Peer-reviewed version available at NeuroImage 2017; doi:10.1016/j.neuroimage.2017.08.010

Principles of Dynamic Network Reconfiguration across Diverse Brain States

James M. Shine [1,2,*] and Russell A. Poldrack [1]

[1] Department of Psychology, Stanford University, Stanford, CA, USA
[2] Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia

* Corresponding author: mac.shine@sydney.edu.au

Abstract: Recent methodological advances have enabled researchers to track the network structure of the human brain over time. Together, these studies provide novel insights into effective brain function, highlighting the importance of the systems-level perspective in understanding the manner in which the human brain organizes its activity to facilitate behavior. Here, we review a range of recent fMRI and electrophysiological studies that have mapped the relationship between inter-regional communication and network structure across a diverse range of brain states. In doing so, we identify both behavioral and biological axes that may underlie the tendency for network reconfiguration. We conclude our review by providing suggestions for future research endeavors that may help to refine our understanding of the functioning of the human brain.

Keywords: network; topology; integration; segregation; fMRI

Introduction

The invention of non-invasive imaging of the human brain has catalyzed a major shift in our understanding of the relationship between brain and behavior. By indirectly imaging activity in distributed neural circuits during the execution of complex, human behavior, neuroscientists have been able to develop a sophisticated understanding of the heterogeneity of specialized function within the human brain. However, the path from measurement to understanding is often frustratingly non-linear. In the case of functional neuroimaging, early studies were designed to determine the particular set of brain regions that were most 'active' in the context of well-controlled psychological experiments (Figure 1). This approach yielded a suite of specialized areas that putatively map onto specific psychological constructs (e.g. consider the role of the fusiform gyrus in facial perception), yet extracting mechanistic specificity from this approach has thus far remained challenging. In particular, it is conceptually difficult to translate the statistically significant 'activation' of a region to its algorithmic implementation in the brain (Poldrack and

Peer-reviewed version available at *NeuroImage* **2017**; doi:10.1016/j.neuroimage.2017.08.010

Yarkoni, 2016; Shine et al., 2016b). It is similarly challenging to understand how relatively isolated groups of specialized regions could coordinate their activity in order to facilitate complex behavior.

One potential solution to this problem is to consider the activity of individual regions within the context of their local (i.e. regional) and global (i.e. the whole brain) neuronal circuitry (McIntosh, 2000). Many modern theories of whole-brain function rely on the fact that cooperation and effective communication between spatially separate neural regions is crucial for the execution of effective behavior (Fries, 2005; Varela et al., 2001). That is, no region works alone (Figure 1). To fully appreciate the utility of a particular region of the brain, one must consider both the local and global architecture that feeds and constrains ongoing activity during behavior.

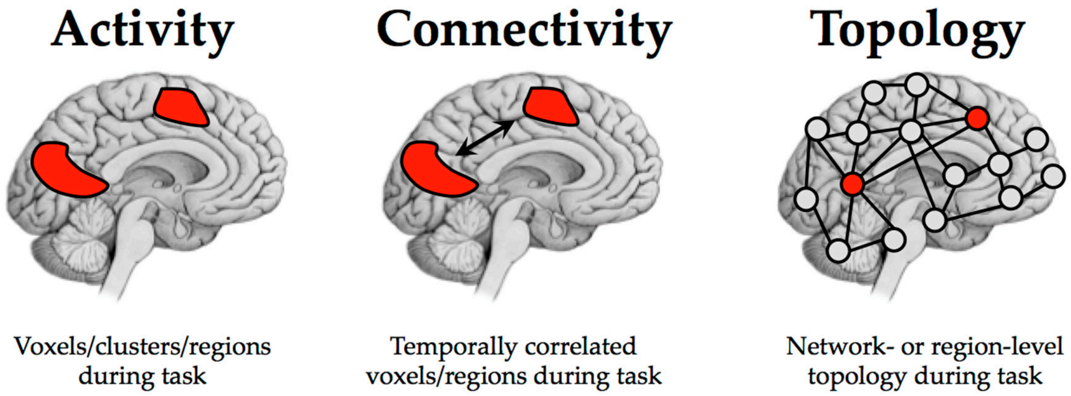

Figure 1 – Different levels of interrogation for neuroimaging studies.

It has been known for some time that coordinated fluctuations between specialist regions of the brain are critical for behavior (Friston, 1994). Although original enthusiasm was dampened by concerns that spurious correlations between regions may have been driven by the temporal constraints imposed by the structure of behavioral tasks, new methods have been developed to account for these issues, demonstrating that interactions between brain regions were indeed related to specific elements of behavioral tasks (Friston, 2011). For instance, using the psychophysiological interaction (PPI) approach, it has been shown that regions in the parietal cortex increase their connectivity with 'lower' visual regions during periods of high attentional load (Büchel and Friston, 1997). Others have used partial least squares (McIntosh et al., 2004;

Spreng et al., 2010), correlation PPI (Fornito et al., 2012), Bayes nets (Ramsey et al., 2010), or background connectivity (Norman-Haignere et al., 2012) to demonstrate interactions between large-scale cortical networks as a function of cognitive task performance. Together, these results shifted the focus from *where* in the brain a particular function resides to *how* the coordinated recruitment of segregated specialist neural regions works together to accomplish the challenges associated with complex behavioral tasks.

However, any meaningful interaction that occurs between two regions within a complex system is necessarily constrained by the global topology of the entire network (Figure 1). Concretely, activating one neuron can constrain the suite of potential actions available to a connected neuron within a broader network (Sporns, 2015). Indeed, perturbation of a network can have many non-linear effects that are difficult to estimate without knowledge of the system as a whole (Bargmann and Marder, 2013). The mathematical formalism of graph theory, a branch of mathematics that quantifies structures at the systems level, has afforded neuroscientists an opportunity to explore these constraints (Sporns, 2015). For instance, a growing number of studies have shown that the human brain is organized according to precise topological rules, displaying a small-world architecture (Bassett and Bullmore, 2006) with a core of densely inter-connected "rich-club" regions (van den Heuvel and Sporns, 2013) that aid in the balance between specialization and global integration (Mišić et al., 2016).

Many of the studies that have applied graph theoretical approaches to understanding the organization of the human brain have investigated the so-called 'structural connectome', calculating topological parameters from white-matter connectivity matrices estimated using diffusion weighted imaging. However, the brain is an inherently dynamic organ, capable of flexible reconfiguration in the face of an evolving world. As such, a new frontier of brain imaging is emerging, in which studies are attempting to coalesce the tools of graph theory with temporal estimates of inter-regional coordination that change over time, both during 'rest' (Allen et al., 2014; Betzel et al., 2016; Calhoun et al., 2014; Shine et al., 2016a; Zalesky et al., 2014) and during task paradigms (Bassett et al., 2013; 2015; Cole et al., 2014).

The balance between integration and segregation

Peer-reviewed version available at *NeuroImage* **2017**; doi:10.1016/j.neuroimage.2017.08.010

Estimating the integrative signature of a network

Although there are many ways in which to describe the topology of a network (Bullmore and Sporns, 2012), the amount of global integration has been shown to be a crucial index for understanding the effective functioning of the human brain. In brief, integration refers to the extent to which a modular network demonstrates interaction amongst its sub-communities or *modules* (see Figure 2a for a simple toy model demonstrating this effect). Conversely, segregation is the topological opposite of network-level integration (Figure 2c), and represents the extent to which a particular network can be readily grouped into relatively isolated sub-communities that are tightly connected within modules but with sparse connected between modules (Figure 2a).

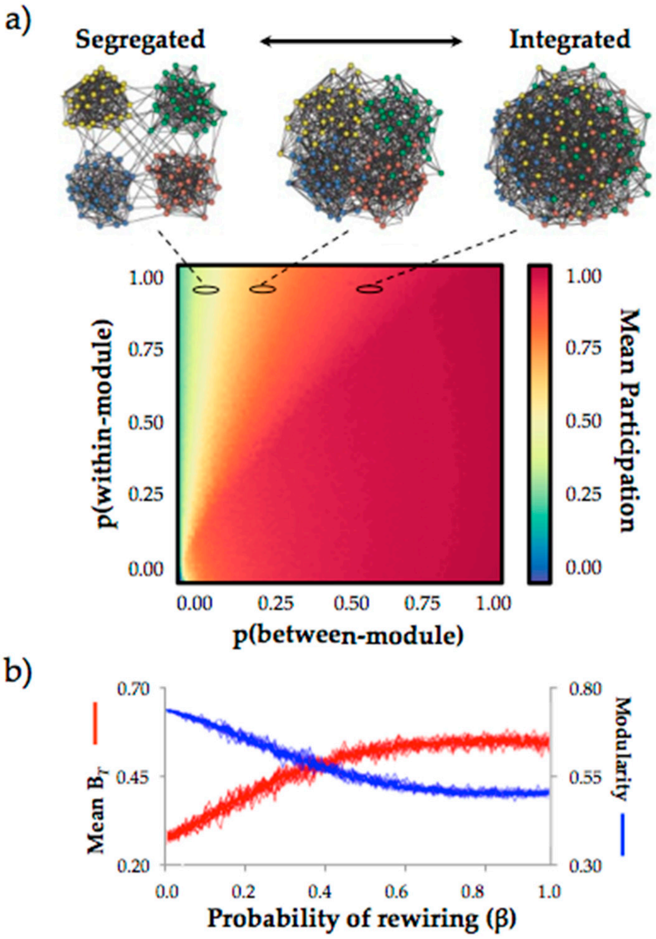

Figure 2 – the balance between Integration and Segregation: a) results of a simulation of the structural network topology of an 120-region network (Guimerà and Nunes Amaral, 2005) with 4 equally sized modules (i.e. 30 regions each), in which we manipulated the probability of within-

(y-axis) and between-module (x-axis) edges between 0 (i.e. no edges between/within a module) and 1 (i.e. full connections within/between modules). The extent of integration within each network was estimated by calculating the mean participation coefficient (which calculates the strength of connections *between* modules) across the parameter space (Bertolero et al., 2017; Power et al., 2013; Rubinov and Sporns, 2010; Shine et al., 2016a). The mean results across 1000 iterations show that integration is maximal when between-module density is greater than within-module density (code is available at http://github.com/macshine/integration/guimera_model.m); b) inverse relationship between mean participation (red) and modularity (blue) as a function of the probability of randomly rewiring (β) a highly clustered "Watts and Strogatz" null model (Watts and Strogatz, 1998).

As demonstrated in Figure 2, it is straightforward to estimate the integrative signature of a network. The first step is to calculate relationships (i.e. 'edges') between a set of brain regions (i.e. 'nodes'). For functional neuroimaging data, networks are generally created by calculating a similarity measure between regions, such as a Pearson's correlation – the correlation strength between regions over time thus defines an 'edge' between two nodes in the graph.

Recent experiments have begun to explore the variability in pairwise connectivity by 'sliding' the estimate of functional connectivity over time using a series of overlapping windows (Hutchison et al., 2013a). Despite compelling differences associated with unique behaviors (see *Relating network reconfiguration to behavior* below), there is currently an ongoing debate in the literature regarding whether the fluctuations observed using these approaches are sensitive to nuisance variables such as head motion or arousal/sleep (Laumann et al., 2016) or to analytic choices such as effects associated with window length (Hindriks et al., 2015; Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015). There are many popular techniques for controlling for the impact of nuisance variables, such as head motion (Power et al., 2014) and arousal (Laumann et al., 2016; Tagliazucchi and Laufs, 2014), but it is currently unclear whether the process of removing these variables from the data also removes meaningful signal (e.g. see Chen and Glover, 2015), particularly in light of recently established links between arousal, cognition and time-resolved network topology (Chang et al., 2016; Shine et al., 2016a).

Some have even questioned whether fluctuations in BOLD data should be described as 'dynamic' at all, since randomly generated with time invariant connectivity structure data can demonstrate patterns typically regarded as dynamic (Laumann et al., 2016; Liegeois et al., 2017). Indeed, the sluggish time scale of BOLD signal activity likely hinders the detection of dynamics on the timescale of human cognitive processes (Hari and Parkkonen, 2015). However, even data indistinguishable from 'stationary' null data can demonstrate behavioral relevance (Liegeois et al., 2017) – for instance, if emergent patterns of coordinated activity between regions coincides above chance with particular elements of a cognitive task (e.g. Figure 3). This suggests that a sensible way to establish the reality and importance of fluctuations in connectivity structure lies in the evaluation of their correspondence with measured behavior. As such, in this review, we have chosen to focus our interrogation on network reconfiguration as a function of behavioral state, irrespective of whether differences were observed within a particular scanning session (Gonzalez-Castillo et al., 2015) or as a function of task performance (Ekman et al., 2012; Sadaghiani et al., 2015).

The result of either of these approaches is a network graph (or set of graphs) for which the topological signature of the network can be estimated using standard graph theoretical tools (e.g. https://sites.google.com/site/bctnet/; https://github.com/networkx/networkx/). Briefly, this involves using one of a suite of algorithms to identify tightly connected *communities* (i.e. clusters) of regions within each graph. From here, it is then possible to calculate the extent of between-module connectivity (e.g. using the participation coefficient (Power et al., 2013), which is commonly used as a proxy for network-integration). In summary, networks that are more extensively integrated have more connections that cross modular boundaries.

As with most neuroimaging analyses, there are a number of critical steps for estimating meaningful graphs. Firstly, it is important to ensure that the network is composed of nodes and edges that reflect a meaningful level of organizational structure of the brain (Fornito et al., 2013). For instance, clusters of voxels are more likely to represent a stable functional unit within the brain than an independent voxel, given that the macroscopic functional organization of the brain appears to be at the scale of roughly one centimeter (Glasser et al., 2016). In addition, as time-series similarity represents by far the most common means for estimating functional networks, it is vital to identify common sources of noise (such as head motion, cardiac/respiratory artifacts, and scanner drift) and also to demonstrate caution when cleaning these sources of noise (e.g. interpolating over missing data may induce variation in the degrees of freedom across windows).

Finally, it is also important to consider the choice of graph theoretical tools used to estimate community structure. In particular, the methods that use modularity maximization to estimate community structure (such as the popular Louvain algorithm) require caution, as the resolution limit and the stochasticity of the most commonly used algorithms can lead to sub-optimal community solutions (Sporns and Betzel, 2015). These problems can be largely minimized using parameter exploration and multiple iterations of each algorithm (Sporns and Betzel, 2015). In addition, the nature of these algorithms is that they will provide a community partition even on completely random graphs, so effort must be taken to compare results to appropriate null models that constrain the hypothesis being tested (Zalesky et al., 2012). Indeed, it is inherently problematic to transform statistics that represent the likelihood and weight of a network connection (such as those estimated using neuroimaging) into the binary edges that are often required for classical graph theoretical algorithms. Fortunately, there is now a suite of suitable tools that leverage the richness of these connections to assist in module detection. Specifically, these approaches alter traditional clustering algorithms to incorporate the continuum of positive and negative edge weights, maximizing the anti-correlations between regions to refine the identification of tight-knit communities in networks with edges defined by statistical relationships over time. In doing so, these algorithms avoid the arbitrary decision of where to threshold a connectivity matrix (Rubinov and Sporns, 2010), leveraging empirical details that would otherwise be lost to better define the network topology of neuroimaging data.

Integration and segregation in brain networks

The balance between segregation and integration is crucial for maintaining the metastability of complex, dynamical systems, such as the brain (Tognoli and Kelso, 2014), essentially striking a balance between local specialization and global organization (Park and Friston, 2013; Tononi and Sporns, 1994). There is a long and storied history of identifying the functional characteristics of specific regions of the brain, but the study of global integration is still in its relative infancy. Indeed, a major challenge for theories that utilize integration is to describe how an integrated brain can maintain information processing selectivity. That is, network topology is relatively ignorant of *what* is being processed by a particular region, but can more easily account for *which* other regions it is temporally coordinated and for *when* this coordination occurs in time.

For example, a region in the ventral temporal cortex may be selective for a particular set of visually identified facial features (Haushofer and Kanwisher, 2007), whereas activation of a similarly sized region in pre-motor cortex would instead trigger the coordinated activation of a particular set of skeletal muscles (Pearce and Moran, 2012). Within a relatively segregated architecture, the execution of each regions capacity should directly relate to its local architecture and its computational properties. However, if the brain were sufficiently integrated while both regions were active, to the extent that the two regions were strongly temporally coordinated, it is plausible that the specific patterns being transmitted by each region might become somehow 'muddled' through their mutual interaction. This begs the question: how can modular regions remain specialized within an integrated network?

A harmonious solution to this problem is that segregation and integration represent competing constraints on higher-level neuronal function (Kelso, 2012; Park and Friston, 2013; Sporns, 2013). That is, if a region becomes too specialized (and as such, becomes less integrated into the global network), then it will likely become maladaptive, impairing the ability to effectively interact with changing circumstances that would normally require substantial flexibility. Conversely, if a particular region becomes too globally integrated, the partners with which the region interacts might become too broad, thus limiting the effectiveness of a particular algorithmic capacity. Indeed, this trade-off between global integration and local segregation essentially maximizes the brain's ability to both exploit learned associations, while also allowing for the exploration of novel opportunities in the environment (Aston-Jones and Cohen, 2005).

Relating network reconfiguration to behavior

Here, we review a range of neuroimaging studies that have used time-resolved analyses to understand the role of network topology in behavior. Due to the breadth of studies, we have chosen to tailor our investigation towards studies that investigate the behavioral state of the individual being scanned, either when there is no perturbation at all (as in the case of the 'resting' state), through the performance of a particular behavioral task (e.g. a motor or cognitive task), or

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 July 2017 doi:10.20944/preprints201707.0014.v1

Peer-reviewed version available at *NeuroImage* **2017**; doi:10.1016/j.neuroimage.2017.08.010

through the causal manipulation of brain states (e.g. via pharmacology or brain stimulation). Due to the necessity for modalities that track network-level changes over time to contain both spatial and temporal resolution, we have focused our review on studies that utilized fMRI, however we have also endeavored to bolster these findings with results from electrophysiology where appropriate. We hope that our review will provide a roadmap for potential future studies to help clarify important issues in the literature.

The extent of integration can be calculated for any network studied using the methods described above. As such, an important question currently facing the field of neuroscience is precisely how functional network architecture maps onto behavior. Traditionally, the approach used by practitioners of fMRI has been to identify regions associated with a contrast of interest on a behavioral task, essentially isolating the segregated regions that are thought to be most crucially involved in the behavior under investigation. In recent years, as the focus has shifted from a locationalist perspective to one in which considers the structure of the entire brain network, a range of studies have been conducted in order to determine the role of network topology in task performance. Here, we report the results of a targeted review of the literature that summarizes a spectrum of these approaches: from resting state, to task-based analyses and finally, to causal manipulation of the brain.

Resting state or unconstrained behavior?

Recent time-resolved functional neuroimaging experiments, which offer an effective method for non-invasively identifying time-sensitive shifts in inter-areal coordination, have shown that there are robust fluctuations in the balance between integration and segregation in the resting brain. For instance, a pioneering study demonstrated that global brain signals transition between states of high and low connectivity strength over time (Zalesky et al., 2014). Since then, it has been shown that the network structure of the brain fluctuates over time (Betzel et al., 2015; Shine et al., 2016a), demonstrating shifts between relatively modular (Betzel et al., 2016) and integrated (Shine et al., 2016a) topological architectures. Given the known inverse relationship between modularity and integration in assortative networks (Figure 2b), it is quite likely that these results reflect the description of topological states that exist as two extremes on a topological spectrum, although this relationship may not necessarily hold for other types of biological networks (Betzel et al.,

Peer-reviewed version available at NeuroImage 2017; doi:10.1016/j.neuroimage.2017.08.010

2017). Either way, the psychological relevance of the fluctuations in network topology remains somewhat of a mystery.

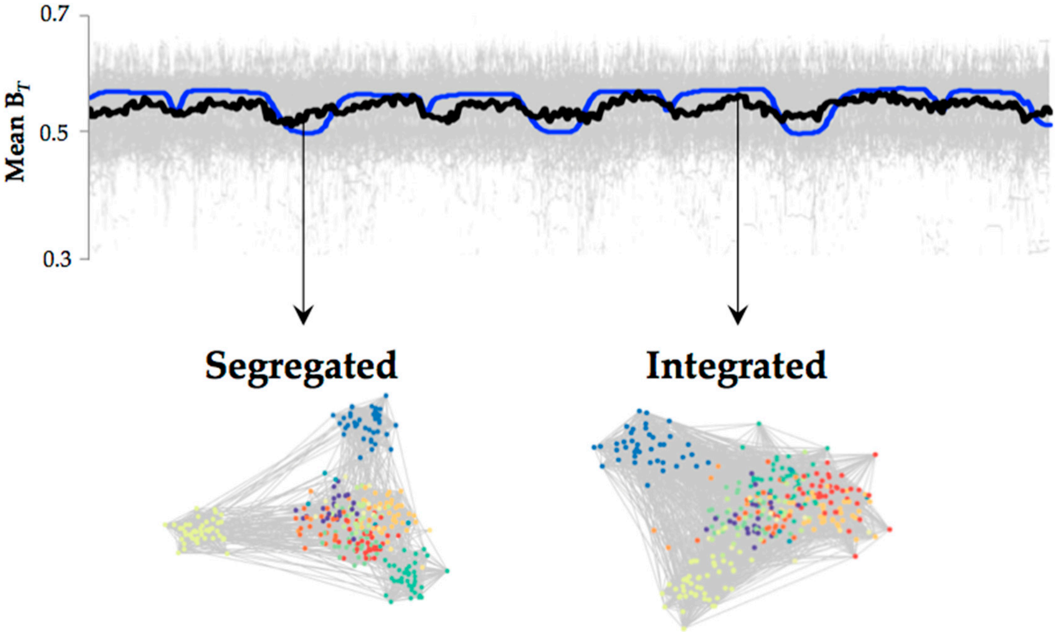

Figure 3 – fluctuations in time-resolved network topology as a function of N-back task performance (see Shine et al., 2016) – the lower panel contains exemplar force-directed plots of both a Segregated (left) and Integrated (right) states. Colors of nodes depict the network identity of individual regions defined using the Gordon atlas (Gordon et al., 2014) and edges represent positive connections between regions.

Importantly, although the resting state is relatively unconstrained behaviorally, it is clear that the ‘resting state’ is not synonymous with a lack of cognitive activity. (Morcom and Fletcher, 2007). On the contrary, participants often have vivid, well-characterized thoughts during resting state sessions (Hurlburt et al., 2015), which can range from somatosensory (e.g. consciously attempting to keep one’s body still) to highly conceptual (e.g. thinking about why the experimenter is scanning one’s brain). Irrespective of the precise thoughts experienced during a scanning session, the logical assumption behind resting state analyses is that individual differences equate to essentially random patterns across a population, and hence that any consistent architecture that is discovered in the analysis of the resting state exists as a ‘baseline’ upon which the coordinated activity of task-constrained behavior should be interpreted. As such, the fluctuations observed in network topology during rest may very well relate directly to ongoing cognitive processing (Hasenkamp et al., 2012), though the unconstrained nature of the resting state makes obtaining evidence for this hypothesis problematic. While thought probes offer some utility (Kucyi and Davis, 2014), they are at best an indirect means for testing the hypothesis that network structure relates to spontaneous cognition.

Integration as a function of task performance

More rigorous testing of the relationship between network topology and cognitive function thus requires the analysis of network structure as a function of task performance (Figure 4). The majority of studies that have demonstrated such a relationship involve experiments that have manipulated specific aspects of cognition, such as working memory or attentional set-shifting. Early studies in this area provided evidence for targeted connectivity involving frontoparietal cortices in cognitive function. For instance, Cole *et al* showed that a flexible frontoparietal architecture across tasks was associated with execution of multiple cognitive tasks (Cole et al., 2013), a finding that has since been replicated using dynamic network analyses (Mattar et al., 2015), which extended earlier work by demonstrating the importance of flexible regional recruitment over time for cognitive function. Others have shown that dynamic patterns of network structure are uniquely related to multiple different tasks (Gonzalez-Castillo et al., 2015), suggesting that the specific patterns of network organization may reflect the information processing requirements of particular tasks. In addition, functional connectivity between frontoparietal and default regions has been shown to reconfigure during cognitive processing (Vatansever et al., 2016) and is also associated with individual differences in cognitive flexibility (Douw et al., 2016). However, the maximization of regional flexibility *per se* is not sufficient to explain the organization of the functional connectome, as the functional connectome is constrained by a structural backbone of connectivity that is relatively stable over time (Lord et al., 2017; Shen et al., 2015).

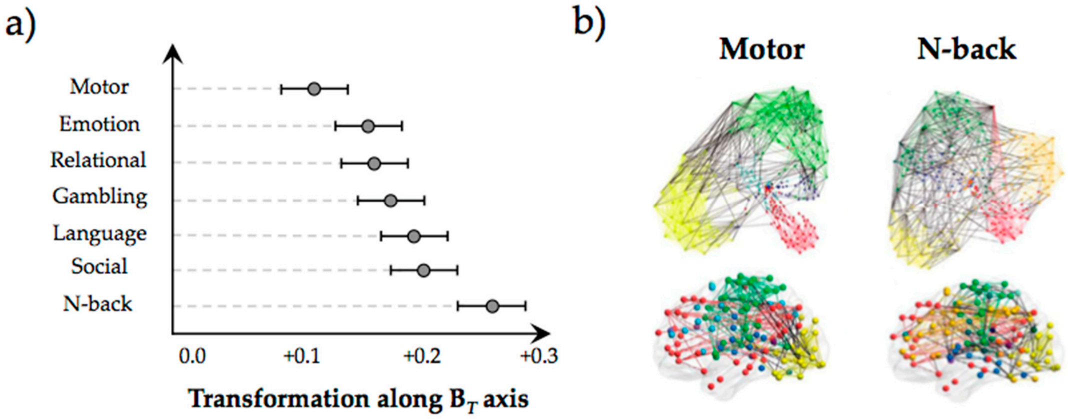

Figure 4 – Reorganization as a function of task: a) the amount of integration (transformation from resting state signature along B_T axis) associated with seven unique tasks from the Human Connectome Project (Shine et al., 2016a); b) network signature of simple motor and cognitively-challenging ('N-back') task (Cohen and D'Esposito, 2016).

At the network level, multiple studies have reported an increase in global integration as a function of cognitive task performance, most notably during the 'N-back' task (Braun et al., 2015; Davison et al., 2015; Finc et al., 2017; Gallen et al., 2016; Shine et al., 2016a; Vatansever et al., 2015; Wendelken et al., 2016) (Figure 4). For instance, Braun and colleagues (Braun et al., 2015) showed that effortful working memory performance was associated with integration between frontoparietal and frontotemporal networks, and that individuals with greater network reconfiguration in frontal cortices demonstrated enhanced memory and had greater cognitive flexibility. Similarly, Shine and colleagues (Shine et al., 2016a) demonstrated that task-related integration in network topology related to fast, effective cognitive performance on the N-back task (Figure 3). This dissolution of modularity during N-back performance has been corroborated by other groups (Alavash et al., 2016; T. Chen et al., 2016; J. R. Cohen and D'Esposito, 2016; Davison et al., 2015; Shine et al., 2016a; Vatansever et al., 2015), demonstrating that brain-wide integration during cognitively complex tasks may act as a predictive signature of individual differences in executive function (Braun et al., 2015; Gallen et al., 2016; Schultz and Cole, 2016; Shine et al., 2016a). Replicating these fMRI results, a number of studies using electrophysiology during N-back tasks have shown similar increases in network-level integration as a function of cognitive performance (Bola and Borchardt, 2016; de Pasquale et al., 2012; Kitzbichler et al., 2011; Zippo et al., 2016). While this replication is extremely important, it raises a number of crucial questions regarding the coordination of network-level interactions across distinct temporal scales (Honey et al., 2012).

Alterations in functional network architecture have also been observed in tasks that manipulate episodic memory. For instance, multiple studies have shown that memory recall is associated with targeted connectivity between frontal and default networks (Fornito et al., 2012; Spreng et al., 2010). Others have shown that successful episodic memory retrieval is associated with a less modular network (Westphal et al., 2017) in which the hippocampal formation, precuneus and frontal cortex acted as highly-connected hubs (Schedlbauer et al., 2014). In keeping with these studies, separate studies have shown that the integrative signature of the hippocampus reconfigures the whole-brain network towards integration during vivid memory recollection (Geib et al., 2015). In contrast, it has been demonstrated that segregation involving nodes of the default network were associated with effective visual semantic memory task (DeSalvo et al., 2014). Based on these differences, it is difficult to draw a conceptual consensus in this area, however one might conjecture that the recall of items that are strongly consolidated into cortex should display a distinct topological signature from items that are poorly learned (O'Reilly et al., 2014).

Attention is another higher cognitive capacity that has been shown to relate to network reconfiguration. For instance, Spadone and colleagues demonstrated that performance on a visuospatial attention task was associated with a targeted increase in dynamic connectivity between parietal and occipital regions (Spadone et al., 2015). It has also been demonstrated that tracking multiple moving objects in their peripheral vision recruits between-network connectivity as a function of increasing attentional load (Alnæs et al., 2015). Others have demonstrated that attention to particular object categories leads to increased connectivity between ventral visual cortex and MTL (Córdova et al., 2016). It has also been shown that higher topological efficiency improved decoding accuracy on a visual perception task (Cocchi et al., 2017). In a longitudinal study, Shine et al. demonstrated that fluctuations in network topology over weeks to months were associated with ‘meta-states’ in which a single individual self-reported heightened attention (Shine et al., 2016c). Similar measures of regional flexibility have also been shown to fluctuate as a function of attentional task performance (Telesford et al., 2016). In support of this result, others have shown that fluctuations of attentional capacity (Kucyi et al., 2016) and vigilance (Wang et al., 2016) are related to dynamic interactions within and between large-scale attentional networks. These results are consistent with a recent study that used EEG to demonstrate that fluctuations in alpha band power were associated with relative impairments in awareness (Lakatos et al., 2016), implying that the capacity for attention may relate to specific states in which connectivity is maximized between regions crucial for the coordination of widespread cortical regions. In keeping with this hypothesis, there is evidence to suggest that integrated network topology is specifically related to trials of an attentional task associated with correct performance, when contrasted with trials in which an error was made (Ekman et al., 2012). Together, these studies suggest that network integration may represent a crucial signature of effective attentional function.

Behavioral tasks that rely on network segregation

Whereas there are clear links between integration and cognitive performance, in some cases it appears that task performance can benefit from increased segregation. In a sustained vigilance task, Sadaghiani and colleagues (Sadaghiani et al., 2015) showed that an increase in network modularity predicted the accurate detection of a rare oddball stimulus, a finding that is in contrast to the relationship between cognition, awareness and global integration. While this might reflect idiosyncratic aspects of the particular task that was studied (which required long periods of hyper-vigilance), it should at the very least serve to highlight the fact that not all behavioral capacities are maximally effective when executed within an integrated network architecture. Indeed, although ubiquitous, attention is an inherently difficult function to define and test. Future studies should therefore aim to decompose attention into qualitatively distinct sub-components (e.g. directed *vs* diffuse; endogenous *vs* exogenous; local *vs* global; overt *vs* covert; visual *vs* corporeal) and measure the resultant functional network architectures associated with the fundamental components of attention, such as alertness, selectivity and processing capacity (Posner and Boies, 1971).

Another behavior that is negatively correlated with network-level integration is the performance of relatively ‘automatic’ motor tasks. The execution of stereotyped, consistent behavior (such as tapping one’s fingers in a particular learned sequence; Figure 4b) has been long known to rapidly improve with training, and in doing so, become relatively immune to interference from other cognitive demands (Shiffrin and Schneider, 1977). As such, one might predict that the effective performance of a motor task might be associated with a relatively segregated architecture. This is precisely what was found when one group scanned subjects over the course of six weeks as they learned a simple visuomotor task (Bassett et al., 2015), revealing a pattern in which the motor and visual networks became more segregated as a function of learning performance. Another recent study showed a similar shift from integration towards segregation with learning (Mohr et al., 2016). It is now of particular interest to determine how these patterns of network-level reorganization relate to long-standing literatures that relate automaticity to neural plasticity within the cortico-basal ganglia circuitry (Balleine and O'Doherty, 2009) and cortico-cerebellar systems (Balsters and Ramnani, 2011). It would also be useful to design experiments to help us understand the potential benefits that segregation as a function of automaticity might confer on the brain – for instance, does segregation 'release' association hubs for more flexible processing (Bassett et al., 2015) or reduce metabolic demands (Bullmore and Sporns, 2012)?

Causal manipulation of network topology

A powerful but relatively underutilized approach is to causally manipulate the behavioral state of an individual using either pharmacological approaches or direct stimulation of the brain, and then estimate the network-level topology of the resultant state. To this end, recent studies using this approach have shown that the network structure of the brain is also related to conscious awareness. One such study administered anesthetic agents to macaques and showed that the emergence from anesthesia was associated with a breakdown in the modularity of the functional connectome (Barttfeld et al., 2015). Corroborative evidence for this effect was observed in separate study in humans using a backwards-masking experiment, whereby an image is rendered probabilistically visible (i.e., at the threshold of awareness), to show that global brain topological efficiency was elevated on trials when individuals consciously perceived a stimulus (Godwin et al., 2015). These results are consistent with the finding that the functional repertoire of brain states is inversely related to the depth of anesthesia (Hutchison et al., 2013b). Indeed, the administration of ketamine, an NMDA receptor antagonist commonly used for anesthesia, has been shown to shift the brain towards a more segregated state (Becker et al., 2016). Together, these studies suggest that an integrated topological structure is closely related to conscious awareness.

Others have used pharmacological fMRI to improve our understanding of the topological reconfigurations associated with particular neurotransmitter systems. For instance, a recent study administered atomoxetine, a potent inhibitor of noradrenaline reuptake in a placebo-based, double-blind, cross-over trial and then measured regional connectivity from resting state fMRI data (van den Brink et al., 2016). The authors observed significant alterations in between-network connectivity, and further analysis has shown that this coincides with a system-wide decrease in network-level integration (Shine et al., 2017). Separate lines of research have manipulated the dopaminergic system, and in doing so have shown a relationship between local and global topological efficiency as a function of dopamine receptor antagonism (Achard and Bullmore, 2007). While there are of course many other neurotransmitter systems to interrogate, this promising approach demonstrates a crucial means for the field to explore the relationship between neurobiology and systems-level network topology.

The brain can also be causally manipulated through electrical stimulation. One common approach is to collect resting state data before and after repetitive transcranial magnetic stimulation, which can be tuned to either excite or inhibit the underlying neural tissue. This technique was recently used to demonstrate that the stimulation of neural hubs (highly interconnected and influential regions within a network) had significantly different effects on network-level topology than the stimulation of topologically isolated regions (Cocchi et al., 2016). Related approaches that use different forms of stimulation (such as optogenetic fMRI in rodents; Liu et al., 2015), or different modalities to collect data (such as studies that combine direct neural stimulation with fMRI; Oya et al., 2017), both hold promise for uncovering the mechanistic basis of network-level dynamics in the brain.

What behavioral axes drive neuronal integration?

The relationship between functional connectivity, network topology and task performance begs the question: what benefit does network reorganization confer to the brain across different behavioral contexts? At its most extreme, integration between all regions of the brain would likely lead to a hyper-synchronous state similar to those associated with epilepsy, which is a state that is devoid of information processing. It is also unlikely that the integrative signatures

Peer-reviewed version available at NeuroImage 2017; doi:10.1016/j.neuroimage.2017.08.010

described in the previous section are simply due to the spatiotemporal constraints imposed by the performance of any psychological task, as differences in network topology have been related to specific performance measurements within task (Ekman et al., 2012; Sadaghiani et al., 2015). Similarly, while the network signatures of sleep and awake states differ in fundamental ways (Tagliazucchi and Laufs, 2014), network-level integration is unlikely to be purely related to arousal, particularly given the range and variation of integrative processes observed across different tasks (Shine et al., 2016a). In the following section, we speculate regarding a range of factors that may impact on network-level reconfiguration in an attempt to determine the next generation of questions that may help to clarify the mechanisms underlying the relationship between network structure and behavior.

Efficient energy expenditure

The systems that control the brain's energy use represent one potential mechanism responsible for controlling network-level reconfiguration. The human brain is both metabolically expensive and globally inter-connected, suggesting that the organization of the brain reflects a trade-off between energy utilization and topological efficiency (Bullmore and Sporns, 2012) that is facilitated by the densely inter-connected 'rich-club' of the structural connectome (van den Heuvel and Kahn, 2012). Recently, work in the mouse structural connectome has provided some empirical support for this notion, with the observation that many of the genes that code for energy turnover coincide spatially with regions of the structural 'rich club' of the brain (Fulcher and Fornito, 2016). This suggests that these highly-interconnected regions act as an information processing highway system across which effective neuronal communication is most likely to occur (Gollo et al., 2015; Senden et al., 2016). However, these relationships between energy efficiency have been most readily apparent when analyzing the structural connectome, often in combination with computational modeling approaches (Honey et al., 2009). Indeed, there is emerging evidence that a different set of regions (the so-called "dynamical workspace of binding nodes") might be more important for maximizing the balance between network-level integration and segregation (Deco et al., 2015; 2017). An extensive treatment of this field is outside the scope of this review, however it is clear that future work is required in order to integrate computational and empirical approaches towards a more complete understanding of this mechanism in the functional brain.

The complexity of task performance

Another axis upon which network topology may relate to behavior is task complexity. For instance, the extent of integration may track with task difficulty, in that a higher number of task-relevant parameters (e.g. choices, perceptual distractions, items to maintain in working memory) could drive interactions between otherwise uncoordinated regions, and hence manifest as network-level integration. This explanation is consistent with the finding that relatively 'simple' tasks, such as a motor tapping task, recruit less network-level integration than more cognitively-challenging tasks, such as the N-back task, which necessarily require the interaction of a larger number of specialist systems of the brain (J. R. Cohen and D'Esposito, 2016; Shine et al., 2016a). Despite these lines of evidence, it remains unclear how to best measure 'complexity' across distinct behavioral domains. One viable approach is to measure subjects across multiple unique task states (Cole et al., 2013; Gonzalez-Castillo et al., 2015; Krienen et al., 2014; Mattar et al., 2015; Shine et al., 2016a) and estimate alterations in connectivity and topology as a function of behavioral performance. An alternative approach involves comparing the network structure of the brain with the signatures of multiple tasks housed within meta-analytic repositories (Bertolero et al., 2015). These studies consistently identify a network of highly interconnected frontoparietal regions that are crucial for task performance across a range of behavioral constraints. However, without systematic exploration of the entire parameter space (which is outside the current scope of cognitive neuroscience), it is difficult to empirically define task complexity, and hence, to draw any firm conclusions about the relationship between complexity and network topology.

Global Workspace Architectures

Many of the studies reviewed here (Bertolero et al., 2015; J. R. Cohen and D'Esposito, 2016; Cole et al., 2014; Finc et al., 2017; Kitzbichler et al., 2011; Shine et al., 2016a; Vatansever et al., 2015) demonstrate results that align with the predictions of theories of consciousness that invoke models of the global workspace (Baars, 2002; Dehaene and Naccache, 2001) or integrated information theory (Oizumi et al., 2014). In brief, these models propose that conscious access to information is related to the extent of integrated information processing within the distributed thalamocortical architecture of the brain (Edelman, 2003). In addition, it has been known since the time of William James that our conscious experience fluctuates over time in *"an alternation of flights and perchings"* (James, 1890), a mechanism that is strikingly similar to the fluctuations observed in topology in the 'resting state' (Betzel et al., 2016; Shine et al., 2016a). As such, it is possible that integrated network states reflect the presence of active thought processes in the brain, with more segregated states reflecting relative cognitive quiescence (such as the states that occur during mindfulness meditation; Tang et al., 2015), however these hypothetical speculations require empirical confirmation.

Goal-directed behavior and automaticity

A similar line of evidence suggests that the balance between integration and segregation may relate to the distinction between goal-directed and automatic/habitual processing. In brief, this axis reflects the differences in behavior associated with task performance over the course of learning: early in the course of learning, behavior is flexible and controlled, whereas behavior tends to automatize over time as the most effective means for executing the behavior are repeated and become well-learned (Shiffrin and Schneider, 1977). Indeed, there is compelling evidence that the functional connectome becomes more segregated over time during motor tasks, with subjects demonstrated a more modular architecture as a function of learning rates (Bassett et al., 2015; Mohr et al., 2016). Conversely, situations that require the most cognitive control (such as during an 'N-back' task, in which items must be continually updated in working memory) have been associated with a relatively integrated brain network (Bola and Sabel, 2015; Shine et al., 2016a; Vatansever et al., 2015). However, it is also clear from studies of multitasking that there are important limits on network interactions, as inappropriate cross-talk can negatively impact performance on multiple simultaneous tasks (Feng et al., 2014). Together, these findings suggest a potentially non-linear relationship between network architecture and performance, though the assimilation of these results with the deep existent literature (e.g. linking automaticity to basal ganglia (Seger and Spiering, 2011) and cerebellar architectures (Balsters and Ramnani, 2011)) remains to be attempted. A direct test of this hypothesis could adopt the logic of traditional automaticity studies (Shiffrin and Schneider, 1977) by comparing performance over time in a consistent environment that supports the development of automaticity to a varied task environment that does not. If controlled processes relates to integration and automatic processing relates to segregation, the consistent mapping condition should support a shift from controlled processing to automatic processes that mirrors a shift from network integration towards segregation, and the varied mapping condition should always require controlled processing, and therefore remain integrated over time.

Modulation of neural gain

A plausible candidate mechanism responsible for driving alterations in higher-level network integration is tonic activity within ascending neuromodulatory nuclei of the brainstem (Robbins and Arnsten, 2009), such as the locus coeruleus (which releases noradrenaline), the ventral tegmental area (dopamine) and the basal nucleus (acetylcholine). While these nuclei are all relatively small in neural terms, their projections ramify across the large portions of the brain, enacting global influence via neuromodulatory mechanisms. By refining the 'gain' of receptive neurons, these neurotransmitters alter the likelihood that regions can interact with one another, thus impacting on the potential for 'functional connectivity' between otherwise disparate neural regions (Aston-Jones and J. D. Cohen, 2005).

The noradrenergic system in particular has received a wealth of recent empirical support, including work in rodents that has shown that noradrenergic tone is related to cortical 'up' states (Joshi et al., 2016; McGinley et al., 2015); work in non-human primates that showed that noradrenergic tone can positively bias attentional performance (Engel et al., 2016); and work in humans that relates higher-level brain function to network topology via the noradrenergic system (Eldar et al., 2013; Shine et al., 2017; 2016a; van den Brink et al., 2016). Together, these studies suggest that manipulating neural gain via ascending neuromodulatory projections may shift a state towards higher levels of integration, perhaps through maximizing the functional involvement of highly-connected regions within the salience network (Young et al., 2017). Despite the link between noradrenaline and integration, the neuromodulatory systems of the brain are complex and inter-connected. For instance, both the cholinergic (Mesulam, 2013) and dopaminergic (Cui et al., 2013) systems have similar neuromodulatory effects to noradrenaline, but are activated in different contexts and demonstrate unique spatial projection patterns, suggesting that the activation of these neurotransmitter systems may manifest as distinct patterns of topological reconfiguration.

Similar mechanisms across distinct brain states?

Based on the lack of an effective generative model of the brain's functional organization, classical approaches to understanding the brain mechanisms underlying behavior have relied upon the isolation of particular behavioral capacities (e.g. attention, cognitive control, motor automaticity, etc.) and the subsequent interrogation of the neural correlates of each behavior. This approach, while successful, has led to a literature that is itself relatively segregated (Poldrack and Yarkoni, 2016). That is, we know a lot about the details of each behavior but are relatively ignorant of how they arise from the same generative architecture. The fact that network level integration has been successfully related to a range of higher-order brain states, such as attention, cognitive control and conscious perception, that are commonly studied in isolation suggests that network reconfiguration may represent a means of integrating mechanisms across multiple unique behaviors.

By re-framing higher-level brain function according to its underlying neurobiology, rather than by the emergent construct under investigation in any given experiment (i.e. attention, cognition, etc.), we could flip the standard practice of investigating the neural basis of a behavior, and instead place the emphasis on the neurobiological mechanisms that give rise to different behaviors under changes in experimental constraints. If network reconfiguration can be demonstrated to exist as the common mechanism upon which a range of higher-order capacities resides, empirical work could then focus on the manipulations of the underlying architecture that manifest as each unique behavior. In this way, network science could act as a powerful generative framework for the field, particularly if it were combined closely with a symbiotic relationship between computational modeling and empirical data.

Concluding Remarks

In this review, we have summarized an emerging literature in human neuroimaging, in which the global network structure of the entire brain is considered as an important constraint on information processing in the context of complex behavior. In the future, we hope that future methodological advances will help to drive our understanding of these relationships in more detail, providing a potential mechanism of brain function that can marry functional specialization with global integration. Together, we predict that by increasing our scope from the modeling of individual regions to circuits and global network properties, that we will improve our fundamental understanding of the human brain.

Acknowledgements

We would like to thank Patrick Bissett, Peter Bell and Kaylena Ehgoetz Martens for their thoughtful comments.

References

1. Achard, S., Bullmore, E., 2007. Efficiency and Cost of Economical Brain Functional Networks. PLoS Comput. Biol. 3, e17.
2. Alavash, M., Thiel, C.M., Giessing, C., 2016. Dynamic coupling of complex brain networks and dual-task behavior. NeuroImage 129, 233–246.
3. Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting state. Cereb. Cortex 24, 663–676.
4. Alnæs, D., Kaufmann, T., Richard, G., Duff, E.P., Sneve, M.H., Endestad, T., Nordvik, J.E., Andreassen, O.A., Smith, S.M., Westlye, L.T., 2015. Attentional load modulates large-scale functional brain connectivity beyond the core attention networks. NeuroImage 109, 260–272.
5. Aston-Jones, G., Cohen, J.D., 2005. An Integrative Theory of Locus Coeruleus-Norepinephrine Function: Adaptive Gain and Optimal Performance. Annu. Rev. Neurosci. 28, 403–450.
6. Baars, B.J., 2002. The conscious access hypothesis: origins and recent evidence. Trends in Cognitive Sciences 6, 47–52.
7. Balleine, B.W., O'Doherty, J.P., 2009. Human and Rodent Homologies in Action Control: Corticostriatal Determinants of Goal-Directed and Habitual Action. Neuropsychopharmacology 35, 48–69.
8. Balsters, J.H., Ramnani, N., 2011. Cerebellar Plasticity and the Automation of First-Order Rules. Journal of Neuroscience 31, 2305–2312.
9. Bargmann, C.I., Marder, E., 2013. From the connectome to brain function. Nat Meth 10, 483–490.
10. Barttfeld, P., Uhrig, L., Sitt, J.D., Sigman, M., Jarraya, B., Dehaene, S., 2015. Signature of consciousness in the dynamics of resting-state brain activity. Proc. Natl. Acad. Sci. U.S.A. 112, 887–892.
11. Bassett, D.S., Bullmore, E., 2006. Small-world brain networks. neuroscientist 12, 512–523.
12. Bassett, D.S., Wymbs, N.F., Rombach, M.P., Porter, M.A., Mucha, P.J., Grafton, S.T., 2013.

Task-based core-periphery organization of human brain dynamics. PLoS Comput. Biol. 9, e1003171.

13. Bassett, D.S., Yang, M., Wymbs, N.F., Grafton, S.T., 2015. Learning-induced autonomy of sensorimotor systems. Nat Neurosci 18, 744–751.
14. Becker, R., Braun, U., Schwarz, A.J., Gass, N., Schweiger, J.I., Weber-Fahr, W., Schenker, E., Spedding, M., Clemm von Hohenberg, C., Risterucci, C., Zang, Z., Grimm, O., Tost, H., Sartorius, A., Meyer-Lindenberg, A., 2016. Species-conserved reconfigurations of brain network topology induced by ketamine. Transl Psychiatry 6, e786.
15. Bertolero, M.A., Yeo, B., D'Esposito, M., 2017. The Diverse Club: The Integrative Core of Complex Networks. arXiv.
16. Bertolero, M.A., Yeo, B.T.T., D'Esposito, M., 2015. The modular and integrative functional architecture of the human brain. Proc. Natl. Acad. Sci. U.S.A. 201510619.
17. Betzel, R.F., Fukushima, M., He, Y., Zuo, X.-N., Sporns, O., 2015. Dynamic fluctuations coincide with periods of high and low modularity in resting-state functional brain networks. NeuroImage 127, 287–297.
18. Betzel, R.F., Fukushima, M., He, Y., Zuo, X.N., Sporns, O., 2016. Dynamic fluctuations coincide with periods of high and low modularity in resting-state functional brain networks. NeuroImage 127, 287–297.
19. Betzel, R.F., Medaglia, J.D., Bassett, D.S., 2017. Diversity of meso-scale architecture in human and non-human connectomes. arXiv.
20. Bola, M., Borchardt, V., 2016. Cognitive Processing Involves Dynamic Reorganization of the Whole-Brain Network's Functional Community Structure. Journal of Neuroscience 36, 3633–3635.
21. Bola, M., Sabel, B.A., 2015. Dynamic reorganization of brain functional networks during cognition. NeuroImage 114, 398–413.
22. Braun, U., Schäfer, A., Walter, H., Erk, S., Romanczuk-Seiferth, N., Haddad, L., Schweiger, J.I., Grimm, O., Heinz, A., Tost, H., Meyer-Lindenberg, A., Bassett, D.S., 2015. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proc. Natl. Acad. Sci. U.S.A. 112, 11678–11683.
23. Bullmore, E., Sporns, O., 2012. The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–349.
24. Büchel, C., Friston, K.J., 1997. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cerebral Cortex 7, 768–778.
25. Calhoun, V.D., Miller, R., Pearlson, G., Adalı, T., 2014. The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in fMRI Data Discovery. Neuron 84, 262–274.
26. Chang, C., Leopold, D.A., Schölvinck, M.L., Mandelkow, H., Picchioni, D., Liu, X., Ye, F.Q., Turchi, J.N., Duyn, J.H., 2016. Tracking brain arousal fluctuations with fMRI. Proc.

Natl. Acad. Sci. U.S.A. 113, 4518–4523.

27. Chen, J.E., Glover, G.H., 2015. BOLD fractional contribution to resting-state functional connectivity above 0.1 Hz. NeuroImage 107, 207–218.
28. Chen, T., Cai, W., Ryali, S., Supekar, K., Menon, V., 2016. Distinct Global Brain Dynamics and Spatiotemporal Organization of the Salience Network. Plos Biol 14, e1002469.
29. Cocchi, L., Sale, M.V., Gollo, L.L., Bell, P.T., Nguyen, V.T., 2016. A hierarchy of timescales explains distinct effects of local inhibition of primary visual cortex and frontal eye fields. elife 2016, e15252.
30. Cohen, J.R., D'Esposito, M., 2016. The Segregation and Integration of Distinct Brain Networks and Their Relationship to Cognition. Journal of Neuroscience 36, 12083–12094.
31. Cole, M.W., Bassett, D.S., Power, J.D., Braver, T.S., Petersen, S.E., 2014. Intrinsic and task-evoked network architectures of the human brain. Neuron 83, 238–251.
32. Cole, M.W., Reynolds, J.R., Power, J.D., Repovs, G., Anticevic, A., Braver, T.S., 2013. Multi-task connectivity reveals flexible hubs for adaptive task control. Nat Neurosci 16, 1348–1355.
33. Córdova, N.I., Tompary, A., Turk-Browne, N.B., 2016. Attentional modulation of background connectivity between ventral visual cortex and the medial temporal lobe. Neurobiology of Learning and Memory 134, 115–122.
34. Cui, G., Jun, S.B., Jin, X., Pham, M.D., Vogel, S.S., 2013. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature 494, 238–242.
35. Davison, E.N., Schlesinger, K.J., Bassett, D.S., Lynall, M.-E., Miller, M.B., Grafton, S.T., Carlson, J.M., 2015. Brain network adaptability across task states. PLoS Comput. Biol. 11, e1004029.
36. de Pasquale, F., Penna, Della, S., Snyder, A.Z., Marzetti, L., 2012. A cortical core for dynamic integration of functional networks in the resting human brain. Neuron 74, 753–764.
37. Deco, G., Tononi, G., Boly, M., Kringelbach, M.L., 2015. Rethinking segregation and integration: contributions of whole-brain modelling. Nat. Rev. Neurosci. 16, 430–439.
38. Deco, G., Van Hartevelt, T.J., Fernandes, H.M., Stevner, A., Kringelbach, M.L., 2017. The most relevant human brain regions for functional connectivity: Evidence for a dynamical workspace of binding nodes from whole-brain computational modelling. NeuroImage 146, 197–210.
39. Dehaene, S., Naccache, L., 2001. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition 79, 1–37.
40. DeSalvo, M.N., Douw, L., Takaya, S., Liu, H., Stufflebeam, S.M., 2014. Task-dependent reorganization of functional connectivity networks during visual semantic decision making. Brain and Behavior 4, 877–885.
41. Douw, L., Wakeman, D.G., Tanaka, N., Liu, H., Stufflebeam, S.M., 2016. State-dependent

variability of dynamic functional connectivity between frontoparietal and default networks relates to cognitive flexibility. Neuroscience 339, 12–21.

42. Edelman, G.M., 2003. Naturalizing consciousness: a theoretical framework. Proc. Natl. Acad. Sci. U.S.A. 100, 5520–5524.
43. Ekman, M., Derrfuss, J., Tittgemeyer, M., 2012. Predicting errors from reconfiguration patterns in human brain networks. Proc. Natl. Acad. Sci. U.S.A. 109, 16714–16719.
44. Eldar, E., Cohen, J.D., Niv, Y., 2013. The effects of neural gain on attention and learning. Nat Neurosci. 16(8), 1146-1153.
45. Engel, T.A., Steinmetz, N.A., Gieselmann, M.A., Thiele, A., Moore, T., Boahen, K., 2016. Selective modulation of cortical state during spatial attention. Science 354, 1140–1144.
46. Feng, S.F., Schwemmer, M., Gershman, S.J., Cohen, J.D., 2014. Multitasking versus multiplexing: Toward a normative account of limitations in the simultaneous execution of control-demanding behaviors. Cognitive, Affective, & Behavioral Neuroscience 14, 129–146.
47. Finc, K., Bonna, K., Lewandowska, M., Wolak, T., Nikadon, J., Dreszer, J., Duch, W., Kühn, S., 2017. Transition of the functional brain network related to increasing cognitive demands. Hum Brain Mapp 3, e17.
48. Fornito, A., Harrison, B.J., Zalesky, A., Simons, J.S., 2012. Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. Proceedings of the National Academy of Sciences 109, 12788–12793.
49. Fornito, A., Zalesky, A., Breakspear, M., 2013. Graph analysis of the human connectome: Promise, progress, and pitfalls. NeuroImage 80, 426–444.
50. Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends in Cognitive Sciences 9, 474–480.
51. Friston, K.J., 2011. Functional and Effective Connectivity: A Review. Brain Connectivity 1, 13–36.
52. Friston, K.J., 1994. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2, 56–78.
53. Fulcher, B.D., Fornito, A., 2016. A transcriptional signature of hub connectivity in the mouse connectome. Proc. Natl. Acad. Sci. U.S.A. 113, 1435–1440.
54. Gallen, C.L., Turner, G.R., Adnan, A., D'Esposito, M., 2016. Reconfiguration of brain network architecture to support executive control in aging. Neurobiology of Aging 44, 42–52.
55. Geib, B.R., Stanley, M.L., Wing, E.A., Laurienti, P.J., 2015. Hippocampal contributions to the large-scale episodic memory network predict vivid visual memories. Cerebral Cortex 27, 680–693.
56. Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178.

57. Godwin, D., Barry, R.L., Marois, R., 2015. Breakdown of the brain's functional network modularity with awareness. Proc. Natl. Acad. Sci. U.S.A. 112, 3799–3804.
58. Gollo, L.L., Zalesky, A., Hutchison, R.M., van den Heuvel, M., Breakspear, M., 2015. Dwelling quietly in the rich club: brain network determinants of slow cortical fluctuations. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 370, 20140165–20140165.
59. Gonzalez-Castillo, J., Hoy, C.W., Handwerker, D.A., Robinson, M.E., Buchanan, L.C., Saad, Z.S., Bandettini, P.A., 2015. Tracking ongoing cognition in individuals using brief, whole-brain functional connectivity patterns. Proc. Natl. Acad. Sci. U.S.A. 112, 8762–8767.
60. Gordon, E.M., Laumann, T.O., Adeyemo, B., Huckins, J.F., Kelley, W.M., Petersen, S.E., 2014. Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. Cereb. Cortex bhu239.
61. Guimerà, R., Nunes Amaral, L.A., 2005. Functional cartography of complex metabolic networks. Nature 433, 895–900. doi:10.1038/nature03288
62. Hari, R., Parkkonen, L., 2015. The brain timewise: how timing shapes and supports brain function. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 370, 20140170.
63. Hasenkamp, W., Wilson-Mendenhall, C.D., Duncan, E., Barsalou, L.W., 2012. Mind wandering and attention during focused meditation: a fine-grained temporal analysis of fluctuating cognitive states. NeuroImage 59, 750–760.
64. Haushofer, J., Kanwisher, N., 2007. In the eye of the beholder: visual experience and categories in the human brain. Neuron 53, 773–775.
65. Hindriks, R., Adhikari, M.H., Murayama, Y., Ganzetti, M., 2015. Can sliding-window correlations reveal dynamic functional connectivity in resting-state fMRI? NeuroImage 127, 242–256.
66. Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences 106, 2035–2040.
67. Honey, C.J., Thesen, T., Donner, T.H., Silbert, L.J., Carlson, C.E., Devinsky, O., Doyle, W.K., Rubin, N., Heeger, D.J., Hasson, U., 2012. Slow cortical dynamics and the accumulation of information over long timescales. Neuron 76, 423–434.
68. Hurlburt, R.T., Alderson-Day, B., Fernyhough, C., Kühn, S., 2015. What goes on in the resting-state? A qualitative glimpse into resting-state experience in the scanner 2015, 1535.
69. Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Penna, Della, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., Handwerker, D.A., Keilholz, S., Kiviniemi, V., Leopold, D.A., de Pasquale, F., Sporns, O., Walter, M., Chang, C., 2013a. Dynamic functional connectivity: Promise, issues, and interpretations. NeuroImage 80, 360–378.
70. Hutchison, R.M., Womelsdorf, T., Gati, J.S., Everling, S., Menon, R.S., 2013b. Resting-state

Peer-reviewed version available at *NeuroImage* **2017**; doi:10.1016/j.neuroimage.2017.08.010

networks show dynamic functional connectivity in awake humans and anesthetized macaques. Hum Brain Mapp 34, 2154–2177.

71. James, W., 1890. Principles of psychology.
72. Joshi, S., Li, Y., Kalwani, R.M., Gold, J.I., 2016. Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex. Neuron 89, 221–234.
73. Kelso, J., 2012. Multistability and metastability: understanding dynamic coordination in the brain. Philosophical Transactions of the Royal Society B: Biological Sciences 367, 906–918.
74. Kitzbichler, M.G., Henson, R.N.A., Smith, M.L., Nathan, P.J., Bullmore, E.T., 2011. Cognitive effort drives workspace configuration of human brain functional networks. J. Neurosci. 31, 8259–8270.
75. Krienen, F.M., Yeo, B.T.T., Buckner, R.L., 2014. Reconfigurable task-dependent functional coupling modes cluster around a core functional architecture. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 369, 20130526–20130526.
76. Kucyi, A., Davis, K.D., 2014. Dynamic functional connectivity of the default mode network tracks daydreaming. NeuroImage 100, 471–480.
77. Kucyi, A., Hove, M.J., Esterman, M., Hutchison, R.M., Valera, E.M., 2016. Dynamic Brain Network Correlates of Spontaneous Fluctuations in Attention. Cereb. Cortex 27, 1831–1840.
78. Lakatos, P., Barczak, A., Neymotin, S.A., McGinnis, T., Ross, D., Javitt, D.C., O'Connell, M.N., 2016. Global dynamics of selective attention and its lapses in primary auditory cortex. Nat Neurosci.
79. Laumann, T.O., Snyder, A.Z., Mitra, A., Gordon, E.M., 2016. On the stability of bold fmri correlations. Cerebral Cortex ePub Ahead of Print.
80. Leonardi, N., Van De Ville, D., 2015. On spurious and real fluctuations of dynamic functional connectivity during rest. NeuroImage 104, 430–436.
81. Liegeois, R., Laumann, T.O., Snyder, A.Z., Zhou, H.J., 2017. Interpreting Temporal Fluctuations In Resting-State Functional Connectivity MRI. bioRxiv.
82. Liu, J., Lee, H.J., Weitz, A.J., Fang, Z., Lin, P., Choy, M., Fisher, R., Pinskiy, V., Tolpygo, A., Mitra, P., Schiff, N., Lee, J.H., 2015. Frequency-selective control of cortical and subcortical networks by central thalamus. elife 4, e09215.
83. Lord, A.R., Li, M., Demenescu, L.R., van den Meer, J., Borchardt, V., Krause, A.L., Heinze, H.-J., Breakspear, M., Walter, M., 2017. Richness in Functional Connectivity Depends on the Neuronal Integrity within the Posterior Cingulate Cortex. Front. Neurosci. 11, 184.
84. Mattar, M.G., Cole, M.W., Thompson-Schill, S.L., Bassett, D.S., 2015. A Functional Cartography of Cognitive Systems. PLoS Comput. Biol. 11, e1004533.

85. McGinley, M.J., David, S.V., McCormick, D.A., 2015. Cortical Membrane Potential Signature of Optimal States for Sensory Signal Detection. Neuron 87, 179–192.
86. McIntosh, A.R., 2000. Towards a network theory of cognition. Neural Networks 13, 861–870.
87. McIntosh, A.R., Chau, W.K., Protzner, A.B., 2004. Spatiotemporal analysis of event-related fMRI data using partial least squares. NeuroImage 23, 764–775.
88. Mesulam, M.M., 2013. Cholinergic circuitry of the human nucleus basalis and its fate in Alzheimer's disease. Journal of Comparative Neurology 521, 4124–4144.
89. Mišić, B., Betzel, R.F., de Reus, M.A., van den Heuvel, M.P., Berman, M.G., McIntosh, A.R., Sporns, O., 2016. Network-Level Structure-Function Relationships in Human Neocortex. Cerebral Cortex 26, bhw089–3296.
90. Mohr, H., Wolfensteller, U., Betzel, R.F., Mišić, B., Sporns, O., Richiardi, J., Ruge, H., 2016. Integration and segregation of large-scale brain networks during short-term task automatization. Nat Commun 7, 13217.
91. Morcom, A.M., Fletcher, P.C., 2007. Does the brain have a baseline? Why we should be resisting a rest. NeuroImage 37, 1073–1082.
92. Norman-Haignere, S.V., McCarthy, G., Chun, M.M., Turk-Browne, N.B., 2012. Category-selective background connectivity in ventral visual cortex. Cereb. Cortex 22, 391–402.
93. O'Reilly, R.C., Bhattacharyya, R., Howard, M.D., 2014. Complementary learning systems. Cognitive Science 38, 1229–1248.
94. Oizumi, M., Albantakis, L., Tononi, G., 2014. From the Phenomenology to the Mechanisms of Consciousness: Integrated Information Theory 3.0. PLoS Comput. Biol. 10, e1003588.
95. Oya, H., Howard, M.A., Magnotta, V.A., Kruger, A., Griffiths, T.D., Lemieux, L., Carmichael, D.W., Petkov, C.I., Kawasaki, H., Kovach, C.K., Sutterer, M.J., Adolphs, R., 2017. Mapping effective connectivity in the human brain with concurrent intracranial electrical stimulation and BOLD-fMRI. J. Neurosci. Methods 277, 101–112.
96. Park, H.-J., Friston, K., 2013. Structural and Functional Brain Networks: From Connections to Cognition. Science 342, 1238411–1238411.
97. Pearce, T.M., Moran, D.W., 2012. Strategy-dependent encoding of planned arm movements in the dorsal premotor cortex. Science 337, 984–988.
98. Poldrack, R.A., Yarkoni, T., 2016. From Brain Maps to Cognitive Ontologies: Informatics and the Search for Mental Structure. Annu Rev Psychol 67, 587–612.
99. Posner, M.I., Boies, S.J., 1971. Components of attention. Psychological review.
100. Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341.
101. Power, J.D., Schlaggar, B.L., Lessov-Schlaggar, C.N., Petersen, S.E., 2013. Evidence for

hubs in human functional brain networks. Neuron 79, 798–813.

102. Ramsey, J.D., Hanson, S.J., Hanson, C., Halchenko, Y.O., Poldrack, R.A., Glymour, C., 2010. Six problems for causal inference from fMRI. NeuroImage 49, 1545–1558.

103. Robbins, T.W., Arnsten, A.F.T., 2009. The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation. Annu. Rev. Neurosci. 32, 267–287.

104. Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: Uses and interpretations. NeuroImage 52, 1059–1069.

105. Sadaghiani, S., Poline, J.-B., Kleinschmidt, A., D'Esposito, M., 2015. Ongoing dynamics in large-scale functional connectivity predict perception. Proc. Natl. Acad. Sci. U.S.A. 112, 8463–8468.

106. Schedlbauer, A.M., Copara, M.S., Watrous, A.J., 2014. Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. Sci Rep 4, 6431.

107. Schultz, D.H., Cole, M.W., 2016. Higher Intelligence Is Associated with Less Task-Related Brain Network Reconfiguration. Journal of Neuroscience. 36(33), 8551-8561.

108. Seger, C.A., Spiering, B.J., 2011. A critical review of habit learning and the Basal Ganglia. Front Syst Neurosci 5, 66.

109. Senden, M., Reuter, N., van den Heuvel, M.P., Goebel, R., Deco, G., 2016. Cortical rich club regions can organize state-dependent functional network formation by engaging in oscillatory behavior. NeuroImage 146, 561–574.

110. Shen, K., Hutchison, R.M., Bezgin, G., Everling, S., McIntosh, A.R., 2015. Network structure shapes spontaneous functional connectivity dynamics. J. Neurosci. 35, 5579–5588.

111. Shiffrin, R., Schneider, W., 1977. Controlled and Automatic Information Processing: I Detection, Search and Attention; II Perceptual Learning, Automatic Attending and a General Theory. Psychological Review.

112. Shine, J.M., Bissett, P.G., Bell, P.T., Koyejo, O., Balsters, J.H., Gorgolewski, K.J., Moodie, C.A., Poldrack, R.A., 2016a. The Dynamics of Functional Brain Networks: Integrated Network States during Cognitive Task Performance. Neuron 92, 544–554.

113. Shine, J.M., Eisenberg, I., Poldrack, R.A., 2016b. Computational specificity in the human brain. Behav. Brain Sci. 39, e131.

114. Shine, J.M., Koyejo, O., Poldrack, R.A., 2016c. Temporal metastates are associated with differential patterns of time-resolved connectivity, network topology, and attention. Proc. Natl. Acad. Sci. U.S.A. 113, 9888–9891.

115. Shine, J.M., van den Brink, R.L., Hernaus, D., Nieuwenhuis, S., Poldrack, R.A., 2017. Catecholaminergic modulation alters dynamic network topology across behavioral states. bioarXiv.

116. Spadone, S., Penna, Della, S., Sestieri, C., Betti, V., Tosoni, A., Perrucci, M.G., Romani, G.L., Corbetta, M., 2015. Dynamic reorganization of human resting-state networks during

visuospatial attention. Proc. Natl. Acad. Sci. U.S.A. 112, 8112–8117.

117. Sporns, O., 2015. Cerebral cartography and connectomics. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 370, 20140173–20140173.

118. Sporns, O., 2013. Network attributes for segregation and integration in the human brain. Current Opinion in Neurobiology 23, 162–171.

119. Sporns, O., Betzel, R.F., 2015. Modular Brain Networks. Annu Rev Psychol 67, annurev–psych–122414–033634.

120. Spreng, R.N., Stevens, W.D., Chamberlain, J.P., Gilmore, A.W., Schacter, D.L., 2010. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. NeuroImage 53, 303–317.

121. Tagliazucchi, E., Laufs, H., 2014. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. Neuron 82, 695–708.

122. Tang, Y.-Y., Hölzel, B.K., Posner, M.I., 2015. The neuroscience of mindfulness meditation. Nat. Rev. Neurosci. 16, 213–225.

123. Telesford, Q.K., Lynall, M.E., Vettel, J., Miller, M.B., Grafton, S.T., 2016. Detection of functional brain network reconfiguration during task-driven cognitive states. NeuroImage 142, 198–210.

124. Tognoli, E., Kelso, J., 2014. The metastable brain. Neuron 81, 35–48.

125. Tononi, G., Sporns, O., 1994. A measure for brain complexity: relating functional segregation and integration in the nervous system. Proc. Natl. Acad. Sci. U.S.A. 91, 5033–5037.

126. van den Brink, R.L., Pfeffer, T., Warren, C.M., Murphy, P.R., Tona, K.-D., van der Wee, N.J.A., Giltay, E., van Noorden, M.S., Rombouts, S.A.R.B., Donner, T.H., Nieuwenhuis, S., 2016. Catecholaminergic Neuromodulation Shapes Intrinsic MRI Functional Connectivity in the Human Brain. J. Neurosci. 36, 7865–7876.

127. van den Heuvel, M.P., Kahn, R.S., 2012. High-cost, high-capacity backbone for global brain communication. Proc. Natl. Acad. Sci. U.S.A. 109, 11372–11377.

128. van den Heuvel, M.P., Sporns, O., 2013. Network hubs in the human brain. Trends in Cognitive Sciences 17, 683–696.

129. Varela, F., Lachaux, J.-P., Rodriguez, E., Martinerie, J., 2001. The brainweb: Phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229–239.

130. Vatansever, D., Manktelow, A.E., Sahakian, B.J., Menon, D.K., Stamatakis, E.A., 2016. Angular default mode network connectivity across working memory load. Hum Brain Mapp 38, 41–52.

131. Vatansever, D., Menon, D.K., Manktelow, A.E., Sahakian, B.J., Stamatakis, E.A., 2015. Default Mode Dynamics for Global Functional Integration. J. Neurosci. 35, 15254–15262.

132. Wang, C., Ong, J.L., Patanaik, A., Zhou, J., 2016. Spontaneous eyelid closures link vigilance fluctuation with fMRI dynamic connectivity states. Proc. Natl. Acad. Sci. U.S.A.

Peer-reviewed version available at NeuroImage 2017; doi:10.1016/j.neuroimage.2017.08.010

113, 9653–9658.

133. Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of “small-world” networks. Nature 393, 440–442.

134. Wendelken, C., Ferrer, E., Whitaker, K.J., Bunge, S.A., 2016. Fronto-Parietal Network Reconfiguration Supports the Development of Reasoning Ability. Cereb. Cortex 26, 2178–2190.

135. Westphal, A.J., Wang, S., Rissman, J., 2017. Episodic memory retrieval benefits from a less modular brain network organization. Journal of Neuroscience 37, 3523–3531.

136. Young, C.B., Raz, G., Everaerd, D., 2017. Dynamic shifts in large-scale brain network balance as a function of arousal. Journal of Neuroscience 2016, 1759.

137. Zalesky, A., Breakspear, M., 2015. Towards a statistical test for functional connectivity dynamics. NeuroImage 114, 466–470.

138. Zalesky, A., Cocchi, L., Fornito, A., Murray, M.M., Bullmore, E., 2012. Connectivity differences in brain networks. NeuroImage 60, 1055–1062.

139. Zalesky, A., Fornito, A., Cocchi, L., Gollo, L.L., Breakspear, M., 2014. Time-resolved resting-state brain networks. Proceedings of the National Academy of Sciences 111, 10341–10346.

140. Zippo, A.G., Rosa, Della, P.A., Castiglioni, I., Biella, G., 2016. Alternating dynamics of segregation and integration in human brain functional networks during working-memory task. bioRxiv.