COMMENTARY

Connectomics Reveals Faulty Wiring Patterns for Depressed Brain

Yanchao Bi and Yong He

Uncovering the neural basis of psychiatric and neurological disorders is the foundation for the development of diagnosis and treatment programs. While disorder-related changes in focal brain areas and specific brain connections have been scrutinized, a recently developed research framework—human brain connectomics (1)—offers the opportunity to study the brain as a complex, integrative network. In a nutshell, a brain network can be constructed on the basis of connections (edges) among brain regions (nodes) derived from a variety of imaging data. The constructed networks can then be viewed as a graph, with mathematical measures available to quantify its various types of topological properties. Such methods reshape how brain structure and function can be conceptualized and studied and provide a whole new perspective of how diseased brain can be understood.

In this issue of *Biological Psychiatry*, Korgaonkar *et al.* (2) present an excellent example of how the connectomic approach advances our knowledge of psychiatric disorders like depression. In this work, they collected diffusion tensor imaging data from a large cohort of 95 individuals with major depressive disorder, who were drug naïve or had undergone a washout period of at least five half-lives of antidepressant medication, and 102 age- and gender-matched control subjects. Individual whole-brain structural networks were first constructed by tracking white matter (WM) connections, representing network edges, across pairs of 84 cortical and subcortical regions, representing network nodes, through a multi-fiber diffusion probabilistic model. Group-based statistical comparisons were then performed on various properties of the network involving connectional, nodal, and global measures.

Using network-based statistical analysis (3), which allows for localization of specific pairs of brain regions with abnormal WM connections in patients, Korgaonkar *et al.* (2) observed that patients with depression had significantly disrupted structural connectivity within two subnetworks: the first was primarily composed of the regions of default mode network including the rostral anterior cingulate cortex, posterior cingulate cortex, and precuneus, and the second mainly contained the frontal-subcortical regions involving the superior and middle frontal cortex, thalamus, and caudate. Regions identified in these two networks correspond well to those in which depressive individuals tend to manifest disruptions. For the default mode network, accumulative evidence has linked it to the processing of self. Regions within this network are more strongly activated and functionally synchronized when subjects are focusing on one's own thoughts and feelings, judging about one's own characters,

planning one's future, and forming one's beliefs (4). Individuals with depression show various types of functional alterations in this network, including hyperactivity during emotion processing tasks and increases of regional cerebral blood flow, cerebral glucose metabolism, and functional connectivity during rest (4). The frontal-subcortical network they observed has been consistently shown to be important in regulating cognition and emotion. Depression-associated changes have also been found in regions of this network, such as increased resting-state functional connectivity in dorsal lateral prefrontal cortex (5) and in caudate (6). The functional alterations of the default mode network and the frontal-subcortical network in patients with depression might underlie their impairments in emotion and cognitive regulation and self-perception, such as failures in effectively toggling between internal emotional and cognitive states and the tasks at hand. Importantly, the study by Korgaonkar *et al.* (2) provides further evidence for the structural basis of these functional deficits.

Notably, while both structural and functional network analysis results point to the critical effects of the default-mode and frontal-regulatory networks in depression, the relationship between these two modals is rather complex (7). The structural connectivity was frequently shown to be reduced in patients with depression (2,8–10); yet, both weakened and enhanced functional connectivities have been reported (5,6). Particularly compelling were findings in de Kwaasteniet *et al.* (9), where depressive patients showed increased resting-state functional connectivity and decreased WM structural connectivity between the subgenual anterior cingulate cortex and the hippocampus. Furthermore, in the depressed patients, and not the control subjects, the structural and functional connectivities were negatively correlated. While the functional hyperconnectivity could in theory be either compensatory or pathologic, a set of studies has shown significant correlation between the functional connectivity and depressive behavior such as severity or duration [e.g., (6)], suggesting that the functional enhancement was at least partly compensatory. One tentative explanation for the different directions of the structural and functional changes is that the structural disruption determines the presence of depression, and in some cases the functional connectivity is elevated to compensate for the structural loss. The severity of the depressive symptoms may thus be better predicted by how much the functional enhancement can make up for the structural impairment. Of course, such speculations are based on loose observations across different studies with varying patient cohorts and analysis methodologies. Multimodal imaging studies that directly examine the structure-function association on the network level in the same depression group are warranted.

Korgaonkar *et al.* (2) also carried out graph theoretical analyses on the whole-brain WM structural networks to evaluate the global and nodal topological properties. Using a stringent statistical threshold, they did not detect any significant changes in either global or regional nodal characteristics. However, the depressive group did show tendency of longer ($p < .05$, uncorrected) characteristic shortest path length (which corresponds to lower

From the State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China.

Address correspondence to Yong He, Ph.D., State Key Laboratory of Cognitive Neuroscience and Learning, and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China; E-mail: yong.he@bnu.edu.cn.

global efficiency of the parallel information transfer in the network) and higher ($p < .01$, uncorrected) nodal centralities in the rostral anterior cingulate cortex and superior and middle frontal cortex. Indeed, other studies have reported similar findings: global network integrity disruption was found in elderly depressed patients, as reflected by reduced network strength, global efficiency, and increased path length (10), and nodal efficiency reduction was reported in the default mode and prefrontal regions in geriatric depression (10) and in a group of depression patients with great age span [age 22 to 53 (8)]. Thus, depression seems to be associated with topological abnormalities of WM structural network. As a general principle, the balance between avoiding type I and type II errors should be carefully considered when choosing the appropriate statistical methods, and the convergent picture over multiple studies is usually more informative.

The study of Korgaonkar et al. (2) has multifaceted implications for depression research. First of all, pathologic structural networks and circuits (default mode and frontal-subcortical) associated with depression were identified, providing novel insights into the pathogenesis of depression. Furthermore, several regions with significant changes in depression (e.g., the anterior and posterior cingulate cortex, precuneus, superior and middle frontal cortex, and thalamus) were so-called brain hubs, which have a large number of connections and are central to large-scale information communication. It is possible that pathology for depression specifically targets certain network hubs and relevant connections, which, in turn, induce system-level alterations. Clinically, these results point to new methods for patient classification on the basis of network changes, providing framework for the biomarker development. These results are also important in aiding effective treatments. The success of treatment programs for depression, especially brain stimulation therapies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and deep brain stimulation, depends on the understanding of the brain circuitry disruption pattern and the ways in which such a pattern may be altered by the stimulation. The key nodes and connections within the two depression-related networks being identified serve as primary targets for stimulation therapies and pharmacologic intervention. Indeed, research has demonstrated that stimulation to the subgenual anterior cingulate cortex and dorsolateral prefrontal cortex extenuated depressive symptoms, coupled with changes in their functional connectivities. Future studies should test the relative importance of the constituent nodes and WM connections within these networks as the candidate targets to stimulate. Furthermore, monitoring the changes of these two networks as the result of intervention and corresponding behavioral consequences would help to evaluate and optimize the effectiveness of the treatment.

Imaging depressive brain networks with connectomics is still at its infancy and there are important methodological issues to be considered. First, diffusion tensor imaging tractography provides an indirect estimate of real fiber connections and is especially prone to errors in resolving fiber crossings. Advanced imaging techniques that cope with these challenges, such as diffusion spectrum imaging and high angular resolution diffusion imaging, are desired. Second, WM structural network can be obtained using different node and edge definitions. Nodes can be defined using various regional parcellations with vastly different numbers of nodes; edges can be generated based on diffusion magnetic resonance imaging data using different tracking methods, such as probabilistic and deterministic tracking, and various physical property measures, such as fractional anisotropy, mean diffusivity, and streamline number. These different network construction and analysis strategies might have different sensitivities in detecting depression-associated circuitry abnormalities. Validations across multiple approaches are also essential for obtaining reliable brain network results. Third, much caution should be taken in patient sampling. Depression is a highly heterogeneous clinical syndrome. Patient demographic variables (such as age and gender), depression symptom classifications, and cognitive profiles, as well as history of drug abuse or childhood neglect, should be carefully considered. Finally, the biological mechanisms of the WM network changes in depression are largely unknown. Studies from various imaging methodologies involving brain morphometry and metabolic and biochemical measures should be jointly advanced to paint a comprehensive picture of depressive brain networks.

1. Sporns O, Tononi G, Kotter R (2005): The human connectome: A structural description of the human brain. *PLoS Comput Biol* 1:e42.
2. Korgaonkar MS, Fornito A, Williams LM, Grieve SM (2014): Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biol Psychiatry* 76:567–574.
3. Zalesky A, Fornito A, Bullmore ET (2010): Network-based statistic: Identifying differences in brain networks. *Neuroimage* 53:1197–1207.
4. Whitfield-Gabrieli S, Ford JM (2012): Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol* 8:49–76.
5. 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.
6. Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, Gong Q (2011): Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biol Psychiatry* 70:334–342.
7. Wang Z, Dai Z, Gong G, Zhou C, He Y (2014): Understanding structural-functional relationships in the human brain: A large-scale network perspective [published online ahead of print June 24]. *Neuroscientist.* doi:10.1177/1073858414537560.
8. Qin J, Wei M, Liu H, Yan R, Luo G, Yao Z, Lu Q (2013): Abnormal brain anatomical topological organization of the cognitive-emotional and the frontoparietal circuitry in major depressive disorder [published online ahead of print November 22]. *Magn Reson Med.* doi:10.1002/mrm.25036.
9. de Kwaasteniet B, Ruhe E, Caan M, Rive M, Olabarriaga S, Groefsema M, et al. (2013): Relation between structural and functional connectivity in major depressive disorder. *Biol Psychiatry* 74:40–47.
10. Bai F, Shu N, Yuan Y, Shi Y, Yu H, Wu D, et al. (2012): Topologically convergent and divergent structural connectivity patterns between patients with remitted geriatric depression and amnestic mild cognitive impairment. *J Neurosci* 32:4307–4318.