The human connectome in health and psychopathology

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A basic tenet of biological psychiatry is that psychiatric disorders are driven by abnormalities in brain function, which in turn reflect abnormalities in the underlying brain circuits, i.e., in the wiring of the brain. These circuit abnormalities presumably reflect a complex interplay between genes and environment. Many psychiatric disorders have strong genetic underpinnings: common or rare variants of genes, individually or in combination, elevate the susceptibility to disorders such as autism (1), schizophrenia (2), and many others.

Most psychiatric disorders are thought to be neurodevelopmental in nature, either because symptoms typically arise during childhood (e.g., autism) or because the interactions between genes and environment begin early, even if the onset of the disorder becomes evident only in adolescence or adulthood.

To better understand, diagnose, and treat psychiatric disorders, it is crucial to obtain deeper insights into brain circuits in health and disease and in humans and animal models. Here, we focus on the relevance of human *in vivo* neuroimaging, particularly involving magnetic resonance imaging (MRI). We briefly address three major points. First, recent neuroimaging studies have already provided important insights about abnormalities related to brain structure, function, and connectivity in psychopathology. Second, recent advances in neuroimaging of healthy adults, including many driven by the Human Connectome Project, offer exciting prospects for accelerated progress in characterizing disease-related brain connectivity abnormalities. Third, methodological limitations of each neuroimaging method, some of which are inadequately appreciated, require critical assessments and careful interpretation of research findings, especially when placed in the context of the extraordinary complexity of brain circuits revealed by studies of laboratory animals.

MEASURING HUMAN BRAIN STRUCTURE, FUNCTION, AND CONNECTIVITY

The human brain contains about 90 billion neurons and 150 trillion synapses. Physically, the dominant structure is the cerebral cortex, a highly convoluted sheet containing most of the synapses but only ~20% of the neurons (3). The cortex is a mosaic containing hundreds of distinct areas (parcels), but accurate mapping of their location, function, and connectivity is an ongoing quest.

Individual variability in cortical structure, function, and connectivity is likely to underlie much of what determines our unique personalities, including behavioral disorders. However, cortical interactions with a complex array of subcortical nuclei (~8% of brain volume but only ~1% of neuronal number) and with the cerebellum (~10% of brain volume, ~80% of the neurons) are extremely important as well (3,4). Data from nonhuman primate studies suggest that there are ~10,000 long-distance pathways between cortical and subcortical parcels ranging widely in their connection strength (5,6). Deciphering even a modest fraction of this circuitry in the human brain is truly a daunting endeavor.

Four major MRI modalities provide views of human brain structure, function, and connectivity. First, structural MRI uses volume-based analyses to estimate the distribution of gray matter regions, and surface-based analyses to assess cortical thickness and folding patterns. Second, task functional MRI (fMRI) identifies regions of increased or decreased fMRI blood oxygen level dependent (BOLD) signal that in turn reflects brain activity (synaptic currents and neuronal spiking) via a complex and still poorly understood mechanism of neurovascular coupling (7). Third, diffusion imaging (dMRI) and tractography enable characterization of "structural connectivity" using preferential diffusion of water molecules along the length of axons to estimate the dominant fiber orientation(s) in each white matter voxel, then inferring long-distance connectivity based on (deterministic or probabilistic) tractography algorithms. Tractography is conceptually the closest approach to inferring direct anatomical connectivity, but it has significant practical limitations owing to the prevalence of crossing fibers, branching fibers, and other methodological confounds that can give rise to false positives and false negatives (6). Fourth, resting-state fMRI (rfMRI) relies on correlated fluctuations in the BOLD signal to infer "functional connectivity", that typically reflects brain regions sharing a history of coactivation. This may reflect anatomically direct connectivity, but coactivation may occur instead or in addition through common inputs or indirect connections (8).

The spatial resolution of each MRI modality depends on the size of individual volume elements ("voxels"), which in turn reflects the signal to noise constraints of each approach. Voxel dimensions are typically 1 mm for structural MRI, ~3 mm for fMRI, and ~2 mm for dMRI, but methodological advances by the Human Connectome Project described below have substantially reduced voxel sizes for each mo-

dality. In the remainder of this paper, we focus mainly on advances revealed by analyses of structural and functional connectivity.

BRAIN CONNECTIVITY IN PSYCHIATRIC DISORDERS: RECENT HIGHLIGHTS

The past decade has seen a burgeoning literature applying currently available methods for assessing functional and structural connectivity to our understanding of course, outcome, treatment response and heterogeneity in psychiatric disorders, as well as their developmental antecedents (9). In many ways these studies are still in their infancy, but here we describe a few examples that highlight the potential utility and power of these methods for helping us to understand the pathophysiology of a range of psychiatric disorders.

Not surprisingly, one major focus has been to assess whether individuals with various forms of psychiatric disorders differ from individuals without psychiatric disorders in either structural and/or functional connectivity. For example, a recent meta-analysis of obsessive-compulsive disorder indicates that this illness is associated with altered structural connectivity between lateral prefrontal and parietal regions (10).

Importantly, the field is now moving beyond basic comparisons to healthy individuals by using measures of functional and structural connectivity to elucidate the progression of brain changes across different stages or phases of illness (11), and between individuals who have putatively different psychiatric disorders (12,13). This offers the prospect of critical insights about potentially dissociable etiological pathways.

A growing number of investigators are examining the relationship between individual differences in specific symptom or cognitive domains and structural and functional brain connectivity, both within and across diagnostic categories (14,15). This aligns well with the Research Domain Criteria (RDoC) initiative (16,17), which focuses on identifying core brain-behavior systems that may be critical for understanding psychopathology.

Another important thrust is to use connectivity measures to understand the predictors and mechanisms of treatment response for psychiatric disorders (18,19), providing insights into both the types of individual difference characteristics and the types of treatments that may facilitate plasticity.

Finally, an exciting new direction is to use structural and functional connectivity measures to elucidate risk factors for and the developmental antecedents of psychiatric disorders (20-22). Such information may provide novel avenues for early intervention or even prevention, as well as clues as to pathophysiology.

THE HUMAN CONNECTOME PROJECT AND BEYOND

The efforts summarized above are starting to provide valuable insights into circuit-based mechanisms of psychiatric disorders, but they represent only the tip of an "information iceberg" that can be better exposed using improved neuroimaging methods. Like many other arenas of neuroscience, neuroimaging has benefited from many recent improvements in data acquisition and analysis that hold promise for advancing our understanding of circuit level dysfunction in psychopathology. Here, we illustrate a few of the advances in human neuroimaging enabled by the Human Connectome Project (23).

Among the many improvements in data acquisition, the two most significant are "multi-band" pulse sequences, which benefit both fMRI and dMRI data acquisition (24,25), and customized scanners with increased maximum gradient strength, which benefits dMRI (24,26). For fMRI, this translates to better resolution in space (2 mm vs. typical ~3 mm voxels; 1.6 mm voxels at 7 Tesla), which enables accurate mapping of data to the cortical ribbon, and in time (0.7 s vs. typical ~2 s for each frame, or image volume), which increases sensitivity to dynamic activity patterns and also helps filter out noise. For dMRI, the improvement is in spatial resolution (1.25 mm vs. typical ~2 mm), which enables better identification of crossing fibers (27), plus the prospect of dealing better with gyral biases (6). Nonetheless, even with improved resolution, given the known densities of neurons and synapses, a fMRI voxel in the Human Connectome Project contains ~250,000 neurons and ~250,000,000 synapses, while a dMRI voxel contains hundreds of thousands of axons. Hence, the gulf between the micro- and macro-connectome domains remains enormous.

Improvements in Human Connectome Project data analysis include concurrent use of appropriate geometric models for cerebral cortex (as a surface mesh) and subcortical structures (as voxels) (28), and improved intersubject alignment using functionally relevant features as well as folding patterns (29). This is critical, given the dramatic individual differences in the physical pattern of cortical convolutions and the variability in size and location of cortical areas relative to folds.

The Human Connectome Project expects to complete data acquisition on 1200 healthy adult twins and nontwin siblings in 2015. Results from the ~500 subjects released to date are already beginning to emerge. The Connectome DB database serves as a user-friendly workhorse platform (http://www.humanconnectome.org) that to date has enabled sharing of nearly a petabyte (1 million gigabytes) of data with the scientific community. For rfMRI, this includes extensively processed data such as parcellations based on functional connectivity and functional connectivity matrices for individuals as well as population averages.

In 2014, the National Institutes of Health announced a Connectomes Related to Human Disease funding opportunity (http://grants.nih.gov/grants/guide/pa-files/PAR-14-281.html) for the study of brain disorders using advanced methods of data acquisition and analysis, with the resultant data to be shared via a Connectome Coordinating Facility that is an extension of Connectome DB. Hopefully, this

promotion of common strategies of acquiring and sharing high-quality neuroimaging data will accelerate progress in characterizing circuit abnormalities.

CONCLUSIONS

While there is reason to be optimistic about continued advances, it is also vital to be realistic about the limits that are attainable using current technologies. Ideally, we would like to see methods that enable diagnosis at the level of individual subjects. Further, it will be increasingly critical in future work to synergistically integrate analyses of both functional and structural connectivity, given their complementary strengths and information content.

In addition, it will be important to appreciate relationships in connectivity across spatial scales, such as understanding how disruption of local circuits (i.e., excitation/inhibition imbalance) may influence both larger scale functional connectivity (29), and even potentially structural connectivity over time.

The degree to which these aspirations will be feasible remains open to question, but we believe that the advances afforded by endeavors such as the Human Connectome Project and related projects are helping to provide the tools and data that are vital for accelerating progress.

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References

1. DeRubeis RJ, Cohen ZD, Forand NR et al. The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. PLoS One 2014;9:e83875.
2. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511:421-7.
3. Azevedo FA, Carvalho LR, Grinberg LT et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol 2009;513:532-41.
4. Pakkenberg B, Pelvig D, Marner L et al. Aging and the human neocortex. Exp Gerontol 2003;38:95-9.
5. Markov NT, Ercsey-Ravasz MM, Ribeiro Gomes AR et al. A weighted and directed interareal connectivity matrix for macaque cerebral cortex. Cereb Cortex 2012;24:17-36.
6. Van Essen DC, Jbabdi S, Sotiropoulos SN et al. Mapping connections in humans and nonhuman primates: aspirations and challenges for diffusion imaging. In: Johansen-Berg H, Behrens T (eds). Diffusion MRI, 2nd ed. Amsterdam: Academic Press, 2014: 337-58.
7. Hillman EM. Coupling mechanism and significance of the BOLD signal: a status report. Annu Rev Neurosci 2014;37:161-81.
8. Dosenbach NU, Fair DA, Miezin FM et al. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci USA 2007;104:11073-8.
9. Castellanos FX, Di Martino A, Craddock RC et al. Clinical applications of the functional connectome. NeuroImage 2013;80:527-40.
10. Piras F, Piras F, Caltagirone C et al. Brain circuitries of obsessive compulsive disorder: a systematic review and meta-analysis of diffusion tensor imaging studies. Neurosci Biobehav Rev 2013;37: 2856-77.
11. Canu E, Agosta F, Filippi M. A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease. Schizophr Res 2015;161:19-28.
12. Baker JT, Holmes AJ, Masters GA et al. Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. JAMA Psychiatry 2014;71:109-18.
13. Anticevic A, Savic A, Repovs G et al. Ventral anterior cingulate connectivity distinguished nonpsychotic bipolar illness from psychotic bipolar disorder and schizophrenia. Schizophr Bull 2015; 41:133-43.
14. Cole MW, Anticevic A, Repovs G et al. Variable global dysconnectivity and individual differences in schizophrenia. Biol Psychiatry 2011;70:43-50.
15. Spielberg JM, Miller GA, Warren SL et al. Transdiagnostic dimensions of anxiety and depression moderate motivation-related brain networks during goal maintenance. Depress Anxiety 2014; 31:805-13.
16. Insel T, Cuthbert B, Garvey M et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010;167:748-51.
17. Cuthbert BN. The RDoC framework: classificating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 2014;13:28-35.
18. Delorenzo C, Delaparte L, Thapa-Chhetry B et al. Prediction of selective serotonin reuptake inhibitor response using diffusion-weighted MRI. Front Psychiatry 2013;4:5.
19. Dichter GS, Gibbs D, Smoski MJ. A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. J Affect Disord 2014;172C:8-17.
20. Luking KR, Repovs G, Belden AC et al. Functional connectivity of the amygdala in early-childhood-onset depression. J Am Acad Child Adolesc Psychiatry 2011;50:1027-41.
21. Clauss JA, Seay AL, VanDerKlok RM et al. Structural and functional bases of inhibited temperament. Soc Cogn Affect Neurosci 2014;9:2049-58.
22. Lewis JD, Evans AC, Pruett JR et al. Network inefficiencies in autism spectrum disorder at 24 months. Transl Psychiatry 2014;4: e388.
23. Van Essen DC, Smith S, Barch D et al. The WU-Minn Human Connectome Project: an overview. Neuroimage 2013;62:1299-310.
24. Ugurbil K, Xu J, Auerbach EJ et al. Pushing spatial and temporal resolution for functional and diffusion MRI in the Human Connectome Project. Neuroimage 2013;80:80-104.
25. Smith SM, Andersson J, Auerbach EJ et al. Resting-state fMRI in the Human Connectome Project. Neuroimage 2013;80:144-68.
26. Setsompop K, Kimmlingen R, Eberlein E et al. Pushing the limits of in vivo diffusion MRI for the Human Connectome Project. Neuroimage 2013;80:220-33.

27. Sotiropoulos SN, Jbabdi S, Xu J et al. Advances in diffusion MRI acquisition and processing in the Human Connectome Project. Neuroimage 2013;80:125-43.
28. Glasser MF, Sotiropoulos SN, Wilson JA et al. The minimal preprocessing pipelines for the Human Connectome Projects. Neuroimage 2013;80:105-24.
29. Anticevic A, Gancsos M, Murray JD et al. NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. Proc Natl Acad Sci USA 2012; 109:16720-5.

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