Commentary

Dysfunctional Connectivity in the Depressed Adolescent Brain

Roselinde H. Kaiser and Diego A. Pizzagalli

Aberration in the coordinated activity of large-scale brain networks, or functional connectivity, is a growing focus of depression research because it may be a key substrate underlying cognitive and emotional symptoms. Consistent with this assertion, numerous studies have shown that individuals with depression 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 and prefrontal systems involved in higher order cognitive control or regulation of affect. However, although many studies 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 gives rise to several important questions. First, to what extent are alterations in functional connectivity unique to specific cognitive or emotional processes? Second, 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 et al. (2) explore several of these questions in a study in the current issue of *Biological Psychiatry*. The authors collected functional magnetic resonance imaging data from adolescents with major depressive disorder (MDD) and healthy control subjects 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 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 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, adolescents with depression and control subjects 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 youth with depression 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 youth with depression 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 indicate that such hyperconnectivity may emerge specifically during goal-directed emotional processing.

Although previous resting-state research conducted in adults with depression repeatedly revealed dysfunctional connectivity of the default network (1), research in adolescents has been equivocal. Ho et al. suggest that altered functional connectivity of midline cortical regions emerges for adolescents with depression 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 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. Alternatively, the chronicity of depression may play 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 multimodal connectivity research.

Research that compares functional connectivity across modalities, such as the study by Ho et al., 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 reflect different contributions of anatomy, arousal, or discrete thoughts (5). 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

---

SEE CORRESPONDING ARTICLE ON PAGE 635

---

modality. In addition, although task-related analyses are designed to examine changes in functional connectivity, standard resting-state analyses typically assess only 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 discovers the anatomic and cognitive influences on functional connectivity at varying time scales will have an opportunity to elucidate these complex relationships.

Multimethod studies are well poised to link the pathophysiology of depression to cognitive and behavioral functioning, and it is hoped that these will 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, adolescents with depression 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 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), whereas on a systems level, anhedonia has been associated with amplified connectivity between default network and striatal regions (9). Accordingly, adolescents with depression who 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, multimodal approach to the study of brain communication in depression not only can provide a nuanced view of the nature of MDD but also can guide translational insights into disease etiology and recovery. In this context, three critical questions 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? Third, how does functional connectivity change over the course of effective treatment? Suggesting answers to the first question, Ho et al. 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 anatomic connectivity are malleable phenomena, which can be normalized with successful treatment.

In conclusion, depression in adolescents 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 et al., are positioned to uncover new dimensions of brain functioning and, it is hoped, reveal targets for prevention and treatment of depression in adolescents.

Article Information

From the Department of Psychiatry, Harvard Medical School, Boston; and the Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, Massachusetts.

Address correspondence to Diego A. Pizzagalli, Ph.D., Center for Depression, Anxiety and Stress Research, McLean Hospital, 115 Mill Street, Belmont, MA 02478; E-mail: dap@mclean.harvard.edu.

Received Aug 18, 2015; accepted Aug 19, 2015.

References

1. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015): Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72:603–611.
2. Ho TC, Connolly CG, Henje Blom E, LeWinn KZ, Strigo IA, Paulus MP, et al. (2015): Emotion-dependent functional connectivity of the default mode network in adolescent depression. Biol Psychiatry 78:635–646.
3. Menon V (2013): Developmental pathways to functional brain networks: Emerging principles. Trends Cogn Sci 17:627–640.
4. Nolen-Hoeksema SG, Girgus JS (1994): The emergence of gender differences in depression during adolescence. Psychol Bull 115:424–443.
5. Bajaj S, Adhikari BM, Dhamala M (2013): Higher frequency network activity flow predicts lower frequency node activity in intrinsic low-frequency BOLD fluctuations. Plos One 8:e64466.
6. Chang C, Glover GH (2010): Time-frequency dynamics of resting-state brain connectivity measured with fMRI. Neuroimage 50:81–98.
7. Normann N, van Emmerik AAP, Morina N (2014): The efficacy of metacognitive therapy for anxiety and depression: A meta-analytic review. Depress Anxiety 31:402–411.
8. Walter M, Henning A, Grimm S, Schulte RF, Beck J, Dydak U, et al. (2009): The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. Arch Gen Psychiatry 66:478–486.
9. Gabbay V, Ely BA, Li QY, Bangaru SD, Panzer AM, Alonso CM, et al. (2013): Striatum-based circuitry of adolescent depression and anhedonia. J Am Acad Child Adolesc Psychiatry 52:628–641.
10. McCauley E, Gudmundsen G, Schloredt K, Martell C, Rhew I, Hubley S, Dimidjian S (2015): The adolescent behavioral activation program: Adapting behavioral activation as a treatment for depression in adolescence [published online ahead of print Jan 20]. J Clin Child Adolesc Psychol. http://dx.doi.org/10.1080/15374416.2014.979933.