated in both healthy and disrupted cognitive control of emotion (1). Coupled with novel psychosocial and physical challenges, these dynamic changes make adolescence a formative period that marks both a window of opportunity and also a window of increased vulnerability. The incidence of psychiatric disorders peaks during adolescence, with mood and anxiety disorders being especially common (2). The onset of these disorders early in life is associated with an increased risk for suicidality, substance abuse, poor academic and social functioning, and chronicity of illness into adulthood (3). Enhancing the prediction of risk to guide diagnosis and facilitate tailored treatment recommendations is therefore vital for optimizing mental health outcomes across the lifespan.

Delineating brain-based alterations associated with risk represents a promising approach to improving clinical prediction early in life. Indeed, neural markers that predict clinical outcomes alone or in combination with traditional behavioral measures have increasingly been identified (4). Yet the majority of research on neuromarkers as predictors of clinical status or treatment response has been conducted in adults. Given the substantial reorganization of corticolimbic circuitry, the potential for developmentally specific interactions between neural and environmental factors, and the heightened salience of specific contextual factors during adolescence, such as social interactions or stressful life events, the strongest predictors of risk for mood and anxiety disorders in adolescents may be different from those factors that are most predictive in adults.

Combining neural markers with investigations into the temporal dynamics of emotion may be an especially fruitful strategy for clinical prediction during adolescence. Parsing emotions into their simplest elements (e.g., magnitude, duration, and habituation) using ecological momentary assessment (EMA) has shed new light on risk for mood and anxiety disorders in adulthood and facilitated mapping these core aspects of emotion to neural processes (5). Adolescents experience intense and frequent emotions and heightened emotional variability relative to children and adults, highlighting the importance of considering how emotional experiences uniquely unfold over time during this period of development (6). In conjunction with rapid advances in mobile technology, the ubiquity of smart phones in adolescents' lives makes EMA a particularly suitable methodology to assess interactions between developmental timing and emotion dynamics in daily life.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Kaiser *et al.* (7) integrate neuroimaging with daily surveys of emotion to examine how frontoinsular network functional connectivity relates to concurrent and prospective mood health during adolescence. Adolescents exhibiting hypoconnectivity between the insula and frontoparietal network and hyperconnectivity between the insula and default mode network showed increases in both lability and intensity of negative affect across a 2-week period. Functional connectivity of the insula was also related to risk for depression. Whereas insula–frontoparietal network hypoconnectivity was associated with higher depressive symptoms at baseline, insula–default mode network hyperconnectivity was associated with increased depressive symptoms over the 2-week period. The study's focus on the insula and its interactions with specific large-scale networks is well grounded in the existing literature on adult depression. Though much remains unknown about the mechanisms linking frontoinsula alterations with depression, these imbalances in insula connectivity may contribute to weaker goal-directed attention and heightened rumination that could interfere with executive functioning in the context of emotional challenges. Moreover, the dissociation between frontoinsular alterations, such that insula–default mode network connectivity was associated only with prospective mood health, whereas insula-frontoparietal connectivity was associated with both prospective and current mood health, raises important questions about potential differences in markers of illness versus vulnerability.

The integration of brain imaging with measures of emotional experiences in daily life outside of the laboratory is an innovative aspect of the present study. Given that the insula has been implicated in salience detection and may direct resources toward or away from large-scale networks depending on significant environmental events (7), the assessment of real-world emotional experiences within the context of an individual's broader environment may be especially well suited to studies of frontoinsular function. Although Kaiser *et al.* (7) did not examine contextual factors, future studies in adolescents could leverage EMA to provide insight into interactions between emotion dynamics and environmental contexts that are highly salient for adolescents, such as social interactions (8) or stressful life events. Previous evidence suggests that adolescents may be particularly sensitive to stressful life events and that variability in emotion interacts with stress to increase risk during adolescence (6). The relatively brief follow-up period (14 days), small subsample ($n$ = 28) of participants who completed at least 7 days (half) of daily diary assessments, and collection of only one time point per day are limitations of the current work to be

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  https://doi.org/10.1016/j.bpsc.2019.06.004
Biological Psychiatry: Cognitive Neuroscience and Neuroimaging August 2019; 4:684–685 www.sobp.org/BPCNNI ISSN: 2451-9022

addressed in future research. Given evidence in adults that the temporal dynamics of emotion and neural processes provide unique information about depression and anxiety (5), richer sampling of emotion dynamics in daily life (e.g., multiple time-points per day) may be especially useful for assessing and predicting mood health among adolescents. Such real-time sampling of negative affect and depressive symptoms may also reduce memory bias and enhance ecological validity.

Identifying network-based alterations that prospectively predict changes in depression holds the potential to inform translational approaches to enhancing risk identification. However, for neural markers to be clinically useful, they must predict risk at the level of the individual and improve predictions over and above traditional clinical or behavioral measures (4). Importantly, the predictive utility of the frontoinsular markers identified by Kaiser *et al.* (7) remains untested in out-of-sample individuals and relative to readily available measures. Future research that works toward a generalizable model to predict risk for depression in new adolescents above and beyond existing measures will be essential for effectively translating the current work into clinical practice. Thus, although integrating neuroimaging assessment may help to enhance precision above clinically observable phenomena, the present findings must be interpreted with caution in regard to clinical prediction.

Precise recommendations for translation will further require testing the specificity of frontoinsular connectivity associated with adolescent mood health. Frontoinsula abnormalities have been implicated across a wide range of psychiatric disorders (9), and it remains to be seen whether the findings are specific to depression or potentially transdiagnostic. Building on the assessment of affect in daily life in the current study, future research assessing emotion dynamics may be particularly useful for distinguishing between risk for anxiety versus depression. For example, evidence in adults suggests that anxiety is associated with greater instability of affect, whereas depressive symptoms are associated with altered mean levels of affect (5). Emotion dynamics may be particularly meaningful for differentially characterizing or predicting disruptions in mental health during periods of heightened plasticity and rapid change, such as adolescence. The extent to which the results of Kaiser *et al.* (7) are developmentally specific is another important area for future study. The present findings converge with previous evidence in adults with depression, and it is not clear whether frontoinsula connectivity and risk for depression are uniquely related during adolescence relative to other stages of development. Although the developmental focus of this study is a major strength, Kaiser *et al.* (7) did not assess age-related change. Frontoinsular networks undergo marked changes across typical development (10), highlighting the importance of a neurodevelopmental approach to delineating the relationship between frontoinsular circuitry and depression. Such a broad age range (13–19 years of age) could be leveraged in studies with larger samples to specifically model the effects of age or puberty. Finally, future research will benefit from pursuing a deeper understanding of the mechanisms linking frontoinsular function with mood health during adolescence. Kaiser *et al.* (7) used an emotional working memory task, and it is unclear to what extent frontoinsular alterations in adolescent depression are specific to emotional working memory or are potentially related to emotion regulation or the cognitive control of emotion more broadly.

Dynamic changes in corticolimbic circuitry and heightened emotional instability characterize adolescence, when mood and anxiety disorders often emerge, and adolescents face a wealth of new social–emotional, cognitive, and physical challenges. This unique developmental stage simultaneously represents a period of immense opportunity and plasticity. Enhancing the prediction of clinical outcomes during adolescence has the potential to facilitate early identification of risk and timely intervention. Given that the biological state of the developing brain and environmental challenges vary widely across the lifespan, optimal predictors of risk are likely to differ for adolescents relative to children or adults. By leveraging unique characteristics of the adolescent period, examining large-scale brain networks in conjunction with temporal dynamics of emotional experiences may provide a powerful approach to predicting risk and resilience at this developmental stage.

## Acknowledgments and Disclosures

This work was supported by a National Institutes of Health Director's Early Independence Award (Grant No. DP5OD021370 [to DGG]), a Brain & Behavior Research Foundation (National Alliance for Research on Schizophrenia and Depression) Young Investigator Award (to DGG), a Jacobs Foundation Early Career Research Fellowship (to DGG), and a Ford Foundation Fellowship (to CC).

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Jun 9, 2019; accepted Jun 10, 2019.

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