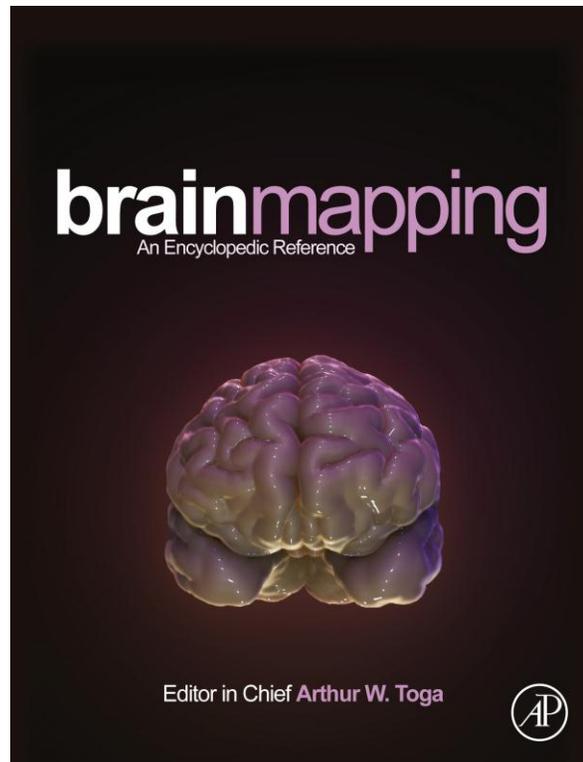


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Large-Scale Functional Brain Organization

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Brain Connectivity and Large-Scale Brain Organization

The first two decades of functional mapping of the human brain were largely focused on the localization of brain responses in relation to specific experimental manipulations (Bandettini, 2012; Huettel, Song, & McCarthy, 2008). It has become increasingly apparent, however, that most cognitive functions require multiple distributed brain regions working in concert, and the original goal of mapping cognitive constructs onto individual brain areas is now widely considered implausible (Fuster, 2006). Consequently, the focus of brain mapping has shifted toward a systematic understanding of large-scale functional organization and its influence on cognitive and affective information processing (Bressler & Menon, 2010).

The human brain is a complex patchwork of interconnected regions, and network approaches have become increasingly useful for understanding how functionally connected systems engender and constrain cognitive functions (Menon, 2011, 2013). The functions of individual cortical and subcortical areas are determined by their intrinsic properties and their extrinsic connections (Passingham, Stephan, & Kotter, 2002). Each brain region likely has a unique fingerprint that distinguishes its pattern of connectivity from that of other brain regions, endowing it with specific functional properties. Understanding the function of any specific brain region therefore requires analysis of how its connectivity differs from the pattern of connections in other functionally related brain areas. Brain connectivity and network analyses are increasingly being used to characterize the large-scale functional organization of the human brain and to understand how intrinsic functional and structural connectivities influence information processing (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Fox & Raichle, 2007; Greicius, Krasnow, Reiss, & Menon, 2003). This article summarizes recent progress in our understanding of functional brain networks, highlights six major principles of large-scale brain organization, and discusses how the brain's intrinsic functional architecture regulates access to networks and neural resources needed for goal-directed behaviors.

Characterizing Large-Scale Functional Brain Organization

A formal characterization of the large-scale organization of the human brain was first developed by Mesulam who proposed that the human brain includes at least five major core networks, each dedicated to a more or less distinct cognitive function (Mesulam, 1998). Examples of such systems are the language network anchored in the middle temporal gyrus – Broca's, Wernicke's, and Geschwind's areas – the working memory–executive function network anchored in the dorsolateral prefrontal and ventral posterior parietal cortices, and the

spatial attention network anchored in dorsal posterior parietal cortex and frontal eye fields. The nodes of such neurocognitive networks were initially identified using lesion studies (Damasio & Damasio, 1989). Although these studies have taken on increasing sophistication over the years with voxel-based lesion–symptom mapping, their anatomical precision remains poor (Bates et al., 2003) and they fail to incorporate measures of interregional connectivity.

Because of their focus on individual cognitive processes, task-based functional and effective connectivity studies, though informative and essential, can sometimes not only miss but also lead to incomplete characterization of functional brain circuits. Recent conceptual and methodological developments in the science of large-scale networks (Bressler & Menon, 2010; Sporns, 2011b) are contributing to our growing understanding of brain organization in a fundamentally different way. Analysis of intrinsic brain architecture is leading to a deeper understanding of functional circuits and the organization of large-scale networks in neurotypical and aberrant brain function (Menon, 2011). A full characterization of the large-scale functional organization of the human brain has required the application of novel quantitative methods for identifying networks, their nodes (functional areas) and edges (connections between them), in a more principled manner. Considerable effort is now being devoted to this from multiple fronts, both functional and anatomical (Behrens & Sporns, 2012; Craddock et al., 2013). A discussion of these quantitative methods is beyond the scope of this article; for such details, the reader is referred to the many excellent original reviews on the topic (Beckmann & Smith, 2004; Sporns, 2011b). Here, the focus is on a summary and synthesis of the major findings and principles from a systems neuroscience perspective.

Six Major Principles of Large-Scale Functional Organization

A wide range of studies using different analytic and conceptual approaches have examined large-scale human brain connectivity. This article synthesizes six major principles of large-scale brain organization that have emerged from these studies. First, large-scale functional organization is characterized by a non-random, small-world, modular global brain architecture with strategic hub regions that regulate communication among different functional systems (Sporns, 2011a, 2011b). Second, strong interhemispheric connectivity between homotopic regions, with a gradient of decreasing left–right connectivity from sensory to association and heteromodal cortices, is a prominent feature of large-scale functional brain organization (Ryali, Chen, Supekar, & Menon, 2012; Stark et al., 2008). Third, the human brain is intrinsically organized into coherent functional networks (Bressler & Menon, 2010), with brain areas that are commonly engaged during cognitive tasks

forming brain networks that can be readily identified using intrinsic functional connectivity (Damoiseaux et al., 2006). Fourth, functional brain organization is characterized by task- and context-dependent activated and deactivated brain systems, pointing to bottlenecks in parallel processing and temporally restricted access to neural resources (Fox et al., 2005; Greicius et al., 2003; Greicius & Menon, 2004; Honey, Kotter, Breakspear, & Sporns, 2007). Fifth, the most widely deactivated regions form a coherent large-scale network, termed the default-mode network, which is a tightly functionally and structurally connected system important for self-referential information processing and monitoring of the internal mental landscape (Greicius et al., 2003; Greicius, Srivastava, Reiss, & Menon, 2004; Qin & Northoff, 2011). Sixth, core prefrontal-parietal control systems can be dissociated into distinct brain networks with distinct roles in cognition. Notably, the salience network, anchored in the insula and anterior cingulate cortex, is a system that plays an important role in attentional capture of biologically and cognitively relevant events while the lateral frontoparietal central executive network, anchored in the dorsolateral prefrontal cortex and supramarginal gyrus, is important for the working memory and higher-order cognitive processes (Menon & Uddin, 2010; Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008).

Global Brain Architecture

Despite its complexity, the functional organization of the human brain is far from random (Achard & Bullmore, 2007; Sporns, 2011a). Several key findings in the area of global architecture have emerged from graph-theoretical analysis of connectivity across the entire brain. This approach views the whole brain as a single network and uses graph-based measures of functional or structural connectivity to characterize overall topology, including path length, clustering, community structure, and connector hubs (Behrens & Sporns, 2012; Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013). The advantage of this approach is that it provides a global snapshot of the functional architecture of the brain.

A wide range of graph-based studies have shown that the brain has a small-world architecture characterized by dense local clustering of connections between neighboring nodes and a short path length between nodes, due to the existence of relatively few long-range connections (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Supekar, Menon, Rubin, Musen, & Greicius, 2008; Supekar, Musen, & Menon, 2009; Figure 1). In the graph theory, 'small-world' architecture refers to a network in which constituent nodes exhibit a large degree of clustering and relatively short distances between any two nodes of the system and is thought to reflect a balance between local processing and global integration of information (Achard & Bullmore, 2007). Small-world networks are economical, tending to minimize wiring costs while supporting efficient processing of complex information (Supekar et al., 2009). The combination of these attributes simultaneously promotes high specialization and high integration within a modular architecture (Bullmore & Sporns, 2012).

An important feature of brain architecture identified by these methods concerns hubs, brain areas (nodes) that are central to communicating information across different brain

systems within a small-world architecture (Power et al., 2013; Van Den Heuvel et al., 2013). The posterior cingulate cortex and insula are two major cortical hubs that have been identified in the human brain (Buckner et al., 2009; Tomasi & Volkow, 2011). Crucially, the functional role of hubs can vary widely depending on their connectivity properties. The posterior cingulate cortex, a hub characterized by the shortest path length to other brain areas (Van Den Heuvel et al., 2013), is well placed to facilitate the rapid integration of information across multiple functional systems. In contrast, the insula is a connector hub that links different subnetworks (Power et al., 2013). Connector hubs such as the insula can help heteromodal regions that integrate complex exogenous and endogenous mental processes (Menon, 2011; Menon & Uddin, 2010; Supekar et al., 2010).

Graded Inter- and Intra-hemispheric Connectivities

The second major principle of large-scale brain organization is that homotopic regions in the left and right hemispheres display strong interhemispheric interactions, when compared with nonhomotopic regions (Figure 2). Crucially, the strength of interhemispheric connectivity is not uniform across the brain. There is a gradient of interhemispheric interaction strength, with the highest correlations across primary sensorimotor cortices, significantly lower correlations across unimodal association areas, and still lower correlations across heteromodal association areas (Stark et al., 2008). The lower levels of synchrony across heteromodal association areas are consistent with the notion of increased functional lateralization and specialization of these regions (Mesulam, 1998). Additionally, the left and right hemisphere connectivities differ in important ways – each hemisphere has a different bias in their pattern of intra- and interhemispheric interactions (Gotts et al., 2013). Left hemisphere regions show a bias toward stronger intra-hemispheric connectivity, particularly for cortical regions involved in language and motor coordination. In contrast, the right hemisphere cortical regions involved in visuospatial and attentional processing display stronger connectivity with homologous regions in the left hemisphere. This bias is consistent with the well-known dichotomy of left hemisphere lateralization for language and bilateral visuospatial attention networks for representing the left and right visual hemifields (Corbetta & Shulman, 2011; Thiebaut De Schotten et al., 2011).

The Human Brain Is Intrinsically Organized into Coherent Functional Networks

A growing number of studies have shown that many of the brain areas engaged during diverse sets of cognitive tasks also form coherent large-scale brain networks that can be readily identified using intrinsic functional connectivity (Greicius & Menon, 2004; Smith et al., 2009). Although these networks can be identified using multiple analytic approaches, model-free analysis of intrinsic connectivity using independent components analysis (Beckmann & Smith, 2004) has turned out to be an elegant tool for identifying large-scale functional brain networks (Damoiseaux et al., 2006; Seeley et al., 2007). These

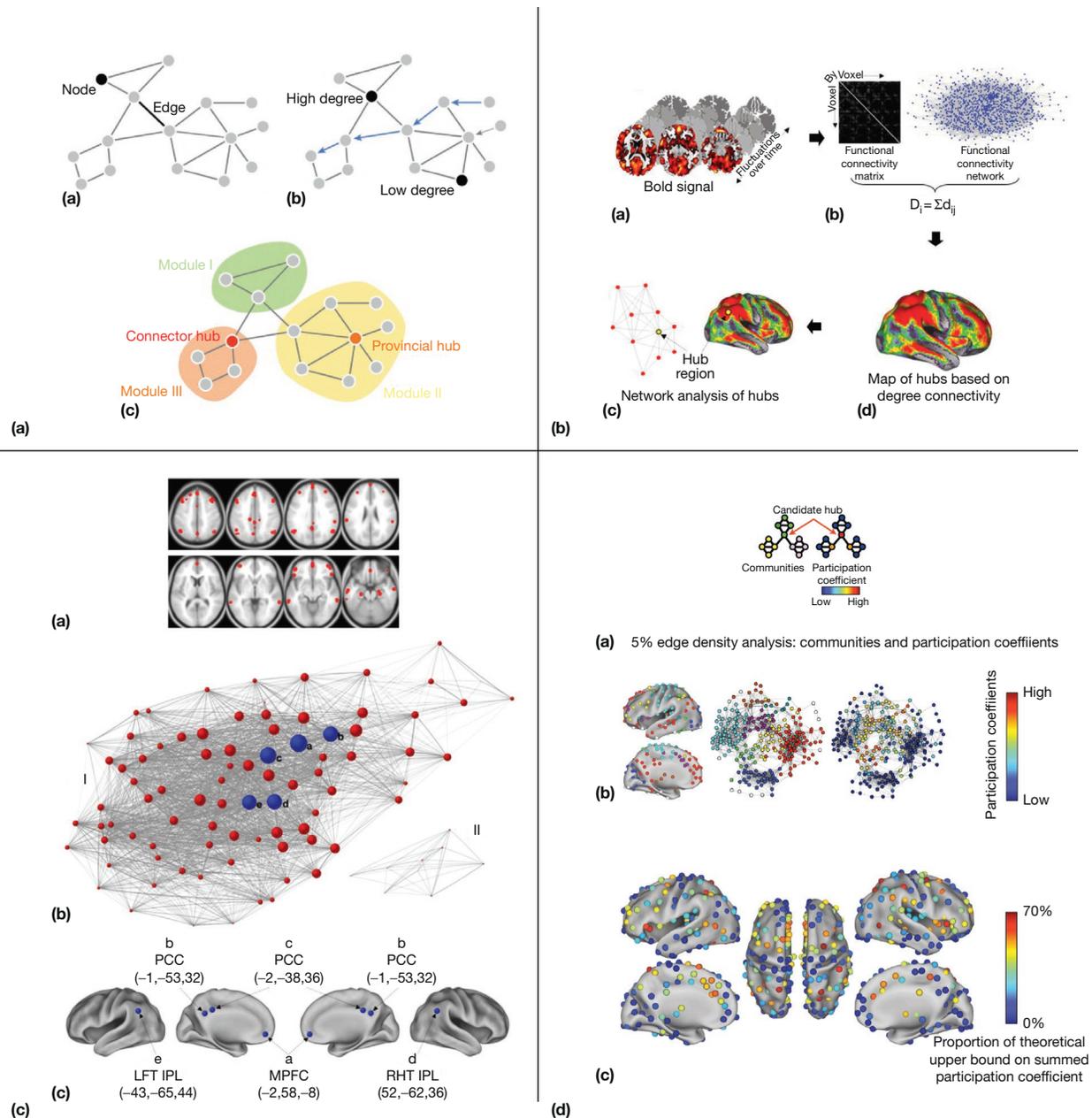


Figure 1 Global brain architecture, nonrandomness, and hubs. (a) Basic network elements. (a) Functional brain networks can be described and analyzed as graphs comprising a collection of brain regions (nodes) and functional connectivity between them (edges). (b) Nodes can have a low or high degree of connected edges. (c) Functional brain organization is characterized by modules, provincial or regional hubs, and connector hubs. (b) Brain connectivity and mapping hubs. Intrinsic fMRI signals over time are used to compute interregional functional connectivity. Maps of hubs are computed using the number of edges associated with each region. Candidate hubs are those regions with disproportionately high connectivity and are plotted in yellow and red. (c) The posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (mPFC) are among the major hubs (most extensively connected nodes) in the brain. (d) Connector hubs. (a) Putative hubs identified by high participation coefficients. (b) Distinct communities (yellow, green, and pink), with nodes colored by participation coefficient. (c) Summed participation identifying major connector hubs in the cortex. Adapted from Van Den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*, *17*, 683–696; Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*, *29*, 1860–1873; and 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.

intrinsic connectivity networks reflect strong coupling of spontaneous fluctuations in ongoing brain activity that is robust under different mental states including sleep, anesthesia, and loss of consciousness (Greicius et al., 2008; Horowitz et al., 2009; Vanhauwhuyse et al., 2010).

About 14 such functional networks can be identified consistently across individuals: (a) auditory, (b) basal ganglia, (c) posterior cingulate cortex and ventromedial prefrontal cortex, (d) secondary visual cortex, (e) language, (f) left dorsolateral prefrontal cortex and left parietal cortex, (g) sensorimotor,

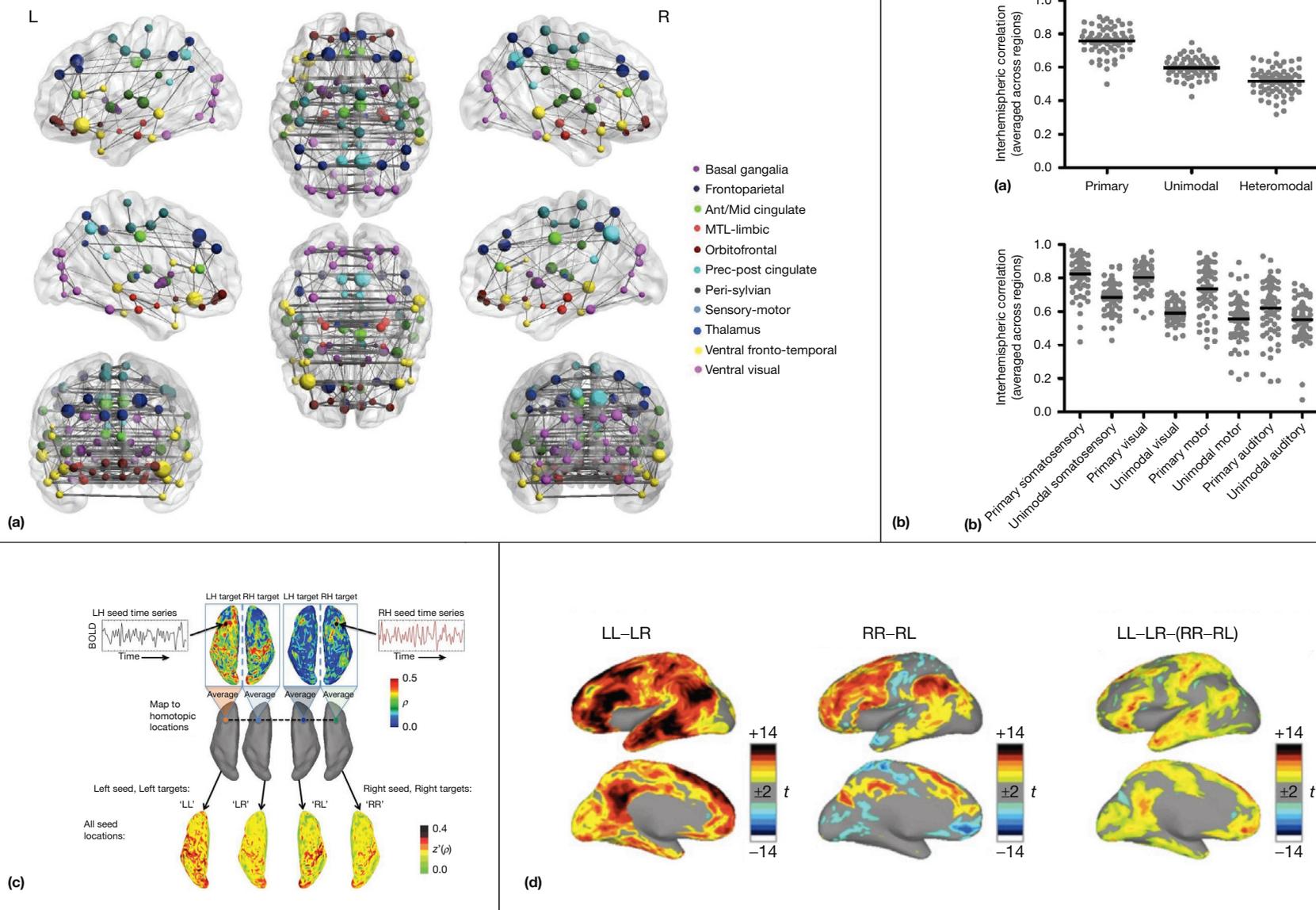


Figure 2 Inter- and intrahemispheric connectivities. (a) Interhemispheric connectivity. Graphic representation of segregated functional subnetworks (modules) derived from whole-brain connectivity analysis. Nodes are sized according to their connectivity profile, with larger nodes representing highly connected ‘hubs.’ Nodes belonging to the same module marked in same color. Each of the 11 subnetworks exhibits strong interhemispheric connectivity. (b) Gradients in interhemispheric connectivity. (a) Each subject’s mean interhemispheric correlation averaged across primary, unimodal, or heteromodal regions. (b) Primary sensorimotor cortices demonstrated a significantly higher degree of interhemispheric correlation than either unimodal association areas or heteromodal association areas. (c) Intra- and interhemispheric connectivities at homotopic locations in each left and right hemisphere voxels. The first letter in the labels ‘LL,’ ‘LR,’ ‘RR,’ and ‘RL’ indicates a seed location in the left (L) or right (R) hemisphere, and the second letter indicates the target hemisphere. (d) Gradients in intrahemispheric connectivity. Differences in intra- and interhemispheric correlations that compose the two lateralization metrics, with all conditions rendered on the left hemisphere. The segregation metric [(LL – LR) – (RR – RL)] emphasizes left hemisphere dominance of language systems. Adapted from Ryali, S., Chen, T., Supekar, K., & Menon, V. (2012). Estimation of functional connectivity in fMRI data using stability selection-based sparse partial correlation with elastic net penalty. *NeuroImage*, 59, 3852–3861; Stark, D. E., Margulies, D. S., Shehzad, Z. E., Reiss, P., Kelly, A. M., Uddin, L. Q., et al. (2008). Regional variation in interhemispheric coordination of intrinsic hemodynamic fluctuations. *Journal of Neuroscience*, 28, 13754–13764; and Gotts, S. J., Jo, H. J., Wallace, G. L., Saad, Z. S., Cox, R. W., & Martin, A. (2013). Two distinct forms of functional lateralization in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 110, E3435–E3444.

(h) posterior insula, (i) precuneus, (j) primary visual cortex, (k) right dorsolateral prefrontal cortex and right parietal cortex, (l) anterior insula and dorsal anterior cingulate cortex, (m) retrosplenial cortex and medial temporal lobe, and (n) intraparietal sulcus and frontal eye fields (Damoiseaux et al., 2006; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2011; Figure 3). These networks are for the most part strongly bilateral with strong interhemispheric connectivity between homotopic brain regions.

These spatially independent networks segregate brain signals while facilitating efficient communication within specific

functional systems. Crucially, these intrinsic networks also demonstrate close correspondence with task-related connectivity patterns (Smith et al., 2009), indicating that network nodes identified using intrinsic functional connectivity are also, for the most part, simultaneously coactivated during a wide range of cognitive tasks. Indeed, these networks can also be readily detected during cognitive information processing and form a useful basis set for examining stimulus-driven information processing (Sridharan, Levitin, Chafe, Berger, & Menon, 2007; Sridharan et al., 2008). It is important to note that even though

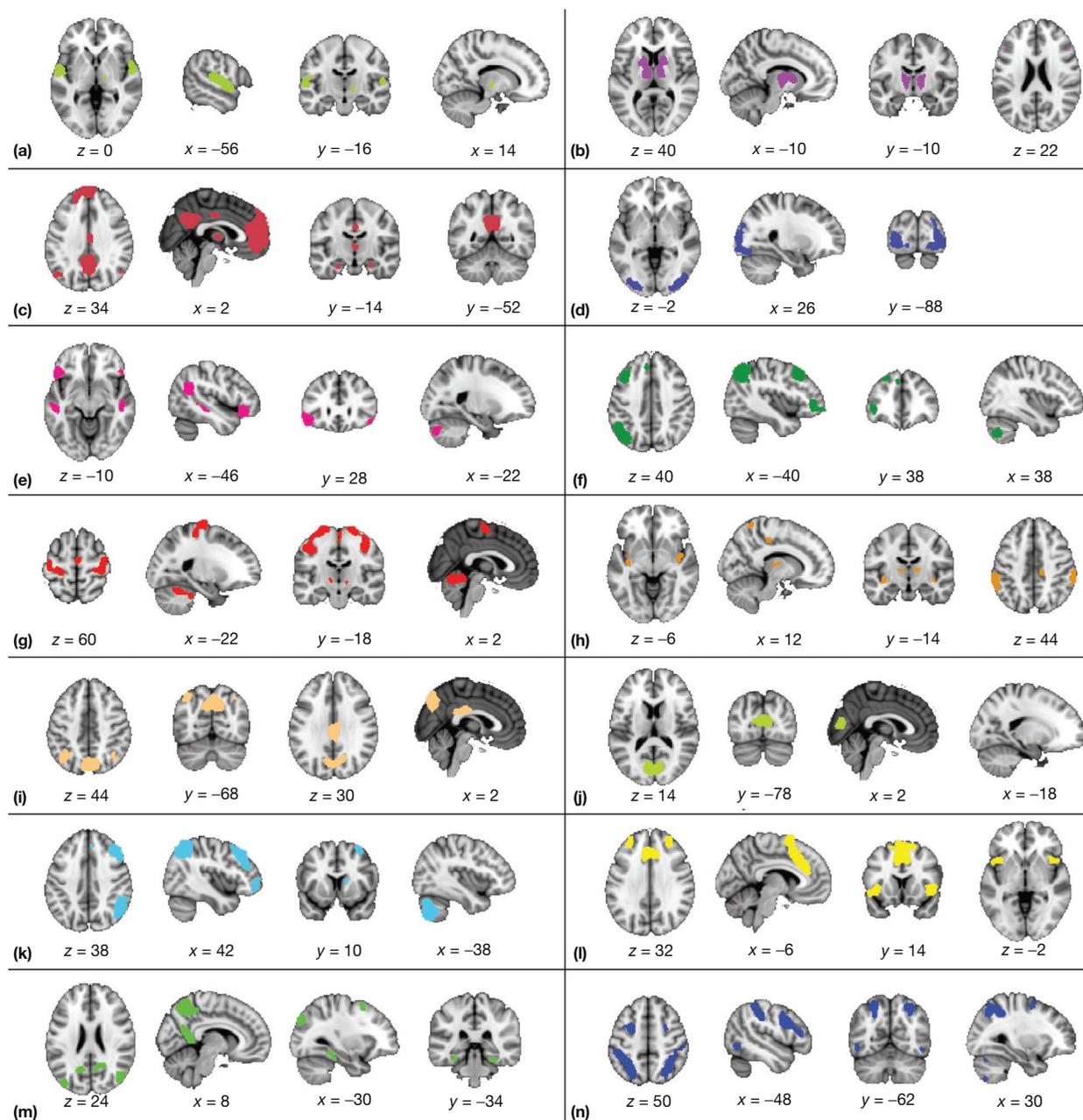


Figure 3 The human brain is intrinsically organized into coherent functional networks. (a) Auditory, (b) basal ganglia, (c) posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (vmPFC), (d) secondary visual cortex (V2), (e) language, (f) left dorsolateral prefrontal cortex (DLPFC) and left parietal lobe, (g) sensorimotor, (h) posterior insula, (i) precuneus, (j) primary visual cortex (V1), (k) right dorsolateral prefrontal cortex (DLPFC) and right parietal lobe, (l) anterior insula and dorsal anterior cingulate cortex (dACC), (m) retrosplenial cortex (RSC) and medial temporal lobe (MTL), (n) intraparietal sulcus (IPS) and frontal eye fields (FEF). Adapted from Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2011). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, 22, 158–165.

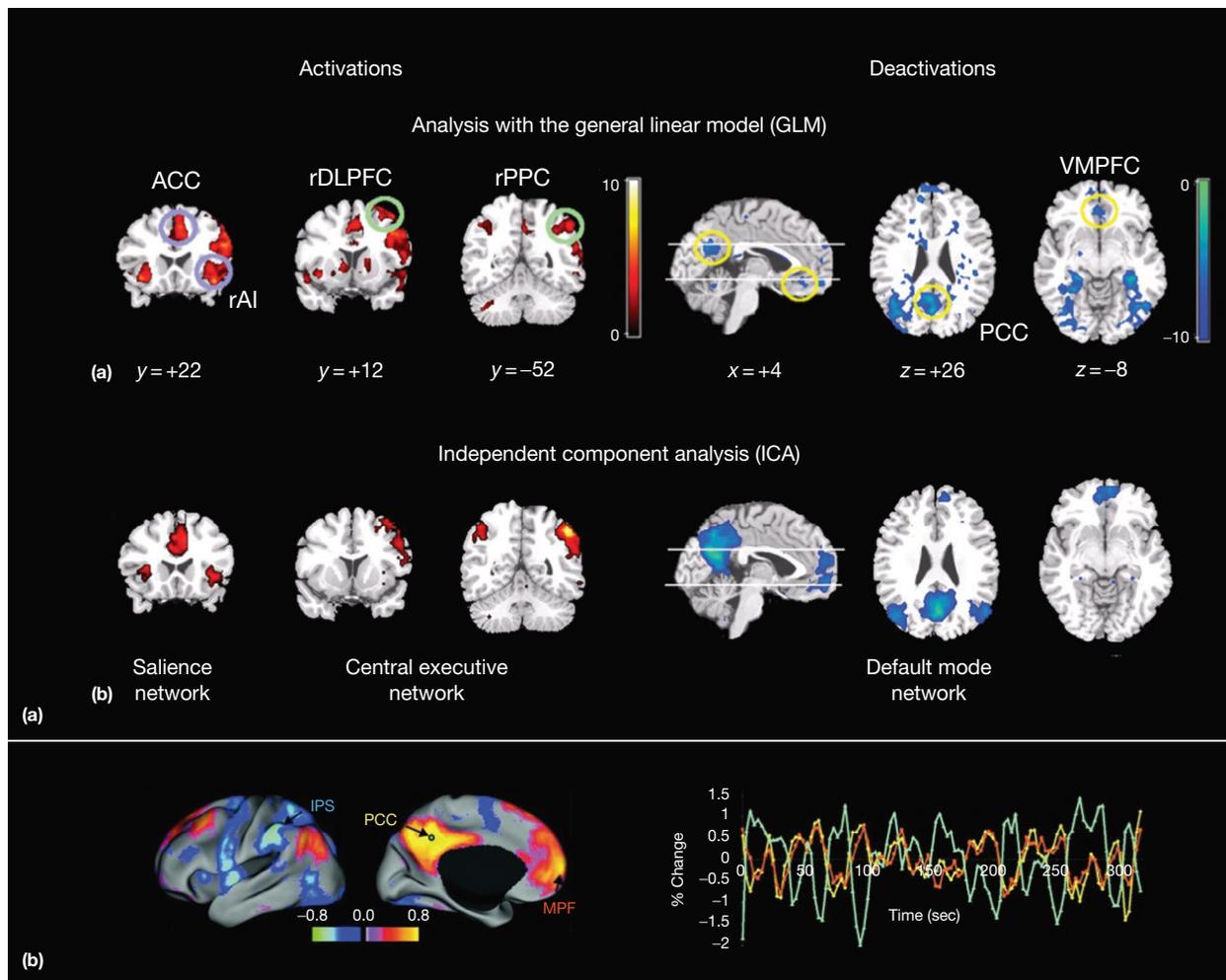


Figure 4 Activated and deactivated brain systems. (a) Canonical activations in the salience and central executive networks and deactivations in the default-mode network. (a) General linear model reveals regional activations (*left*) in the right hemispheric AI and ACC (blue circles); DLPFC and PPC (green circles) and deactivations (*right*) in the vmPFC and PCC during event transitions. (b) Activated and deactivated brain systems form distinct spatially independent networks. From left to right: salience network (rAI and ACC), central executive network (rDLPFC and rPPC), and default-mode network (vmPFC and PCC). (c) Intrinsic correlations between a seed region in the PCC and all other voxels in the brain for a single subject during resting fixation. The spatial distribution of correlation coefficients shows both correlations (positive values) and anticorrelations (negative values). The time course for a single run is shown for the seed region (PCC, yellow), a region positively correlated with this seed region in the vmPFC (orange), and a region negatively correlated with the seed region in the IPS (green). Adapted from Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 12569–12574 and Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 9673–9678.

these connectivity networks are intrinsically segregated spatially, the individual nodes of these networks can flexibly interact to facilitate cross network signaling based on task demands (Sridharan et al., 2007, 2008; Van Den Heuvel & Sporns, 2013). In sum, the brain is intrinsically organized into large-scale brain networks that facilitate segregation and integration of functional systems and impose constraints on signaling and information processing.

Activated and Deactivated Brain Systems

A prominent general feature of functional imaging studies is the cooccurrence of activation and deactivation across distributed

brain areas (Figure 4; Fox et al., 2005; Greicius et al., 2003; Greicius & Menon, 2004; Honey et al., 2007). Although the precise configuration of brain areas that show activations below or above 'resting' baseline varies considerably with task context, extant findings highlight an important principle of large-scale brain organization: Neural activity in some brain systems is suppressed while other systems are preferentially actively engaged in processing task-relevant information (Dastjerdi et al., 2011). Importantly, brain responses within these regions increase and decrease proportionately and often antagonistically in relation to specific cognitive demands and subjective task difficulty.

Crucially, brain areas that are typically activated, or deactivated, together form temporally synchronized networks, and the pattern of engagement and disengagement of these

networks during cognition typically mirrors this intrinsic network organization. For example, two midline brain structures – the posterior cingulate cortex and the medial prefrontal cortex – typically demonstrate below ‘resting’ baseline activation, whereas the dorsolateral prefrontal cortex and the supramarginal gyri show increased activation during a wide range of cognitive tasks (Greicius & Menon, 2004; Raichle et al., 2001). In contrast, the posterior cingulate cortex and medial prefrontal cortex show above resting baseline activation when access to self-referential and autobiographical memory recall is critical (Spreng, Mar, & Kim, 2009). From the viewpoint of large-scale brain networks highlighted earlier in the text, it is noteworthy that these regions map onto two distinct intrinsic networks – the default-mode network and the fronto-parietal central executive network. It is important to note, however, that the components of these networks can flexibly interact with one another based on task demands. The key organizing principle is not that there are dedicated ‘task-positive’ or ‘task-negative’ networks (Spreng, 2012), but that the antagonistic nature of brain networks imposes bottlenecks and limits access to neural resources that are needed for goal-directed behaviors while suppressing irrelevant ones.

Default-Mode Network, A System Important for Self-Referential Mental Processes

The discovery of the default-mode network highlights several important aspects of large-scale functional brain organization (Greicius et al., 2003; Raichle et al., 2001). This network consists of a set of brain regions that are deactivated during a wide range of cognitive tasks (Figure 5). It is anchored in the posterior cingulate cortex and medial prefrontal cortex, with prominent nodes in the medial temporal lobe and the angular gyrus (Greicius et al., 2003; Raichle et al., 2001). A range of functions, some based on above ‘resting’ baseline activations and others based on reduced levels of deactivation with respect to control tasks, have been ascribed to these regions in the functional imaging literature, leading to the notion that they form a default mode of brain function (Greicius et al., 2003; Raichle et al., 2001). Only after it was demonstrated that these areas form an interconnected network with activity levels that are strongly synchronized over time did the functional interrelations between these regions become apparent (Greicius et al., 2003). Subsequent research has shown that the default-mode network is a robust network that can be readily identified in each individual.

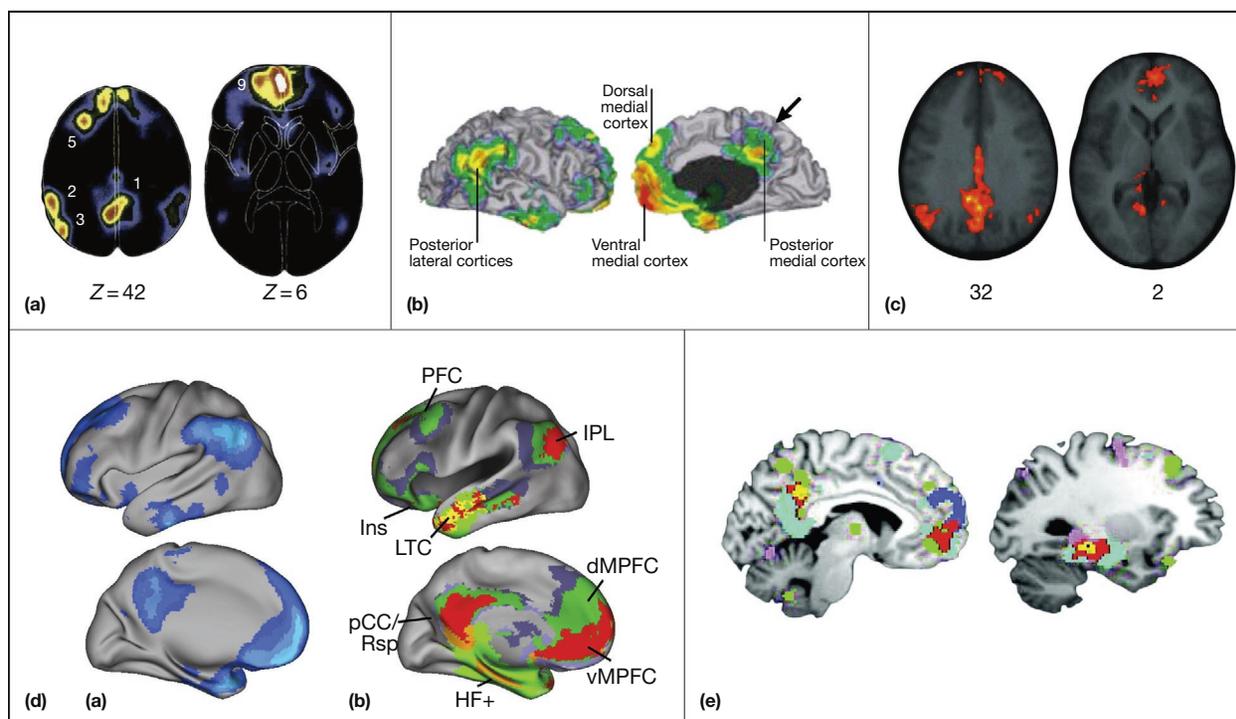


Figure 5 Default-mode network. (a, b) Meta-analysis of 10 studies illustrating brain areas with elevated PET signals during ‘resting baseline.’ (c) First identification of the default-mode network as a set of brain regions with strong temporal synchrony with each other, suggesting it forms a large-scale intrinsic functional network. The images show regions functionally correlated with the posterior cingulate. (d) (a) Surface rendering of key nodes of the default-mode network identified by intrinsic functional connectivity of the posterior cingulate, dorsomedial prefrontal cortex (dmPFC), and hippocampal formation (HF). These analyses reveal heterogeneity with the default-mode network and point to multiple, functionally interacting subsystems within it. (b) Surface rendering of the key nodes of brain areas shown in (a) for comparison. (e) Meta-analysis of 130 studies showing convergence of brain regions implicated in memory, prospection, navigation, and theory of mind on the default-mode network. Adapted from Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98, 676–682. Greicius, M., Krasnow, B., Reiss, A., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 253–258; and Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain’s default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, 1124, 1–38.

The default-mode network comprises an integrated system for autobiographical, self-monitoring value judgments, and other cognitive functions that support self-referential mental activity (Buckner, Andrews-Hanna, & Schacter, 2008). Its key nodes have been variously linked to episodic memory retrieval (Sestieri, Corbetta, Romani, & Shulman, 2011; Vannini et al., 2011), autobiographical memory (Dastjerdi et al., 2011; Spreng et al., 2009), and internal speech (Binder, Desai, Graves, & Conant, 2009), whereas specific nodes in the medial prefrontal cortex have been differentially associated with self-related and social cognitive processes (Amodio & Frith, 2006; Spreng et al., 2009), value-based decision making (Rangel, Camerer, & Montague, 2008), and emotion regulation (Etkin, Egner, & Kalisch, 2011). Collectively, these regions and their network interaction help in the construction of mental models of personally significant events (Andrews-Hanna, 2012). Abnormalities in intrinsic functional connectivity within the default-mode network have now been identified in virtually every major psychiatric disorder including Alzheimer's disease, schizophrenia, and depression, in which self-related processing and monitoring are known to be disrupted (Broyd et al., 2009; Qin & Northoff, 2011). Critically, knowledge of the intrinsic architecture of the network now plays an important role in how we conceptualize the functions of each of the brain regions that comprise this network.

Dissociable Fronto-Opercular–Parietal Control Systems

Another major feature of large-scale functional organization is that multiple frontal and parietal regions that are commonly activated across a wide range of cognitive tasks can be dissociated into distinct networks. In task-based functional imaging, coactivations of the anterior insula, anterior cingulate cortex, and the dorsolateral and the ventrolateral prefrontal cortices, as well as the supramarginal gyrus, intraparietal sulcus, and superior parietal lobules of the lateral parietal cortex are common across a wide range of cognitive tasks (Figure 6).

Detailed analyses of connectivity profiles of neighboring areas such as the supramarginal gyrus, angular gyrus and intra-parietal sulcus, and the dorsal and ventrolateral prefrontal cortices each have distinct fingerprints of connectivity with partially overlapping but largely distinct, target brain regions (Uddin et al., 2010; Yeo et al., 2011). Analysis of independent connectivity networks (see section 'Default-Mode Network, A System Important for Self-Referential Mental Processes') has provided the clearest evidence for dissociable systems involving these frontoparietal cortical regions. The salience and central executive networks have highly distinct patterns of connectivity across cortical and subcortical areas. The salience network, anchored in the anterior insula and anterior cingulate cortex, has strong

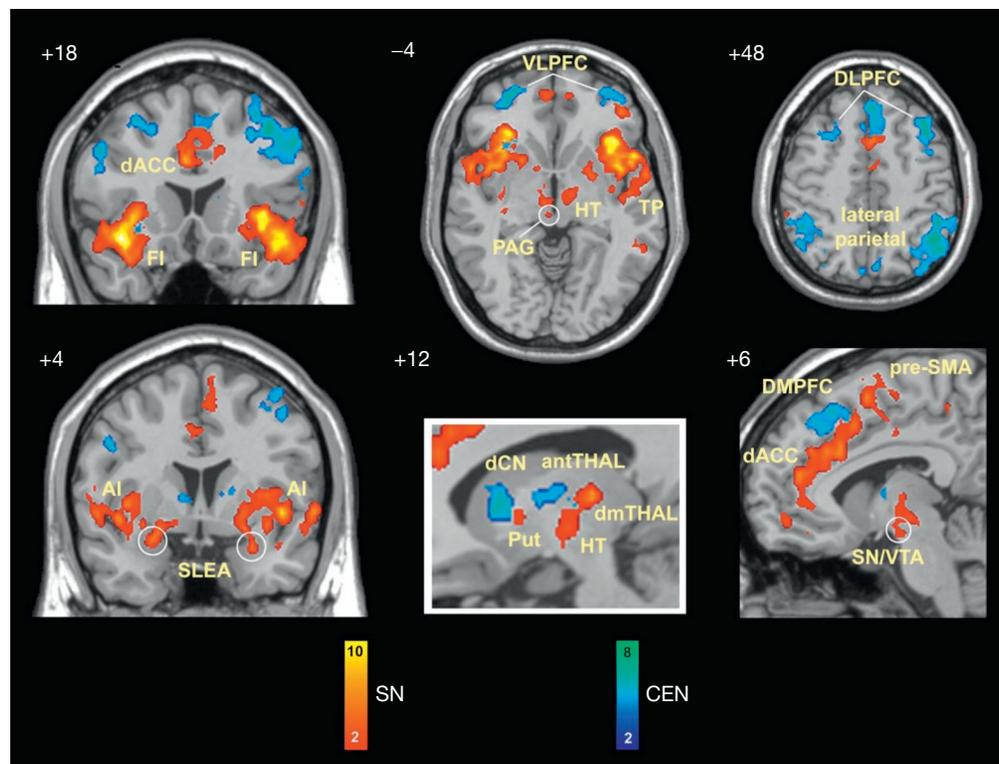


Figure 6 Dissociable prefrontal–opercular–parietal control networks. The salience network (SN; shown in red) is important for monitoring the saliency of external inputs and internal brain events, and the central executive network (CEN; shown in blue) is engaged in higher-order cognitive control. The SN is anchored in the fronto-insular (FI) cortex and dorsal anterior cingulate cortex (dACC) and features extensive connectivity with subcortical and limbic structures involved in reward and motivation. The CEN links the DLPFC and PPC and has subcortical coupling that is distinct from that of the SN. antTHAL, anterior thalamus; dCN, dorsal caudate nucleus; dmTHAL, dorsomedial thalamus; HT, hypothalamus; PAG, periaqueductal gray; Put, putamen; SLEA, sublenticular extended amygdala; SN/VTA, substantia nigra/ventral tegmental area; TP, temporal pole. Adapted from Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, 27, 2349–2356.

links with paralimbic and limbic areas including the anterior temporal cortex, sublenticular extended amygdala, ventral striatopallidum, dorsomedial thalamus, hypothalamus, periaqueductal gray, and substantia nigra/ventral tegmental area (Seeley et al., 2007). This network integrates brain signals involved in conflict monitoring, interoceptive–autonomic, and reward-processing areas into a common ‘salience network.’ It should be noted that this paralimbic–limbic salience network is distinct from the dorsal spatial attention network, a system anchored in the intraparietal sulcus and frontal eye fields that helps maintain a stable ‘saliency’ or priority map of the visual environment (Egner et al., 2008; Fecteau & Munoz, 2006; Ptak, 2012; Szczepanski, Pinsk, Douglas, Kastner, & Saalman, 2013).

Like the salience network, the central executive network is another amodal system, anchored in the dorsolateral and ventrolateral prefrontal cortices and the supramarginal gyrus in the lateral parietal cortex (Seeley et al., 2007). This frontoparietal central executive network is functionally coupled to the dorsal caudate and anterior thalamus but crucially lacks connectivity with limbic, hypothalamic, and midbrain structures. Critically, the identification of these distinct fronto-opercular–parietal networks has played an important role in clarifying their functional roles in cognition. The salience network is involved in detecting, integrating, and filtering relevant interoceptive, autonomic, and emotional information (Menon & Uddin, 2010; Seeley et al., 2007). A key function of the salience network is to identify the most homeostatically relevant among several internal and extrapersonal stimuli in order to guide behavior (Lovero, Simmons, Aron, & Paulus, 2009; Menon & Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008). The salience network is integrally involved in attentional capture of biologically and cognitively relevant ‘salient’ events and then signaling other brain systems, including the frontoparietal central executive network, for additional, more sustained, goal-directed processing (Menon & Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008). In contrast, the central executive network is critical for actively maintaining and manipulating information in the working memory, for rule-based problem solving, and for decision-making in the context of goal-directed behavior (Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Muller & Knight, 2006; Petrides, 2005). Dynamic interactions between these networks regulate shifts in attention and access to goal-relevant cognitive resources (Dosenbach et al., 2008, 2007; Ham, Leff, De Boissezon, Joffe, & Sharp, 2013; Sridharan et al., 2008). These processes have important implications for understanding the basic aspects not only of cognitive function but also of psychopathology (Bonnelle et al., 2012; Menon, 2011). Critically, this example illustrates how knowledge of large-scale brain organization can provide novel insights into distinct, domain-general, cognitive control systems in the human brain.

Conclusion

Network approaches have become increasingly useful for understanding the large-scale functional organization of the human brain. Analysis of intrinsic brain connectivity and networks provides a systematic framework for understanding the fundamental aspects of human brain architecture, independent of specific cognitive and experimental manipulations

and individual differences in behavior. This article has highlighted six important features of functional brain organization. First, as evidenced by graph-theoretic studies of whole-brain connectivity, globally, the brain has a nonrandom ‘small-world’ organization characterized by optimal connectivity for synchronization and information transfer with minimal rewiring cost. Second, the brain has a modular architecture dominated by strong interhemispheric connectivity between homologous regions in the left and right hemispheres. Third, the brain is intrinsically organized into multiple coherent networks that segregate functional systems and constrain information processing. Fourth, brain areas that show common patterns of activation and deactivation during cognition are generally organized into distinct intrinsic brain systems that impose bottlenecks arising from network access, conflict, and resources. Fifth, the most commonly deactivated brain regions form a default-mode network, a functional brain system important for self-referential information processing. Sixth, fronto-opercular–parietal brain regions implicated in a wide range of cognitive tasks, including cognitive control, form dissociable intrinsic functional systems that play distinct roles, cognition and control. Crucially, the salience network, anchored in the insula and anterior cingulate cortex, plays an important role in transient attentional capture of biologically and cognitively relevant ‘salient’ events. In contrast, the frontoparietal central executive network is important for more sustained goal-relevant and adaptive processing, such as maintaining and manipulating information in the working memory. Collectively, these six principles provide important insights into how the intrinsic functional architecture of the human brain facilitates segregation of neural signals while at the same time allowing flexible interactions for goal-directed behavior.

Building on these findings, efforts are now underway to more fully characterize the functional nodes spanning the entire human brain and their structural and functional interconnectivity, collectively the ‘connectome’ (Behrens & Sporns, 2012; Craddock et al., 2013; Sporns, 2011a; Van Essen et al., 2012). These efforts will eventually lead to a better understanding of how large-scale functional circuits facilitate information processing in the brain. More broadly, neurocognitive network models are helping to synthesize extant findings of brain response and connectivity across disparate tasks into a common framework and offer new avenues for synthesis of disparate findings in the cognitive neuroscience literature.

See also: **INTRODUCTION TO ACQUISITION METHODS:** Functional MRI Dynamics; Temporal Resolution and Spatial Resolution of fMRI; **INTRODUCTION TO ANATOMY AND PHYSIOLOGY:** Cytoarchitecture and Maps of the Human Cerebral Cortex; Functional Connectivity; The Resting-State Physiology of the Human Cerebral Cortex; **INTRODUCTION TO METHODS AND MODELING:** Resting-State Functional Connectivity; **INTRODUCTION TO SYSTEMS:** Autonomic Control; Brain Mapping of Control Processes; Hubs and Pathways; Network Components; Salience Network; Working Memory.

Bibliography

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLoS Computational Biology*, 3, e17.

- Achard, S., Salvador, R., Whitcher, B., Suckling, J., & Bullmore, E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *Journal of Neuroscience*, *26*, 63–72.
- Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience*, *7*, 268–277.
- Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist*, *18*, 251–270.
- Bandettini, P. A. (2012). Twenty years of functional MRI: The science and the stories. *NeuroImage*, *62*, 575–588.
- Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., et al. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience*, *6*, 448–450.
- Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, *23*, 137–152.
- Behrens, T. E., & Sporns, O. (2012). Human connectomics. *Current Opinion in Neurobiology*, *22*, 144–153.
- Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, *19*, 2767–2796.
- Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., et al. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 4690–4695.
- Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, *14*, 277–290.
- Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience and Biobehavioral Reviews*, *33*, 279–296.
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38.
- Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*, *29*, 1860–1873.
- Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, *13*, 336–349.
- Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, *34*, 569–599.
- Craddock, R. C., Jbabdi, S., Yan, C. G., Vogelstein, J. T., Castellanos, F. X., Di Martino, A., et al. (2013). Imaging human connectomes at the macroscale. *Nature Methods*, *10*, 524–539.
- Damasio, H., & Damasio, A. R. (1989). *Lesion analysis in neuropsychology*. New York: Oxford University Press.
- Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., et al. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 13848–13853.
- Dastjerdi, M., Foster, B. L., Nasrullah, S., Rauschecker, A. M., Dougherty, R. F., Townsend, J. D., et al. (2011). Differential electrophysiological response during rest, self-referential, and non-self-referential tasks in human posteromedial cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 3023–3028.
- Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, *12*, 99–105.
- Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A., et al. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 11073–11078.
- Egner, T., Monti, J. M., Trittschuh, E. H., Wieneke, C. A., Hirsch, J., & Mesulam, M. M. (2008). Neural integration of top-down spatial and feature-based information in visual search. *Journal of Neuroscience*, *28*, 6141–6151.
- Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*, 85–93.
- Fecteau, J. H., & Munoz, D. P. (2006). Salience, relevance, and firing: A priority map for target selection. *Trends in Cognitive Sciences*, *10*, 382–390.
- Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*, 700–711.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 9673–9678.
- Fuster, J. M. (2006). The cognit: A network model of cortical representation. *International Journal of Psychophysiology*, *60*, 125–132.
- Gotts, S. J., Jo, H. J., Wallace, G. L., Saad, Z. S., Cox, R. W., & Martin, A. (2013). Two distinct forms of functional lateralization in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, E3435–E3444.
- Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpaa, V., Alahuhta, S., Reiss, A. L., et al. (2008). Persistent default-mode network connectivity during light sedation. *Human Brain Mapping*, *29*, 839–847.
- Greicius, M., Krasnow, B., Reiss, A., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 253–258.
- Greicius, M. D., & Menon, V. (2004). Default-mode activity during a passive sensory task: Uncoupled from deactivation but impacting activation. *Journal of Cognitive Neuroscience*, *16*, 1484–1492.
- Greicius, M., Srivastava, G., Reiss, A., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 4637–4642.
- Ham, T., Leff, A., De Boissezon, X., Joffe, A., & Sharp, D. J. (2013). Cognitive control and the salience network: An investigation of error processing and effective connectivity. *Journal of Neuroscience*, *33*, 7091–7098.
- Honey, C. J., Kotter, R., Breakspear, M., & Sporns, O. (2007). Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 10240–10245.
- Horowitz, S. G., Braun, A. R., Carr, W. S., Picchioni, D., Balkin, T. J., Fukunaga, M., et al. (2009). Decoupling of the brain's default mode network during deep sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 11376–11381.
- Huettel, S. A., Song, A. W., & McCarthy, G. (2008). *Functional magnetic resonance imaging*. Sunderland, MA: Sinauer Associates.
- Koechlin, E., & Summerfield, C. (2007). An information theoretical approach to prefrontal executive function. *Trends in Cognitive Sciences*, *11*, 229–235.
- Lovero, K. L., Simmons, A. N., Aron, J. L., & Paulus, M. P. (2009). Anterior insular cortex anticipates impending stimulus significance. *NeuroImage*, *45*, 976–983.
- Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*, 483–506.
- Menon, V. (2013). Developmental pathways to functional brain networks: Emerging principles. *Trends in Cognitive Science*, *17*, 627–640.
- Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*, 655–667.
- Mesulam, M. M. (1998). From sensation to cognition. *Brain*, *121*(Pt 6), 1013–1052.
- Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.
- Muller, N. G., & Knight, R. T. (2006). The functional neuroanatomy of working memory: Contributions of human brain lesion studies. *Neuroscience*, *139*, 51–58.
- Passingham, R. E., Stephan, K. E., & Kotter, R. (2002). The anatomical basis of functional localization in the cortex. *Nature Reviews Neuroscience*, *3*, 606–616.
- Petrides, M. (2005). Lateral prefrontal cortex: Architectonic and functional organization. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *360*, 781–795.
- 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.
- Ptak, R. (2012). The frontoparietal attention network of the human brain: Action, saliency, and a priority map of the environment. *The Neuroscientist*, *18*, 502–515.
- Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? *NeuroImage*, *57*, 1221–1233.
- Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 676–682.
- Rangel, A., Camerer, C., & Montague, P. R. (2008). A framework for studying the neurobiology of value-based decision making. *Nature Reviews Neuroscience*, *9*, 545–556.
- Ryali, S., Chen, T., Supekar, K., & Menon, V. (2012). Estimation of functional connectivity in fMRI data using stability selection-based sparse partial correlation with elastic net penalty. *NeuroImage*, *59*, 3852–3861.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*, 2349–2356.
- Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: Functional and topographic analyses. *Journal of Neuroscience*, *31*, 4407–4420.
- Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2011). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, *22*(1), 158–165.

- Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 13040–13045.
- Sporns, O. (2011a). The human connectome: A complex network. *Annals of the New York Academy of Sciences*, *1224*, 109–125.
- Sporns, O. (2011b). *Networks of the brain*. Cambridge, MA: MIT Press.
- Spreng, R. N. (2012). The fallacy of a "task-negative" network. *Frontiers in Psychology*, *3*, 145.
- Spreng, R. N., Mar, R. A., & Kim, A. S. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: A quantitative meta-analysis. *Journal of Cognitive Neuroscience*, *21*, 489–510.
- Sridharan, D., Levitin, D. J., Chafe, C. H., Berger, J., & Menon, V. (2007). Neural dynamics of event segmentation in music: Converging evidence for dissociable ventral and dorsal networks. *Neuron*, *55*, 521–532.
- Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 12569–12574.
- Stark, D. E., Margulies, D. S., Shehzad, Z. E., Reiss, P., Kelly, A. M., Uddin, L. Q., et al. (2008). Regional variation in interhemispheric coordination of intrinsic hemodynamic fluctuations. *Journal of Neuroscience*, *28*, 13754–13764.
- Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*, *4*, e1000100.
- Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. *PLoS Biology*, *7*, e1000157.
- Supekar, K., Uddin, L. Q., Prater, K., Amin, H., Greicius, M. D., & Menon, V. (2010). Development of functional and structural connectivity within the default mode network in young children. *NeuroImage*, *52*, 290–301.
- Szczepanski, S. M., Pinsk, M. A., Douglas, M. M., Kastner, S., & Saalman, Y. B. (2013). Functional and structural architecture of the human dorsal frontoparietal attention network. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 15806–15811.
- Thiebaut De Schotten, M., Dell'acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G., et al. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience*, *14*, 1245–1246.
- Tomasi, D., & Volkow, N. D. (2011). Functional connectivity hubs in the human brain. *NeuroImage*, *57*, 908–917.
- Uddin, L. Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., et al. (2010). Dissociable connectivity within human angular gyrus and intraparietal sulcus: Evidence from functional and structural connectivity. *Cerebral Cortex*, *20*, 2636–2646.
- Van Den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*, *17*, 683–696.
- Van Den Heuvel, M. P., Sporns, O., Collin, G., Scheewe, T., Mandl, R. C., Cahn, W., et al. (2013). Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA Psychiatry*, *70*, 783–792.
- Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T. E., Bucholz, R., et al. (2012). The Human Connectome Project: A data acquisition perspective. *NeuroImage*, *62*, 2222–2231.
- Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L. J., Bruno, M. A., Boveroux, P., Schnakers, C., et al. (2010). Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain*, *133*, 161–171.
- Vannini, P., O'Brien, J., O'Keefe, K., Pihlajamaki, M., Laviolette, P., & Sperling, R. A. (2011). What goes down must come up: Role of the posteromedial cortices in encoding and retrieval. *Cerebral Cortex*, *21*, 22–34.
- Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*, 1125–1165.