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Commentary

Resting-State Functional Connectivity Abnormalities in Adolescent Depression

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Major depressive disorder (MDD) is the single greatest cause of disability and frequently emerges during adolescence, which can lead to devastating social, personal, and medical consequences (Cullen et al., 2014). It is critical to understand how departure from typical brain development patterns impacts the incidence of depression, as it allows us to develop more effective treatments and better clinical interventions to prevent recurrent, chronic episodes.

It is currently unclear how and why MDD frequently emerges during adolescence. Different theories including dual-process models have been reviewed to explain certain aspects of adolescent depressive disorders (Hagan et al., 2015). In dual-process models, the so-called hot and cold neural systems that underlie both typical and atypical human behavior are proposed. The bottom-up hot systems are represented by emotional processing arising from lower brain regions, passing upward through the limbic system and emerging as reactive or reflexive behaviors (Hagan et al., 2015). The top-down cold systems underlie cognitive processes arising from frontal and prefrontal brain regions, passing down towards the limbic system and emerging as proactive or reflective behaviors. Previous studies suggest that exaggerated neurodevelopmental imbalances between hot and cold systems contribute to the incidence of affective disorders in adolescence (Casey et al., 2010).

Evidence from imaging studies suggests altered functional connectivity in adults with MDD, such as increased physiological activity in regions of hot emotional processing and reduced activity in regions of cold cognitive control (Anand et al., 2009). However, it remains unclear whether similar dysfunction is present in adolescents with MDD due to the limited number of studies and small sample sizes of the studies conducted. Pathophysiology of MDD in adolescents can be different than in adults, due to maturation changes in the adolescent brain (Cullen et al., 2014).

Chattopadhyay and co-workers examined differences in resting-state functional connectivity (rsFC) between adolescent patients with MDD and matched healthy controls as well as changes in rsFC following cognitive behavioral therapy (CBT) (Chattopadhyay et al., 2017-in this issue). This is one of the largest studies of adolescent MDD to date and the first to examine hypothesized changes in functional connectivity due to depressive illness, and the amelioration of these changes as a result of CBT. The cross-sectional sample with 82 patients and 34 healthy controls was used for case–control comparison on rsFC with seed regions including amygdala, anterior cingulate cortex (ACC), and prefrontal cortex (PFC). Findings of significant seed regions from the cross-sectional sample were used as a mask for the longitudinal sample analyses (17 patients and 30 controls). The effect of CBT on rsFC was examined for seed regions that showed significant between-group differences in the cross-sectional sample. The independence of the patients in the cross-sectional and longitudinal samples is another strength of the study design.

Chattopadhyay and co-workers report that depressed adolescents showed significantly greater rsFC to left amygdala, bilateral supragenual ACC but not with PFC. The results partially support the putative dual-system hypothesis believed to underlie disorders such as major depression. Specifically, it may suggest that unlike adults with depression, adolescents have aberrant, bottom-up processing in hot limbic regions without the concomitant differences in cognitive control in cold prefrontal regions. Furthermore, elevated functional connectivity in right insula connected to left supragenual ACC in patients was lowered towards values seen in controls following CBT. In addition, changes in functional connectivity were significantly associated with changes in symptom severity. This indicates that symptom recovery may be at least partially associated with normalization of rsFC in hot emotional brain systems, and their restoration is critical for successful therapeutic interventions (*e.g.*, CBT).

It is worth noting that the rationale for maintaining the same seed regions in the cross-sectional and longitudinal analyses was to constrain the narrative, and to avoid suggestions of gaming the analysis by using consistent, independently defined regions. However, it is possible that in the longitudinal analysis connectivity can change in regions that are not different between groups cross-sectionally. The choice of a limited number of seed regions is both a weakness

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and a strength of this technique. In the literature, most neuroimaging studies examining resting-state functional activity utilize *a priori* restrictions on specific networks or seed regions, which may bias analysis results (Zhang et al., 2016). The selection of appropriate seed regions has been a challenging methodological issue for examining resting-state fMRI data and is especially difficult when the underlying pathology or regional pattern is unknown. Future studies can explore data-driven analysis methods such as independent component analysis-derived connectivity and functional connectivity density mapping to minimize input of prior knowledge (Zhang et al., 2016).

Disclosure

No conflict of interest to declare.

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