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Resting State Functional Connectivity in the Human Connectome Project: Current Status and Relevance to Understanding Psychopathology

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Abstract

A key tenet of modern psychiatry is that psychiatric disorders arise from abnormalities in brain circuits that support human behavior. Our ability to examine hypotheses around circuit level abnormalities in psychiatric disorders has been made possible by advances in human neuroimaging technologies. These advances have provided the basis for recent efforts in the field to develop a more complex understanding of the function of brain circuits in health and of their relationship to behavior, which in turns provides a foundation for our understanding of how disruptions in such circuits contribute to the development of psychiatric disorders. The focus of this review will be on the use of resting state functional connectivity (rsfMRI) to assess brain circuits, the advances in this field generated by the Human Connectome Project, and the relevance of these advances for understanding neural circuit dysfunction in psychopathology. I focus on the methods developed by the Human Connectome Project that may be particularly relevant to studies of psychopathology, outline some of the key findings in terms of what constitutes a brain region, and highlight new information about the nature and stability of brain circuits. I then describe some of the new findings from the Human Connectome Project about neural circuits and their relationships to behavior that may be particularly relevant to psychopathology. Finally, I end on future directions in terms of extensions of the Human Connectome Project methods across the lifespan and into manifest illness, as well as a discussion of potential treatment implications.

A core principal of modern “Biological Psychiatry” is that psychiatric disorders arise from abnormalities in brain function – in other words, dysfunction of brain circuits that support human behavior. Such circuit level abnormalities clearly reflect a complex interplay between genes and environment, with most, if not all, psychiatric disorders reflecting both genetic underpinnings^{1–5} and a host of environmental factors^{6–10}. Further, most psychiatric disorders are likely to be neurodevelopmental in nature, either because symptoms arise during childhood (e.g., autism) or because the interactions between genes and environment that shape brain circuits and their function begin early in life, even if the onset of the disorder becomes evident only in adolescence or adulthood.

Our ability to empirically examine hypotheses around circuit level abnormalities in psychiatric disorders has been made possible by advances in human neuroimaging technologies. In turn, such technological advances have provided the genesis for major efforts in the field to develop a clearer understanding of the normative function of brain

circuits in health, which many consider to be critical in order to understand how disruptions in such circuits contribute to the development of psychiatric disorders. These efforts include initiatives such as the Human Connectome Project ^{11, 12}, the United Kingdom Biobank Project ¹³ and the recent Adolescent Brain and Cognitive Development study. The Human Connectome Project (HCP) was an National Institutes of Health funded project designed to improve methods for assessing brain structure and function and to acquire a large data set in relatively healthy adults that would enhance our understanding of normative patterns of brain connectivity and their relationships to behavior relevant to understanding psychopathology (i.e., depression, anxiety, substance use, cognitive function, social function, etc.).

Projects such as the HCP and related efforts incorporate four or more magnetic resonance imaging (MRI) modalities to understand the human brain: 1) structural MRI, which uses volumetric and surface based methods to understand both gray and white matter distributions; 2) task-based functional MRI, using blood oxygen level dependent (BOLD) signal as an indirect measure of neural activity while individuals engage in various cognitive, emotional, or sensory demands ¹⁴; 3) resting state functional connectivity fMRI (rsfcMRI), which measures the coordination of spontaneous fluctuations in BOLD activity across the brain ¹⁵; and 4) diffusion MRI (dMRI), which measures the diffusion of water along axons in the brain, which forms the basis for various deterministic and probabilistic assessments of white matter “tracts” in the brain ¹⁶. Each of these modalities provides unique and important information about the human brain.

The focus of this review will be on the use of rsfcMRI to assess human brain circuits, the advances in this domain afforded by the recently completed HCP, and the relevance of these advances for understanding neural circuit dysfunction in psychopathology. dMRI measures of white matter tracts are relevant to this question, and in part constrain rsfcMRI, though the two are not isomorphic. However, we focus on rsfcMRI rather than dMRI because of a particular interest in how brain circuits *function* together to support human behavior. Examining activity and connectivity during specific task states is also highly relevant to understanding how brain circuits function together. Further, it is important to point out that “rest” is not necessarily a special state and may simply be one type of task state. Nonetheless, the focus here is on rsfcMRI and does not include a focus on fcMRI or activity during task because of space constraints. This review will start with a very brief history of the development of methods to measure and understand human functional brain connectivity. This review will then describe the HCP and its advances, review some of the knowledge being generated by the HCP about neural circuits that may be particularly relevant to psychopathology, and discuss some of the findings from the HCP that directly relate rsfcMRI to behavioral dimensions relevant to psychopathology.

Functional Connectivity

Functional connectivity was originally studied in the context of simultaneous recordings of neuronal spike trains ^{17–19}, which are thought to contribute to the functional connectivity observed in human using non-invasive neuroimaging methods. If two regions have highly correlated neuronal activity (i.e. have high functional connectivity), then one inference is

that they are more likely to be relevant to a shared or common set of processing mechanisms. If so, then functional connectivity provides a tool for understanding which brain regions may be communicating during the completion of cognitive or affective demands, and therefore which brain circuits support performance in different domains of cognition, emotion, and/or social processing ²⁰.

A major shift in the way we study human brain functional connectivity came when Biswal and colleagues reported that spontaneous activity from regions in the right and left motor cortices were highly correlated even while an individual was resting ¹⁵. This finding highlighted the fact that there was “functional” connectivity between brain regions, even when people are not performing a specifically targeted task. Importantly, such resting brain state activity may consume a major portion of the body’s energy (~20%), despite the brain only being 2% of the body’s total mass ²¹. To put this in context, changes in metabolism due to engagement in a specific task are typically less than 5%, which suggests that ongoing resting state activity may provide a critical and rich source of disease-related variability ²¹. Further, there is also work suggesting that much of the trial-to-trial variability in task related activity reflects these spontaneous fluctuations in brain activity ²², providing another piece of evidence that these spontaneous fluctuations are a meaningful source of variation in human brain function.

The Human Connectome Project

There are a number of different ways in which the HCP rsfMRI methods, data and related efforts are important for our understanding of psychopathology. These include: 1) methodological advances; 2) advances in our understanding and identification of what constitutes a brain “region;” 3) advances in our understanding of the nature of brain networks and their stability; and 4) the generation of a large data set by which we can explore the relationships between individual differences in behaviors relevant to understanding psychopathology and individual differences in the organization and function of brain networks.

Methodological Advances

The HCP has generated a number of methodological advances relevant to the use of rsfMRI in the context of work both on health and psychopathology. This includes the creation of “multi-band” pulse sequences that allow for the rapid acquisition of whole brain high resolution BOLD activity in a short time frame ^{23–27}. The HCP used a version of the multi-band BOLD sequence that acquired an image of the whole brain at a 2mm isotropic voxel resolution in 720 milliseconds ²⁷. This compares to a typical whole-brain acquisition protocol for a single-band sequence with 3 to 4 mm isotropic voxel resolution in 2 to 3 seconds. In theory, the development of such multi-band sequences could have a potential practical application to psychopathology, in that one might be able to shorten the time needed to acquire resting state data in children or adult clinical populations, for which long acquisition periods might be prohibitive. For example, if we focused only on acquiring a specific number of whole-brain acquisitions (i.e., frames), one could acquire 1000 frames of a multi-band sequence, like the one used in the HCP, in 12 minutes. Even if you used a

higher spatial resolution (3 mm isotropic) for a whole-brain single-band acquisition, the TRs are typically ~2 seconds, meaning that 1000 frames would take 33 minutes. Thus, if one only considered the number of frames, the acquisition time could be reduced by almost two-thirds. However, there has yet to be a direct comparison of these two scan types (e.g., match on number of frames rather than total duration) in terms of outcomes such as test-retest reliability or network identification. Further, a focus on shorter durations would need to be balanced against a variety of competing factors, such as the somewhat lower signal-to-noise ratio of the multi-band sequences for any single individual acquisition²⁸ and the loss of signal-to-noise at higher spatial resolutions. Some of the signal-to-noise loss associated with higher multi-band factors can be gained back by acquiring more acquisitions in a fixed time, and some analysis approaches benefit from an increase in temporal resolution²³. However, recent work suggests that acquisitions of at least 20–30 minutes might be needed to obtain highly reliable individual subject estimates of rsfMRI even using multi-band sequences, depending on one's criterion for adequate reliability²⁹. In part, the length of time necessary to obtain robust single subject estimates of rsfMRI may reflect the intrinsic variability in the human brain over time, which may necessitate a minimum scan duration to obtain a good “central tendency” estimate²⁹. Thus, short rsfMRI acquisitions may not be appropriate for all applications and questions. At the same time, the higher spatial-resolution possible with multi-band sequences facilitates testing hypotheses that require finer-grained localization, such as hypotheses about the role of specific basal ganglia nuclei or thalamus^{30,31} or subregions of the amygdala or hippocampus in psychopathology^{32,33}, or the examination of small structures with rsfMRI that may have relevance to psychopathology, such as the habenula^{34,35}.

The HCP also developed a number of new processing and analyses approaches that reduce the amount of smoothing needed for accurate alignment of images³⁶, both across time within an individual and across individuals, and that support the use of surface based as well as volume based alignment of images^{36–38}. These advances are reviewed in detail in a number of published manuscripts^{16,36,39–41}, including a recent overview by Glasser et al³⁷. The HCP has provided added evidence of the pernicious influence of movement on rsfMRI, as well as information on important correlates of head movement (i.e., cognitive function) and its heritability^{42,43}. Fortunately, the HCP has also provided new tools and approaches for reduction of artifact and noise in multi-band rsfMRI data, including movement related artifact, as outlined in these published manuscripts^{44–46}. In addition, since the data from the HCP is publically released, many other groups have used it to generate new processing and analysis approaches for rsfMRI data^{47–56}. Although such enhancements in processing and analyses are not specific in benefiting research on psychopathology, they make possible high quality data acquisition and processing for all applications relevant to understanding human brain connectivity, including those focused on psychiatric disorders.

What Constitutes A Brain “Region”

Our search to understand neural circuits in the brain is constrained in important ways by our understanding of what the building blocks of such circuits are – in other words, what are the brain “regions” that form these circuits. Much of the early work in the domain used either more anatomically based definitions of regions, such as regions based on canonical

Brodmann areas⁵⁷ or automated anatomical labeling maps⁵⁸. While these parcellations have been very helpful to the field, they are based on structural or anatomical information that may or may not have functional relevance and are also based on limited information (i.e. a single individual). Thus, a number of researchers have explored alternative ways of defining brain regions, including those based on similarity or homogeneity in patterns of task related brain activation⁵⁹ or rsfMRI^{60–63}. In work supported in part by the HCP, Gordon and colleagues⁶⁴ used a boundary mapping technique with rsfMRI data to identify a parcellation of 356 regions that showed greater homogeneity in patterns of rsfMRI than either anatomically based regions or other rsfMRI parcellations, such as those reported in prior work^{60–62}. This parcellation was developed based on group-averaged data, but showed stability in many, though not all, individuals. Further, work has now begun on applying parcellation approaches to individual subjects^{65,66}.

Using data from the HCP, Glasser and colleagues also used boundary mapping approaches to identify brain regions using a multi-modal parcellation approach⁶⁷. This method used maps of myelin content, cortical thickness, task activation from seven tasks, and rsfMRI maps to identify 180 regions at the group level. However, they have also shown that this can be done in individual subjects with sufficient data, and that common regions can be mapped across individuals. These methods for defining brain regions may have relevance to psychopathology, as one could hypothesize that altered brain structure, connectivity, or function could lead to disrupted formation of brain regions, as defined by parcellations such as that of Glasser and colleagues. If so, this could, in turn, alter the formation of neural networks. The ability to identify brain regions in individuals and to map common regions across individuals can help test such hypotheses, by determining whether the shape, size, or location of “regions” themselves are altered in certain forms of psychopathology, and by examining the degree to which this may or may not contribute to alterations in the architecture and function of circuits formed from multiple brain regions.

Advances In Our Understanding Of The Nature of Brain Networks

Analyses of the data generated by the HCP have helped to confirm our growing understanding of core rsfMRI networks in the human brain⁴⁰ and to replicate prior work that previously identified a number of robust functional brain networks in the human brain e.g.,^{59,60,68–72}. Each of the commonly identified human brain networks using rsfMRI are likely relevant in some way to the understanding of psychopathology. However, there are several that may be particularly relevant to the functions and processes often found to be impaired in psychopathology. The *frontal-parietal* (FPN) and the *cingulo-opercular* (CON) networks have been repeatedly associated with a variety of cognitive control functions^{73,74}. The frontal-parietal network includes dorsal regions of both the lateral prefrontal cortex and parietal cortex. The cingulo-opercular network includes the dorsal anterior cingulate cortex, bilateral dorsal anterior insula, and in some work, both thalamic regions and anterior prefrontal regions. The *dorsal* and *ventral attention* networks have also been associated with cognitive function, including both stimulus driven and endogenous attention in particular^{75,76}. The dorsal attention network is related to the frontal parietal network in that it also includes both dorsal frontal and parietal regions, though typically not the same frontal and parietal regions found in the FPN. Further, the dorsal attention network also includes

more dorsal supplementary motor and eye field areas. The ventral attention system includes the temporal-parietal junction and the ventrolateral prefrontal cortex, and has been associated with attention to salient events in the environment, often activated when events (?) disrupt ongoing processing occur^{75,76}. The *default mode network* (DMN) has been linked to a number of different functions. One hypothesis is that the DMN is associated with attention to internal emotional states and the ability to distinguish or shift between internal and external modes of attention⁷⁷. Further, there is a large body of literature showing that the default mode network decreases activity during engaged task states, and some clues that the ability to successfully “shut down” the default mode network may be important for effective cognitive function^{78–81}. The default mode network includes the medial prefrontal cortex, medial posterior cingulate and precuneus regions. The *salience* network is one that has been identified somewhat more recently than some of the other networks⁷², and includes more rostral regions of the anterior cingulate and insula than typically allocated to the cingulo-opercular network, though both have connectivity with limbic and subcortical regions. Connectivity of the salience network has been associated with anxiety and arousal and is hypothesized to be a network of regions that serve to process and coordinate reactions to salient events in the environment⁸². Further, the salience network has been hypothesized to regulate the relationship between the FPN and DMN⁸³.

The data generated by the HCP has been used to advance our understanding of the nature of these networks in several ways. One active area of investigation with the HCP data, afforded in part by the relatively long acquisitions and a large amount of data, has been the examination of “dynamic” rsfMRI or changes in the patterns of connectivity over time within an individual. This work has attempted to identify various “states” or patterns in rsfMRI that may vary in structured ways over time^{84–88}. Further, others have linked variation in such dynamic rsfMRI to behavior, including executive function⁸⁹. However, recent work by Laumann and colleagues suggested that measures of dynamic rsfMRI are susceptible to confounding influences of factors such as arousal state and head motion⁹⁰. Importantly, there is much debate about the appropriate statistical models for assessing the presence of dynamic rsfMRI^{91,92} and thus much remains to be learned about the source of such dynamics in order to determine how clearly they can be interpreted as reflecting meaningful aspects of brain function and organization.

Another interesting advance by Cole and colleagues using HCP data has been to highlight the strong similarity in the networks identified at rest and those identified in data acquired during multiple task states⁹³. This similarity exists even when comparing data during any single task to rest, but is particularly strong when the aggregation of multiple task states is compared to rest. This may be because such aggregation “washes out” unique variation associated with any particular task, leaving the patterns shared across tasks⁹⁴. This finding has both theoretical and practical considerations for psychopathology research. At the theoretical level, it suggests that either (or both) that rsfMRI networks present during task states are strongly constrained by putatively intrinsic networks that are present even at rest, or that such resting state networks arise in part out of the activity dependent processes that drive task related activation. At a practical level, it suggests that much can be learned about fMRI networks from data acquired during tasks, potentially allowing task activation paradigms to do double duty in populations that may find it difficult to tolerate long rsfMRI

acquisitions, such as individuals with some forms of psychopathology. One caveat though is that we do not yet know the optimal number of different task states to combine in order to balance providing an unbiased estimate of intrinsic network connectivity with efficient data acquisition. For example, Bolt et al. compared rsfMRI to fcMRI in each of the same tasks examined by Cole et al., and found in general lower overall similarity between each individual task and rest (average r of .72 versus .83 for Cole et al.), and significant differences in a number of graph theoretic metrics (e.g., global efficiency, network clustering, etc.)⁹⁵. One hypothesis is that the differences across these two studies may reflect the fact that Bolt et al. did not regress out the influence of deterministic task design signals that could lead fcMRI in task data to appear less similar to rsfMRI, while Cole et al. did. Gratton et al. also removed task design signals in a different dataset and again found strong overall similarity between fcMRI network organization and topology during task as compared to rest, whether examining individual tasks or data aggregated across three tasks⁹⁶. However, at the same time, they also found interesting differences across tasks and rest⁹⁶. Thus, the idea of examining fcMRI during task states as a way mitigate subject demand in psychopathology populations is an intriguing one, but more work will be needed to determine optimal processing streams (e.g., whether to remove task design signals) and how much aggregation across multiple tasks is needed to best approximate rsfMRI. Further, it will be important to determine whether or not differences as a function of psychopathology or relationships to individual differences in behavior are equally apparent in either rsfMRI or task aggregated fcMRI, which could be true even if there are mean level differences in fcMRI across states⁹⁷.

rsfMRI and Behavior in the HCP: Relevance to Psychopathology

As noted above, one of the goals of the HCP was to generate and release to the public a large data set in which to explore relationships between individual differences in functional connectivity and behavior. Individuals who had a documented history of being diagnosed with and treated for a psychiatric condition by a professional for 12 months or longer were excluded from participation in the HCP, but there was considerable variation in cognitive and emotional function of the participants who were enrolled in the study, including some individuals who met diagnostic criteria for a psychiatric disorder at some point in their life. A growing number of studies have been using the HCP data to examine a wide variety of behavioral factors relevant to psychopathology, including cognitive function, mood, emotion, and substance use/abuse, with many creative studies addressing diverse questions. For example, in work by the HCP consortium itself, Steve Smith led an analysis identifying a central “mode” of functional connectivity that was related to many different individual difference attributes, ranging from fluid intelligence, use of substances, educational level, and depression⁹⁸. A focus on fluid IQ has been particularly popular, with a number of studies identifying aspects of functional brain connectivity relevant to IQ⁹⁹, such as connectivity in the frontal-parietal network, which shows stable individually identifiable patterns or rsfMRI that predict IQ¹⁰⁰.

In other work, investigators are also examining rsfMRI patterns that predict individual differences in depression, negative mood states, and anxiety, with evidence for relationships to connectivity of the habenula³⁴ and connectivity among the dorsal attention, default mode

and frontal-parietal networks¹⁰¹. In our own work, we have examined the interrelationships among cognitive function, psychotic-like experiences and rsfcMRI¹⁰². We found that global efficiency of the cingulo-opercular network (a measure of efficient network integration) predicted better overall cognition (first principal component from a factor analyses of many cognitive measures), that psychotic-like experiences were related to worse cognitive function, and that cingulo-opercular network global efficiency mediated the relationship between cognition and psychotic-like experiences. This set of findings followed up on prior work in individuals with manifest psychosis⁹⁴ to suggest that such relationships may extend across the spectrum of clinical psychosis and non-clinical psychotic-like experiences.

This work on individual difference relationships in the HCP data set is just starting, as the final release of the full data set just occurred in the spring of 2017. Importantly the design of the participant population includes many sets of siblings that contain pairs of monozygotic and dizygotic twins along with their siblings, a feature that will allow investigators to examine questions about the heritability of rsfcMRI metrics and their relationships, as well as questions about environmental versus genetic influences using family data¹⁰³ and discordant twin analyses^{104–106}. These findings will hopefully help generate novel hypotheses about the potential contributions of altered rsfcMRI to psychopathology, as they begin to identify individual difference relationships that may extend across various dimensions of health and disease.

Future Directions

We are just at the beginning of exploring the full possibilities provided by the methods and data generated by the HCP and without a doubt, many new analyses of rsfcMRI, other modalities, and the integration across modalities will be published in the upcoming years. The hope is that these analyses will shed new light on the ways in which behavior of many different forms is related to functional brain connectivity, providing a launching point for application of such results to understanding psychopathology. In conducting such analyses, many of which will be data-driven investigations designed to generate novel insights, it will be crucial for investigators to pay careful attention to the need to incorporate replicability analyses into their work, such as the use of k-fold cross validation, holding out subsets of participants for replication, or even attempting to replicate in other data sets. Importantly, the acquisition of new data sets has already started, with a number of projects underway applying the methods developed by the HCP to understanding a variety of forms of psychopathology, including projects funded as part of the “Connectomes of Disease” RFA on depression/anxiety, early psychosis, dementia, and Alzheimer’s Disease, to name a few. Further, three new HCP projects in relatively healthy populations have started, one to extend our understanding of the normative development of functional and structural brain networks from birth to age 5 (“the baby connectome”), one to extend our understanding from ages 5 to 21 (HCP Development) and one to extend our understanding from ages 35 to 100 (HCP Aging).

As described above, there are already a number of published studies examining dimensions of psychopathology within the HCP data itself (e.g., anxiety, depression, psychotic-like experiences, substance abuse) and a number of ongoing studies using the HCP methods to

examine rsfcMRI in samples with greater levels of manifest psychopathology. Thus, the methods and data generated by the HCP are already being used to inform clinical neuroscience research on the correlates of psychopathology. However, a further question is whether these methods will be able to inform treatment and patient care. There is good reason to hope that they will, potentially in several ways. First, it is possible that the advances in knowledge about the relationships between brain circuitry and behavior may lead to new targets for treatment development. As one example, I described work above linking cingulo-opercular network global efficiency to both cognitive function and psychotic-like experiences. One hypothesis stemming from this work is whether stimulation or cognition remediation treatments focused on cingulo-opercular network function and connectivity might be useful in improving cognition and or preventing progression from psychotic-like experiences to full blown psychotic experiences. Second, it possible that advances in the analysis of rsfcMRI may lead to novel methods to examine the effectiveness of treatment interventions. For example, current studies of the impact of treatment on rsfcMRI as a mediator of behavior change primarily focus on static patterns of rsfcMRI. It is possible that if the work on dynamic rsfcMRI supports interpretable patterns, this approach may provide alternative measures to index treatment related modulation of functional connectivity.

Third, and perhaps most importantly, the focus on individual subject level analyses of rsfcMRI in the HCP may be the most relevant in terms of patient care and treatment. There is a growing body of work from the HCP and related efforts such as the “My Connectome Project” showing that individually defined patterns of rsfcMRI can be highly stable in a person over time and cognitive states^{29,100,107,108} as well as showing variation in relationship to factors such as metabolic profile and gene expression¹⁰⁸. This allows for the possibility that patterns of fcMRI could be used to identify patients that might benefit from particular forms of treatment. Further, it also allows for the possibility that we can examine unique within person changes in fcMRI as a way to evaluate treatment effectiveness in psychopathology research, predict the emergence or worsening of symptoms, or even identify unique etiological pathways. To the skeptic, these suggestions may sound like a pipe dream, but the rapid pace of advances in this area suggests that it is a potential path by which advances developed from the HCP and related projects may translate to improvements in both our understanding of the neural correlates of psychopathology and improvements in treatment and outcome.

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