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Control and Connectivity

Dynamic Networks in the Human Brain

Michael W. Cole

The human brain is an extremely complex network consisting of billions of nodes and trillions of connections (Azevedo et al., 2009). Somehow, the complex spatiotemporal dynamics that play out on this network architecture produce cognitive control—a broad domain composed of goal-directed thoughts and behaviours. Until recently, however, even those who conceptualised cognitive control in terms of brain network mechanisms nonetheless continued to exclusively use localisation tools such as single-unit electrophysiology and functional MRI (fMRI) general linear models to investigate its neural basis. Here I will cover recent developments that are allowing for proper characterisation of the brain network basis of cognitive control. This includes methodological advances in characterising human brain connectivity, such as resting-state and task-state functional connectivity MRI and diffusion weighted imaging (DWI), as well as advances in identifying more descriptive network components such as brain hubs. Finally, I will cover theoretical insights gained from these advances, such as the nested organisation of cognitive control brain networks and the role of hub dynamics in implementing cognitive control functionality.

Applying Network Science to Neuroscience

Recent advances in network science have begun to facilitate our ability to characterise complex brain network properties underlying cognitive control. Network science is an interdisciplinary field built on graph theory (a branch of mathematics) to investigate complex interactive processes such as occur within the Internet and social networks (Bullmore & Bassett, 2011; Newman, 2008; Watts & Strogatz, 1998). For example, highly connected nodes in a network are called hubs (Berlingerio, Coscia, Giannotti, Monreale, & Pedreschi, 2011; Guimera, Mossa, Turtschi, & Amaral, 2005), with a variety of graph theoretical measures estimating different properties thought to characterise hubs (Figure 18.1). Google.com is an example of a hub website on the Internet, while a successful politician might be considered a social network hub. Network science also develops algorithms for identifying sub-networks (called modules) within a larger network, such as clusters of websites on related topics or social cliques (Figure 18.1).

These and other graphical approaches have been applied to the brain (Buckner et al., 2009; Bullmore & Bassett, 2011; Sporns, Honey, & Kötter, 2007), as part of ongoing developments in network science being adapted for neuroscience. A major challenge for applying

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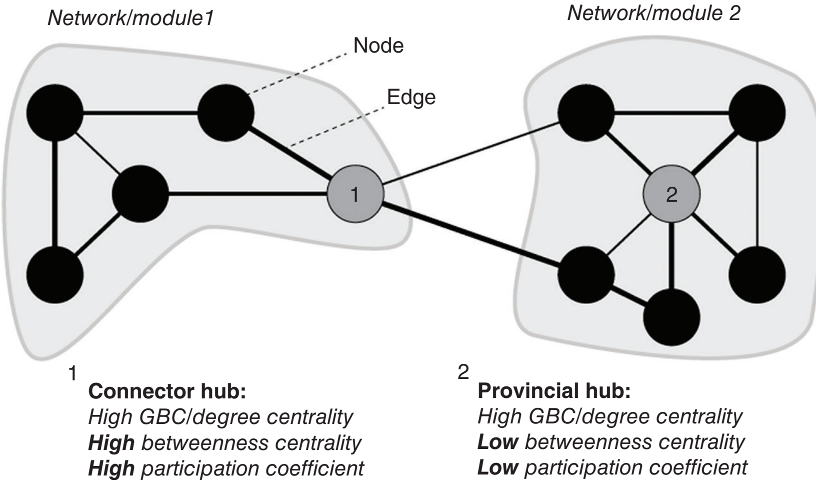

Figure 18.1 Hubs and modules. There are many graph theoretical constructs (and associated measures) that can be used to characterise networks. Particularly useful constructs include hubs, which are highly connected nodes, and modules, which are clusters of interconnected nodes. A hub that is primarily highly connected outside its own module is a connector hub (grey node 1 above). A hub that is primarily highly connected within its own module is a provincial hub (grey node 2 above). Graph theoretical measures that can (and cannot) be used to distinguish these hub subtypes are listed. Degree centrality simply counts the number of connections with a node, whereas global brain connectivity (GBC) averages the weighted connectivity (giving that node's average connection strength). Participation coefficient counts the number of between-module connections relative to within-module connections, therefore reflecting how well distributed a node's connections are across modules. Betweenness centrality counts the number of shortest paths between all nodes that pass through the node of interest, such that high betweenness centrality indicates that a node is on many of the most efficient/direct routes in a network. In practice, nodes with high betweenness centrality tend to have many between-module connections. See Cole, Ito, & Braver, 2015, for more details.

network science to the brain, however, is obtaining accurate and interpretable data regarding brain networks. Initial interest in this area focused on the brain's structural network—the comprehensive collection of white matter tracts connecting neurons termed the structural 'connectome' (Sporns, Tononi, & Kötter, 2005). An initial source of comprehensive large-scale structural connectivity data for the mammalian brain came from the CoCoMac database (Kötter, 2004), which was built from published tract tracing studies of the macaque monkey brain. This database was used along with graph theoretical measures to identify brain hubs (Sporns et al., 2007) and other network properties (Passingham, Stephan, & Kötter, 2002; Rubinov & Sporns, 2010) of the primate brain.[1]

Two primary approaches are used to estimate network structure in the living human brain. The first—DWI—uses MRI to detect white matter tracts via estimation of the diffusion of water along those tracts (Johansen-Berg & Rushworth, 2009). The second major method estimates functional connectivity—the statistical associations between brain activity time series—typically via correlation of activity across distinct brain locations (B. Biswal, Yetkin, Haughton, & Hyde, 1995; Friston, 1994). A variety of (primarily noninvasive) neuroimaging methods have been used to estimate functional connectivity in humans, such as fMRI, electroencephalography, and magnetoencephalography.

DWI involves the collection of multiple MRI images, each sensitive to a different direction of water diffusion (Figure 18.2). White matter tract directions are estimated on the basis of

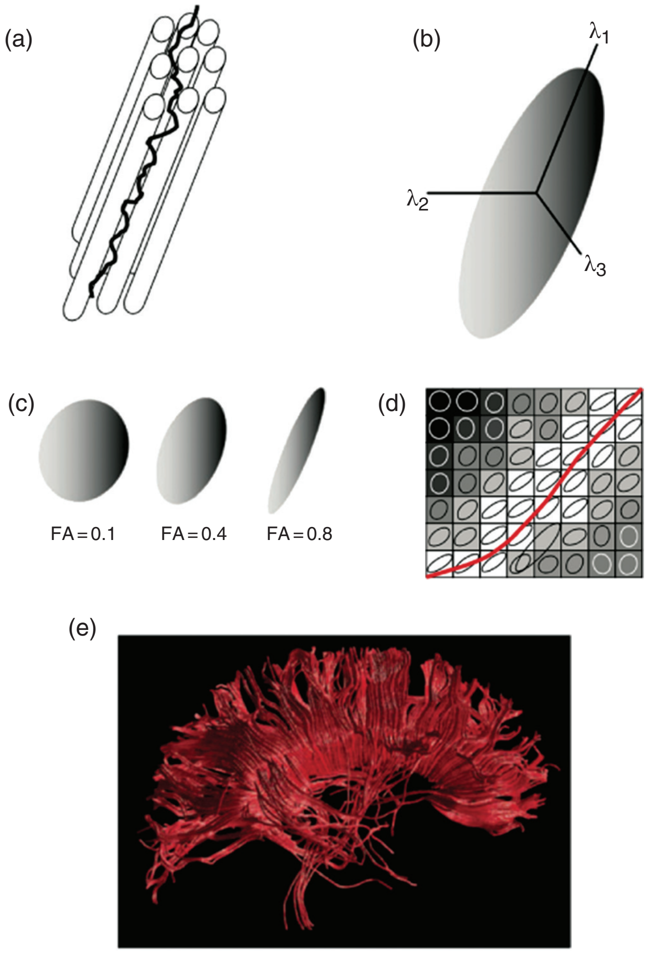

Figure 18.2 Structural connectivity estimated via diffusion weighted imaging (DWI). **a**) Diffusion weighted imaging (DWI) is sensitive to the direction of water diffusion within a measured brain volume. Water moves along an axon, producing a dominant diffusion direction as measured by DWI. b) The dominant direction of diffusion can be measured using a tensor with three axes, as shown here. More sophisticated models are available as well. These more sophisticated models are recommended, given the likelihood of fibre crossings (multiple dominant directions) within a given volume of measurement. c) As a given direction of diffusion increases in dominance, so does fractional anisotropy (FA). d) Each volume's FA (or equivalent) can be linked together to infer tracts over multiple volumes. e) These fibre tracts can then be analysed statistically and visualised. Figure adapted from (Johansen-Berg & Rushworth, 2009).

the principle that water is more likely to diffuse in the direction of tracts than other directions (Johansen-Berg & Rushworth, 2009). At least six DWI directions are necessary to estimate tracts, though many more directions (e.g., 64 or 264) are typically used to increase the accuracy of tract tracing. Even with many more directions than necessary, however, there are issues with movement during data collection that changes estimated tract directions (Mukherjee, Chung, Berman, Hess, & Henry, 2008; Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2013). The best way to model tracts is also unclear (Dell'Acqua & Catani, 2012)—especially

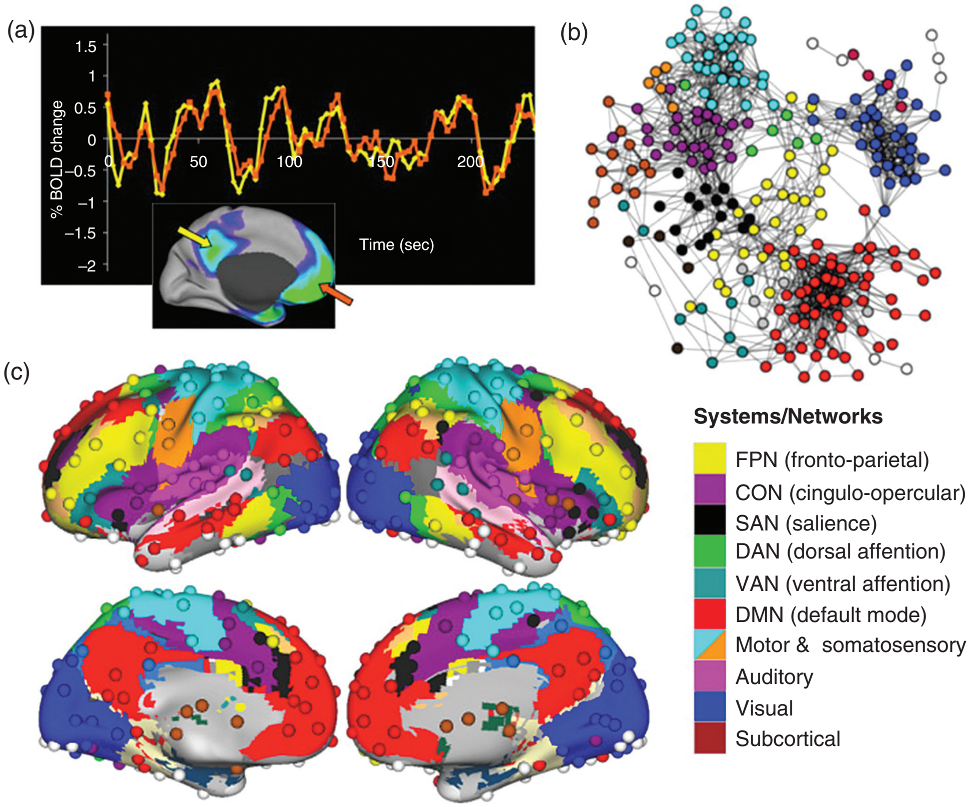

Figure 18.3 Community detection with resting-state functional connectivity. a) Resting-state functional connectivity with fMRI. Time series from two default-mode network regions are shown, indicating their high correlation (functional connectivity). Adapted with permission from (Raichle, 2010). **b**) A graph of regions from throughout the brain, with spatial proximity of regions based on the strength of their resting-state functional connectivity (closer regions = stronger connectivity). They are colour-coded on the basis of their network/module affiliation. Adapted with permission from (Power et al., 2011). **c**) The locations of the regions from panel B, along with their network/module affiliations, and equivalent network assignments based on a voxel-wise analysis. Source: Power 2011. Reproduced with permission of Elsevier.

at fibre crossings in single voxels. Indeed, there may be some fundamental limit to the accuracy of DWI data (C. Thomas et al., 2014; Van Essen et al., 2013). For instance, several tracts known to exist within the macaque monkey brain are not detectable using DWI even with especially high-resolution images (C. Thomas et al., 2014).

A common functional connectivity approach infers network structure on the basis of coordinated spontaneous fMRI activations while subjects are at rest (B. B. Biswal et al., 2010; B. Biswal et al., 1995; Raichle, 2010; Figure 18.3a). This resting-state functional connectivity method was developed after high correlations between each hemisphere's somatomotor cortices were observed even though subjects were at rest (B. Biswal et al., 1995). This paralleled these subjects' somatomotor activations during a motor task. Subsequent research has verified and extended those initial observations to the rest of the brain, determining that resting-state functional connectivity is functionally meaningful (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Laird et al., 2013; S. M. Smith et al., 2009; Waites, Stanislavsky, Abbott, & Jackson, 2005), highly reproducible (Shehzad et al., 2009), and related (but not identical) to structural connectivity (as measured using DWI tractography; Honey et al., 2009). These studies have recently culminated in the identification of all major networks in the human brain via network partitioning—clustering of highly connected brain regions into communities (Power et al., 2011; Yeo et al., 2011; Figures 18.3b & 18.3c). However, there is uncertainty regarding exactly how to interpret resting-state functional connectivity results. One possibility consistent with existing data is that resting-state functional connectivity reflects spontaneous activity dynamics playing out on the brain's structural network (Deco et al., 2013; Goñi et al., 2014), perhaps modulated by synaptic strengths (Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009; Cole et al., 2016). Thus, this approach may reveal the likelihood of activity flowing across structural connections (and their synapses), even if multiple connections are involved in a chain—a kind of network pattern that is difficult to identify using structural data alone (Dum & Strick, 2013).

Cognitive Control as a Network Phenomenon

The above connectivity methods have been used to identify network properties related to cognitive control. Prior to this, however, a set of brain regions distributed across prefrontal and parietal cortices was found to be co-activated across various cognitive control demands (Duncan & Owen, 2000; Schneider & Chein, 2003; Wager & Smith, 2003; Figure 18.4a). These regions include the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC; also called anterior mid-cingulate cortex), anterior insula cortex (AIC), posterior parietal cortex (PPC), and pre-motor cortex (PMC). Some additional regions may be included such as the pre-supplementary motor area (pre-SMA) and the rostrolateral prefrontal cortex,

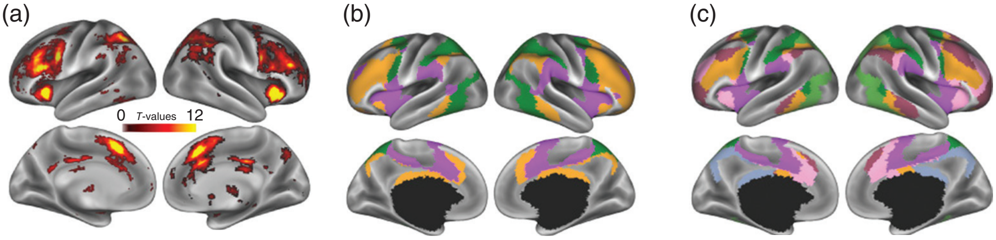

Figure 18.4 The cognitive control network and nested sub-networks. **a**) A meta-analysis of the fMRI literature using the term 'cognitive control' with Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). The activation pattern is consistent, with many individual studies of cognitive control assessing a variety of cognitive control demands. The statistical map ($p < 0.01$, false discovery rate corrected for multiple comparisons; forward inference) was generated by Neurosynth (which is periodically updated with new studies) on June 9, 2015. As many as 377 studies including the term 'cognitive control' contributed. **b**) Resting-state functional connectivity fMRI was used to parcellate the brain into seven networks (Yeo et al., 2011), of which three corresponding to the cognitive control co-activation pattern identified in panel A are shown. The orange network roughly corresponds to the frontoparietal control network, the green network roughly corresponds to the dorsal attention network, and the magenta roughly corresponds to the cingulo-opercular network. **c**) Nested within the coarse partition of the cognitive control network (three networks), seven networks are identified (based on a whole-brain 17-network solution; Yeo et al., 2011). B and C adapted with permission from Yeo et al. (2011).

depending on one's means of defining the set of co-active regions. Several groups speculated at the time that this set of regions forms a distinct brain network, yet it might have been that each region was no more connected with this set of regions as with any others.

Initial hints of a coherent cognitive control network had been identified over a decade earlier in non-human primates (Friedman & Goldman-Rakic, 1994; Pandya, Van Hoesen, & Mesulam, 1981; Quintana & Fuster, 1999; Selemon & Goldman-Rakic, 1988). These studies used structural connectivity and multi-site electrophysiological recordings to identify a distributed network across lateral frontal, medial frontal, and parietal cortices in macaque monkeys. Most of this work had been in the context of eye movement control and associated attentional shifts (Colby & Goldberg, 1999), leaving open the possibility that this frontoparietal network was really a specific eye movement control system rather than a general cognitive control system. Further, it might have been that this frontoparietal system—if not simply an eye movement system—was specifically an attentional system rather than something more general. Thus, even if a non-human primate investigators knew of this frontoparietal network, it was unknown if an analogue also existed in humans and if it corresponded to the co-activation patterns seen in humans across diverse cognitive control demands.

Subsequent studies have used resting-state functional connectivity to determine that these frontoparietal regions are not only highly interconnected in humans, but that their high connectivity continues during rest, when control processes are at a minimum (Cole & Schneider, 2007; Dosenbach et al., 2007; Fox et al., 2005; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). This demonstrated the existence of the frontoparietal cognitive control network in humans, as well as its intrinsic (non-task-dependent) nature.

Note that very little work has been done to investigate cognitive control network connectivity using DWI (relative to resting-state functional connectivity). One such study investigated the structural connectivity organisation of the prefrontal cortex (Croxson, 2005). Another study combined fMRI with DWI, linking a prefrontal region sensitive to inhibitory control with the subthalamic nucleus (Aron, Behrens, Smith, Frank, & Poldrack, 2007). A more recent study used probabilistic tractography along with individual difference correlations with behaviour to identify differential contributions of tracts to cognitive control (Strenziok, Greenwood, Santa Cruz, Thompson, & Parasuraman, 2013). The limited number of published DWI studies of cognitive control suggests there is much to learn from more such studies.

Dissociations within the Cognitive Control Network

Parallel to (and perhaps in theoretical opposition to) the discovery of an intrinsic cognitive control network, the dominant paradigm for understanding the neural basis of cognitive control was in terms of specialisation (i.e., dissociations) among cognitive-control-related regions (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Henson, 2005; Saxe, Brett, & Kanwisher, 2006). This followed from the traditional assumption that all brain regions constitute functionally specialised 'modules', such that each cognitive-control-related region should have a unique function if we could just find the right cognitive manipulation to reveal it. This was effective for some portions of the cognitive control network, but not (so far) for others. Note, however, that both of these perspectives can be subsumed into a single framework characterising the nested organisation of cognitive control networks.

One particularly important task dissociation was hypothesised between the DLPFC the ACC (cf. Chapter 10 by Kool et al. in this volume; Chapter 4 by Egner in this volume). The difficulty in demonstrating this dissociation was made apparent in a meta-analysis showing the co-activation of these two distant prefrontal regions across a wide variety of tasks

(Duncan & Owen, 2000). This is in contrast to several other studies that did find dissociations between these regions (Barch et al., 1997; Braver et al., 1997; Macdonald, Cohen, Stenger, & Carter, 2000). These studies suggested that the DLPFC is involved in both sustained and transient working memory processes, whereas the ACC is involved in transient conflict monitoring/resolution processes (Botvinick, Cohen, & Carter, 2004; Braver, Reynolds, & Donaldson, 2003). Because of their emphasis on working memory tests, we will refer to this as the 'working memory' theoretical perspective on these regions.

Soon after these distinct roles for the DLPFC the ACC were posited, however, another study came to essentially the opposite conclusion (Dosenbach et al., 2006). They used a unique activity modelling approach to separate sustained from transient task-evoked activations (a mixed blocked/event-related fMRI design; Visscher et al., 2003), finding that ACC activity was sustained (and possibly transient as well), whereas DLPFC activity was only transient across a variety of tasks. This suggested that the ACC implements sustained processing for each task set, whereas the DLPFC implements transient changes in the task set. Because of their emphasis on changes in task set, we will refer to this as the 'task set' theoretical perspective on these regions.

These two views are yet to be resolved. One important consideration is that both accounts suggest a role for the DLPFC in highly dynamic cognitive control, such as task switches or possibly working memory manipulation. This is in contrast to, for example, simple working memory maintenance, which the accounts disagree on. This still leaves disagreement regarding the role of the ACC. One possibility supported by a subsequent study is that the ACC is involved in transient attentional processes as well as anticipatory attentional processes, such that ACC activity is not truly sustained but rather 'fills the gap' between trials in anticipation for the need for attention (Cole & Schneider, 2007). This anticipatory role for the ACC is supported by studies emphasising a role for the ACC in predicting the need for cognitive control (Alexander & Brown, 2011; Brown & Braver, 2005; Shenhav, Botvinick, & Cohen, 2013; Chapter 15 by Brown in this volume; Chapter 10 by Kool et al. in this volume). This role is also consistent with evidence that ACC activity is associated with arousal/vigilance, rather than maintaining task information per se (Sadaghiani & D'Esposito, 2014). Further research is necessary to resolve these theoretical and empirical discrepancies regarding the ACC, as well as the DLPFC.

Nested Cognitive Control Networks: From One Network to Many Sub-Networks

The popular 'working memory' theoretical perspective on the DLPFC and ACC emphasises their highly interactive nature (J. Cohen, Botvinick, & Carter, 2000), suggesting they should be part of the same network. For example, a now classic model suggests that the ACC detects decision conflict and signals the DLPFC to increase cognitive control during decision making (Botvinick et al., 2001). In contrast, however, the 'task set' account suggests that the DLPFC and ACC should be part of separate networks (Dosenbach et al., 2006). Determining whether these regions are in separate networks could therefore serve to adjudicate between these competing theoretical perspectives.

The resting-state functional connectivity studies above provided evidence that the DLPFC and ACC are nested within the same large-scale network (Cole & Schneider, 2007; Vincent et al., 2008). This was based on strongly above-chance correlations between the resting-state fMRI time series of these regions. However, advocates for the 'task set' account used graph theory to find that these regions segregate into separate networks once higher thresholds are applied (Dosenbach et al., 2007). This approach places the PPC along with the DLPFC, and the AIC separately along with the ACC. Thus, there is evidence for both perspectives.

These findings can be reconciled by considering a nested organisation: Portions of the ACC and DLPFC are part of separate sub-networks (Figure 18.4c) within a single higher-order frontoparietal control network (Figure 18.4b). This reflects the strongly above-chance functional connectivity between the ACC and DLPFC (Cole & Schneider, 2007; Vincent et al., 2008), while acknowledging that each of these regions has even stronger functional connectivity with other regions (Dosenbach et al., 2007). This also appears to reflect the frequency of observed task activation-based dissociations in the literature; the DLPFC and ACC appear to be more frequently dissociated than the DLPFC and the PPC or the ACC and the anterior insula (Dosenbach et al., 2006; Yeo et al., 2015). This tentative characterisation of the co-activation patterns of the DLPFC and ACC in the literature is consistent with a large meta-analysis of the fMRI literature (Figure 18.5), which finds that a co-activation component

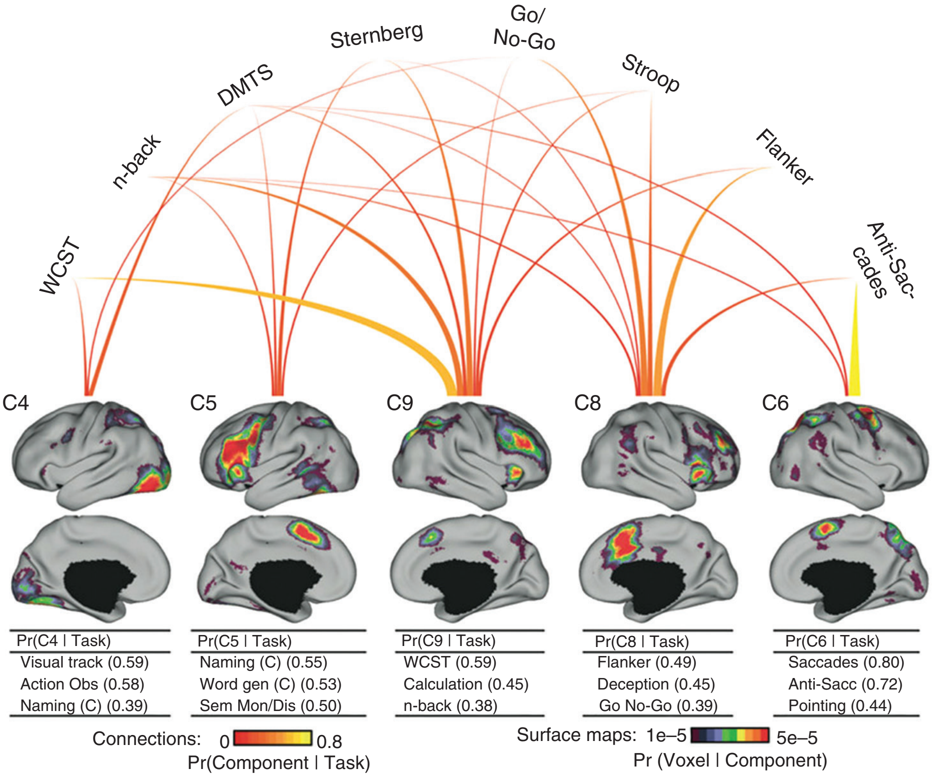

Figure 18.5 Task fMRI meta-analysis reveals co-activation pattern components related to cognitive control. A 13-component model was used to identify separate co-activation patterns across task demands (Yeo et al., 2015). Five components are shown that contributed prominently to activation patterns during cognitive control task performance. Of note, components 8 and 9 (C8 and C9) each contributed to all but one cognitive control task. C8 appears to correspond to the cingulo-opercular or salience resting-state functional connectivity network, whereas C9 appears to correspond to the fronto-parietal control network. When a 12-component model was used (rather than a 13-component model), C8 and C9 collapsed into a single component, suggesting that these components/networks have a nested organisation. The values along the top are names of cognitive control tasks. WCST = Wisconsin Card Sorting Test. DMTS = delayed match to sample. Adapted with permission from Yeo et al. (2015).

dominated by the ACC and anterior insula (component 8 in Figure 18.5) is separate from a co-activation component dominated by the DLPFC and PPC (component 9 in Figure 18.5; Yeo et al., 2015). Simultaneously, however, the ACC is present in the DLPFC component (component 9) in the same meta-analysis. Further, when a 12-component model was used instead of a 13-component model, the DLPFC and ACC components (components 8 and 9) were collapsed into a single component. Thus, the sub-network structure apparent in resting-state functional connectivity is reflected in co-activation patterns: regions in separate sub-networks are more readily dissociable, yet (reflecting their relationship in the higher-order network structure) are also often co-activated.

Identification of Cognitive Control Sub-Networks

Multiple cognitive control sub-networks have been identified (Figure 18.3c). First, a dorsal attention network (PMC and anterior PPC) and a ventral attention network (ventrolateral prefrontal cortex and temperoparietal junction) were identified using task co-activation patterns (Corbetta & Shulman, 2002) and verified by subsequent resting-state functional connectivity (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). The dorsal attention system appears to be specialised for eye movement control and goal-directed, or 'top-down', attention to external stimuli, whereas the ventral attention system appears to be specialised for stimulus-driven, or 'bottom-up', shifts in attention. Subsequently, as already mentioned, resting-state functional connectivity was used to separate the frontoparietal control network (the DLPFC and PPC) from the cingulo-opercular network (the ACC and AIC; Dosenbach et al., 2007). Simultaneously, another group dissociated these regions into essentially identical sets, but chose to label the cingulo-opercular network the 'salience' network (Seeley et al., 2007; but see below for evidence that they may be nearby separate networks).

At this point, with at least four cognitive control sub-networks, it became unclear how they all related to one another and to other networks in the brain. Further, it was unclear if each of the networks had been mapped comprehensively, or if extraneous regions had been added to one or more networks because of theoretical biases. What was necessary was a comprehensive map of all of the brain's networks at once, applying a single method uniformly to all networks to identify network affiliations throughout the brain.

As mentioned previously (see Figure 18.3), two groups of researchers took on this challenge (Power et al., 2011; Yeo et al., 2011). Power et al. (2011) applied a graph theoretical community detection algorithm to a large whole-brain resting-state functional connectivity dataset, identifying a variable but largely consistent set of brain networks across multiple thresholds (Figure 18.3c). In the same year, Yeo et al. (2011) used a similar dataset with an alternate clustering algorithm (involving projecting the data into a higher-dimensional space to facilitate segmentation into networks), identifying nearly identical networks as Power et al. (Figure 18.4c). Importantly, both studies threw out all but the very highest functional connections and applied multiple strict thresholds in order to force their algorithms to segment the data into a variety of separate networks. This suggests that it remains possible for higher-order network structures to exist (combining the identified networks at more liberal thresholds), as suggested above, to form an overarching cognitive control network.

Both the Power and Yeo studies found evidence for at least five cognitive control sub-networks. This included a dorsal attention network, a ventral attention network, a frontoparietal control network, a cingulo-opercular network and, perhaps surprisingly, a separate salience network. The cingulo-opercular and salience networks have a very similar connectivity pattern and are nearby spatially, yet they appear to be separate networks. This is especially illustrative of the importance of characterising all brain networks simultaneously: even hard-to-distinguish networks can thus be identified. Note, however, that both studies reported multiple network sets because of the need to use multiple thresholds for segmenting network affiliations. This presents a current limitation in our understanding, and leaves open the possibility of a nested organisation of cognitive control networks, as described above. Consistent with this, Yeo et al. (2011) found that several control networks collapsed between their 17-network and 7-network solutions (Figures 18.4b and 18.4c).

Beyond Networks to Network Mechanisms: Biased Competition and Guided Activation

If we are ever going to say we truly understand the neural basis of cognitive control, we will need to move beyond identifying the component parts underlying cognitive control in the brain. This means moving beyond identifying cognitive control-related brain regions and their networks. Instead, we need to map these and other constituent components to *mechanisms.*

Mechanisms are sets of causal relations explaining a phenomenon of interest. Mechanisms can be at any level of organisation, but in neuroscience they typically refer to a relationship between levels (Craver, 2007). Mechanism is inherent in our desire to map neural properties at one level to mental properties at another level. However, there are many levels between these fundamental two levels. One might begin at the ion channel level, move to synapses and axons, then entire neurons. Neurons then form local circuits such as cortical columns or cell assemblies, which form brain areas, which form sub-networks that in turn constitute entire distributed networks/systems, which then compose the entire brain. From interactions among these parts, mental phenomena emerge at yet another higher level of organisation. A mechanistic focus with the goal of eventual understanding of the neural basis of cognition should therefore focus on all of these levels and how the constituent parts produce the higher-order phenomena of interest—in this case, cognitive control.

Identifying the cognitive control network and the sub-networks that compose that network, then, is only the first step towards mechanistically understanding the neural basis of cognitive control. The ideal mechanistic explanation would involve a particular set of interactions among neural components that produce behavioural output consistent with a cognitive control process of interest.[2]

An excellent example of such a mechanism is the biased competition theory of visual attention (Desimone & Duncan, 1995; Desimone, Wessinger, Thomas, & Schneider, 1990). This theory suggests that potential attentional foci constantly compete for dominance, with both top-down and bottom-up properties influencing the eventual outcome of what is attended to. This involves distributed visual representations throughout the dorsal and ventral streams of the visual system, such that both spatial locations and objects compete for attention. Further, the theory speculates that the DLPFC is involved in biasing attentional selection based on current goals (Stokes et al., this volume). This goal-directedness is thought to be implemented via connectivity between the DLPFC and the visual system.

Simultaneous with the development of the biased competition theory, theoretical work applying connectionist modelling to the Stroop task revealed important related insights (J. D. Cohen, Dunbar, & McClelland, 1990). In this model, key nodes were able to overcome response conflict by biasing activity according to current goal-like activity patterns in those nodes. These key nodes were subsequently considered a model of the prefrontal cortex (Botvinick et al., 2001). Combining these insights with the biased competition theory led to a new theoretical account of the role of the prefrontal cortex in cognitive control called the guided activation theory (Miller & Cohen, 2001). Rather than being restricted to visual attention (or even attention at all), the account suggests that the prefrontal cortex maintains goal representations and uses its extensive connectivity to interact with a variety of task-relevant regions to bias processing towards goal-relevant outcomes (Figure 18.6a). Thus, the guided activation theory was a substantial extension of the biased competition theory. Further, this theory represents something close to an ideal in network-level neuroscience (as well as cognitive neuroscience) research: going beyond simply elucidating the regions and networks associated with cognitive phenomena to specify network interaction mechanisms underlying those phenomena.

Flexible Hubs as a Network Mechanism for Cognitive Control

With the discovery of the cognitive control network—with its strong integration between the prefrontal cortex and other distributed regions—the guided activation theory's sole focus on the prefrontal cortex may no longer be warranted. Further, recent studies have found that regions within the cognitive control network serve as 'hubs' with extensive functional (Cole, Pathak, & Schneider, 2010b; Cole & Schneider, 2007; Power et al., 2011) and structural (Modha & Singh, 2010; Van Den Heuvel & Sporns, 2011) connectivity throughout the brain. This both supports the guided activation theory and calls for further refinement of the theory with regard to how a distributed network of hub regions could implement cognitive control processes.

This line of reasoning led to the recently formulated flexible hub theory (Cole et al., 2012, 2013b; Cole, Laurent, & Stocco, 2013a; Cole, Repovs, & Anticevic, 2014; Zanto & Gazzaley, 2013). This theory posits that cognitive control network regions are hubs that shift their global functional connections depending on current task goals, biasing distributed goal-relevant processes (consistent with the guided activation theory). This allows for a balance between distributed and localised control: A network of highly integrated regions work together to implement control processes in a domain-general fashion. The domain generality of the network is made possible by its hub status, because it can shift its influences by biasing any of a wide variety of specialised brain networks.

A recent study carried out by my group provided strong evidence for this theory (Cole et al., 2013b). We tested the theory by looking at rapid functional connectivity updates across dozens of tasks, using a recently developed paradigm in which tasks are learned from instructions during fMRI scanning (Cole, Bagic, Kass, & Schneider, 2010a). We found that frontoparietal control network regions (one of the sub-networks within the cognitive control network) on average had the highest global variability coefficients among all major brain networks (Figure 18.7). The global variability coefficient is a graph theoretical measure created to test the flexible hub theory. It involves calculating the standard deviation of the strength of each functional connection for a region across tasks, followed by averaging all of that region's standard deviations—thereby summarising each region's overall tendency for global functional connectivity changes across tasks.

This supports a role for the frontoparietal control network in implementing the hypothesised global functional connectivity changes. However, it remained unclear if these changes were systematically related to the currently implemented task. We therefore used an approach related to representational similarity analysis (Kriegeskorte et al., 2008)—in which the relationship between connectivity patterns are matched to the relationship between mental representations—finding that the similarity of the frontoparietal control network's functional connections across tasks was related to the rule similarity across tasks. This suggests that

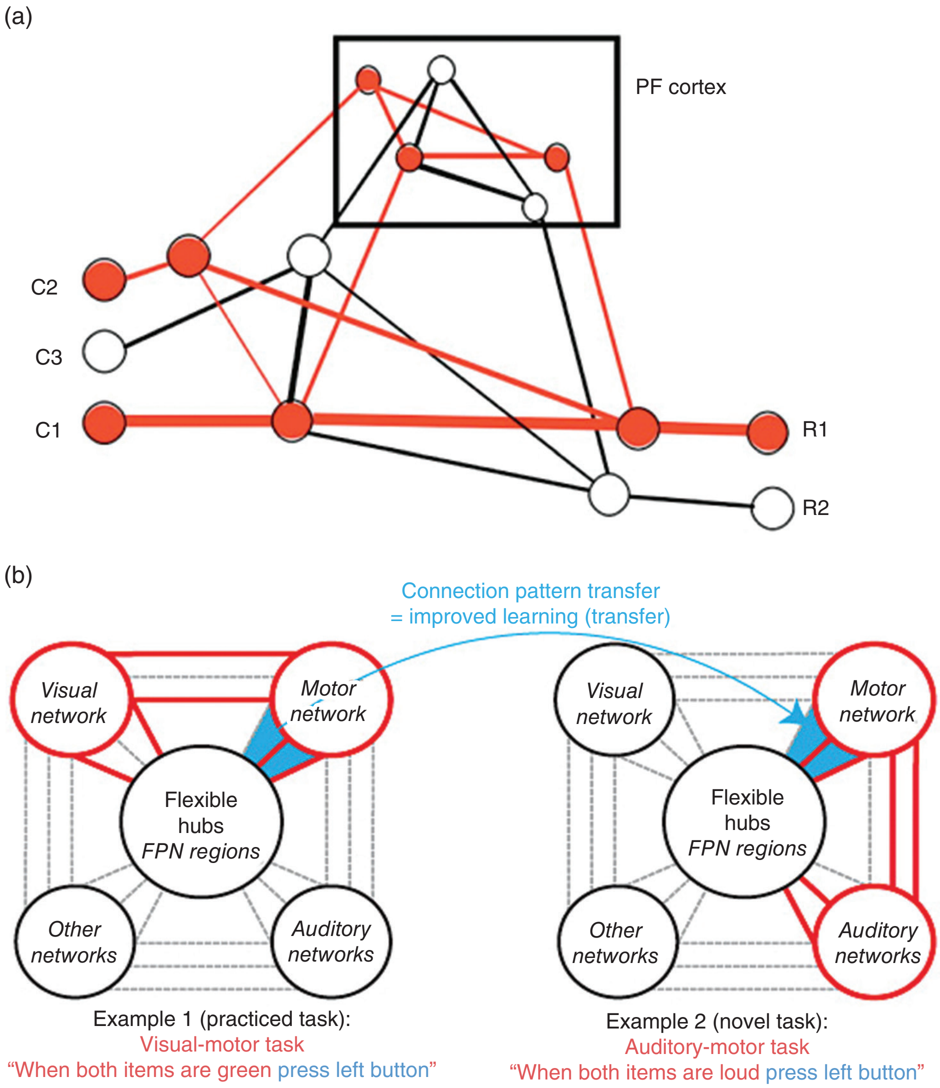

Figure 18.6 The guided activation and flexible hub theories as dynamic brain network accounts of cognitive control. a) The primary mechanisms of the guided activation theory are shown (Miller & Cohen, 2001). Activity and connectivity patterns within the prefrontal cortex are associated with large-scale influences on hidden units/neurons between sensory inputs (C1, C2, and C3) and motor outputs (R1 and R2). These enhancements are thought to specify particular behaviours required by current task demands. Figure adapted from Miller & Cohen (2001). b) A depiction of mechanisms of the flexible hub theory (Cole et al., 2013b). This theory is highly compatible with the guided activation theory, but expands functionality to the entire frontoparietal network (FPN), emphasises hub connectivity as a primary property allowing for these mechanisms, and provides a possible explanation for rapid instructed task learning via connection pattern transfer (see Cole et al., 2013b).

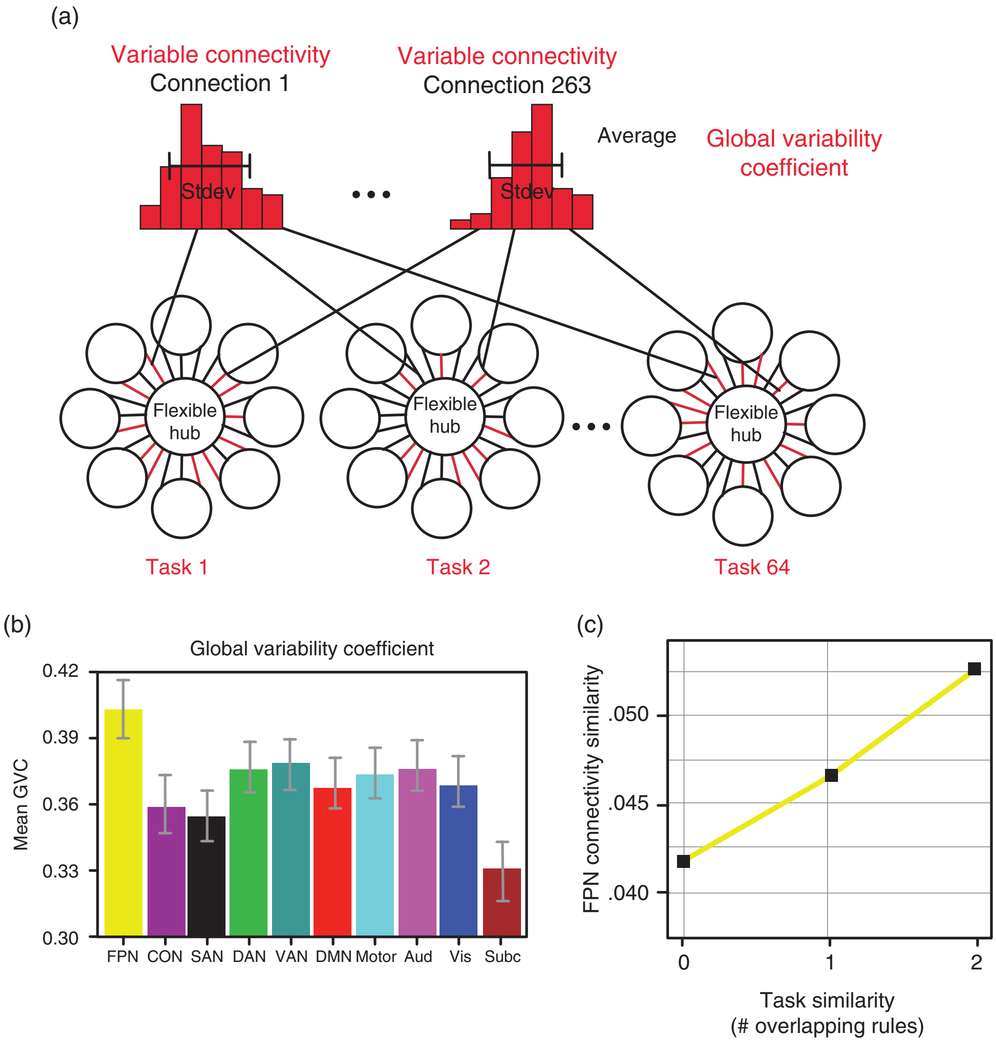

Figure 18.7 Evidence for flexible hub dynamics and task representation via the frontoparietal control network. The PRO (permuted rule operations) cognitive paradigm was used along with a new graph theoretical measure and multivariate pattern analysis (machine learning) to investigate novel task learning across 64 distinct cognitive tasks. a) A new dynamic graph theoretical measure for estimating global brain variability hypothesised to underlie flexible hub dynamics during learning (see text). b) The frontoparietal network (FPN) had the highest global variability of all major brain networks. See Figure 18.3c for brain network definitions used here. c) Multivariate pattern analysis (Kriegeskorte, Mur, & Bandettini, 2008) was used to determine that fine-grained task information (task rule identity) was contained in FPN functional connectivity patterns, consistent with the flexible hub hypothesis. Source: Adapted Cole 2013b.

functional connections between the frontoparietal control network and the rest of the brain represent the task rules composing the tested tasks. Further, we used support vector machines to successfully predict which task was being performed on the basis of the pattern of frontoparietal control network functional connections.

These analyses support the mechanism proposed in the guided activation theory as well as the extensions made by the flexible hub theory, moving beyond the DLPFC to include other portions of the frontoparietal control network: the PPC, the rostrolateral prefrontal cortex, and a small portion of the ACC. This also includes the extension of the theory to emphasise the hub status of the involved regions, as well as the representation of task information in global functional connections.

Outstanding Questions Regarding the Brain Network Basis of Cognitive Control

There are many outstanding questions in network science, applications of network science to neuroscience, and how these relate to the brain basis of cognitive control. For instance, the relationship between structural connectivity and functional connectivity remains unclear (Deco et al., 2013; Honey et al., 2009). This is an especially important issue in the context of cognitive control, as the cognitive control network and its sub-networks appear to have only been characterised in terms of functional connectivity. DWI (see Figure 18.2) has been applied to cognitive control questions only a handful of times (Aron et al., 2007; Forstmann et al., 2008), and these studies tended to focus on only small portions of the cognitive control network. It will be important for future research to map the structural connections of the cognitive control network so we can begin to address the structural basis of this network, and how structural connectivity may constrain the possible patterns of functional connections during cognitive control processes.

Another major question is whether brain regions are meaningful units of function, or if networks/sub-network should subsume the role of region in structure–function mapping within cognitive neuroscience. The frequent co-activation of control network regions, and the clear dissociation of sub-networks rather than individual regions (see above), suggests that individual regions may not be very meaningful functionally. This would appear to be a strange design by evolution—why would it distribute portions of an undifferentiated functional unit over vast cortical distances? Yet, evolution is known to be highly suboptimal in other circumstances (Olshansky, Carnes, & Butler, 2015), such that it may be suboptimal with regard to brain organisation. A perhaps more likely scenario is that the nested brain network organisation characterised above continues to the level of individual regions (i.e., each region has a unique function within a sub-network). This would imply that functional dissociations will be possible but much more difficult (and perhaps less functionally relevant) among regions within the same sub-networks.

Considering this issue with respect to the frontoparietal control network, it remains unclear if each frontoparietal region is equally involved in a wide variety of functions (domain general). Alternatively, frontoparietal regions could pool their (relatively broad) functionalities together such that the network as a whole is domain general. This would imply a nested organisation with an emergent property—domain generality—due to the coordinated interactions among regions within a network. It will be difficult to test this possibility, owing to the need to test a wide variety of functions in many individual brains. Nonetheless, some clues from large meta-analyses of fMRI activation data suggest that this may be true (Niendam et al., 2012; Yeo et al., 2015).

In other cases—such as the ACC/pre-SMA—there may be questions regarding how many functional regions comprise a portion of the cortex (Cole, Yeung, Freiwald, & Botvinick, 2009). ACC/pre-SMA is often considered to be a single region in the literature, with activations in that general portion of the cortex used to constrain inferences regarding possible functions of that region (Ridderinkhof, Nieuwenhuis, & Braver, 2007). This has led to particularly broad functional characterisations of the ACC/pre-SMA (Botvinick et al., 2001; Brown & Braver, 2005; Grinband, Hirsch, & Ferrera, 2006; Shenhav et al., 2013; Chapter 15 by Brown in this volume; Chapter 10 by Kool et al. in this volume), as well as some heated debates with relatively little resolution over time. However, cytoarchitecture (B. A. Vogt, Nimchinsky, Vogt, & Hof, 1995), receptor densities (Palomero-Gallagher, Mohlberg, Zilles, & Vogt, 2008), and other criteria (Picard & Strick, 2001; Power et al., 2011; Yeo et al., 2015) have identified a variety of distinct regions within the ACC/pre-SMA. It is especially noteworthy that the ACC/pre-SMA sits at the convergence of at least five large-scale functional networks (Power et al., 2011; Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013), with portions of each in the vicinity of what many in the literature assume to be a single region. Proper characterisation of functional subdivisions within the ACC/pre-SMA could substantially improve our understanding of the regions and the functional network associations that comprise this portion of the cortex.

Moving up a level from cognitive-control-related brain regions, the distinct and overlapping functions of the cognitive control sub-networks remain unclear. As outlined above, there is evidence for top-down control of attention via the dorsal attention network, and sensitivity to task salience in the salience network. There is also evidence for especially dynamic top-down cognitive control processes occurring in the frontoparietal network, whereas the cingulo-opercular network appears to maintain activation levels over the entire duration of a task (Dosenbach et al., 2006; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). However, it remains unclear whether task information is actually being maintained by these sustained activations, or if these activations are rather maintaining arousal or sustained vigilance (Sadaghiani & D'Esposito, 2014). This is an example of the kind of questions that remain to be answered regarding the particular functions of each cognitive control sub-network.

Even after answering these kinds of questions, however, we would not have a complete theory of the neural basis of cognitive control. A set of interrelated functional mechanisms involving (in part) highly distributed network dynamics would also be necessary, which would bind the properties discovered in the process of answering these questions. Frameworks such as the guided activation theory and the flexible hub theory can act as these types of binders, though even these frameworks currently lack the detail necessary for a comprehensive explanation of cognitive control in the brain. What may be necessary is a kind of feedback loop between these types of theories and pragmatic empirically driven approaches—perhaps led by the novel data collection and network science methods described in the first section above—to answer outstanding questions. These questions would be driven in part by these theoretical frameworks (and possibly associated computational models; O'Reilly, Herd, & Pauli, 2010), while answering these questions would lead to refinement of the theoretical frameworks to incorporate that new information. Ultimately this process would help identify key mechanisms binding levels of organisation between lower-order brain processing (such as within-region dynamics) to higher-order brain processes (such as large-scale network dynamics) to cognition and behaviour.

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Notes

1 Note that while impressively comprehensive and accurate, this large-scale connectome lacks the detail of micro-connectomes characterizing neuron-level connectivity, such as is available in the aplysia sea slug and (for a subset of brain regions) the mouse.

2 Note that it may be impractical to start at certain levels of organization for explaining a given phenomenon of interest (e.g., the molecular level, or quantum mechanics level), because features often shift independently of the phenomenon of interest at certain levels (e.g., potassium molecules constantly being replaced in the prefrontal cortex).

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