



# 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 to develop a more complex understanding of the function of brain circuits in health and of their relationship to behavior—providing, in turn, a foundation for our understanding of how disruptions in such circuits contribute to the development of psychiatric disorders. This review focuses on the use of resting-state functional connectivity MRI to assess brain circuits, on the advances generated by the Human Connectome Project, and on how these advances potentially contribute to understanding neural circuit dysfunction in psychopathology. The review gives particular attention to the methods developed by the Human Connectome Project that may be especially relevant to studies of psychopathology; it outlines some of the key findings about what constitutes a brain region; and it highlights new information about the nature and stability of brain circuits. Some of the Human Connectome Project’s new findings particularly relevant to psychopathology—about neural circuits and their relationships to behavior—are also presented. The review ends by discussing the extension of Human Connectome Project methods across the lifespan and into manifest illness. Potential treatment implications are also considered.

**Keywords:** brain, functional connectivity, network, neuroimaging, psychopathology

A core principle of modern biological psychiatry is that psychiatric disorders arise from abnormalities in brain function; in other words, from dysfunction of brain circuits that support human behavior. Such circuit-level abnormalities reflect a complex interplay between genes and environment, with most, if not all, psychiatric disorders reflecting both genetic underpinnings<sup>1–5</sup> and a host of environmental factors.<sup>6–10</sup> 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 foundation 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 for understanding how disruptions in such circuits contribute to the development of psychiatric disorders. These efforts include initiatives such as the Human Connectome Project (HCP),<sup>11,12</sup> United Kingdom Biobank Project,<sup>13</sup> and Adolescent Brain and Cognitive Development study. HCP, funded by the National Institutes of Health (U.S.), was 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 (e.g., depression, anxiety, substance use, cognitive function, social function).

Projects such as 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 (fMRI), which uses blood oxygen level-dependent (BOLD) signals as an indirect measure of neural activity while individuals engage in various cognitive, emotional, or sensory tasks;<sup>14</sup> (3) resting-state functional connectivity

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MRI (rsfMRI), which measures the coordination of spontaneous fluctuations in BOLD activity across the brain;<sup>15</sup> 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.<sup>16</sup> Each of these modalities provides unique and important information about the human brain.

The focus of this review will be on the use of rsfMRI 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 rsfMRI, though the two are not isomorphic. We focus on rsfMRI rather than dMRI, however, because of a particular interest in how brain circuits *function* together to support human behavior. 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, because of space constraints, the focus here is on rsfMRI and does not include a focus on functional connectivity MRI (fcMRI) or activity during tasks. This review will start with a brief history of the development of methods to measure and understand human functional brain connectivity. It will then describe HCP and its advances, review some of the knowledge about neural circuits being generated by HCP that may be particularly relevant to psychopathology, and discuss some of the findings from HCP that directly relate rsfMRI to behavioral dimensions relevant to psychopathology.

### FUNCTIONAL CONNECTIVITY

Functional connectivity was originally studied in the context of simultaneous recordings of neuronal spike trains,<sup>17–19</sup> which are thought to contribute to the functional connectivity observed in human using noninvasive 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, or social processing.<sup>20</sup>

A major shift in the way we study human brain functional connectivity came when Biswal and colleagues<sup>15</sup> reported that spontaneous activity from regions in the right and left motor cortices was highly correlated even while an individual was resting. This finding highlighted that there was “functional” connectivity between brain regions, even when people are not performing a specifically targeted task. Importantly, such resting-state activity of the brain may consume a major portion of the body’s energy (~20%), despite the brain being only 2% of the body’s total mass.<sup>21</sup> To put this percentage 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.<sup>21</sup> Further, some research suggests that much of the trial-to-trial variability in task-related activity reflects these spontaneous fluctuations in brain activity,<sup>22</sup> 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 HCP’s 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 through which we can explore the relationships between (a) individual differences in behaviors relevant to understanding psychopathology and (b) individual differences in the organization and function of brain networks.

#### Methodological Advances

HCP has generated a number of methodological advances relevant to using rsfMRI in the context of work both on health and on psychopathology. These advances include the creation of “multiband” pulse sequences that allow for the rapid acquisition of whole-brain, high-resolution BOLD activity in a short time frame.<sup>23–27</sup> In particular, HCP used a version of the multiband BOLD sequence that acquired an image of the whole brain at a 2 mm isotropic voxel resolution in 720 milliseconds.<sup>27</sup> By comparison, a typical whole-brain acquisition protocol for a single-band sequence with 3 to 4 mm isotropic voxel resolution requires 2 to 3 seconds. In theory, the development of such multiband sequences could have a practical application to our understanding of 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 multiband sequence, like the one used in HCP, in 12 minutes. Even if one used a higher spatial resolution (3 mm isotropic) for a whole-brain single-band acquisition, the repetition times are typically ~2 seconds, meaning that 1000 frames would take 33 minutes. Thus, if one considered only the number of frames, the acquisition time could be reduced by almost two-thirds. These two scan types have yet to be directly compared (e.g., match on number of frames rather than total duration), however, in terms of outcomes such as test-retest reliability or network identification. Further, a focus on shorter durations would need to be balanced against various competing factors, such as the somewhat lower signal-to-noise ratio of the multiband

sequences for any single individual acquisition<sup>28</sup> and the loss of signal-to-noise at higher spatial resolutions. Some of the signal-to-noise loss associated with higher multiband factors can be gained back by acquiring more acquisitions in a fixed time, and some analytical approaches benefit from an increase in temporal resolution.<sup>23</sup> Recent work suggests, however, that—depending on one’s criterion for adequate reliability—acquisitions of at least 20–30 minutes might be needed to obtain highly reliable single-subject estimates of rsfMRI, even using multiband sequences.<sup>29</sup> 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” estimate.<sup>29</sup> Thus, short rsfMRI acquisitions may not be appropriate for all applications and questions. That said, the higher spatial resolution possible with multiband sequences facilitates testing hypotheses that require finer-grained localization, such as hypotheses about the role of the thalamus,<sup>30,31</sup> specific basal ganglia nuclei,<sup>31</sup> or subregions of the amygdala or hippocampus in psychopathology,<sup>32,33</sup> or the examination of small structures with rsfMRI that may have relevance to psychopathology, such as the habenula.<sup>34,35</sup>

HCP also developed a number of new processing and analytical approaches that reduce the amount of smoothing needed for accurate alignment of images,<sup>36</sup> 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.<sup>36–38</sup> These advances are reviewed in detail in various published manuscripts,<sup>16,36,39–41</sup> including a recent overview by Glasser and colleagues.<sup>37</sup> HCP has provided added evidence of the pernicious influence of movement on rsfMRI and also information on important correlates of head movement (i.e., cognitive function) and its heritability.<sup>42,43</sup> Fortunately, HCP has also provided new tools and approaches for reducing artifact and noise in multiband rsfMRI data, including movement-related artifact.<sup>44–46</sup> In addition, since the data from HCP are publicly released, many other groups have used those data to generate new processing and analytical approaches for rsfMRI data.<sup>47–56</sup> Such enhancements in processing and analysis 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 areas<sup>57</sup> or automated anatomical labeling maps.<sup>58</sup> While these parcellations have helped, they are

based on structural or anatomical information that may or may not have functional relevance and also on limited information (i.e., a single individual). Thus, researchers are exploring alternative ways of defining brain regions, including those based on similarity or homogeneity in patterns of task-related brain activation<sup>59</sup> or rsfMRI.<sup>60–63</sup> In work supported in part by HCP, Gordon and colleagues<sup>64</sup> 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.<sup>60–62</sup> 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.<sup>65,66</sup>

Using data from HCP, Glasser and colleagues<sup>67</sup> used boundary-mapping approaches to identify brain regions using a multimodal parcellation approach. 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. The same researchers also showed that this mapping 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, such disruptions 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 such altered regions 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 HCP have helped to confirm our growing understanding of core rsfMRI networks in the human brain<sup>40</sup> and to replicate prior work that identified a number of robust functional brain networks in the human brain.<sup>59,60,68–72</sup> Each of the commonly identified human brain networks using rsfMRI is likely relevant in some way to the understanding of psychopathology. Several may be particularly relevant, however, 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.<sup>73,74</sup> 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.<sup>75,76</sup> 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 frontal-parietal network. Further, the dorsal attention network 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 such events disrupt ongoing processing.<sup>75,76</sup> The *default mode network* (DMN) has been linked to numerous 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 attention.<sup>77</sup> Further, a large body of literature shows that the DMN decreases activity during engaged task states, and some studies suggest that the ability to successfully “shut down” the DMN may be important for effective cognitive function.<sup>78–81</sup> The DMN includes the medial prefrontal cortex, medial posterior cingulate, and precuneus. The *salience network* is one that has been identified somewhat more recently than some of the other networks,<sup>72</sup> 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. It is hypothesized that the salience network serves to process and coordinate reactions to salient events in the environment.<sup>82</sup> Increased connectivity of the salience network has been associated with anxiety and arousal. Further, the salience network has been hypothesized to regulate the relationship between the frontal-parietal network and DMN.<sup>83</sup>

The data generated by HCP have 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—that is, the 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.<sup>84–88</sup> Others have linked variation in such dynamic rsfMRI to behavior, including executive function.<sup>89</sup> Recent work by Laumann and colleagues,<sup>90</sup> however, suggests that measures of dynamic rsfMRI are susceptible to the confounding influences of factors such as arousal state and head motion. Importantly, there is much debate about the appropriate statistical models for assessing the presence of dynamic rsfMRI,<sup>91,92</sup> and much remains to be learned about the source of such dynamics and whether, and to what extent, they can be interpreted as reflecting meaningful aspects of brain function and organization.

In another interesting advance using HCP data, Cole and colleagues<sup>93</sup> found a strong similarity in the networks identified at rest and those identified in data acquired during multiple task states. 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; a possible explanation is that such aggregation “washes out” unique variation associated with any particular task, leaving the patterns that are shared across tasks.<sup>94</sup> This finding has both theoretical and practical implications for psychopathology research. At the theoretical level, it suggests 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 the 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 achieve a balance between efficient data acquisition and the need to obtain an unbiased estimate of intrinsic network connectivity. For example, Bolt and colleagues<sup>95</sup> compared rsfMRI to fMRI in each of the same tasks examined by Cole and colleagues,<sup>93</sup> 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). One hypothesis is that the differences across these two studies may reflect the fact that Bolt and colleagues, unlike Cole and colleagues, did not regress out the influence of deterministic task-design signals that could lead fMRI in task data to appear less similar to rsfMRI. Gratton and colleagues<sup>96</sup> also removed task-design signals in a different data set and again found strong overall similarity between fMRI network organization and topology during tasks versus rest, whether examining individual tasks or data aggregated across three tasks. They also found interesting differences, however, across tasks and rest. Thus, although examining fMRI during task states as a way to mitigate subject demand in psychopathology populations is an intriguing possibility, 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 differences as a function of psychopathology or in relationship to individual differences in behavior are equally apparent in either rsfMRI or task-aggregated fMRI—which could be true even if there are mean-level differences in fMRI across states.<sup>97</sup>

### rsfMRI and Behavior in the HCP: Relevance to Psychopathology

As noted above, one of the goals of HCP was to generate and release to the public a large data set in which to explore relationships between behavior and individual differences in functional connectivity. 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. Nevertheless, the cognitive and emotional function of the participants in the study varied widely and included some individuals who met diagnostic criteria for a psychiatric disorder at some point in their lives. A growing number of studies have been using HCP data to examine various behavioral factors relevant to psychopathology, including cognitive function, mood, emotion, and substance use/abuse. For example, in work by the HCP consortium itself, Stephen Smith<sup>98</sup> led an analysis identifying a central “mode” of functional connectivity that was related to many different individual attributes, ranging from fluid intelligence, use of substances, educational level, and depression. A focus on fluid IQ has been particularly popular, with a number of studies identifying aspects of functional brain connectivity relevant to IQ,<sup>99</sup> such as connectivity in the frontal-parietal network, which shows stable individually identifiable patterns or rsfMRI that predict IQ.<sup>100</sup>

In other work, investigators are examining rsfMRI patterns that predict individual differences in depression, negative mood states, and anxiety, with evidence for relationships to connectivity of the habenula<sup>34</sup> and to connectivity among the dorsal attention, default mode, and frontal-parietal networks.<sup>101</sup> In our own work, we have examined the interrelationships among cognitive function, psychotic-like experiences, and rsfMRI.<sup>102</sup> 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 analysis 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, in combination with prior work in individuals with manifest psychosis,<sup>94</sup> suggests that such relationships may extend across the spectrum of clinical psychosis and nonclinical psychotic-like experiences.

This work on individual differences in the HCP data set is just starting, as the full data set was released 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 rsfMRI metrics and their relationships, as well as questions about environmental versus genetic influences using family data<sup>103</sup> and discordant twin analyses.<sup>104–106</sup> It is hoped that these findings will help generate novel hypotheses about the potential contributions of altered rsfMRI to

psychopathology, as they begin to identify relationships between individual differences 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 HCP. Without doubt, many new analyses of rsfMRI, other modalities, and relationships across modalities will be published in the upcoming years. The hope is that these analyses will shed new light on how behavior of many different forms is related to functional brain connectivity, ultimately providing a new window for 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 using 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 already under way to apply methods developed by HCP to various forms of psychopathology, including projects funded as part of the “Connectomes of Disease” requests for applications 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, ones to extend our understanding of the normative development of functional and structural brain networks from birth to age 5 (“the baby connectome”), ages 5 to 21 (HCP Development), and ages 35 to 100 (HCP Aging).

As described above, some published studies have already examined dimensions of psychopathology (e.g., anxiety, depression, psychotic-like experiences, substance abuse) within the HCP data itself, and some ongoing studies are using the HCP methods to examine rsfMRI in samples with greater levels of manifest psychopathology. Thus, the methods and data generated by HCP are already being used to inform clinical neuroscience research on the correlates of psychopathology. A further question, however, 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 these findings is whether stimulation or cognition-remediation treatments focused on cingulo-opercular network function and connectivity might be useful in improving cognition or preventing progression from psychotic-like experiences to full-blown psychotic experiences.

Second, it is possible that advances in the analysis of rsfMRI may lead to novel methods for examining the

effectiveness of treatment interventions. For example, in current studies of the impact of treatment on rsfcMRI as a mediator of behavior change, the primary focus has been on static patterns of rsfcMRI. It is possible that, if the work on dynamic rsfcMRI supports interpretable patterns, those patterns may provide alternative means of indexing treatment-related modulation of functional connectivity.

Third, and perhaps most importantly, the focus on individual-level analyses of rsfcMRI in HCP may be the most relevant in terms of patient care and treatment. A growing body of work from HCP and related efforts such as the “My Connectome Project” shows that individually defined patterns of rsfcMRI can be highly stable in a person over time and cognitive states<sup>29,100,107,108</sup> and also that such patterns vary in relationship to factors such as metabolic profile and gene expression.<sup>108</sup> These results allow for the possibility that patterns of fcMRI could be used to identify patients who might benefit from particular forms of treatment. Further, they allow for the possibility that we can examine unique within-person changes in fcMRI as a way to evaluate treatment effectiveness in psychopathology research, to predict the emergence or worsening of symptoms, or even to 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 the work of HCP and related projects may translate to improvements in both our understanding of the neural correlates of psychopathology and improvements in treatment and outcomes.

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