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Dysfunctional connectivity in the depressed adolescent brain

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Aberration in the coordinated activity of large-scale brain networks, or *functional connectivity*, is a growing focus of depression research, as it may be a key substrate underlying cognitive and emotional symptoms. Consistent with this assertion, a number of studies have shown that depressed individuals exhibit abnormal functional connectivity in brain systems previously implicated in socioemotional and cognitive processes relevant to depressive symptoms (1). These neural regions include midline cortical areas of the default network involved in self-referential and autobiographical thinking, as well as prefrontal systems involved in higher-order cognitive control or regulation of affect. However, although a number of studies have examined functional connectivity either at rest when cognition is undirected or during tasks relevant to depressive symptoms, few studies have combined these modalities. This gap in our understanding of dysfunctional connectivity in depression engenders several important questions: to what extent are alterations in functional connectivity unique to specific cognitive or emotional processes? What can the comparison of functional connectivity across multiple modalities reveal about markers of psychiatric illness? Finally, are abnormalities in functional connectivity malleable – do they change over development or normalize during treatment?

Ho and colleagues explore several of these questions within a study reported in the current issue of *Biological Psychiatry* (2). The authors collected functional magnetic resonance imaging (fMRI) data from adolescents with major depressive disorder (MDD) and healthy controls during two paradigms: an unconstrained period of rest and an emotion-identification task in which participants identified the emotional category of morphing faces (fearful, happy, sad). Critically, this design allowed the researchers to interrogate functional connectivity during both directed emotional processing using psychophysiological interaction analyses and undirected thought using resting-state functional connectivity analyses. Several intriguing results emerged. *First*, when engaged in task-directed emotional processing, depressed adolescents exhibited greater functional connectivity than healthy

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youth in regions of the default network, and between medial prefrontal and posterior cingulate “hubs” of the default network and cingulate or striatal regions involved in cognitive control or affective/salience processing. *Second*, during unconstrained rest, depressed and control adolescents showed comparable functional connectivity among these regions. When inspecting the patterns of results across groups and connectivity modalities, both groups exhibited robust functional connectivity within the default network at rest; however, among depressed youth only, this network remained active and functionally connected during explicit emotional processing. Similarly, at rest, both groups exhibited moderate functional connectivity between midline hubs of the default network and cingulate or striatal regions, but depressed youth also showed elevated functional connectivity between these regions during the emotion-identification task. Together, these findings provide evidence for default network hyperconnectivity in adolescent depression, and they also indicate that such hyperconnectivity may emerge specifically during goal-directed emotional processing.

Although previous resting-state research conducted with depressed adults has repeatedly revealed dysfunctional connectivity of the default network (1), research with adolescents has been equivocal. Ho and colleagues suggest that altered functional connectivity of midline cortical regions emerge for depressed adolescents when they are confronted with salient emotional material, hinting at a trajectory in which connectivity abnormalities tend to emerge within distinct modalities at particular developmental stages or as markers of disease progression. Adolescence is a critical period for the formation of large-scale brain networks, and therefore, may be a time in which these networks are most vulnerable to hormonal, social, or acute emotional influences (3). For example, children exposed to chronic stress or socioeconomic adversity may experience repeated emotional challenge, taxing neural systems involved in emotion regulation and leading to dysfunctional connectivity that is most apparent during explicit affective processing but ultimately extends to unconstrained resting-state. Alternately, it may be that the chronicity of depression plays a role in dysfunctional connectivity, e.g., over the course of repeated episodes of MDD, dysfunctional connectivity becomes more deeply engrained and persists across task and resting-state modalities. Collectively, the view that adolescence is a key time of brain network development, together with evidence for increased MDD prevalence during adolescence (especially for girls and children exposed to adversity (4)), points to this developmental period as a key focus for multi-modal connectivity research.

Studies that compare functional connectivity across modalities, such as that of Ho and colleagues, provide useful insight but also draw attention to unanswered questions and methodological challenges. For example, resting-state and task-related analytic strategies may differ in their ability to capture correlated activity at slow or fast frequency bands; critically, connectivity at different frequencies may in turn reflect different contributions of anatomy, arousal, or discrete thoughts (5). Therefore, it is unclear whether distinct patterns of resting-state or task-related functional connectivity are driven by differences in the cognitive activities of each modality (unconstrained vs. task-directed), or differences in the nature of functional connectivity that is assessed by each modality. In addition, whereas task-related analyses are designed to examine changes in functional connectivity, standard

resting-state analyses typically only assess static (overall) functional connectivity. Exciting new evidence for dynamic fluctuations in functional connectivity at rest (6) suggests the importance of exploring these facets of resting-state functioning in depression. Ultimately, future research that unpacks the anatomical and cognitive influences on functional connectivity, and at varying timescales, will have an opportunity to elucidate these complex relationships.

Multi-method studies are well-poised to link the pathophysiology of depression to cognitive and behavioral functioning, and hopefully provide much-needed guidance for treatment selection in the near future. New studies may build on this integrated approach by including additional measures that probe neurotransmitter function or depressive phenotypes more explicitly. For example, depressed adolescents with broad impairments in executive functioning may be more likely to exhibit altered functional connectivity in cortical regions involved in regulating emotion and attention. As a result, they might be especially likely to benefit from interventions that target executive function, including metacognitive therapy (7) or mindfulness-based treatments. In addition, investigating clinical subtypes of depression as they relate to unique patterns of abnormal connectivity may also shed new light on the heterogeneous nature of mood disorders. On a molecular level, anhedonia-related abnormalities in the activity of midline cortical regions have been linked to disrupted glutamatergic function (8), while on a systems level, anhedonia has been associated with amplified connectivity between default network and striatal regions (9). Accordingly, depressed adolescents that experience more severe anhedonia may particularly benefit from pharmacotherapy that targets glutamatergic systems, or from interventions that increase contact with positive reinforcement for healthy behaviors such as behavioral activation (10). By including neurobiological methods that probe multiple facets of functional connectivity and molecular mechanisms, along with behavioral methods that precisely define depressive phenotypes, the field is poised to gain a better grasp of the diverse manifestations of this disorder.

An integrated, multi-modal approach to the study of brain communication in depression cannot only provide a nuanced view of the nature of MDD, but also guide translational insights into disease etiology and recovery. In this context, three critical questions will need to be addressed. First, how do functional connectivity abnormalities relate to the onset and progression of depression? Second, how does disease trajectory relate to developmental trajectory? And third, how does functional connectivity change over the course of effective treatment? Suggesting answers to the first question, Ho and colleagues highlight a relationship between depression onset, developmental stage, and brain function, as earlier age of onset was associated with greater abnormalities. Future longitudinal work may be useful for tracking functional connectivity in at-risk children, and may clarify the neural signature of depression onset during particular developmental windows. In addition, clinical trials that include connectivity methods may begin to shed light on the degree to which functional or anatomical connectivity are malleable phenomena, which can be normalized with successful treatment.

In sum, adolescent depression is characterized by dysfunctional connectivity especially of regions of the large-scale default network; however, these abnormalities may depend on the

modality of functional connectivity and nature of cognitive or emotional activities. Innovative studies that incorporate multiple theoretically-motivated methods for studying brain communication, such as the study by Ho and colleagues, are positioned to uncover new dimensions of brain functioning and hopefully reveal targets for prevention and treatment of depression among adolescents.

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