Commentary

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Functional and Structural Brain Connectivity in Psychopathology

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Since the advent of modern "biological psychiatry" in the 1950s, much work on understanding the etiology of mental illness has focused on identifying the neural mechanisms that contribute to the development and maintenance of varying forms of psychopathology. This work has been aided by advances in neuroimaging technologies, such as the use of single photon emission computed tomography, positron emission tomography, and magnetic resonance imaging for the assessment of structural and/or functional characteristics of the human brain. Basic and translational research on task-related brain activation has been hugely informative in terms of understanding of the neural substrates of particular cognitive and affective processes and how these may go awry in psychopathology. However, it is now clear that a particular task never activates a single brain region, and rarely is any particular domain of psychopathology associated with abnormal activation in only a single brain region. Furthermore, basic neuroscience research has long made it clear that activity in any individual brain region (or any individual neuron) is the result of inputs from and outputs to different areas of the brain. Such realizations have led to a shift in focus to questions regarding neural circuits, rather than a focus only on specific brain regions. More specifically, this shift has been to questions about the relationship between and among different brain regions in producing successful cognitive and affective function in health and the ways in which abnormalities at the level of circuits contribute to the development and maintenance of specific dimensions of psychopathology.

The growing work on the role of brain oscillations in coordinating activity among and between neutral networks (1–4) is consistent with hypotheses that localize impairment in psychopathology at the circuit level of function, rather than within specific individual brain regions (5). Furthermore, in many ways, it is easier to connect circuit level hypotheses with the larger literature on impairments at other levels of analysis in psychopathology (e.g., neurotransmitter availability, receptors, dendritic spine density, excitatory-inhibitory balance). Such impairments are frequently not regionally specific (6) and involve processes and mechanisms that would reasonably be expected to alter interregional communication, either with cortex or between cortical and subcortical regions (6).

Aimed at highlighting this conceptual shift, this special issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* has three goals. The first is to address some of the methodological issues relevant to understanding human functional and structural brain connectivity as well as to highlight certain methodological advances that provide novel pathways for investigating large-scale circuit level dysfunction associated with psychopathology. As discussed in many of the reviews in this special issue, a major methodological challenge facing studies of both functional and structural brain connectivity relevant to psychopathology is movement-related confounds. As noted by Castellanos and Aoki (7), movement may be a particularly serious problem for studies working with populations in whom difficulties with cognitive control and/or inhibition, such as individuals with attention-deficit/hyperactivity disorder (ADHD), may make remaining still enormously challenging. Movement can confound functional (8,9) and structural (10) measures of brain connectivity and is something that needs to be carefully addressed in both the analysis of data and its interpretation (i.e., when might group differences in connectivity reflect group differences in movement). Novel methods that can help address movement-related confounds in the analysis stage continue to emerge (9–12).

The articles in this special issue also highlight other methodological advances that move forward our understanding of brain connectivity in psychopathology. For example, Collin *et al.* (13) and Chase and Phillips (14) each point out the usefulness of applying graph theory approaches to the analysis of functional and structural connectivity data, allowing novel insights into brain organization and function through concepts such as efficiency and hubs. In addition, Chase and Phillips (14) allude to the growing literature on dynamic changes in functional connectivity over time as a potentially interesting direction for future research. Furthermore, Calhoun and Sui (15) highlight the utility of multimodal fusion methods that allow researchers to directly link findings across modalities. Such an approach may have particular utility for linking across structural and functional connectivity levels of analysis, an approach important for a fuller understanding of the mechanisms of large-scale circuit level dysfunction associated with psychopathology.

A second goal of this special issue is to address the current state of knowledge in regard to alterations in functional and structural connectivity in various forms of psychopathology. To this end, the articles by Collin *et al.* (13), Karlsgodt (16), Calhoun and Sui (15), and Sutcliffe *et al.* (17) each provide a different perspective on the literature regarding structural and functional brain connectivity in psychosis, including an illuminating discussion of the history behind concepts related to altered connectivity in schizophrenia by Collin *et al.* (13). Similarly, Fischer *et al.* (18), Smagula and Aizenstein (19), and Chase and Phillips (14) each provide reviews of different aspects of mood pathology, including adult depression (18), late life depression (19), and bipolar forms of depression (14). In addition, Castellanos and Aoki (7) provide a review of the literature on functional connectivity in ADHD, MacNamara *et al.* (20) provide a review on both resting-state and task-based

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connectivity in various forms of anxiety, and Vasa *et al.* (21) provide a review of both structural and functional connectivity studies in autism. There are several themes that emerge across these reviews. One theme is that although there is growing, and at least somewhat consistent, evidence in some areas for certain types of connectivity abnormalities, such as the abnormal functional connectivity between the amygdala and the lateral regions of the ventral prefrontal cortex in bipolar disorder described by Chase and Phillips (14), there is still considerable variability across the results of different studies of putatively the same phenotype. As such, there is a need for work that closely examines possible meaningful sources of this variability in results, such as developmental stage, medication status, sex, symptom severity, or comorbidity.

A second theme is that many of the same networks appear to show at least some evidence of altered connectivity across putatively different forms of psychopathology. One excellent example in this regard is connectivity of the default mode network. Eight of the articles in this special issue describe some evidence for altered default mode network connectivity in forms of psychopathology including autism, ADHD, anxiety, depression, and psychosis. In some cases, the nature of the alteration in default mode network connectivity may vary across forms of psychopathology, such as evidence for increased connectivity in the default mode network in depression (18) versus decreased connectivity of the default mode network in anxiety (20) and ADHD (7), and altered coupling of the default mode network with other networks, such as the frontal-parietal system in schizophrenia (7). However, the findings of at least some evidence of similar alterations in connectivity (e.g., in frontoparietal and cingulo-opercular or salience networks) across what might appear to be relatively different manifestations of psychopathology raise intriguing questions about whether such changes might be related to core dimensions that may cut across traditional diagnostic boundaries, a question of high importance for future research efforts in this area.

A third goal of this special issue is to illustrate the ways in which functional and structural brain connectivity may be novel targets for intervention. For example, Karlsgodt (16) discusses the potential uses of polyunsaturated fatty acids, which determine the rate of phospholipid synthesis, a key component of the pathway to increased myelination. In addition, both Karlsgodt (16) and Fischer *et al.* (18) discuss the potential use of transcranial magnetic stimulation or other interventions (e.g., transcranial direct current stimulation) that may influence myelination or other forms of plasticity.

In conclusion, we believe that the articles presented in this special issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* provide an important entryway into the burgeoning literature on the role of large-scale circuit level abnormalities in a variety of forms of psychopathology as well as some of the important current directions in methods and data analysis of structural and functional connectivity. As noted in several of the articles, the work on human brain connectivity continues to evolve as both the acquisition and the analysis methods develop and expand. The existing evidence points to the functional relevance of these networks to understanding variation in cognition and emotion in a wide range of manifestations of psychopathology and even points to altering connectivity as a potential novel target of intervention. As discussed by Vasa *et al.* (21), a next key step in the evolution of this field will be to begin to link circuit level abnormalities at the scale measured with diffusion and functional neuroimaging with more microlevel circuit abnormalities, such as local oscillations and interregional phase coherence to build bridges that allow us to understand, predict, and, it is hoped, intervene in the development of connectivity abnormalities across levels of analysis in psychopathology.

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