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What Do Network Approaches Add to Our Understanding of Prefrontal Cortex and Executive Function?

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Abstract

Regions in the human frontal lobe form distributed large-scale brain networks, with connections to one another and other locations in the cortex, striatum, thalamus, and cerebellum. Here, evidence is reviewed that multiple networks lie side by side in the frontal lobe, and these networks are largely (but not entirely) parallel, or separate, from one another. These network findings improve our understanding of frontal lobe organization and help constrain theories of executive function and the impact of brain disorders. Ongoing challenges in the study of frontal lobe networks are discussed related to tracking functional associations of brain networks, individual differences, and changes in networks over time.

Introduction

Many approaches used to study the frontal lobe focus on the characteristics of isolated regions. In contrast, another class of approaches examines the frontal lobe through a distributed processing lens, characterizing how regions relate to one another and to other parts of the brain. In this chapter, we discuss the value of this "network" perspective.

Large-scale networks or "systems" of the human brain can be defined in various ways but most often refer to sets of brain regions that are interconnected anatomically or exhibit covarying activity patterns (referred to as structural and functional connectivity, respectively) (see Sporns 2016 and Appendix 11.1). These properties are taken as evidence that neurons in these regions frequently interact to complete different aspects of brain function (Petersen

and Sporns 2015). Large-scale networks represent an important scale of brain organization (Churchland and Sejnowski 1988), and connectivity is often considered a defining feature for delineating brain areas, together with cytoarchitectonics, function, and topography (Van Essen and Glasser 2018).

We argue here that network approaches are crucial to the study of the frontal lobe, in particular the prefrontal cortex (PFC). The frontal lobe contains many distinct but closely juxtaposed networks with stereotyped patterns of connections across the cortex and subcortex. Several of these networks are linked to executive functions—the set of functions that allow one to control thoughts and actions in the pursuit of a goal, overriding automatic behavior. Thus, network characteristics can constrain theories of both function and dysfunction of the frontal lobes.

What Do Network Approaches Add to Our Understanding of the Frontal Lobe?

In this section, we review four insights gained from using network approaches to study the frontal lobe. We describe (a) principles of frontal lobe network integration and segregation: different regions in the frontal lobe are reciprocally connected within networks with a stereotyped spatial topography, but these networks are largely distinct, or parallel, to one another. These findings provide a platform (b) to examine how executive function is supported by multiple distributed networks, (c) to situate PFC networks within a whole-brain complex system, and (d) to understand the consequences of PFC disorders from the lens of network connectivity.

Regions of the Frontal Lobe Form Multiple Distributed and Parallel Networks

Early observations of large-scale networks in the frontal lobe were grounded in tract-tracing work in macaques (e.g., Goldman-Rakic 1988; Mesulam 1981, 1990; Selemon and Goldman-Rakic 1988). These influential studies mapped the afferent and efferent connections of PFC subregions and found evidence for parallel segregated networks, which involved interconnected parietal, frontal, temporal, and subcortical regions (Figure 11.1). For example, Mesulam (1981) proposed that spatial attention is not supported by a single region, as had been previously hypothesized, but is instead supported by a distributed system of reciprocally connected brain regions, including the posterior parietal cortex, frontal cortex, cingulate cortex, and subcortical areas in the intralaminar thalamic nucleus, brainstem raphe nuclei, and locus coeruleus. He proposed that while different components of that system may support different components of behavior (thus lesions to different areas within the network may create slightly different deficits), attention emerges as a property of the network as a

whole. Goldman-Rakic (1988) furthered this view, showing that when areas of the parietal and PFC are anatomically connected, they often sent convergent connections to the same temporal, midline, and subcortical regions, forming a densely interconnected system. However, while regions in these networks have strong connectivity to each other, they have minimal connectivity outside of their network. This led Goldman-Rakic (1988) to propose that a fundamental property of these distributed networks is their largely parallel or independent nature from one another.

Modern tract-tracing work has characterized connectivity of large-scale networks further, partly thanks to the creation of large databases of tract-tracing results (Giarrocco and Averbeck 2023; Stephan et al. 2001; Wang et al. 2020). This work has extended earlier observations of structurally distinct networks (e.g., Hilgetag et al. 2000) and led to an understanding of how these networks function using a complex systems lens; for example, by identifying hub regions of the brain with distributed network connections (Markov et al. 2013; Sporns et al. 2007), map-like topographic patterns of organization that are mirrored across regions (Averbeck et al. 2014; Haber et al. 2006), and nested models of cortical connectivity, with subnetworks breaking up larger network systems (Giarrocco and Averbeck 2021). As the collection and analysis of macaque connectomes grows, this work will continue to influence the analysis of human connectomes based on fMRI that is the focus of the remainder of this chapter.

We focus on networks measured with fMRI functional connectivity, which measures patterns of covariation in BOLD activity between different brain
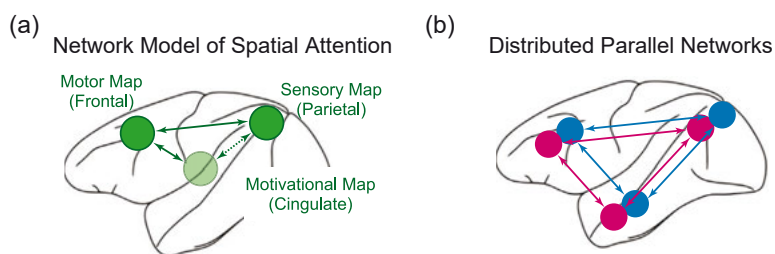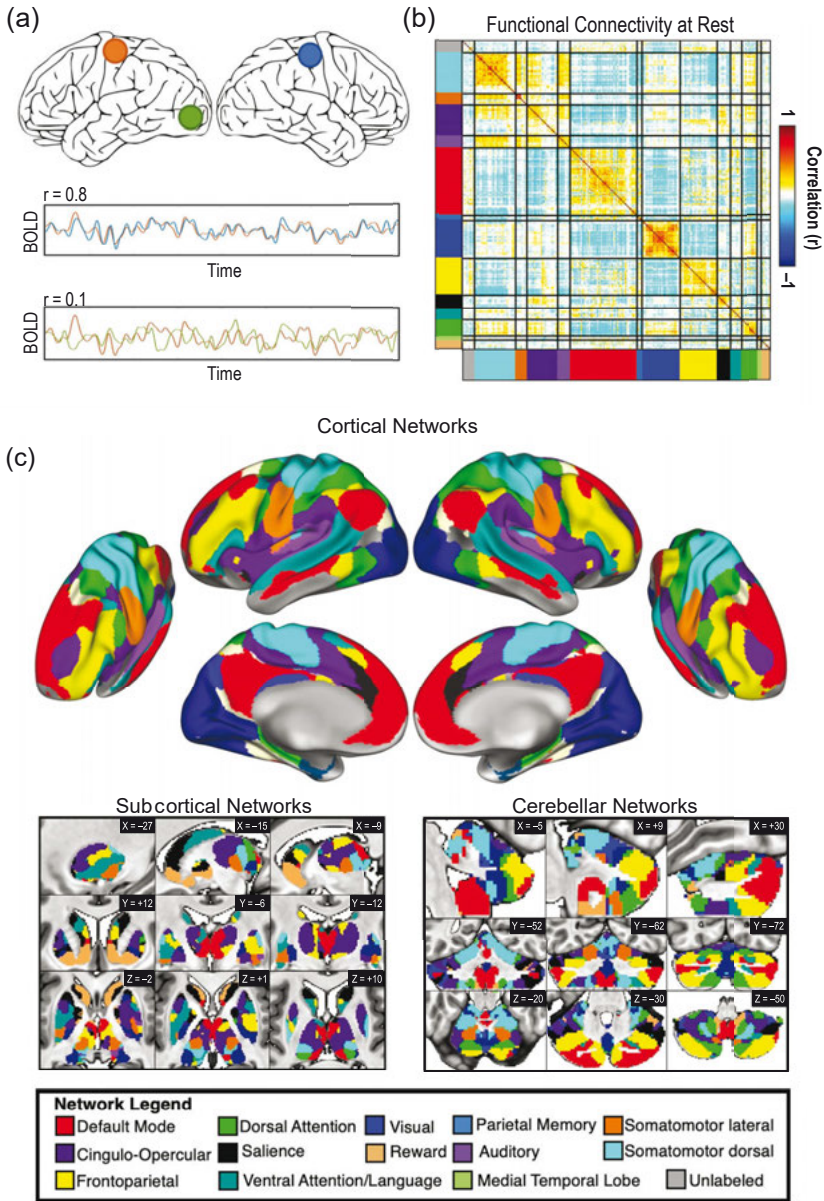

Figure 11.1 Early observations of large-scale networks were made using tract-tracing techniques in macaques and lesion studies in humans. (a) On the basis of axonal tracing and analysis of patients with focal cortical damage, Mesulam (1981) proposed that spatial attention is emergent from a network of distributed regions including frontal, parietal, and cingulate cortex. He proposed each node of the network supports a slightly different representation (sensory, motor, and motivational) of spatial attention. (b) Using axonal tracing, Goldman-Rakic (1988) identified that parietal area 7A and frontal area 46 in the macaque sent projections to many of the same regions, defining a large-scale connected network. Further, she found that regions which lie side by side in parietal cortex often project to regions that lie side by side in other parts of the brain, thus supporting a model of segregated, parallel networks. Figures were drawn by the authors based on work from Goldman-Rakic (1988) and Mesulam (1981).

regions, because it has emerged as a dominant approach to track brain networks in humans. Our working hypothesis is that large-scale networks measured with functional connectivity represent relatively stable organizational elements of the brain and, as such, they should converge with other methods of identifying brain systems, although it is important to remember that they are not the same.[1] For further discussion, see Appendix 11.1.

Using functional connectivity methods, substantial evidence has provided an extended account of distinct networks, components of which are in the human frontal lobe. This includes the delineation of the default, cingulo-opercular, and frontoparietal networks, among others (Figure 11.2). The existence and topography of these networks has been consistently found in several different datasets in different populations, different scanners, and using different network techniques (e.g., Gordon et al. 2017; Power et al. 2011; Smith et al. 2009; Sporns 2016; Yeo et al. 2011). In contrast with the more spatially proximal sensorimotor systems, association networks of the PFC are linked to cortical parietal, temporal, and midline regions, as well as with distinct subregions of the basal ganglia, thalamus, and cerebellum (Figure 11.2c) (Seitzman et al. 2020), forming a distributed pattern.

Figure 11.2   Using functional connectivity to define large-scale human brain networks. (a) Functional connectivity is a measure of the temporal association between the patterns of activity of two brain regions. If the two regions are functionally related, such as the left (orange) and right (blue) motor cortex, the correlation between their BOLD timeseries will be high (top box). In contrast, if the two regions are not functionally related, like the left motor cortex and the left visual cortex (green), then their activity correlations will be low (bottom box). See Appendix 11.1 for an extended description of functional connectivity measures from resting-state fMRI. (b) Functional connectivity across all regions in the brain can be displayed in a correlation matrix, where each cell represents the relationship between a pair of regions. In these matrices, we see a characteristic structure where the within-network correlations (on-diagonal) are high, whereas the between-network correlations (off-diagonal) are lower. These patterns can be used to group regions into networks with data-driven clustering methods (marked by lines in the matrix). (c) Functional connectivity can be used to map the network organization of the cerebral cortex, subcortex, and the cerebellum; different colors represent different networks and mapping onto rows in (b). A description of network terminology is provided in Table 11.1. Figures were drawn using conventions from Power et al. (2011), Seitzman et al. (2020), and Van Dijk et al. (2010).

[1]   For example, functional connectivity from fMRI is moderately correlated to anatomical connectivity measured with diffusion MRI (Honey et al. 2009). While this relationship suggests a link between structure and function, a number of differences are also present. Some differences may have functional significance, but differences can also arise for methodological reasons (Mnih et al. 2015). For example, correlational measures from resting state measure indirect as well as direct connections (Petersen and Sporns 2015), and signals may be unreliable without sufficient data (Gordon et al. 2017); diffusion based measures of anatomical connectivity have difficulty tracking branching, turning, and crossing fibers (Grisot et al. 2021); head motion can bias both measures (Baum et al. 2018; Power et al. 2015). An avenue for continued research will be to study the relationships across these techniques and the merits of joining information across modalities.

(a)

r = 0.8

BOLD

Time

r = 0.1

BOLD

Time

(b) Functional Connectivity at Rest

Correlation (r)

1

−1

Cortical Networks

(c)

Subcortical Networks

X = −27   X = −15   X = −9

Y = +12   Y = −6   Y = −12

Z = −2   Z = +1   Z = +10

Cerebellar Networks

X = −6   X = +9   X = +30

Y = −52   Y = −62   Y = −72

Z = −20   Z = −30   Z = −50

Network Legend

Default Mode	Dorsal Attention	Visual	Parietal Memory	Somatomotor lateral
Cingulo-Opercular	Salience	Reward	Auditory	Somatomotor dorsal
Frontoparietal	Ventral Attention/Language	Medial Temporal Lobe	Unlabeled

Notably, a source of confusion in the literature on human brain networks is that there is limited consensus in the field on the proper terminology (and taxonomy) with which to refer to these networks (Uddin et al. 2022). Some of the disagreement stems from differences in resolution: an apparent network at one resolution may divide into two or more separate components when examined at another. Different definition methods may also give rise to distinctions: e.g., single task contrasts may not correspond to full resting-state networks or may join multiple networks together. Finally, lack of anatomical specificity in published works, as well as anatomical variation in functional network locations across individuals, adds to the ambiguity of separating closely interposed systems. As the literature currently stands, it can be difficult to determine which network someone is referring to by name unless it is accompanied by an anatomical map (Uddin et al. 2019, 2022). Recent efforts aim to address these issues by providing quantitative representations of the variability in functional network definitions, delineating regions that commonly fall into these networks across most individuals as compared to brain regions that show variability in the network they belong to across individuals (Dworetsky et al. 2021).

Moving forward, these tools will aid researchers in addressing some of the ambiguity that has plagued past reports. For clarity, we provide a taxonomy for the large-scale networks of the PFC that we follow, see Table 11.1, based on Gordon et al. (2017), Power et al. (2011), and Seitzman et al. (2020), together with some common variations (e.g., Yeo et al. 2011). We also provide a visual representation of these networks and their typical (group average) anatomical patterns (Figure 11.2c) and point the interested reader to materials associated with the following references for full downloadable maps (Dworetsky et al. 2021; Power et al. 2011; Seitzman et al. 2020; Yeo et al. 2011).

Table 11.1   Large-scale networks of the PFC and their nomenclature.

Network	Terminological description
Frontoparietal network	Sometimes called the "central executive" or "cognitive control" network, it corresponds with the Yeo et al. (2011) "frontoparietal" network (7-network parcellation) and Control A from Kong et al. (2019). It is sometimes joined with the dorsal attention or cingulo-opercular networks (e.g., Fox et al. 2005). However, the cingulo-opercular and frontoparietal networks actually have very low (near zero, and often negative) intercorrelations, suggesting that they are unlikely to be closely related brain systems. Relative to the dorsal attention network, the frontoparietal network is more positively correlated with the default, and less to visual and somatomotor networks. Adding to confusion in descriptions of this network, it is consistently identified as highly variable across individuals (Gordon et al. 2017; Kong et al. 2019; Seitzman et al. 2019). This suggests that individual-level mapping is necessary to distinguish accurately the frontoparietal from other interdigitated systems (see Challenge 2, below).

Network	Terminological description
Cingulo-opercular	Many studies refer to networks with this distribution as the "salience," but we separate this network from another nearby system with that name but slightly differing anatomical distribution (Gordon et al. 2017; Power et al. 2011). While intercorrelated, the network we call cingulo-opercular has stronger relationships to somatomotor systems and weaker relationships to the default network than does the salience (Figure 11.2). In Yeo et al. (2011), this network is called "ventral attention" (7-network parcellation). As described, some studies join the cingulo-opercular and frontoparietal network into a single system, despite their low intercorrelations.
Default	This network is relatively consistently named and identified (Power et al. 2011; Uddin et al. 2022; Yeo et al. 2011) but can vary substantially in extent across papers; sometimes it encompasses regions of the ventral attention, language, and salience networks (note that these three networks are smaller and more variable in position across people, which may contribute to these differences). Recent evidence suggests that the default network is composed of at least two separable subnetworks (Andrews-Hanna et al. 2010). Due to anatomical variability, these most clearly differentiate in individuals (Braga and Buckner 2017).
Dorsal attention	This network was first described by Corbetta and Shulman (2002) on the basis of common task activations and monkey electrophysiological responses. In functional connectivity, it is sometimes joined with the frontoparietal, but differs in its connectivity to the default, visual, and somatomotor systems. In Yeo et al. (2011), it is also referred to as the dorsal attention network (separate from the frontoparietal network).
Language/ventral attention	Originally, we termed this network "ventral attention" (Power et al. 2011) in relation to the influential work by Corbetta and Shulman (2002). However, this network shows considerable overlap in distribution with language localizers (Braga et al. 2020) and has been labeled as "language" in more recent work. In general, this network is variable across individuals and not always consistently identified in group maps with data-driven methods. A network with this distribution is not identified in the 7-network parcellation (Yeo et al. 2011), although components emerge in the 17-network parcellation. Kong et al. (2019) name this the "temporal parietal" network.
Salience network	We identify a small network, "salience," which has a similar but distinct anatomical distribution from the cingulo-opercular network. This network appears in ventral regions of the anterior insula, and in more rostral components of the anterior cingulate, often extending further along the anterior cingulate gyrus in patterns that differ across individuals (Gordon et al. 2017). This network shows relatively higher correlations with the default and lower correlations with the somatomotor systems than the cingulo-opercular network. A network with this distribution was not identified by Yeo et al. (2011), but a similar network in Kong et al. (2019) is labeled "Control C."

As seen in Figure 11.2c, multiple networks have components in the PFC, including the frontoparietal (yellow), cingulo-opercular (purple), salience (black), default mode (red), dorsal attention (green), and language/ventral attention (teal). These networks are consistently separable across datasets and methodologies, and appear largely parallel to one another, with limited exceptions (e.g., see Figure 11.2b, off diagonals). These observations of a distributed but primarily parallel organization to PFC brain networks have implications for their function.

Executive Function Is Supported By Multiple Distributed Networks

Until recently, efforts to divide the frontal lobe into specialized components were dominated by a localization of function view, in which individual brain regions were the foci for specific functions. These studies linked the frontal lobe with executive functions (e.g., Banich 2009; Botvinick et al. 2001; Corbetta and Shulman 2002; D'Esposito et al. 1998a; Duncan and Owen 2000; Koechlin et al. 2003; Stuss and Alexander 2000). It has been difficult, however, to identify specialization within the frontal lobe, partly because these areas are less likely to show a one-to-one association with specific tasks. Many regions of lateral PFC are activated by a range of tasks tapping working memory, attention, inhibition, task set, and novelty (Duncan and Owen 2000). This led these regions to be labeled as part of a single "multiple demand" system (Duncan and Owen 2000). Network approaches provide new insights into this organization.

First, these approaches suggest that, rather than a single multiple demand system, there are at least[2] two networks central to executive functions (Dosenbach et al. 2008): the frontoparietal network and the cingulo-opercular network, sometimes called salience (Table 11.1). These networks were first segregated based on resting-state fMRI (Dosenbach et al. 2008; Seeley et al. 2007). The networks are activated in many tasks, especially tasks with executive function demands (Dosenbach et al. 2008; Nelson et al. 2010) (Figure 11.3). However, detailed analyses suggest they differ in their specific activation patterns associated with cues, error and ambiguity, task set maintenance, and decision making (reviewed in Gratton et al. 2018b). Notably, resting-state functional connectivity between the two networks is near zero, suggesting they function largely separately. These correlations are raised slightly during controlled task periods, but still remain low relative to correlations within each network (Cohen et al. 2014; Gratton et al. 2016). Focal lesion studies provide

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[2]   Additional networks (e.g., default, dorsal attention, ventral attention, salience; see Table 11.1) in the frontal lobe add further complexities to this view. At least a portion of these (dorsal and ventral attention) have been reported to show signals consistent with a role in sustained attention and shifts in attention (Corbetta and Shulman 2002), and others (e.g., default network) show signals that scale inversely with executive function demands (McKiernan et al. 2003). Executive function performance is likely supported by the cumulative processes of these large-scale systems.
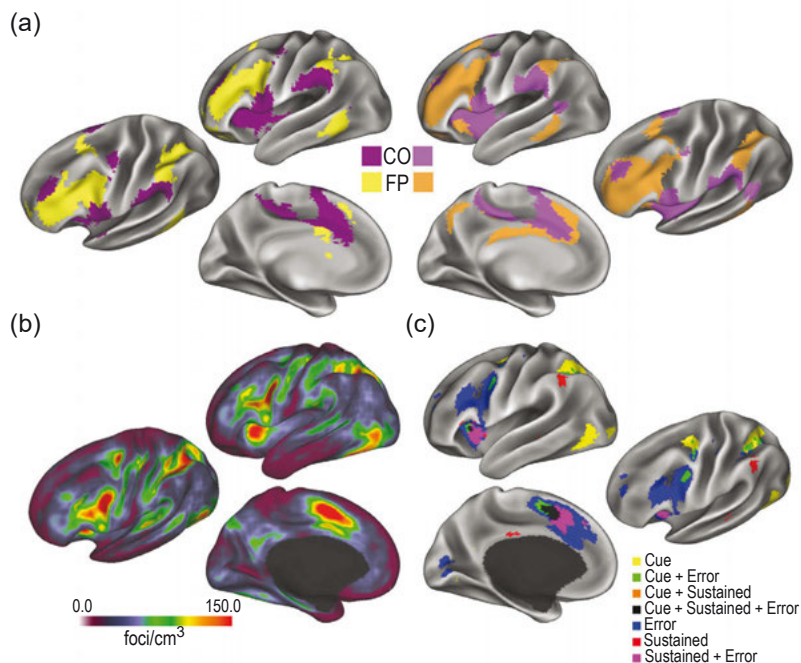
Figure 11.3 The cingulo-opercular and frontoparietal networks have been linked to executive function. (a) The frontoparietal (FP, yellow/orange) and cingulo-opercular (CO, purple/pink) networks are reproducibly identified across studies of large-scale networks of the human brain, shown here based on Power et al. (2011) and Yeo et al. (2011). (b) These networks are activated across many tasks; color bar shows the frequency of activation in a meta-analysis of 1000 task contrasts, based on Nelson et al. (2010). (c) These networks show activations related to task set, including for task cues, errors, and sustained across task periods. Figure reproduced with permission from Gratton et al. (2018b).

evidence for the independence of the networks: individuals with damage to the cingulo-opercular network have decreased functional connectivity extending throughout that system, but leave the frontoparietal network largely intact, and vice versa (Nomura et al. 2010).

This dissociation revealed by network approaches implies that there are subdivisions of executive function associated with spatially distinct neuroanatomical units. The function of each subdivision and how it supports goal-directed and context-dependent implementations of executive function remains an area of debate (see Challenge 1, below), with multiple proposed theories. For example, some suggest the cingulo-opercular (or sometimes labeled "salience") network acts as a "switch" that engages default or frontoparietal networks, depending on current goals and the import of incoming information (Menon and Uddin 2010). We have suggested that the cingulo-opercular network is

involved in maintaining task sets while the frontoparietal network rapidly adjusts control as needed, based on differences in task set responses (Dosenbach et al. 2008; Gratton et al. 2018b). A related, but distinct theory suggests that the cingulo-opercular and frontoparietal networks are involved in the control of tonic and phasic awareness, respectively, based again on differences in task activations and linked EEG signatures (Sadaghiani and D'Esposito 2015; Sadaghiani et al. 2012). These ideas also connect with other models of goal-directed functions, which propose that separate regions monitor for the need for control and implement top-down control biases (Banich 2019; Botvinick et al. 2001). An ongoing challenge in the field is to design experiments to tease apart these different interpretations. Regardless, network studies add to prior work by emphasizing that multiple distributed networks are associated with executive functions, each likely subserving distinct roles.

Second, brain networks are linked to individual differences in cognition. In an influential study, Finn et al. (2015) examined "fingerprints" of brain networks that were characteristic of different individuals. They found that these fingerprints were particularly unique in the frontoparietal network and could be used to predict fluid intelligence. The observation that brain network variability—especially of frontal-associated networks—can predict a range of cognitive abilities has been replicated by several groups (e.g., Cui et al. 2020; Kong et al. 2019; Marek et al. 2022). In a developmental sample, Cui et al. (2020) demonstrated that variability in brain network layout (especially in the two control networks noted above) could be used to predict executive function performance. While the levels of prediction were modest (~15–20% variance explained), they tend to be higher than those seen from anatomical measures and similar to task fMRI (Marek et al. 2022). Further improvements are likely to come from techniques addressing the precision of individual brain measures (Challenge 2, below).

Situating PFC Networks within a Whole-Brain Complex System

Early work on networks of the frontal lobe studied these networks in relative isolation, leaving open the question of how networks are interrelated. A complex systems approach provides a means to characterize network connections throughout the brain simultaneously and to understand properties of the brain's communication architecture (Sporns 2016). At a basic level, graph theoretical approaches reformulate brain network data as a graph, in which brain regions are represented as nodes of the graph and connections between brain regions are represented as links or "edges" in the graph (Figure 11.4). Graphs can be analyzed and contrasted with one another to reveal different properties of brain network organization. Graphs can help quantify properties of brain network structure through diverse metrics (e.g., path length, global and local efficiency, modularity, segregation) developed from the study of other complex networks such as the internet, social networks, and biological systems. These metrics
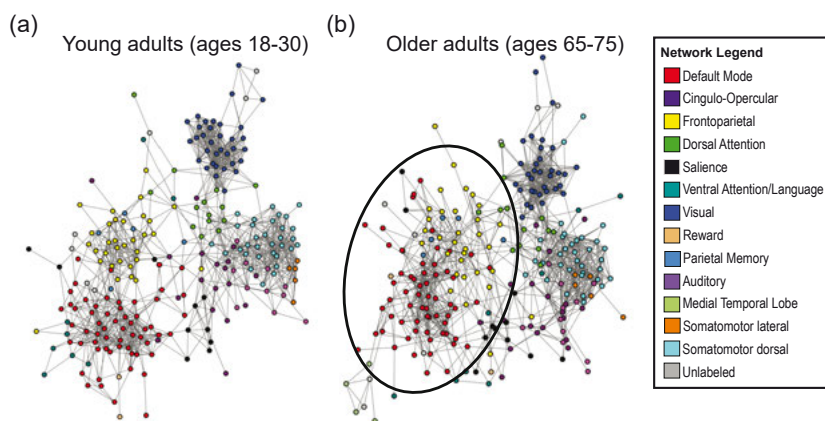
Figure 11.4 A complex systems representation of networks of the human brain. In these graphs, called spring embedding plots, each brain region (or node) is represented by a dot; the lines (or edges) represent high functional connectivity between pairs of brain regions. (a) Nodes that belong to the same network (same color in the plot) cluster together and lie separate from other networks. (b) In older adults, this segregation decreases, especially in association systems, such as the default and frontoparietal networks (black circle). This effect is known as desegregation. This figure illustrates unpublished results from our research group, reproducing similar findings from Chan et al. (2014).

can quantify global properties of the brain (e.g., identifying brain organization layouts that are more or less efficiently organized for transferring information), properties specific to particular networks (e.g., the degree of association, or closeness, between a pair of networks) and the roles of specific brain regions (e.g., identifying hubs, either based on their number of connections or the distribution of connections across different brain networks).

When considered within this context, a number of observations can be made about whole-brain systems organization, the positionality of particular networks within this organization, and the roles of individual brain regions. First, the complex systems approach highlights properties of whole-brain organization, including how efficiently the organization supports the transfer of local and/or global information, and the degree of modularity within a system. Modularity—or the extent to which the system (brain) can be separated into separable subunits (networks)—has been well characterized within the brain. This separability can be observed within graph theoretical depictions of brain connectivity (Figure 11.4), where nodes from a given network (marked with a distinct color) are clustered closely with one another and separate from other networks. This is true for the default (red), frontoparietal (yellow), and cingulo-opercular (purple) networks along with roughly a dozen others. This property underlies the parallel network identification findings cited earlier in

this chapter. Using graph theory, modularity can be systematically quantified and compared across systems with statistics like Newman's Q (Newman 2006), which provides a unitary statistic that quantifies the extent to which a given complex system (brain) divides into modules, with higher values (closer to 1) indicating higher modularity, and values close to 0 indicating a nonmodular organization similar to that seen in randomly interconnected systems. Interestingly, a decrease in the segregation between brain networks (Chan et al. 2014) is one of the best replicated changes seen in brain networks with aging, and is particularly prominent for the default, frontoparietal, and cingulo-opercular networks (Figure 11.4b). Moreover, modularity (and its reconfiguration) has been linked to executive function (Eichenbaum 2017) and complex task performance (Bertolero et al. 2015, 2018; Braun et al. 2015; Cohen and D'Esposito 2016). Thus, graph metrics provide a means to quantify the macrolevel architecture of brain organization, how it may differ across populations, and how these differences are linked to executive function.

Second, we can use these methods to assess relationships between specific networks. For example, despite their general parallel nature, some networks lie "closer together" in graph space, with more interconnections. This information constrains theories about how large-scale networks interact. For example, as introduced in the previous section, several theories posit that control networks are in competition, and that "switches" between their activity are important to aspects of executive function; deficits in the ability of these networks to switch modes is thought to underlie psychiatric disorders ranging from anxiety to autism (e.g., Dosenbach et al. 2008; Menon and Uddin 2010; Seeley et al. 2007). The network interactions seen in Figure 11.4 suggests that the frontoparietal network is well positioned to mediate between the default and cingulo-opercular system, while the cingulo-opercular network is well positioned to mediate interactions between somatomotor and default systems (for a different viewpoint on the relative positions of these networks, see Menon and Uddin 2010).

Third, in addition to considering entire networks, these approaches can be used to highlight the roles of specific regions within these networks (Sporns 2016). These measures can improve our understanding of executive functions. For example, we and others have proposed that connector "hub" regions of the brain are important for controlled behavior (Gratton et al. 2018b). Connector hub regions (by definition) have connections distributed across multiple networks that can be quantified with the participation coefficient statistic (e.g., nodes with connections across networks in Figure 11.4). This property makes connector hubs particularly well suited to regulating interactions between systems, as is likely needed for flexible, goal-driven behavior. Perhaps not surprisingly, connector hubs are found with high density in frontal and parietal brain regions (Gratton et al. 2018b).

Supporting the importance of connector hub regions for executive function, lesions to hub regions have particularly widespread consequences on

modularity throughout the brain, even in regions remote from the sites of damage (Gratton et al. 2012). Disruption of hub regions occurs across a range of neurological and psychiatric disorders (Crossley et al. 2014), and lesions to hubs are associated with widespread deficits on neuropsychological tasks (Warren et al. 2014). Bertolero et al. (2015) demonstrated that these regions are activated in many task contrasts and we have shown that they also exhibit altered functional connectivity during tasks, that differs systematically relative to non-hub regions (Gratton et al. 2016). These pieces of evidence support the idea that connector hubs are important sites for coordinating effective complex behavior, an essential element of executive function.

Understanding the Consequences of Brain Disorders from the Lens of Network Connectivity

Many advances in cognitive neuroscience have come from linking specific behavioral deficits to localized damage to the brain, and cases like Phineas Gage, Tan, and H. M. permeate introductory textbooks. While lesion studies provide insights into the function of the frontal lobe (e.g., Stuss and Alexander 2000), deficits from damage to frontal regions can often be diffuse and hard to characterize. Indeed, it has also long been recognized that damage to connections between brain regions can also cause behavioral impairments and that localized damage can cause disruptions in the function of remaining intact regions (i.e., diaschisis) (Geschwind 1974).

Recent work has used network approaches as a way of characterizing these distributed effects of damage to the brain. These observations have borrowed from insights gained in the study of other complex systems, such as air transportation networks. When travel at one airport is disrupted due to bad weather, for example, this disruption can spread to other connected airports. If the airport is relatively isolated, the effects will be minimal, but if it is well connected to others, especially on an international level, then the effects can be particularly detrimental (e.g., as occurred in 2010 after volcanic eruptions in Iceland impacted European airport hubs). So, too, can we view damage in the brain: certain regions will have more extensive effects than others by virtue of their position within the network structure.

For example, we have shown that focal lesions which caused damage to (non-hub) nodes of the cingulo-opercular network were related to functional connectivity disruptions throughout the network but did not influence connectivity of the frontoparietal network (Nomura et al. 2010). Similar effects were seen in reverse after frontoparietal network damage. In contrast, damage to connector hubs (Gratton et al. 2012) produced more extensive disruptions that affected widespread multi-network organization. These findings suggest that network approaches can provide a way to contextualize and understand nonlocalized, but still selective, effects of brain lesions, in terms of how they extend across interconnected complex systems.

Network models are also relevant to the study of neurodegenerative diseases. Seeley et al. (2009) found that neurodegenerative disorders, including Alzheimer disease and frontotemporal dementia, exhibited distinct atrophy patterns and that these patterns corresponded to specific functional brain networks present in healthy individuals (Figure 11.5). Atrophy in Alzheimer disease tracked with the default network, while frontotemporal dementia shows a profile that overlaps substantially with the cingulo-opercular or salience networks. Seeley et al. (2009) proposed that this pattern arises because neurodegenerative diseases target and spread through specific large-scale networks. Just as with lesion studies, disruptions from neurodegeneration at key nodes (hubs) of these networks, with disproportionately numerous and long-distance
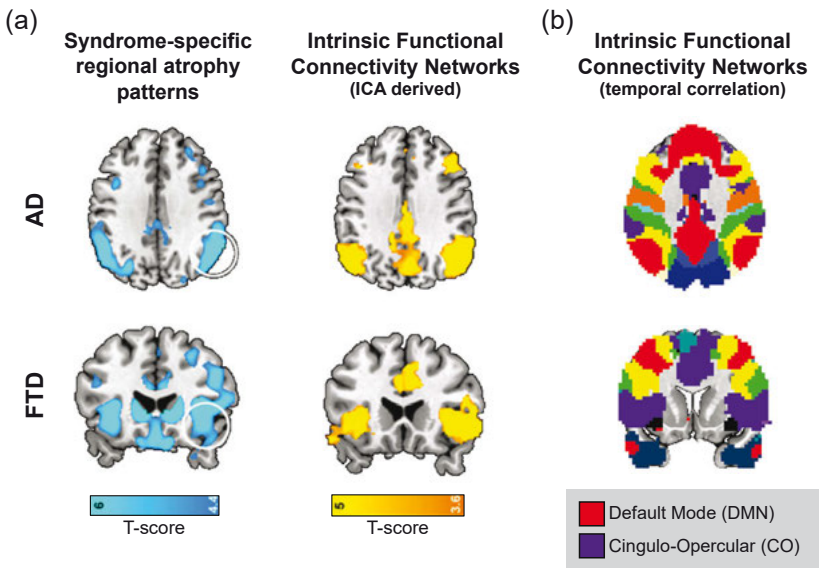

Figure 11.5 Neurodegenerative disorders affect specific networks. (a) Work from Seeley et al. (2009) demonstrated that subtypes of neurodegenerative disorders, like Alzheimer disease (AD) and frontotemporal dementia (FTD), exhibit syndrome-specific atrophy patterns (left column) that correspond spatially with intrinsic functional connectivity networks defined using independent component analysis (ICA). (b) The two networks shown in (a) overlap spatially with networks defined using temporal correlation. Namely, the atrophy pattern associated with AD overlaps with the default network (in red) and the pattern associated with FTD overlaps with the cingulo-opercular network (in purple). Results were reproduced with permission (Seeley et al. 2009) or redrawn.

connections, may produce a cascade of deleterious effects resulting in a weakening of functional circuits.

In addition to neurological disorders, psychiatric disorders ranging from depression to schizophrenia, ADHD, and autism have also been linked to disruptions in large-scale brain networks. To take depression as an example, a recent meta-analysis of lesions identified a distributed set of brain regions, rather than a single location, which contribute to depression when damaged (Padmanabhan et al. 2019). Similarly, depression symptoms are linked with abnormal functional connectivity between the default mode network, frontoparietal network, dorsal attention network, and cingulo-opercular network (Kaiser et al. 2015). Intriguingly, the success of an increasingly common form of depression treatment, transcranial magnetic stimulation, is linked to the functional connectivity between the stimulation site in the left dorsolateral PFC and the subgenual cingulate (Fox et al. 2012). These studies emphasize the importance of understanding connectivity of frontal regions in at least some psychiatric conditions.

Challenges and New Frontiers for Large-Scale Networks of the Frontal Lobe

Network methods allow researchers to place frontal regions in the context of a distributed, stereotyped, and complex set of large-scale networks. This information provides a means to frame and constrain hypotheses about frontal function. However, a number of outstanding questions remain, posing challenges that must be met with further research.

Challenge 1: Linking Frontal Networks to Specific Executive Function Processes

Perhaps the largest outstanding challenge to the network perspective of the frontal lobe is an ongoing gap in understanding the "function" of each network. The presence of distinct, largely parallel networks suggests that there are distinct functions for each network that cause their segregated pattern of activity. Moreover, while regions within a given network are thought to share a common functional association, each region presumably makes unique contributions to the underlying processing, much like regions in the visual system each contribute to visual processing but have unique (and multifaceted) specialization.

However, the functional association of each "executive function" network and the processes that differentiate their subregions are still largely undetermined. Despite the advances reviewed above, unambiguous differentiation of the functions of the cingulo-opercular and frontoparietal networks (and the

regions comprising these networks) has not yet been achieved to our knowledge.[3] Most task contrasts that tap executive function processes activate multiple frontal regions spanning both networks (Figure 11.3). As with task fMRI, task variables measured with electrophysiological recordings from nonhuman primates are also frequently represented across multiple PFC regions, showing low dissociation (see Rich and Averbeck, this volume). Thus, while clear distinctions are seen between the cingulo-opercular and frontoparietal network in functional connectivity, these distinctions have thus far been missing from task responses. It is unclear why sharp dissociations are seen in functional network measures, but not task responses.

Notably, many theories of executive processes do not seem to map those processes easily or clearly onto the major network in PFC nor their divisions. To take a few case examples: Friedman and Miyake (2017), on the basis of behavioral performance, have proposed that executive function includes both common processes (associated with a general executive function ability) and specialized properties associated with updating and shifting. Braver (2012) proposed that control functions can be separated into those associated with pro-active and re-active control. Yet others (Badre and Nee 2018; Koechlin et al. 2003) suggest that the lateral PFC encodes a progressive control hierarchy based on abstraction, that lateral PFC regions are associated with a progressive cascade of selection processes (Banich 2009), or that divisions of lateral PFC are associated with different forms of working memory processing (e.g., maintenance vs. manipulation) (D'Esposito et al. 1998a; Petrides 1994) or content (spatial vs. nonspatial) (Wilson et al. 1993). At present, these proposed divisions have not been cleanly mapped onto distinct networks identified with the network methods described above (e.g., Reineberg et al. 2018).

The lack of strong task dissociation for networks of the frontal lobe may reflect our limited understanding into the processes that differentiate these networks. Integration of information from computational modeling (e.g., see Koechlin and Wang, this volume) may help identify dimensions that are more likely to differ across these large-scale networks (see Shenhav et al., this volume). For example, recent work has used detailed tract-tracing results to develop sophisticated circuit-level models of executive function (for a review, see Wang 2022). These models have proven successful in reproducing a range of working memory and decision related responses in the PFC, suggesting that

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[3]   Interestingly, separate domains of inquiry have reported functional dissociations along the medial wall of the PFC that may correspond to distinct functional networks (Shenhav et al. 2018; Venkatraman and Huettel 2012). For example, Ritz and Shenhav (2024) show two distinct areas of the dorsal medial PFC that encode distractor and target information, respectively. They also demonstrate that these areas correspond closely to the borders of "Salience" and "Control C" network representations from (Kong et al. 2019) (cingulo-opercular and salience in our terminology from Table 11.1). However, it is not clear that these tasks differentiate the cingulo-opercular from the frontoparietal network ("Control A" in (Kong et al. 2019); this network has a more dorsal aspect along the medial wall in group averages, but varies across individuals as shown in (Smith et al. 2021, Figure 3).

this may be a useful avenue for considering and uniting information regarding network structure and function.

Additional limitations may be driven by study approaches: fMRI task responses and functional network measures at rest are not frequently collected in the same participants and directly compared. More rapid progress is likely to be made with studies that combine resting-state fMRI with task data. Importantly, anatomical imprecision, as well as individual differences in network boundaries, can have a major impact on the ability to dissociate functions cleanly, since distinct networks lie anatomically juxtaposed with one another (Figure 11.6).
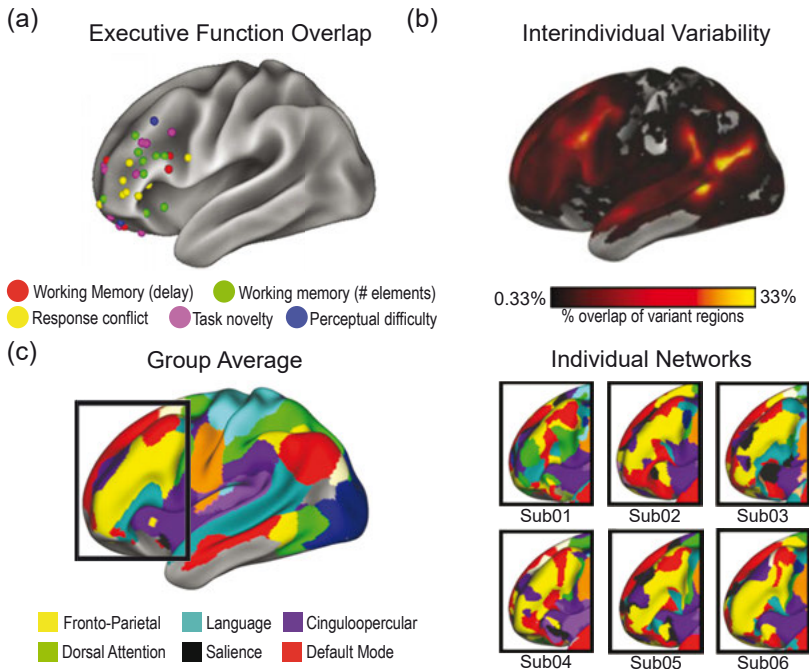

Figure 11.6 Despite many theories which distinguish types of cognitive control, it has been difficult to find functional dissociations in the PFC. (a) In a meta-analysis, Duncan and Owen (2000) showed that many different executive function tasks seem to have overlapping activation patterns in lateral PFC. (b) One potential confound is that the PFC is a particularly variable area of cortex across people, shown here in terms of locations with high variability between each individual and group average ("variants") (Seitzman et al. 2019). (c) Gordon et al. (2017) showed that each individual has a unique pattern of network organization that can be reliably mapped with sufficient data; here we highlight the variability in locations of the lateral PFC (in this case, based on 10 sessions of data from each participant). Panels (a) and (b) are reproduced with permission from (Smith et al. 2021).

Challenge 2: Understanding the Impact of Individual Differences of Brain Networks

Resting-state fMRI has often been collected in short, 5–10 minute scans from individual participants. With this amount of data, functional connectivity measures have low reliability (Gordon et al. 2017). Historically, this practice has led to a reliance on group approaches in functional connectivity studies, that average fMRI data across participants after anatomical normalization (Power et al. 2011; Yeo et al. 2011) and assume voxel-level correspondence across individuals. While these studies provide insights into typical patterns of network organization, they also obscure features that differ across individuals.

This is problematic, as the lateral frontal cortex is among the most variable in organization across individuals (see Figure 11.6b; Finn et al. 2015; Gordon et al. 2017; Kong et al. 2019; Seitzman et al. 2019). This individual variability suggests that group studies of the PFC are likely mixing together signals from different networks across individuals (Figure 11.6c). The mixing of signals across networks (and regions) in the PFC will limit our ability to know which aspects of function are dissociated or overlapping, and to use this knowledge to link the PFC to cognition, behavioral outcomes, and disease processes.

One way to address this issue is to shift toward individual-level mapping of brain networks. Precise individual-level mapping of networks depends on having sufficient high-quality resting-state fMRI data, that is properly de-noised from artifacts, to overcome inherent sampling variability and sources of systematic bias. This "precision" data can then be used to map individual brain networks with high reliability, yielding improved overlap with individual task activations and correspondence to anatomical features (Braga and Buckner 2017; Gordon et al. 2017).

Approaches using individual-level mapping have already provided improved understanding of networks in the frontal lobe (Braga and Buckner 2017; Braga et al. 2020; Gordon et al. 2017). For example, these approaches have identified subnetworks in the default (Braga and Buckner 2017) and cingulo-opercular networks (Gratton et al. 2022); subnetworks are likely to be present for other networks of the PFC as well. These initial studies suggest that these more fine-scale subnetworks link more clearly to function. For example, the two default subnetworks show a double dissociation for episodic projection and social cognition functions, respectively (DiNicola et al. 2020; see also Fedorenko et al. 2011; Michalka et al. 2015) for other specializations associated with frontal regions).

Challenge 3: Measuring Rapid Temporal Variation in Brain Networks

A final challenge in the study of large-scale networks is to improve our understanding of how network interactions (both within and between networks) change over time. In controlled behavior, different functions need to be united

and updated flexibly to meet task goals, suggesting the need for modifications in how different regions interact with one another. It is natural to ask how network models support these rapid interactions, on the order of seconds, and whether rapid dynamics in functional networks may be revealing regarding these processes.

However, evidence suggests that functional networks measured with fMRI remain largely stable across fairly distinct tasks (e.g., Gratton et al. 2018a). Much of the variation in the magnitude of functional connectivity over shorter time windows (<1 min.) can be attributed to sampling variability or physiological artifacts from motion and respiration (Ladwig et al. 2022; Laumann et al. 2017; Liegeois et al. 2017).

Thus, the question remains of how large-scale networks support ongoing and flexible cognition. One possibility is that only relatively small differences in functional networks are needed for these processes. Indeed, small but significant variation in between-network interactions can be found across different task states, riding on top of a largely stable network backbone (e.g., Cohen et al. 2014; Gratton et al. 2016; Gratton et al. 2018a). These changes are consistent enough that they can be used to accurately decode task state from functional network patterns alone (e.g., Shirer et al. 2012). However, the precise links between these distributed changes and particular executive function processes remain unclear. One productive avenue of future work may be to unite network studies with computational models of brain state changes during executive function. Connectionist models may be well suited to this need, as they can help make inferences about the representational states of networks needed for the initiation of control as well as the need for optimization in the balance for cognitive flexibility and stability (Musslick and Cohen 2021).

A second possibility is that network function is changed at temporal or spatial scales that are not easily measured with standard fMRI techniques. Methods with higher spatial resolution (e.g., ultra-highfield 7T fMRI), spatiotemporal resolution (e.g., ECOG), or combinations across methods (e.g., fMRI + EEG) may be used to explore this possibility. Ultra-high field MRI, for example, has been used to show finer scale distinctions among subnetworks of the default network (Braga et al. 2019) and parietal memory network (Kwon et al. 2023). Layer-specific studies (Bandettini et al. 2021) may add further nuance to our understanding of the PFC (Finn et al. 2019) and its networks (Huber et al. 2021), by allowing investigators to separate feedforward and feedback connections found in distinct cortical layers (although challenges remain in the collection and analysis of whole-brain layer data (Bandettini et al. 2021; Huber et al. 2021). Networks have also been examined across multiple methods, finding similar parallels between fMRI findings and invasive electrophysiological recordings (Kucyi et al. 2018), stimulation (Fox et al. 2020), and noninvasive methods such as EEG/MEG (see review by Sadaghiani and Wirsich 2020). Interestingly, at least some of this evidence suggests that large-scale networks

are largely stable across a wide range of frequency bands in ECOG recordings (e.g., Mostame and Sadaghiani 2021).

A final possibility is that flexible cognition is not mediated by changes in long-range cortical interactions, but is associated more with local interactions, perhaps aided by neuromodulatory signals. These possibilities are not mutually exclusive and must jointly be explored to improve our understanding of how flexible cognition can arise in the face of (what appears to be) a largely stable large-scale network architecture.

Conclusion

Network approaches add novel insights into frontal lobe organization and its contribution to executive function. These approaches have shown that the frontal lobe includes many distinct networks, connected with other cortical and subcortical regions. These networks show correlated, integrative activity, but are largely parallel to one another. These observations suggest that executive function is supported by multiple distinct networks, embedded within a complex architecture of whole-brain interactions, that have consequences for how damage and disease spread throughout the system. However, challenges remain in the study of large-scale networks of the frontal lobe. There is a need to improve our understanding of how network models relate to other cognitive and functional models of the frontal lobe and executive function, a need to address the substantial individual variability in large-scale network organization in the PFC, and a need to improve our understanding of temporal scales of variation in networks. Future advances are likely to come from studies with an increased focus on integrating different measures and obtaining reliable individual-level representations of networks in the frontal lobe.

Acknowledgments

Appendix 11.1: Measuring Large-Scale Brain Networks with Resting-State fMRI

The focus of this chapter is on networks measured with functional connectivity MRI, often during what is termed a "resting state." In resting-state fMRI, participants are asked to lie quietly at "rest" inside an MRI, typically with

only a cross to fixate on, while letting their mind wander.[4] Experimenters then measure spontaneous BOLD activity across the brain and search for patterns of covariation between regions, termed "functional connectivity." Different measures can be used to quantify these statistical dependencies in brain activity (e.g., correlation, coherence, ICA, lagged covariance) (Sporns 2016). An advantage of resting-state fMRI is that it is relatively easy for experimenters to collect and participants to complete; this has led to it being widely adopted in consortia imaging projects and clinical populations.

While it appears quite unconstrained, resting-state fMRI can produce robust maps of large-scale brain networks, both at the level of groups (Power et al. 2011; Yeo et al. 2011) and individuals (Braga and Buckner 2017; Gordon et al. 2017), given sufficient data and appropriate de-noising methods. Notably, resting-state fMRI can simultaneously map networks both for sensorimotor regions as well as association regions like the frontal lobe (Power et al. 2011; Yeo et al. 2011). These spontaneous "resting-state" maps mimic activation patterns seen in a range of tasks (Smith et al. 2009) and can be used to predict individual activation patterns in many task contrasts (Gordon et al. 2017; Tavor et al. 2016). Indeed, recent work has highlighted that large-scale networks only differ subtly across task states (Gratton et al. 2018a), are stable across sessions of a participant (Gratton et al. 2018a) and are even present across states of consciousness (sleep, anesthesia), albeit with some alterations (Heine et al. 2012; Palanca et al. 2015; Sämann et al. 2011). Recent trends have led to improvements in the spatial and temporal resolution of resting-state fMRI (e.g., via multiband data acquisition), signal quality of noncortical regions (e.g., via multi-echo sequences), and the size and extent of samples (e.g., via large N consortia datasets such as the HCP, ABCD, and UK Biobank, as well as extended acquisition "precision" fMRI approaches of single individuals).

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[4] Participants likely engage in a range of internally-driven cognition during rest. However, it is unclear to what extent this internally-driven cognition alters functional connectivity measurements (Fox and Raichle 2007). Functional connectivity patterns (including each of the large-scale networks discussed in detail in this chapter) remain very similar during resting-state and a wide variety of explicit cognitive tasks (Gratton et al. 2018a). Thus, differences in internally-driven cognition during resting-state likely only have a subtle influence on functional connectivity.