Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com

Subcortical contributions to large-scale network communication

Peter T. Bell [a, b, *], James M. Shine [b, c, d]

[a] University of Queensland Centre for Clinical Research, University of Queensland, Brisbane, QLD, Australia
[b] Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia
[c] Neuroscience Research Australia, Neuroscience Research Australia, University of New South Wales, Sydney, NSW, Australia
[d] Psychology Department, Stanford University, Stanford, CA, USA

ARTICLE INFO

Article history:
Received 30 December 2015
Accepted 29 August 2016
Available online xxx

Keywords:
Basal ganglia
Connectivity
Dopamine
Hub
Integration
Striatum
Thalamus

ABSTRACT

Higher brain function requires integration of distributed neuronal activity across large-scale brain networks. Recent scientific advances at the interface of subcortical brain anatomy and network science have highlighted the possible contribution of subcortical structures to large-scale network communication. We begin our review by examining neuroanatomical literature suggesting that diverse neural systems converge within the architecture of the basal ganglia and thalamus. These findings dovetail with those of recent network analyses that have demonstrated that the basal ganglia and thalamus belong to an ensemble of highly interconnected network hubs. A synthesis of these findings suggests a new view of the subcortex, in which the basal ganglia and thalamus form part of a core circuit that supports large-scale integration of functionally diverse neural signals. Finally, we close with an overview of some of the major opportunities and challenges facing subcortical-inclusive descriptions of large-scale network communication in the human brain.

1. Introduction

Concepts of functional localization and specialization have shaped modern perspectives of neuroscience. These principles view the brain as a complex multi-scale system composed of specialized neural sub-systems that are themselves responsible for executing specialized neural computations and cognitive operations. Extensive evidence for the concept of functional specialization has been observed across multiple levels of spatial description from neuronal circuits through to large-scale neural systems, firmly cementing this principle in theoretical accounts of brain organization.

However, the recent emergence of sophisticated methods for the acquisition and analysis of neuroanatomical data has led to an increasing recognition that functional specialization does not occur in isolation. Instead, higher brain function also requires the integration of distributed neuronal activity across specialized brain systems (Tononi et al., 1994; Mesulam, 1998; Sporns, 2013).[1] Indeed, accumulating evidence suggests that integration across distributed neural systems supports diverse cognitive processes including language (Friederici and Gierhan, 2013), visual recognition (Behrmann and Plaut, 2013), emotion (Pessoa, 2012), cognitive control (Power and Petersen, 2013) and learning (Bassett et al., 2011; Bassett et al., 2015). The overall picture emerging from this work is that a dynamic and coordinated balance between functional integration and segregation is essential for the operation of distributed brain networks underlying cognition and adaptive behaviour (Tononi et al., 1994; Fox and Friston, 2012; Sporns, 2013).

Grounding the theoretical principle of functional integration in a neuroanatomical framework has been of major neuroscientific interest over the past 30 years. Fundamental insights into cortical organization have been gained from detailed examination of tract-tracing data in experimental vertebrate organisms and neuroimaging data in humans. This body of work has demonstrated that the vertebrate brain is organized into a complex hierarchical network in which specialized neural communities communicate via putative transmodal convergence zones (Damasio, 1989; Mesulam, 1998; Sepulcre et al.,

Abbreviations: BG, basal ganglia; CBG, cortico-basal ganglia; MRI, magnetic resonance imaging; STN, subthalamic nucleus

* Corresponding author at: University of Queensland Centre for Clinical Research, University of Queensland, QLD, Australia.
Email address: p.bell4@uq.edu.au (P.T. Bell)

[1] The principles of functional integration and segregation scale with brain organization. For instance, functional integration can be understood at the synaptic and cellular level through the temporal and spatial summation of incoming synaptic inputs. Equally, functional integration may be understood at the *systems*-level through 'binding' of multimodal information (Mesulam, 1998) and communication across large-scale neural communities (Sporns, 2013). In this article, we examine functional integration and segregation at the systems-level. Although this discussion invariably requires consideration of mechanisms on the scale of cells and circuits, our primary focus will be on macroscopic neural *systems*.

http://dx.doi.org/10.1016/j.neubiorev.2016.08.036
0149-7634/

2012; Bell and Shine, 2015; Braga and Leech, 2015) and network *hub* regions [for review, see van den Heuvel and Sporns, 2013b] (Glossary).

Despite insights into *cortical* substrates underpinning systems-level integration in the brain, the subcortex has been underrepresented in prior descriptions of whole-brain anatomical connectivity (Pessoa, 2014). This omission may in part reflect a pervasive 'corticocentric' view of higher brain function, in which the neocortex is considered the key structure for higher function, while deep gray-matter structures simply subserve cortical demands (Parvizi, 2009). Contrary to this viewpoint however, cortico-subcortical circuits are linked to a diverse range of limbic, cognitive and motor control functions (Chudasama and Robbins, 2006; Pennartz et al., 2009). Furthermore extensive reciprocal and non-reciprocal circuits connect the cortex with the basal ganglia (BG), thalamus, cerebellum and brainstem (Alexander et al., 1986; Shepard and Grillner, 2010). Thus, from both an anatomical and functional standpoint, a complete and accurate description of brain structure and function necessarily requires consideration of the extensive cortico-subcortical architecture.

In this *Review,* we examine recent evidence suggesting that subcortical macrocircuits connecting the BG, thalamus and cortex are involved in large-scale functional integration. We begin by examining findings from anatomical work revealing that the BG and thalamus support the convergence of information arriving from cortical, subcortical and neuromodulatory systems. Following this, we discuss complementary results from recent literature that has adopted an explicit network perspective to examine structural brain organization. In synthesizing these findings, we arrive at a new view of the subcortex in which large-scale communication and information integration is a key computational priority. Finally, we conclude with an overview of the opportunities and challenges facing subcortical-inclusive descriptions of large-scale network communication in the human brain.

2.1. Integration in basal ganglia & thalamic circuits

Interactions between the cortex and BG support goal-directed behaviours, including decision-making, motor control, action selection, learning, and habit formation (Graybiel et al., 1994; Houk and Wise, 1995; Pennartz et al., 2009). These interactions take place throughout large-scale anatomical loops that link the cortex, BG and thalamus (Alexander et al., 1986), and are essential for vertebrate forebrain function.

2.1.1. Cortical–basal ganglia loop architecture

Projections from the cortex terminate in the striatum, the major BG input structure. BG output is then channeled back to cortex via the thalamus; thereby completing the cortical–basal ganglia (CBG) 'loop' architecture (Fig. 1a). CBG circuits are organized according to a general functional topography, whereby limbic cortex projects to the ventral striatum, associative cortex projects to the ventromedial caudate, and motor cortex projects to the dorsolateral striatum (Alexander et al., 1986). This functional topography is also maintained in extra-striatal BG nuclei (i.e. pallidum and subthalamic nucleus) and thalamus, suggesting that a general topographic organization is preserved at all stations of the CBG loop (Alexander et al., 1986). The discovery of functional topography throughout the CBG loop architecture led to the segregated loop model, which proposed that functionally specialized information remains segregated throughout parallel 'closed' CBG streams (limbic, associative and motor

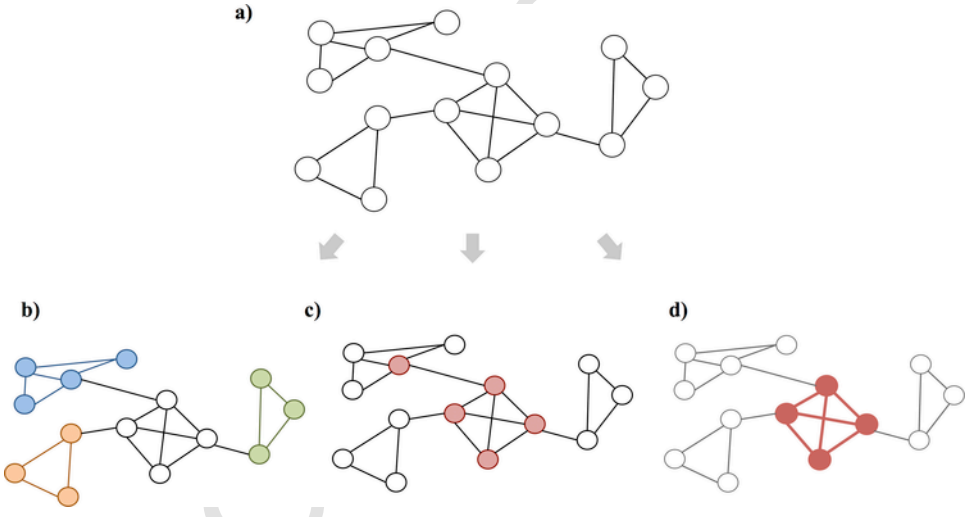

Fig. 1. a Schematic illustration depicting the general organization of the cortico-basal ganglia (CBG) loop architecture (Alexander et al., 1986). The connections between the cerebral cortex and the basal ganglia (BG) form a series of parallel macrocircuits conveying limbic (red), associative (yellow) and motor (blue) information. Cortical projections terminate in the striatum, which represents the major input structure of the BG. BG output is subsequently channeled via subthalamic and pallidal BG nuclei towards the thalamus, which then projects to the back to the cortex completing the CBG 'loop'. Pointed arrowheads denote excitatory projections, circular arrowheads represent inhibitory projections. b – Areas of Corticostriatal Terminal Overlap in the Striatum. Figure denotes the number of distinct prefrontal cortical regions (i.e., vmPFC, OFC, dACC, dPFC, vlPFC) that converge at each site across the topography of the striatal complex based on data from an invasive tract tracing experiment in rhesus macaques (Averbeck et al., 2014). Colour on each section indicates voxels that receive projections from 0 to 5 distinct prefrontal cortical regions. For illustrative purposes we present only a representative sample of the striatal slices originally published by (Averbeck et al., 2014). Striatal slices (i) 7.2 mm, (ii) 4.2 mm, and (iii) 1.8 mm, anterior to the anterior commissure respectively. b adapted from (Averbeck et al., 2014) with permission. Abbreviations: GP, Globus pallidus; STN, subthalamic nucleus; vmPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex; dACC, dorsal anterior cingulate cortex; dPFC, dorsal prefrontal cortex; vlPFC, ventrolateral prefrontal cortex. c – Schematic representation of a hypothetical connectome. Subcortical-inclusive connectome mapping has demonstrated that the striatum and thalamus form part of an integrated core circuit of tightly interconnected brain hubs. The topological embedding of cortical (blue) and subcortical (green) hubs renders them attractive candidates for integration and distribution of diverse and global signal traffic. The subcortex is positioned to support the convergence and distribution of diverse cortical and subcortical afferents, as well as abundant ascending neuromodulatory (dopaminergic and non-dopaminergic) signals from the brainstem (red) (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

channels, respectively) (Alexander and Crutcher, 1990; Hoover and Strick, 1993).

Although the segregated loop model has proven a useful heuristic for understanding BG function, accumulating evidence over the past two decades suggests that BG and thalamic nuclei are not merely relay stations for propagating signals throughout isolated macrocircuits. Instead, CBG architecture represents a complex dual organizational system, supporting both segregated and integrative information processing across functional channels (Haber, 2010). In the following section, we review recent work highlighting the importance of CBG circuitry in the integration of information across distributed neural systems.

2.1.2. Neural systems converge in CBG architecture

While corticostriatal projections terminate in the striatum according to a general functional topography (Fig. 1a), there is also an intricate non-topographic organization. Tract-tracing work in non-human primates has demonstrated convergence between corticostriatal terminals projecting from functionally diverse cortical regions (Haber et al., 2006; Calzavara et al., 2007; Averbeck et al., 2014). These converging terminals contravene the general striatal topography by crossing putative functional boundaries in the striatum (Haber et al., 2006; Calzavara et al., 2007; Averbeck et al., 2014), suggesting that the striatal complex may provide a neuroanatomical substrate for the integration of convergent input from limbic, associative and motor systems. In a recent tract-tracing study in non-human primates, Averbeck et al. (2014) quantified striatal projection zones from distinct injection locations in the prefrontal cortex. Results revealed that specific striatal regions receive highly convergent inputs from multiple functionally distinct prefrontal regions (Fig. 1b), leading to the proposal that striatal convergence zones play a role in synchronizing information across multiple functional domains (Haber et al., 2006; Averbeck et al., 2014). Evidence for corticostriatal convergence zones has since been extended to humans using structural neuroimaging data (Draganski et al., 2008; Jarbo and Verstynen, 2015), however unlike histological approaches [e.g. (Averbeck et al., 2014)], limitations in the spatial resolution of MRI preclude the examination of synaptic terminal fields in humans. Intriguingly, striatal convergence zones share conceptual similarity with network hubs observed in large-scale cortical networks (Power et al., 2013; van den Heuvel and Sporns, 2013a), suggesting that systems-level integrative computations may not be exclusive to the cortex.

Another intriguing feature of CBG organization is the progressive reduction of cell numbers throughout the BG. The striatum receives afferent inputs from a range of cortical areas, but has far fewer neurons (Wilson, 1995; Bar-Gad et al., 2003). In turn, striatal neurons project to an even smaller neuronal population in the pallidum (Bar-Gad et al., 2003). Previous authors have proposed that, by virtue of a progressive reduction in cell number throughout the CBG loop, synaptic terminals from adjacent fields come into contact as they are compressed into smaller and smaller structures (Bar-Gad et al., 2003). This organization may be particularly useful for integrating information at putative functional boundaries of BG nuclei where topographical overlap between different functional zones is most prominent (Haber, 2010; Haynes and Haber, 2013).

In addition to corticostriatal terminals, the striatum also receives convergent subcortical innervation (Sesack and Grace, 2010). There is anatomical (French and Totterdell, 2002, 2003) and electrophysiological (O'Donnell and Grace, 1995) evidence to suggest that single neurons in the ventral striatum receive convergent input from the hippocampus, amygdala and prefrontal cortex (O'Donnell and Grace, 1995; French and Totterdell, 2002, 2003). Previous investigators have proposed that, through connectivity with the amygdala and hippocampus, the ventral striatum provides a gateway for subcortical limbic drives to enter the BG system, and subsequently bias cognitive planning and motor control (Grace et al., 2007; Pennartz et al., 2009). Moreover, the striatal complex also receives convergent glutamatergic input directly from the thalamus (McFarland and Haber, 2002). Together, these findings emphasize the importance of the BG nuclei in orchestrating interactions between convergent cortical and subcortical systems.

In addition to striatal mechanisms discussed above, there is also some evidence for systems-convergence in the pallidum (Yelnik et al., 1984; Percheron and Filion, 1991) [but see Selemon and Goldman-Rakic, 1991], subthalamic nucleus (Bevan et al., 1997; Kolomiets et al., 2001; Haynes and Haber, 2013) and thalamus (Sherman and Guillery, 1996; McFarland and Haber, 2002; Sherman, 2007; Theyel et al., 2010), suggesting that integration occurs at multiple levels of the CBG loop. It is important to re-emphasize however, that functional integration is not the sole computational priority of CBG circuitry. Indeed, each level of the CBG loop also demonstrates a degree of functional specialization (Francois et al., 1994; Kolomiets et al., 2001; Middleton and Strick, 2002; Draganski et al., 2008; Averbeck et al., 2014; Oh et al., 2014), a finding consistent with the dual processing model of the CBG loop.

2.1.3. Neuromodulation in CBG architecture

Ascending neuromodulatory structures arising from the caudal brainstem also provide dense innervation of the striatum and thalamus. In particular, the striatal complex receives extensive dopaminergic input from ventral midbrain nuclei (Haber et al., 2000), which provides potent modulatory control over striatal activity (Surmeier et al., 2007). This arrangement enables a system in which convergent glutamatergic cortical and subcortical afferents are modulated by dopaminergic neurons from the midbrain. Such an organization has important functional properties. Phasic bursting firing from the dopaminergic midbrain provides instructive signals about reward seeking, engaging motivationally salient situations, or responding to alerting stimuli in the environment (Schultz et al., 1997; Bromberg-Martin et al., 2010). Overall, these dopamine signals provide moment-to-moment contextual information that enables the organism to flexibly adapt and learn in a dynamic environment (Schultz et al., 1997; Bromberg-Martin et al., 2010). Thus, the convergence of diverse cortical and subcortical afferents, combined with their common modulation by dopamine, has led to the proposal that the striatum provides a neuroanatomical substrate for the integration of dopaminergic signals about environmental context, with incoming information in limbic, cognitive and motor control circuits (Belin and Everitt, 2008; Haber and Knutson, 2010; Sesack and Grace, 2010; Aarts et al., 2011; Haber, 2014). At a more protracted time-scale, dopamine regulates activity-dependent neuroplasticity at corticostriatal synapses (Calabresi et al., 2007), which has been implicated in motor learning, cognition and reward processes (Wickens et al., 2003; Mahon et al., 2004). Thus, in addition to providing real-time signals about environmental context, dopamine may also influence systems-level integration by regulating long-lasting changes in corticostriatal synaptic connectivity.

Further to the proposed role of dopamine in modulating activity of convergent glutamatergic afferents in the striatal complex, there have also been suggestions that the dopaminergic neurons may directly mediate interactions across limbic, associative and motor CBG streams. Originally discovered in rodents (Nauta et al., 1978; Ikemoto, 2007) and later in non-human primates (Haber et al., 2000), a cascade-like 'spiraling' dopamine pathway links the ventral stria-

tum with progressively more dorsal striatal areas via serial non-reciprocal connections with the ventral midbrain [see (Haber et al., 2000)]. Thus, based on the serial arrangement of this circuitry, it has been proposed that this spiraling dopaminergic cascade connecting the striatum and the ventral midbrain provides a substrate for the feed-forward integration of limbic, associative and motor signals across CBG macrocircuits (Haber et al., 2000). Placed into a behavioural framework, this hypothesis posits that the spiraling dopamine projections represent a possible mechanism for the serial flow of information from structures involved in reward and motivation to influence goal-directed cognition and subsequently drive motor output (Belin and Everitt, 2008; Haber and Knutson, 2010; Sesack and Grace, 2010; Aarts et al., 2011; Haber, 2014).

While dopamine is currently the most widely studied biogenic amine neuromodulator, other ascending projection systems also provide intricate patterns of innervation to the BG and thalamus, along with more diffuse innervation of neocortical regions. Ascending serotonergic, cholinergic and noradrenergic projection systems provide a unique combination of interacting neuromodulators that influence neuronal excitability and synaptic transmission in the BG and thalamus. Thus, interacting dopaminergic and non-dopaminergic neuromodulatory inputs are likely to influence integrative computations within the CBG loop architecture.

2.1.4. Role of the thalamus within the CBG loop

The thalamus is highly heterogeneous structure, composed of up to 50 discrete nuclei (Jones, 2012). The thalamic complex forms extensive bidirectional connections with visual, sensorimotor, limbic and associative neocortical regions as well as other subcortical structures including the striatum (Oh et al., 2014). In recent years, an abundance of evidence from rodents though to primates has supported the concept that transthalamic pathways are critical for actively orchestrating information flow throughout cortico-cortical networks (Guillery, 1995; Sherman, 2007; Sherman and Guillery, 2011; Saalmann et al., 2012; Oh et al., 2014). Indeed, the thalamus is now believed to enable large-scale inter-regional cortical communication via non-reciprocal cortico-thalamo-cortical pathways. These pathways are formed by the non-reciprocal arrangement of projection fibers in which thalamic nuclei receive afferent input from different cortical areas (and different cortical layers) to which they project, enabling feed-forward inter-areal information flow [see (Sherman and Guillery, 2011)]. Furthermore, recent evidence in slice preparations has demonstrated that thalamic silencing can block communication between distinct cortical areas (Theyel et al., 2010). Thus, it is clear that the transthalamic conduit provides an important channel for large-scale flow of information between distributed cortical areas and distinct cortical layers (Sherman and Guillery, 1996; McFarland and Haber, 2002; Sherman, 2007; Theyel et al., 2010; Saalmann et al., 2012).

2.1.5. Summary of convergence in the CBG architecture

The anatomical connectivity of the BG and thalamus implies central involvement of these structures in systems-level integration – whereby converging cortical and subcortical signals are integrated under potent neuromodulatory control. Together the above findings are consistent with a dual processing model of the CBG loop in which coordinated behaviour can be maintained and focused (through parallel CBG circuitry), but also flexibly modified (through integrative CBG networks) in response to dynamic environmental cues (Haber and Calzavara, 2009; Haber and Knutson, 2010).

Although the above work provides insights into the convergent organization of specific projection systems within the CBG architecture, consideration of how the CBG system is embedded within the global brain network requires an alternative approach. The following section will discuss findings from recent network-analytic studies that have begun to shed light on the how the CBG system is embedded within the global brain network.

2.2. Subcortical membership in the 'Rich-Club'

2.2.1. Introduction to the science of brain networks

The search for fundamental organizational principles in anatomical brain networks has a long history in the neuroscience literature (Goldman-Rakic, 1988; Damasio, 1989; Felleman and Van Essen, 1991; Mesulam, 1998). However, the recent application of quantitative data-driven tools, adopted from a branch of mathematics known as graph theory, has revolutionized the study of large-scale brain organization. Network models of brain organization provide an abstract representation of brain connectivity in which discrete neural elements (nodes) and their connections (edges) are represented in the form of a connectivity graph (see Glossary & Fig. 2). The collective structure of interconnected nodes and edges defines the topology of the network (Glossary), which can be further examined using a range of quantitative metrics to mathematically describe elements of the local and global connectivity profile [see (Bullmore and Sporns, 2009)].

Quantitative network tools have been applied to invasive tract-tracing data in mammalian model organisms and noninvasive neuroimaging data in humans, providing unprecedented insights into brain organization. This literature has revealed that a prominent organizational feature of vertebrate cortical networks is the presence of community and hub structure (van den Heuvel and Sporns, 2013b). Network communities represent densely interconnected neural elements in which local computations are highly segregated, whereas network hubs connect communities, enabling information integration (Sporns, 2013) (see Glossary & Fig. 2). These organizational principles are thought to balance the specialization of function with the integration of information (Tononi et al., 1994; Sporns, 2013), and this balance gives rise to complex neural dynamics that span multiple spatiotemporal scales (Breakspear and Stam, 2005).

In this section, we will examine recent evidence suggesting that the topological embedding of the BG and thalamus place these regions among an exclusive collection of putative network hubs. The *rich* connectivity structure of these subcortical hubs suggests their involvement in large-scale integration of diverse and global neural signals. These findings dovetail with work reviewed above (Section 2.1) suggesting the convergent CBG architecture supports integration across multiple neural systems. Finally, the implications of these findings along with the major opportunities and challenges of studying subcortical contributions to large-scale network communication are discussed.

2.2.2. Network hubs in cortical brain networks

Examination of mammalian *cortical* networks has revealed the existence of an exclusive collection of putative hub regions that act to link specialized communities (Glossary & Fig. 2c). The topological embedding of network hubs renders them important candidates for supporting integration and distribution of diverse and global signal traffic (van den Heuvel and Sporns, 2013b). Intriguingly, network hubs appear to be arranged into a topological *core* (Hagmann et al., 2008; Modha and Singh, 2010; Markov et al., 2013b) or *rich-club* (Zamora-López et al., 2010; Harriger et al., 2012; van den Heuvel et al., 2012; Collin et al., 2013; van den Heuvel and Sporns, 2013a; Ball et al., 2014; Grayson et al., 2014) (Glossary & Fig. 2d). Rich-club nodes are more densely interconnected than predicted on the basis of

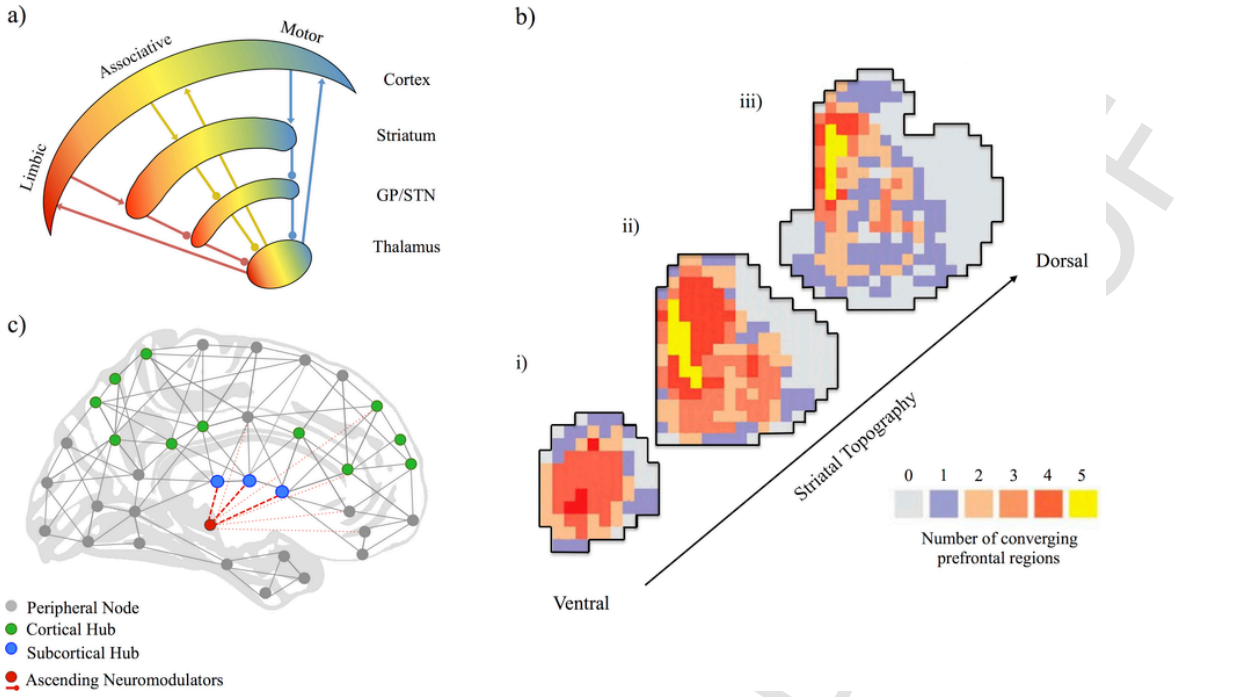

Fig. 2. Schematic illustration depicting graph-theory concepts. The arrangement of a graphs nodes and edges defines the network topology (a), which is comprised of network communities (b), network hubs (c) and rich-club ordering (d). See Glossary for further elaboration of these network concepts.

their degree of topological connectivity alone (Colizza et al., 2006), and rich-club organization acts to further enhance the influence of its exclusive members by facilitating interactions between them (Colizza et al., 2006; van den Heuvel and Sporns, 2013b). Compelling evidence for the importance of cortical rich-club nodes in efficient global integrative processing has been provided by recent empirical and computational modeling work (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2013a , 2013b; Senden et al., 2014; Mišić et al., 2015). Such work has shown that a fundamental property of rich-club nodes is that they act to cross-link specialized large-scale functional systems (Zamora-Lopez et al., 2010; van den Heuvel and Sporns, 2013a), providing a high-capacity backbone for systems-level integration in the brain (van den Heuvel et al., 2012).

2.2.3. Subcortical hubs: 'Rich' contributions to large-scale integration

Although prior network-analytic work has largely focused on cortico-cortical topology − possibly in part due to technical limitations inherent in studying connectivity of subcortical nuclei (see Section 3.1.1) – recent examples in the literature have incorporated subcortical nodes into their analysis of rich-club patterning in human structural tractography data (van den Heuvel and Sporns, 2011; McColgan et al., 2015; Owen et al., 2015). Results from these studies reveal that the striatum and thalamus form part of the neural 'rich-club' (van den Heuvel and Sporns, 2011; McColgan et al., 2015; Owen et al., 2015) and are in-line with findings from tract-tracing work in Macaque monkeys demonstrating that striatal and thalamic nuclei belong to an integrated core circuit (Modha and Singh, 2010) (Fig. 1c). Furthermore, recent analysis of the complete mesoscopic mouse connectome has shown that the striatum and thalamus belong to a subset of neural regions that participate in multiple neural communities (Rubinov et al., 2015). Taken together, these data suggest that the topological embedding of these deep gray-matter nuclei endows them with exclusive access to global information arriving from multiple neural communities (van den Heuvel et al., 2012). Although the above findings lack the spatial resolution required to examine the specific geometric patterns of terminal field overlap in deep nuclei [as seen in histological work (Averbeck et al., 2014), see Fig. 1b], they do highlight the topological centrality of the striatum and thalamus within the macroscopic connectome.

2.2.4. Network fragmentation in 'Subcortical Hub-Opathy'

A complementary paradigm used to examine the functional significance of brain hubs has been to observe the consequences of hub lesions on network topology in both clinical disorders and *in silico* models. Mounting evidence suggests that lesions to *cortical* network hubs result in profound network disruption (Honey and Sporns, 2008; Alstott et al., 2009; Stam, 2014; Warren et al., 2014; Fornito et al., 2015) and hub lesions are associated with more severe and widespread neuropsychological impairments relative to non-hub lesions (Warren et al., 2014). Thus, converging findings from clinical, computational and neuroanatomical data suggest that network hub regions are essential for large-scale network communication.

Although scarce at present, a small number of studies have begun to incorporate subcortical nodes in network descriptions of disease pathology. In particular, a recent meta-analytic study has provided an initial indication of the clinical consequences of subcortical hub pathology across multiple brain disorders. In this study, Crossley et al. (2014) mapped the location of gray-matter lesions associated with a total of 26 different brain disorders onto a common 'disorder-general' map. Results revealed that pathological gray-matter lesions were concentrated in hub regions (in particular, rich-club hubs) (Crossley et al., 2014). Interestingly, the striatum and thalamus were among the most significantly affected hub regions, suggesting that subcortical hubs represent key pathological foci across multiple brain disorders (Crossley et al., 2014). Empirical findings linking subcortical pathology to brain disorders have been supported by recent modeling studies that have begun to incorporate subcortical nodes into their compu-

tational models (Iturria-Medina et al., 2008; Irimia and Van Horn, 2014). Data from this computational work indicates that simulated attack on striatal and thalamic nodes and their direct connections substantially alters global network topology *in silico* (Iturria-Medina et al., 2008; Irimia and Van Horn, 2014). Although the relationship between subcortical hub pathology and brain disorders awaits validation with more direct and causal evidence, the above findings suggest that subcortical dysfunction may contribute to profound fragmentation of network structure (Glossary) and breakdown in large-scale network communication.

It is also of clinical interest that neurodegenerative disorders that are characterized by early and selective CBG neuropathology − such as Parkinson's disease and Huntington's disease − are associated with a severe and pervasive clinical impairments that extend across affective, cognitive and motoric domains (Chaudhuri et al., 2006; O'Callaghan et al., 2014; Ross et al., 2014). Furthermore, network analyses of clinical neuroimaging data has demonstrated that these pathological conditions are associated with fragmentation of global network topology in early-stage disease (Dubbelink et al., 2014; Harrington et al., 2015; Luo et al., 2015; McColgan et al., 2015; Sang et al., 2015), and network topology continues to deteriorate with disease progression (Dubbelink et al., 2014; Harrington et al., 2015; McColgan et al., 2015). Although neuropathology in these clinical disorders is not exclusively confined to subcortical circuits, the major focus of neuropathology resides within CBG structures, particularly in early-stage disease (Vonsattel et al., 1985; Braak et al., 2003). Thus, examples of network fragmentation in disorders characterized by severe and early subcortical pathology provide further, albeit indirect evidence, for a role of the subcortex in systems-integration.

3. Synthesis: subcortical contributions to large-scale network communication

Studies reviewed above suggest that the BG and thalamus support convergence of diverse afferents from the neocortex, subcortex and neuromodulatory brainstem (Section 2.1). Furthermore, the topological embedding of these subcortical structures within the global connectivity network suggests that they belong to an exclusive rich-club circuit (Section 2.2). Taken together, these findings emphasize a new view of the BG and thalamus, in which communication across large-scale systems is a key computational priority. This framework may have important clinical implications, as emerging data suggest that subcortical insult (i.e. 'subcortical hub-opathy') is associated with fragmentation of large-scale communication and multi-domain clinical sequelae. Although, many outstanding questions face the study of large-scale integration, subcortical-inclusive descriptions of brain connectivity will be an important step in advancing whole-brain descriptions of spatiotemporal dynamics in health and disease.

3.1. Outstanding questions & future directions

The inclusion of subcortical projection systems into models of whole-brain connectivity "dramatically alters the computational landscape of the brain" (Pessoa, 2014) and will be critical for advancing models of brain structure and function. Below, we provide a succinct overview of some of the opportunities and challenges facing the study of subcortical-inclusive connectomics in the human brain. Specifically, we discuss technical challenges associated with human subcortical neuroimaging, and how the development of more sensitive neuroimaging methods will enable increasingly detailed characterization of human subcortical topology and geometry. We also consider the importance of capturing dynamic (time-varying) aspects of brain connectivity in future studies examining the neurobiology of integration and segregation within the human brain.

3.1.1. Technical challenges of subcortical connectomics

Much of our understanding of human connectomics has come from analyses of data acquired using Magnetic Resonance Imaging (MRI). Indeed, the possibility of noninvasively examining brain connectivity and network organization *in vivo* has ignited immense interest across disciplines of cognitive and clinical neuroscience. Despite the impact of MRI, several noteworthy limitations currently render the anatomical analysis of human deep nuclei challenging. For instance, detailed examination of the multinuclear structure of subcortical anatomy has been limited by the spatial resolution of MRI. To further compound this issue, MR signal is often extracted from group-averaged anatomical templates, which can result in signal blurring across spatial boundaries as a consequence of inter-individual variability in subcortical morphology (Keuken et al., 2014), as well as a side-effect of analysis protocols including spatial smoothing and normalization (de Hollander et al., 2015). These issues may be particularly problematic in the context of small subcortical nuclei with neighboring regions that reside in close proximity [i.e. the 'subcortical cocktail problem' (de Hollander et al., 2015)], where high spatial precision is required for accurate signal localization. Similarly, reconstruction of white matter pathways that traverse subcortical structures is difficult, as a high density of white matter bundles pass through close-proximity subcortical nuclei, rendering accurate reconstruction of subcortical white-matter architecture challenging.

Despite these limitations, recent developments in data acquisition at ultra-high resolution, MR acquisition protocols and automated analytical protocols for MR-data segmentation hold promise for circumventing many of these contemporary challenges. In addition, the application of analytic tools from network science to gold-standard invasive quantitative tract-tracing represents a powerful complementary method for non-human mammalian connectome mapping − and has been recently applied to Macaque monkeys (Modha and Singh, 2010; Markov et al., 2013a,b, 2014; van den Heuvel et al., 2015) and other mammalian model organisms (Scannell et al., 1995; Zamora-Lopez et al., 2009; Zamora-López et al., 2010; Oh et al., 2014; Bota et al., 2015). The incorporation of cortico-subcortical and subcortico-subcortical fiber systems into tract-tracing connectome mapping [e.g. (Modha and Singh, 2010; Rubinov et al., 2015)] and MR neuroimaging studies, will also help to develop and advance subcortical-inclusive representations of the mammalian connectome.

3.1.2. Subcortical hub discovery

In this review, we have focused on the BG and thalamus as major subcortical sites of large-scale communication – given the substantial body of supportive empirical evidence reviewed above. With future development of more sensitive methods for estimating the topology and geometry of subcortical nuclei, it will be interesting to see whether other subcortical projection systems display similar integrative capacities. Indeed, previous authors have proposed that the hippocampus (Mišić et al., 2014) and amygdala (Pessoa, 2014) may possibly also play important roles in functional integration across large-scale neural systems, however direct empirical data for these claims are currently limited. Thus, characterizing the details of subcortical connectivity with greater spatial precision will be an important area for future neuroanatomical investigation.

3.1.3. Dynamics of functional integration and segregation

While anatomical descriptions of brain connectivity provide a necessary initial framework for grounding neurobiological accounts

of functional integration and segregation, higher brain functions such as perception and cognition depend upon dynamic coordination of neuronal activity operating at multiple timescales (Voytek and Knight, 2015). Thus, understanding information exchange requires, not only detailed knowledge of structural connectivity, but also an understanding of time-varying spatiotemporal patterns of neural activity that unfold within the anatomical scaffold.

Recent scientific innovations in the acquisition and analysis of noninvasive functional brain imaging data have enabled researchers to examine time-varying patterns of synchronous oscillatory activity, termed *functional* brain networks [see (Hutchison et al., 2013; Calhoun et al., 2014)]. These studies have shown that dynamic reconfigurations in large-scale functional network assemblies accompany changes in learning (Bassett et al., 2011; Bassett et al., 2015), cognitive task (Fornito et al., 2012; Cole et al., 2014; Krienen et al., 2014; Braun et al., 2015), cognitive load (Kitzbichler et al., 2011; Hearne et al., 2015), and also occur spontaneously in the absence of exogenous stimuli or task demands (Zalesky et al., 2014; de Pasquale et al., 2015; Laumann et al., 2015). Furthermore, transient reconfigurations in functional network architecture have been observed following noninvasive stimulation of human cortical networks (Dayan et al., 2013) and pharmacological manipulation of neuromodulatory systems (Achard and Bullmore, 2007; Schaefer et al., 2014a). Together, these data suggest that the brain exists in a continuous state of flux, in which large-scale spatiotemporal patterns of neural activity are shaped, not only by the underlying structural scaffolding (Honey et al., 2009; Shen et al., 2015), but also by moment-to-moment fluctuations in the external and internal state of the organism (Sporns, 2012; Bargmann and Marder, 2013; Deco et al., 2015). Thus, from a relatively 'static' structural connectome emerges a dynamical repertoire of large-scale context-dependent functional networks that are critical for flexible cognition and behaviour.

Through the study of large-scale network *dynamics* it is possible to examine how segregated and integrated information exchange is supported by a temporally evolving functional architecture (Calhoun et al., 2014; Deco et al., 2015). While large-scale cortico-cortical communication dynamics remain poorly understood at present, even less understood are the contributions of subcortical structures to dynamic information flow. However, recent advances in human neuroimaging and computational modeling have made probing subcortical contributions to large-scale functional network dynamics increasingly more tractable. Indeed, several recent functional MRI (fMRI) studies have begun to include subcortical nodes in their descriptions of network dynamics (Allen et al., 2012; Schaefer et al., 2014b; Zalesky et al., 2014; Shine et al., *under review*), providing a promising avenue for noninvasive examination of subcortical contributions to large-scale functional integration in the human brain. Beyond purely descriptive methods, causal mechanistic insights can be obtained by 'perturb and measure' approaches (Dayan et al., 2013) in which subcortical circuitry can be experimentally manipulated while brain activity is measured using noninvasive neuroimaging methods. Such approaches could perturb subcortical activity through pharmacological manipulation of neurotransmitter systems [e.g. (Achard and Bullmore, 2007; Kelly et al., 2009; Bell et al., 2015)] or via electrical stimulation of subcortical grey matter structures in patient cohorts that have undergone neurosurgical implantation of subcortical electrodes for symptom management (Kringelbach et al., 2007; Kahan et al., 2014; van Hartevelt et al., 2014).

Finally, whole-brain computational modeling approaches offer important tools for understanding emergent macroscopic network dynamics in the human brain. Generative whole-brain computational models which are constrained by neuroanatomical connectivity data can be used to probe dynamics of integration and segregation in the brain [for comprehensive discussion, see (Deco et al., 2015)]. These whole-brain computational models combine empirical neuroanatomical connectivity data with neurodynamic models of brain activity to simulate and predict dynamic large-scale network behaviour (Honey et al., 2009; Cabral et al., 2014; Mišić et al., 2015). Furthermore, such models can be used to test specific hypotheses about mechanisms underpinning large-scale network dynamics by systematically tuning model parameters and altering local connectivity. Given that the inclusion of subcortical neuroanatomy is likely to drastically alter the neuroanatomical connectivity landscape of *in silico* models, future subcortical-inclusive computational models may provide new information into the dynamics of integration and segregation in the brain.

4. Conclusion

A review of recent work operating at the interface of network science, cognitive science and brain anatomy suggests a new view of the subcortex, in which the BG and thalamus form part of a core circuit that supports large-scale integration of functionally diverse neural signals. Subcortical-inclusive descriptions of brain connectivity will be important for refining our understanding of large-scale network communication in health and disease.

Conflict of interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

There is no funding to declare.

Author contributions

All authors contributed to the writing of this manuscript.

Acknowledgements

We would like to thank Prof. Russell A. Poldrack, Assoc. Prof. Simon J.G. Lewis, Dr. Claire O'Callaghan, Prof Charlie Wilson and Moran Gilat for their constructive comments on the manuscript.

References

Aarts, E., van Holstein, M., Cools, R., 2011. Striatal dopamine and the interface between motivation and cognition. Front. Psychol. 2, 163.

Achard, S., Bullmore, E., 2007. Efficiency and cost of economical brain functional networks. PLoS Comput. Biol. 3 (2), 174–183.

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13 (7), 266–271.

Alexander, G.E., Delong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2012. Tracking whole-brain connectivity dynamics in the resting state. Cereb. Cortex

Alstott, J., Breakspear, M., Hagmann, P., Cammoun, L., Sporns, O., 2009. Modeling the impact of lesions in the human brain. PLoS Comput. Biol. 5 (6).

Averbeck, B.B., Lehman, J., Jacobson, M., Haber, S.N., 2014. Estimates of projection overlap and zones of convergence within frontal-striatal circuits. J. Neurosci. 34 (29), 9497–9505.

Ball, G., Aljabar, P., Zebari, S., Tusor, N., Arichi, T., Merchant, N., 2014. Rich-club organization of the newborn human brain. Proc. Natl. Acad. Sci. 111 (20), 7456–7461.

Bar-Gad, I., Morris, G., Bergman, H., 2003. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. Prog. Neurobiol. 71 (6), 439–473.

Bargmann, C.I., Marder, E., 2013. From the connectome to brain function. Nat. Methods 10 (6), 483–490.
Bassett, D.S., Wymbs, N.F., Porter, M.A., Mucha, P.J., Carlson, J.M., Grafton, S.T., 2011. Dynamic reconfiguration of human brain networks during learning. Proc. Natl. Acad. Sci. 108 (18), 7641–7646.
Bassett, D.S., Yang, M., Wymbs, N.F., Grafton, S.T., 2015. Learning-induced autonomy of sensorimotor systems. Nat. Neurosci. 18 (5), 744–751.
Behrmann, M., Plaut, D.C., 2013. Distributed circuits: not circumscribed centers, mediate visual recognition. Trends Cogn. Sci. 17 (5), 210–219.
Belin, D., Everitt, B.J., 2008. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron 57 (3), 432–441.
Bell, P.T., Shine, J.M., 2015. Estimating large-scale network convergence in the human functional connectome. Brain Connect 5 (9), 565–574.
Bell, P.T., Gilat, M., O'Callaghan, C., Copland, D.A., Frank, M.J., Lewis, S.J.G., 2015. Dopaminergic basis for impairments in functional connectivity across subdivisions of the striatum in Parkinson's disease. Hum. Brain Mapp. 36 (4), 1278–1291.
Bevan, M.D., Clarke, N.P., Bolam, J.P., 1997. Synaptic integration of functionally diverse pallidal information in the entopeduncular nucleus and subthalamic nucleus in the rat. J. Neurosci. 17 (1), 308–324.
Bota, M., Sporns, O., Swanson, L.W., 2015. Architecture of the cerebral cortical association connectome underlying cognition. Proc. Natl. Acad. Sci. U. S. A. 112 (16), E2093–101.
Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24 (2), 197–211.
Braga, R.M., Leech, R., 2015. Echoes of the brain: local-Scale representation of whole-brain functional networks within transmodal cortex. Neuroscientist
Braun, U., Schafer, A., Walter, H., Erk, S., Romanczuk-Seiferth, N., Haddad, L., 2015. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proc. Natl. Acad. Sci. U. S. A. 112 (37), 11678–11683.
Breakspear, M., Stam, C.J., 2005. Dynamics of a neural system with a multiscale architecture. Phil. Trans. R. Soc. B: Biol. Sci. 360 (1457), 1051–1074.
Bromberg-Martin, E.S., Matsumoto, M., Hikosaka, O., 2010. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 68 (5), 815–834.
Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 (3), 186–198.
Cabral, J., Luckhoo, H., Woolrich, M., Joensson, M., Mohseni, H., Baker, A., 2014. Exploring mechanisms of spontaneous functional connectivity in MEG: How delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. Neuroimage 90, 423–435.
Calabresi, P., Picconi, B., Tozzi, A., Di Filippo, M., 2007. Dopamine-mediated regulation of corticostriatal synaptic plasticity. Trends Neurosci. 30 (5), 211–219.
Calhoun, Vince D., Miller, R., Pearlson, G., Adalı, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84 (2), 262–274.
Calzavara, R., Mailly, P., Haber, S.N., 2007. Relationship between the corticostriatal terminals from areas 9 and 46, and those from area 8A, dorsal and rostral premotor cortex and area 24c: an anatomical substrate for cognition to action. Eur. J. Neurosci. 26 (7), 2005–2024.
Chaudhuri, K.R., Healy, D.G., Schapira, A.H.V., 2006. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 5 (3), 235–245.
Chudasama, Y., Robbins, T.W., 2006. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. Biol. Psychol. 73 (1), 19–38.
Cole, Michael W., Bassett Danielle, S., Power Jonathan, D., Braver Todd, S., Petersen Steven, E., 2014. Intrinsic and task-evoked network architectures of the human brain. Neuron 83 (1), 238–251.
Colizza, V., Flammini, A., Serrano, M.A., Vespignani, A., 2006. Detecting rich-club ordering in complex networks. Nat. Phys. 2 (2), 110–115.
Collin, G., Sporns, O., Mandl, R.C., van den Heuvel, M.P., 2013. Structural and functional aspects relating to cost and benefit of rich club organization in the human cerebral cortex. Cereb. Cortex (New York, NY : 1991)
Crossley, N.A., Mechelli, A., Scott, J., Carletti, F., Fox, P.T., McGuire, P., et al., 2014. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain
Damasio, A.R., 1989. The brain binds entities and events by multiregional activation from convergence zones. Neural Comput. 1 (1), 123–132.
Dayan, E., Censor, N., Buch, E.R., Sandrini, M., Cohen, L.G., 2013. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat. Neurosci. 16 (7), 838–844.
de Hollander, G., Keuken, M.C., Forstmann, B.U., 2015. The subcortical cocktail problem; mixed signals from the subthalamic nucleus and substantia nigra. PLoS One 10 (3), e0120572.
de Pasquale, F., Penna, S.D., Sporns, O., Romani, G.L., Corbetta, M., 2015. A dynamic core network and global efficiency in the resting human brain. Cereb. Cortex
Deco, G., Tononi, G., Boly, M., Kringelbach, M.L., 2015. Rethinking segregation and integration: contributions of whole-brain modelling. Nat. Rev. Neurosci. 16 (7), 430–439.
Draganski, B., Kherif, F., Kloeppel, S., Cook, P.A., Alexander, D.C., Parker, G.J.M., 2008. Evidence for segregated and integrative connectivity patterns in the human basal ganglia. J. Neurosci. 28 (28), 7143–7152.
Dubbelink, K., Hillebrand, A., Stoffers, D., Deijen, J.B., Twisk, J.W.R., Stam, C.J., 2014. Disrupted brain network topology in Parkinson's disease: a longitudinal magnetoencephalography study. Brain 137, 197–207.
Felleman, D.J., Van Essen, D.C., 1991. Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex (New York, NY: 1991) 1 (1), 1–47.
Fornito, A., Harrison, B.J., Zalesky, A., Simons, J.S., 2012. Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. Proc. Natl. Acad. Sci. U. S. A. 109 (31), 12788–12793.
Fornito, A., Zalesky, A., Breakspear, M., 2015. The connectomics of brain disorders. Nat. Rev. Neurosci. 16 (3), 159–172.
Fox, P.T., Friston, K.J., 2012. Distributed processing; distributed functions?. Neuroimage 61 (2), 407–426.
Francois, C., Yelnik, J., Percheron, G., Fenelon, G., 1994. Topographic distribution of the axonal endings from the sensorimotor and associative striatum in the macaque pallidum and substantia nigra. Exp. Brain Res. 102 (2), 305–318.
French, S.J., Totterdell, S., 2002. Hippocampal and prefrontal cortical inputs monosynaptically converge with individual projection neurons of the nucleus accumbens. J. Comp. Neurol. 446 (2), 151–165.
French, S.J., Totterdell, S., 2003. Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. Neuroscience 119 (1), 19–31.
Friederici, A.D., Gierhan, S.M., 2013. The language network. Curr. Opin. Neurobiol. 23 (2), 250–254.
Goldman-Rakic, P.S., 1988. Topography of cognition: parallel distributed networks in primate association cortex. Annu. Rev. Neurosci. 11, 137–156.
Grace, A.A., Floresco, S.B., Goto, Y., Lodge, D.J., 2007. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 30 (5), 220–227.
Graybiel, A.M., Aosaki, T., Flaherty, A.W., Kimura, M., 1994. The basal ganglia and adaptive motor control. Science 265 (5180), 1826–1831.
Grayson, D.S., Ray, S., Carpenter, S., Iyer, S., Dias, T.G.C., Stevens, C., et al., 2014. Structural and functional rich club organization of the brain in children and adults. PLoS One 9 (2), e88297.
Guillery, R.W., 1995. Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review. J. Anat. 187 (Pt 3), 583–592.
Haber, S.N., Calzavara, R., 2009. The cortico-basal ganglia integrative network: the role of the thalamus. Brain Res. Bull. 78 (2-3), 69–74.
Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35 (1), 4–26.
Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci. 20 (6), 2369–2382.
Haber, S.N., Kim, K.S., Mailly, P., Calzavara, R., 2006. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. J. Neurosci. 26 (32), 8368–8376.
Haber, S.N., 2010. Chapter 24 – integrative networks across basal ganglia circuits. In: Heinz, S., Kuei, Y.T. (Eds.), Handbook of Behavioral Neuroscience. Elsevier, pp. 409–427.
Haber, S.N., 2014. The place of dopamine in the cortico-basal ganglia circuit. Neuroscience 282 (0), 248–257.
Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., et al., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6 (7), e159.
Harriger, L., van den Heuvel, M.P., Sporns, O., 2012. Rich club organization of macaque cerebral cortex and its role in network communication. PLoS One 7 (9), e46497.
Harrington, D.L., Rubinov, M., Durgerian, S., Mourany, L., Reece, C., Koenig, K., 2015. Network topology and functional connectivity disturbances precede the onset of Huntington's disease. Brain 138 (Pt 8), 2332–2346.
Haynes, W.I.A., Haber, S.N., 2013. The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for basal ganglia models and deep brain stimulation. J. Neurosci. 33 (11), 4804–4814.
Hearne, L., Cocchi, L., Zalesky, A., Mattingley, J.B., 2015. Interactions between default mode and control networks as a function of increasing cognitive reasoning complexity. Hum. Brain Mapp. 36 (7), 2719–2731.
Honey, C.J., Sporns, O., 2008. Dynamical consequences of lesions in cortical networks. Hum. Brain Mapp. 29 (7), 802–809.
Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. 106 (6), 2035–2040.
Hoover, J.E., Strick, P.L., 1993. Multiple output channels in the basal ganglia. Science 259 (5096), 819–821.
Houk, J.C., Wise, S.P., 1995. Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. Cerebral Cortex (New York, NY: 1991) 5 (2), 95–110.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80 (0), 360–378.
Ikemoto, S., 2007. Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. Brain Res. Rev. 56 (1), 27–78.
Irimia, A., Van Horn, J.D., 2014. Systematic network lesioning reveals the core white matter scaffold of the human brain. Front. Hum. Neurosci. 8, 51.
Iturria-Medina, Y., Sotero, R.C., Canales-Rodriguez, E.J., Aleman-Gomez, Y., Melie-Garcia, L., 2008. Studying the human brain anatomical network via diffusion-weighted MRI and Graph Theory. Neuroimage 40 (3), 1064–1076.
Jarbo, K., Verstynen, T.D., 2015. Converging structural and functional connectivity of orbitofrontal: dorsolateral prefrontal, and posterior parietal cortex in the human striatum. J. Neurosci. 35 (9), 3865–3878.
Jones, E.G., 2012. The Thalamus. Springer Science & Business Media.
Kahan, J., Urner, M., Moran, R., Flandin, G., Marreiros, A., Mancini, L., 2014. Resting state functional MRI in Parkinson's disease: the impact of deep brain stimulation on 'effective' connectivity. Brain
Kelly, C., de Zubicaray, G., Di Martino, A., Copland, D.A., Reiss, P.T., Klein, D.F., 2009. L-Dopa modulates functional connectivity in striatal cognitive and motor networks: a double-blind placebo-controlled study. J. Neurosci. 29 (22), 7364–7378.
Keuken, M.C., Bazin, P.L., Crown, L., Hootsmans, J., Laufer, A., Muller-Axt, C., 2014. Quantifying inter-individual anatomical variability in the subcortex using 7 T structural MRI. Neuroimage 94, 40–46.
Kitzbichler, M.G., Henson, R.N., Smith, M.L., Nathan, P.J., Bullmore, E.T., 2011. Cognitive effort drives workspace configuration of human brain functional networks. J. Neurosci. 31 (22), 8259–8270.
Kolomiets, B.P., Deniau, J.M., Mailly, P., Menetrey, A., Glowinski, J., Thierry, A.M., 2001. Segregation and convergence of information flow through the cortico-subthalamic pathways. J. Neurosci. 21 (15), 5764–5772.
Krienen, F.M., Yeo, B.T.T., Buckner, R.L., 2014. Reconfigurable task-dependent functional coupling modes cluster around a core functional architecture. Phil. Trans. R. Soc. B: Biol. Sci. 369 (1653).
Kringelbach, M.L., Jenkinson, N., Owen, S.L., Aziz, T.Z., 2007. Translational principles of deep brain stimulation. Nat. Rev. Neurosci. 8 (8), 623–635.
Laumann, Timothy O.., Gordon Evan, M., Adeyemo, B., Snyder Abraham, Z., Joo Sung, J., Chen, M.-Y., 2015. Functional system and areal organization of a highly sampled individual human brain. Neuron 87 (3), 657–670.
Luo, C.Y., Guo, X.Y., Song, W., Chen, Q., Cao, B., Yang, J., 2015. Functional connectome assessed using graph theory in drug-naive Parkinson's disease. J. Neurol. 262 (6), 1557–1567.
Mahon, S., Deniau, J.M., Charpier, S., 2004. Corticostriatal plasticity: life after the depression. Trends Neurosci. 27 (8), 460–467.
Markov, N.T., Ercsey-Ravasz, M., Lamy, C., Ribeiro Gomes, A.R., Magrou, L., Misery, P., 2013. The role of long-range connections on the specificity of the macaque interareal cortical network. Proc. Natl. Acad. Sci. U. S. A. 110 (13), 5187–5192.
Markov, N.T., Ercsey-Ravasz, M., Van Essen, D.C., Knoblauch, K., Toroczkai, Z., Kennedy, H., 2013. Cortical high-density counterstream architectures. Science 342 (6158).
Markov, N.T., Ercsey-Ravasz, M.M., Ribeiro Gomes, A.R., Lamy, C., Magrou, L., Vezoli, J., 2014. A weighted and directed interareal connectivity matrix for macaque cerebral cortex. Cerebral Cortex (New York, NY: 1991 24 (1), 17–36.
McColgan, P., Seunarine, K.K., Razi, A., Cole, J.H., Gregory, S., Durr, A., 2015. Selective vulnerability of Rich Club brain regions is an organizational principle of structural connectivity loss in Huntington's disease. Brain
McFarland, N.R., Haber, S.N., 2002. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. J. Neurosci. 22 (18), 8117–8132.
Mesulam, M., 1998. From sensation to cognition. Brain 121 (6), 1013–1052.
Mišić, B., Goñi, J., Betzel, R.F., Sporns, O., McIntosh, A.R., 2014. Network convergence zone in the hippocampus. PLoS Comput. Biol. 10 (12), e1003982.
Mišić, B., Betzel Richard, F., Nematzadeh, A., Goñi, J., Griffa, A., Hagmann, P., 2015. Cooperative and competitive spreading dynamics on the human connectome. Neuron 86 (6), 1518–1529.
Middleton, F.A., Strick, P.L., 2002. Basal-ganglia 'Projections' to the prefrontal cortex of the primate. Cereb. Cortex 12 (9), 926–935.
Modha, D.S., Singh, R., 2010. Network architecture of the long-distance pathways in the macaque brain. Proc. Natl. Acad. Sci. 107 (30), 13485–13490.
Nauta, W.J.H., Smith, G.P., Faull, R.L.M., Domesick, V.B., 1978. Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience 3 (4-5), 385–401.
O'Callaghan, C., Bertoux, M., Hornberger, M., 2014. Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. J. Neurol. Neurosurg. Psychiatry 85 (4), 371–378.
O'Donnell, P., Grace, A.A., 1995. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J. Neurosci. 15 (5 Pt 1), 3622–3639.
Oh, S.W., Harris, J.A., Ng, L., Winslow, B., Cain, N., Mihalas, S., 2014. A mesoscale connectome of the mouse brain. Nature 508 (7495), 207–214.
Owen, J.P., Chang, Y.S., Mukherjee, P., 2015. Edge density imaging: mapping the anatomic embedding of the structural connectome within the white matter of the human brain. Neuroimage 109, 402–417.
Parvizi, J., 2009. Corticocentric myopia: old bias in new cognitive sciences. Trends Cogn. Sci. 13 (8), 354–359.
Pennartz, C.M., Berke, J.D., Graybiel, A.M., Ito, R., Lansink, C.S., van der Meer, M., 2009. Corticostriatal interactions during learning: memory processing, and decision making. J. Neurosci. 29 (41), 12831–12838.
Percheron, G., Filion, M., 1991. Parallel processing in the basal ganglia: up to a point. Trends Neurosci. 14 (2), 55–59.
Pessoa, L., 2012. Beyond brain regions: network perspective of cognition-emotion interactions. Behav. Brain Sci. 35 (3), 158–159.
Pessoa, L., 2014. Understanding brain networks and brain organization. Phys. Life Rev. 11 (3), 400–435.
Power, J.D., Petersen, S.E., 2013. Control-related systems in the human brain. Curr. Opin. Neurobiol. 23 (2), 223–228.
Power, Jonathan D., Schlaggar Bradley, L., Lessov-Schlaggar Christina, N., Petersen Steven, E., 2013. Evidence for hubs in human functional brain networks. Neuron 79 (4), 798–813.
Ross, C.A., Aylward, E.H., Wild, E.J., Langbehn, D.R., Long, J.D., Warner, J.H., 2014. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat. Rev. Neurol. 10 (4), 204–216.
Rubinov, M., Ypma, R.J.F., Watson, C., Bullmore, E.T., 2015. Wiring cost and topological participation of the mouse brain connectome. Proc. Natl. Acad. Sci.
Saalmann, Y.B., Pinsk, M.A., Wang, L., Li, X., Kastner, S., 2012. The pulvinar regulates information transmission between cortical areas based on attention demands. Science 337 (6095), 753–756.
Sang, L., Zhang, J., Wang, L., Zhang, J., Zhang, Y., Li, P., et al., 2015. Alteration of brain functional networks in early-stage Parkinson's disease: a resting-state fMRI study. PLoS One 10 (10), e0141815.
Scannell, J.W., Blakemore, C., Young, M.P., 1995. Analysis of connectivity in the cat cerebral cortex. J. Neurosci. 15 (2), 1463–1483.
Schaefer, A., Burmann, I., Regenthal, R., Arélin, K., Barth, C., Pampel, A., 2014. Serotonergic modulation of intrinsic functional connectivity. Curr. Biol. 24 (19), 2314–2318.
Schaefer, A., Margulies, D.S., Lohmann, G., Gorgolewski, K.J., Smallwood, J., Kiebel, S.J., et al., 2014. Dynamic network participation of functional connectivity hubs assessed by resting-state fMRI. Front. Hum. Neurosci. 8 (195).
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275 (5306), 1593–1599.
Selemon, L.D., Goldman-Rakic, P.S., 1991. Reply. Trends Neurosci. 14 (2), 56–59.
Senden, M., Deco, G., de Reus, M.A., Goebel, R., van den Heuvel, M.P., 2014. Rich club organization supports a diverse set of functional network configurations. Neuroimage 96, 174–182.
Sepulcre, J., Sabuncu, M.R., Yeo, B.T.T., Liu, H.S., Johnson, K.A., 2012. Stepwise connectivity of the modal cortex reveals the multimodal organization of the human brain. J. Neurosci. 32 (31), 10649–10661.
Sesack, S.R., Grace, A.A., 2010. Cortico-basal ganglia reward network: microcircuitry. Neuropsychopharmacology 35 (1), 27–47.
Shen, K., Hutchison, R.M., Bezgin, G., Everling, S., McIntosh, A.R., 2015. Network structure shapes spontaneous functional connectivity dynamics. J. Neurosci. 35 (14), 5579–5588.
Shepard, G., Grillner, S., 2010. Handbook of brain microcircuits. Oxford University Press Inc.
Sherman, S.M., Guillery, R.W., 1996. Functional organization of thalamocortical relays. J. Neurophysiol. 76 (3), 1367–1395.
Sherman, S.M., Guillery, R.W., 2011. Distinct functions for direct and transthalamic corticocortical connections. J. Neurophysiol. 106 (3), 1068–1077.
Sherman, S.M., 2007. The thalamus is more than just a relay. Curr. Opin. Neurobiol. 17 (4), 417–422.
Shine, J.M., Bell, P.T., Koyejo, O., Gorgolewski, K.J., Moodie, C.A., Poldrack, R.A., Dynamic fluctuations in integration and segregation within the human functional connectome. Manuscript Under Review.
Sporns, O., 2012. Discovering the Human Connectome.
Sporns, O., 2013. Network attributes for segregation and integration in the human brain. Curr. Opin. Neurobiol. 23 (2), 162–171.
Stam, C.J., 2014. Modern network science of neurological disorders. Nat. Rev. Neurosci.
Surmeier, D.J., Ding, J., Day, M., Wang, Z., Shen, W., 2007. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends Neurosci. 30 (5), 228–235.
Theyel, B.B., Llano, D.A., Sherman, S.M., 2010. The corticothalamocortical circuit drives higher-order cortex in the mouse. Nat. Neurosci. 13 (1), 84–88.
Tononi, G., Sporns, O., Edelman, G.M., 1994. A measure for brain complexity – relating functional segregation and integration in the nervous-System. Proc. Natl. Acad. Sci. U. S. A. 91 (11), 5033–5037.

van Hartevelt, T.J., Cabral, J., Deco, G., Moller, A., Green, A.L., Aziz, T.Z., et al., 2014. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. PLoS One 9 (1), e86496.
van den Heuvel and Sporns, 2011. M.P. van den Heuvel, O. Sporns, Rich-Club organization of the human connectome, J. Neurosci. 31 (44) (2011) 15775–15786.
van den Heuvel, M.P., Sporns, O., 2013. An anatomical substrate for integration among functional networks in human cortex. J. Neurosci. 33 (36), 14489–14500.
van den Heuvel, M.P., Sporns, O., 2013. Network hubs in the human brain. Trends Cogn. Sci. 17 (12), 683–696.
van den Heuvel, M.P., Kahn, R.S., Goni, J., Sporns, O., 2012. High-cost: high-capacity backbone for global brain communication. Proc. Natl. Acad. Sci. U. S. A. 109 (28), 11372–11377.
van den Heuvel, M.P., de Reus, M.A., Feldman Barrett, L., Scholtens, L.H., Coopmans, F.M., Schmidt, R., 2015. Comparison of diffusion tractography and tract-tracing measures of connectivity strength in rhesus macaque connectome. Hum. Brain Mapp. 36 (8), 3064–3075.
Vonsattel, J.P., Myers, R.H., Stevens, T.J., Ferrante, R.J., Bird, E.D., Richardson Jr., E.P., 1985. Neuropathological classification of Huntington's disease. J. Neuropathol. Exp. Neurol. 44 (6), 559–577.
Voytek, B., Knight, R.T., 2015. Dynamic network communication as a unifying neural basis for cognition: development, aging, and disease. Biol. Psychiatry 77 (12), 1089–1097.
Warren, D.E., Power, J.D., Bruss, J., Denburg, N.L., Waldron, E.J., Sun, H., et al., 2014. Network measures predict neuropsychological outcome after brain injury. Proc. Natl. Acad. Sci. U. S. A.
Wickens, J.R., Reynolds, J.N., Hyland, B.I., 2003. Neural mechanisms of reward-related motor learning. Curr. Opin. Neurobiol. 13 (6), 685–690.
Wilson, C., 1995. The contribution of cortical neurons to the firing pattern of striatal spiny neurons. Models of Information Processing in the Basal Ganglia. 29–50.
Yelnik, J., Percheron, G., Francois, C., 1984. A Golgi analysis of the primate globus pallidus: II. Quantitative morphology and spatial orientation of dendritic arborizations. J. Comp. Neurol. 227 (2), 200–213.
Zalesky, A., Fornito, A., Cocchi, L., Gollo, L.L., Breakspear, M., 2014. Time-resolved resting-state brain networks. Proc. Natl. Acad. Sci.
Zamora-López, G., Zhou, C., Kurths, J., 2010. Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. Front. Neuroinf. 4, 1.
Zamora-Lopez, G., Zhou, C., Kurths, J., 2009. Graph analysis of cortical networks reveals complex anatomical communication substrate. Chaos (Woodbury, NY) 19 (1), 015117.
Zamora-Lopez, G., Zhou, C., Kurths, J., 2010. Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. Front. Neuroinf. 4, 1.

Glossary

Connectome:

A term used to describe the complete description of the structural connections between neural elements in the brain.

Topology:

Graph-theory is a branch of mathematics that is concerned with describing properties of complex networks. a graph is described as a set of nodes (neural elements) linked by edges (connections). the arrangement of the graph defines its network topology (Fig. 2a).

Community:

Communities refer to densely interconnected sets of nodes that support the segregation and specialization of information processing (Fig. 2b).

Hub:

A highly connected node, topologically central node that connects different neural communities, thereby enabling the integration and dissemination of information across specialized systems (Fig. 2c).

Rich-Club Organization:

Rich-club organization of a network is characterized by a level of inter-connectivity between hub nodes above what can be predicted by chance (Colizza et al., 2006). rich-club nodes are therefore a unique subclass of network hubs, defined by their high degree interconnectivity (Fig. 2d).

Centrality:

A measure of the relative importance of a node in a topological network based on its pattern and extent of connectivity. various measures for centrality exist, the most common including; degree centrality, betweenness centrality and eigenvector centrality.

Network Fragmentation:

Splitting of the network into subsets of nodes leading to impaired communication between nodes and neural communities