

Resting State Functional Connectivity and Depression: In Search of a Bottom Line

Ellen Leibenluft and Daniel S. Pine

Over the past 5 years, the increase in the number of studies examining resting-state functional connectivity (RSFC) has been nothing short of astonishing. This upsurge is fueled by the fundamental insights such studies provide regarding the organization of neural circuitry in health and disease and the fact that the technique is relatively easy to use. In concert with other techniques used to assess connectivity, the RSFC literature has shifted the field's approach to pathophysiology, such that investigators now focus less on functioning within individual brain regions and more on the ways in which these regions interact to function as part of an integrated circuit.

This edition of *Biological Psychiatry* includes an important addition to the RSFC literature from Connolly *et al.* (1). The investigators compare RSFC in a sample of 23 adolescents with major depressive disorder (MDD) and 36 healthy subjects. The sample is remarkable because patients were medication-free for at least 2 weeks, and patients and comparison subjects were well matched for IQ, socioeconomic status, age, sex, ethnicity, and pubertal stage. Such adolescent samples are difficult to recruit and study, but it is particularly important to study RSFC in adolescents with depression because most cases of adult depression begin in adolescence. Thus, adolescence is characterized both by marked brain plasticity and by rising risk for depression, providing a potential inflection point for treatments designed to alter the life-course trajectory of depressive illness.

Connolly *et al.* (1) use a seed-based analysis focused on the subgenual anterior cingulate cortex (sgACC). In MDD versus healthy subjects, the authors find increased functional connectivity between the sgACC and both the amygdala and the insula. In addition, the authors report increased negative connectivity between the sgACC and the precuneus in MDD versus healthy subjects. Figure 1 depicts the relationships among these structures. The precuneus, adjacent posterior cingulate and retrosplenial cortex, and sometimes the sgACC (discussed subsequently), are considered important nodes in the default mode network (DMN), a distributed neural network whose fundamental importance was most persuasively elucidated through RSFC studies. This network is centered in midline structures (Figure 1) and tends to show increased activity during rest and decreased activity during cognitively demanding tasks. The authors also find that increased rumination is associated with decreased connectivity between the sgACC and the middle and inferior frontal gyri.

The results in Connolly *et al.* (1) include both expected and unexpected findings. The investigators' choice of a sgACC seed was extremely well supported because studies using a variety of

imaging approaches converge on the conclusion that sgACC dysfunction plays an important role in the pathophysiology of depression. Such work has led to clinical trials with results suggesting that deep brain stimulation in this region may have a therapeutic effect in MDD (2). Thus, one important contribution in Connolly *et al.* (1) is to extend to adolescents a focus on the sgACC that has been a staple of research in adult MDD. Moreover, as detailed subsequently, some form of perturbed RSFC would be expected in adolescent MDD, given the longitudinal continuity between adolescent and adult MDD.

The RSFC literature treats both the ventral medial prefrontal cortex and the precuneus as vital nodes within the DMN. However, studies vary as to whether they consider the DMN to extend as far ventrally and posteriorly as the sgACC (shown in Figure 1, lying on the posterior and inferior edge of the DMN). Whether the sgACC is viewed as part of the DMN, studies in MDD do, with some consistency, find abnormally increased functional connectivity within the DMN or between the DMN and the sgACC (3–6). Thus, Connolly *et al.*'s finding of increased connectivity between the sgACC and the precuneus is expected. However, there is one unexpected aspect of this finding: Connolly *et al.* (1) report increased negative connectivity between the precuneus and sgACC, but RSFC networks such as the DMN have historically been conceptualized as encompassing the regions in Figure 1 with high positive connectivity; negative connectivity among regions that compose a network is therefore unexpected.

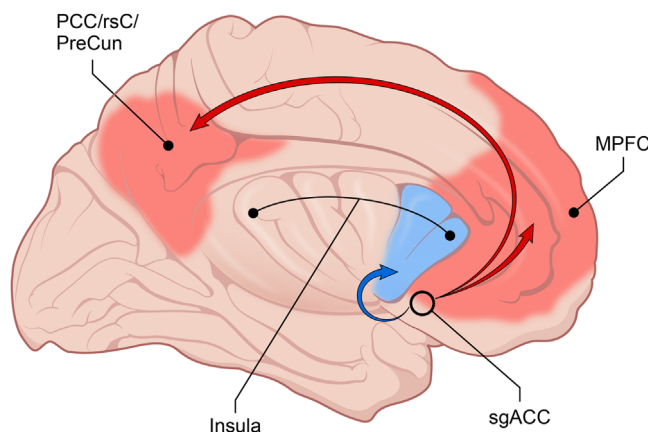


Figure 1. The figure depicts components of the default mode network (DMN) in red shading. These components include the subgenual anterior cingulate cortex (sgACC), the medial prefrontal cortex, and the posterior cingulate cortex/retrosplenial cortex/precuneus (PCC/rsC/PreCun). The red arrow displays connectivity between the sgACC and other components of the DMN, including medial prefrontal cortex (MPFC) and PCC/rsC/PreCun. In Connolly *et al.* (1), adolescents with major depressive disorder exhibited abnormal connectivity between the sgACC and PreCun. The figure also depicts the insula, where the anterior expanse is shaded in blue. The blue arrow displays connectivity between the sgACC and anterior insula, which is a node in another network, the salience network. In Connolly *et al.* (1), adolescents with major depressive disorder exhibited abnormal connectivity between the insula and the sgACC, a DMN node.

From the Emotion and Development Branch, Division of Intramural Research Programs, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland.

Address correspondence to Ellen Leibenluft, M.D., Building 15K Room 210, MSC 2670, 15K North Drive, Bethesda MD 20892-2670; E-mail: leibs@mail.nih.gov.

Received Oct 1, 2013; accepted Oct 2, 2013.

Beyond abnormal sgACC–precuneus connectivity, Connolly *et al.* (1) also find increased positive connectivity between the sgACC and the insula in MDD versus healthy subjects, as also depicted in Figure 1. Because the insula, rather than the DMN, is commonly viewed as part of an affective salience-monitoring network, this finding differs from previous studies reporting increased connectivity within the DMN of depressed subjects. However, Connolly *et al.*'s (1) finding does have precedent: several studies in MDD report abnormal coupling not only within but also between neural networks. For example, using graph analysis, Zhang *et al.* (7) found greater global integration across networks in depressed versus healthy subjects. Using a different approach, Sheline *et al.* (4) reported that, in depressed versus healthy subjects, there was greater connectivity between a region in the dorsal medial prefrontal cortex and three major neural networks (cognitive control, default mode, and affective networks), so that this “dorsal nexus” functioned as a central hub only in the patients. Although Connolly *et al.* use yet a third analytic approach, their finding can be viewed as broadly consistent with these earlier studies. Taken together, this work suggests that the sgACC, a central region in the pathophysiology of depression, may be the site of perturbed connectivity between the salience and default mode networks.

Finally, Connolly *et al.* (1) add to the literature by showing associations between RSFC and clinical measures, including depression severity, level of impairment, and amount of rumination. The latter is particularly interesting given its theoretical relevance to RSFC, that is, anterior regions of the DMN are thought to mediate self-referential thought, including rumination. Because rumination is a prominent symptom in depression, a number of RSFC studies in subjects with MDD have examined associations between rumination and connectivity within the DMN. For example, Berman *et al.* (8) found that, compared with healthy subjects, those with MDD showed increased connectivity within the DMN (specifically, between sgACC and the posterior cingulate cortex) during rest but not task periods. Furthermore, in depressed subjects, connectivity during rest correlated with measures of rumination. Hamilton *et al.* (9) devised a quantitative method for estimating the relative dominance of the DMN and a task-activated network and reported that, in patients with MDD, there was a positive correlation between DMN dominance and depressive rumination. Of note, although the literature tends to support an association between rumination in depressed subjects and increased connectivity within the DMN, Connolly *et al.*'s (1) finding links rumination with decreased connectivity across neural networks. Specifically, Connolly *et al.* (1) report an association between rumination and decreased connectivity between the sgACC and both the inferior and medial frontal gyri, with the latter regions being components of the central executive network (CEN) that mediates cognition. The authors suggest that the CEN may function to decrease rumination, so that patients with relatively low connectivity between the CEN and sgACC therefore show more prominent rumination.

This growing work on RSFC in MDD has yielded tantalizing findings, but the devil is very much in the details. That is,

although many studies in MDD find abnormal connectivity, there is considerable variation across studies in the nature of the findings, hindering attempts to distill a clear message from the growing number of studies. Clearer conclusions might emerge more quickly if one goal of future work was to increase cross-study coherence in analytic methods. Clearly, it is reasonable for each research group to use an analytic approach that is ideally tailored to test their specific hypotheses. However, the beauty of RSFC is that it also can support shared analytic approaches that could generate consensus on connectivity in MDD. Given the relative simplicity of acquisition, RSFC data are well suited for sharing across sites, and the RSFC research community is to be commended for actively pursuing open-access data sharing (10). On the analytic side, after testing study-specific hypotheses with one analytic approach, RSFC-focused investigators might consider adopting a second analytic approach that would be implemented uniformly across all studies of MDD. This could reveal the extent to which any inconsistency in RSFC findings across age groups and patient samples arises from inconsistencies in analytic approaches. In this way, investigators would facilitate cross-institution collaborations that could generate a consistent message from the impressive and rapidly growing series of RSFC studies on MDD and other psychopathologies across the life span.

The authors report no biomedical financial interests or potential conflicts.

1. Connolly CG, Wu J, Ho TC, Hoeft F, Wolkowitz O, Eisendrath S, *et al.* (2013): Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biol Psychiatry* 74:898–907.
2. Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, *et al.* (2012): *Arch Gen Psychiatry* 69:150–158.
3. Wang L, Hermens DF, Hickie LB, Lagopoulos J (2012): A systematic review of resting-state functional-MRI studies in major depression. *J Affective Dis* 142:6–12.
4. Sheline YI, Price JL, Yan Z, Mintun MA (2010): Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A* 107: 11020–11025.
5. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, *et al.* (2007): Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry* 62:429–437.
6. Davey CG, Harrison BJ, Yücel M, Allen NB (2012): Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. *Psychol Med* 42:2071–2081.
7. Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, Gong Q (2011): Disrupted brain connectivity networks in drug-naïve, first-episode major depressive disorder. *Biol Psychiatry* 70:334–342.
8. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J (2011): Depression, rumination and the default network. *Soc Cogn Affect Neurosci* 6:548–555.
9. Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH (2011): Default-mode and task-positive network activity in major depressive disorder: Implications for adaptive and maladaptive rumination. *Biol Psychiatry* 70:327–333.
10. Mennes M, Biswal BB, Castellanos FX, Milham MP (2013): Making data sharing work: The FCP/INDI experience. *Neuroimage* 82:683–691.