Chapter 17
Organisational Principles of Connectomes: Changes During Evolution and Development

Roman Bauer and Marcus Kaiser

Abstract The set of neural connections in an organism is now called the connectome. Using recent noninvasive techniques such as diffusion tensor imaging and traditional invasive techniques for tract tracing has uncovered a wide range of connectomes from *Caenorhabditis elegans* and *Drosophila melanogaster* to cat, mouse, rat, macaque, and human. We can therefore start to look at organisational changes during evolution. At the same time cell lineage information and measurements at different time steps allow us to observe network changes during individual, ontogenetic development. We find that the structure of a network is closely linked to its function, with distinct functional components first leading to network modules and, after the rise of further specialisation, to a hierarchical architecture with modules at different levels of network organisation. We first describe concepts that are used to characterize complex networks, then move on to briefly discuss computational models for development and evolution, before showing how network features change during the evolution and development of brain networks. We conclude with future challenges in the field of connectome development and evolution.

Keywords Complex networks • Connectome • Neuronal network • Network structure • Topology • Modelling • Development • Evolution

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S. Shigeno et al. (eds.), *Brain Evolution by Design*, Diversity and Commonality in Animals, DOI 10.1007/978-4-431-56469-0_17

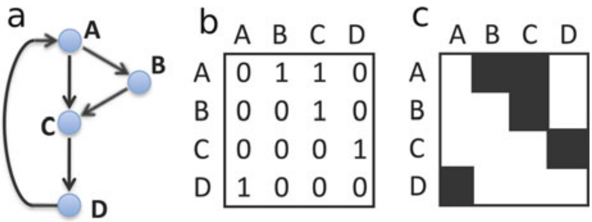
17.1 Representing Brain Connectivity as a Network

The nodes of a neural network can be neurons, populations of neurons, or brain regions, depending on the scale under examination. Synaptic connections between such nodes can be of chemical or electrical nature. Neuronal activity is transmitted in only one direction by chemical synapses (A–>B), whereas electrical synapses allow for bidirectional communication (A<–>B). These networks or graphs can be represented in an adjacency matrix (Fig. 17.1), based on which various measures can be computed. Also, the network structure can be in weighted or binarized form, depending on the knowledge of connection strength (e.g., the number of chemical synapses between two neurons).

The synaptic connectivity reflects the structure of the neural network and shapes its function. Also this functional aspect can be captured using the network formalism, by establishing links between nodes that show similar activity patterns. Such similarity could, for example, be measured in the correlation of the activity patterns between two brain regions or two neurons. Again, the link could be a continuous value of correlation strength, or could be binarized in that connection weights are set to one if the corresponding correlation is above a certain threshold and zero otherwise. Importantly, a functional connection might indicate that two nodes are structurally connected, but it might also arise if both nodes are driven by common input. In this chapter, we focus on the structural connectivity, that is, the 'connectome' (Sporns 2013).

17.2 Properties of Complex Networks

Before we describe the organisation of biological neural networks, we first need to describe some concepts that are used to study complex networks. We only give a brief overview; a more complete list of network measures can be found in (Costa et al. 2007; Rubinov and Sporns 2010; Kaiser 2011).



$$\begin{array}{c|cccc} & A & B & C & D \\ \hline A & 0 & 1 & 1 & 0 \\ B & 0 & 0 & 1 & 0 \\ C & 0 & 0 & 0 & 1 \\ D & 1 & 0 & 0 & 0 \end{array}$$

Fig. 17.1 Network representations of neural networks. (**a**) Network with four nodes and feedforward paths (A–>C, A–>B–>C) and feedback (A–>C–>D–>A) loops. (**b**) Representation in an adjacency matrix where '1' represents an existing connection and '0' stands for a connection that either has not been discovered yet or which is known to be absent. (**c**) For visualization, such binary matrices can be represented with *black squares* for existing and *white squares* for nonexisting connections

17.2.1 Modularity

Networks often show topological modules, also called clusters or communities. There is a relatively higher density of connections within modules than between modules. This difference allows rapid flow and integration of information within densely connected modules whereas information flow between modules can only use fewer links that form a potential bottleneck for passing information.

The measure of modularity Q is a reflection of the segregation within a network (Newman 2006), and serves as a tool in identifying the structural modules within. It quantifies how well a parcellation into nonoverlapping modules or communities represents the architecture of a network. Given two parcellations into distinct modules for the same network, the parcellation with the higher value of Q would be preferred.

From a biological aspect, modularity is an evolutionary beneficial network property because it allows for robustness and evolvability (Hintze and Adami 2008). Nonmodular network topologies entail strong interdependence among individual sub-networks, and so local changes can have detrimental effects on a more global level. It is therefore not surprising that modularity is a common feature of biological networks.

17.2.2 Hierarchy

A pervasive property of most complex networks is a hierarchical structure among nodes and/or modules. Usually, hierarchical networks are also modular, and the hierarchical composition can involve different functional levels or temporal orders. For example, a network might consist of several modules, where each module consists of several sub-modules, which again consist of several sub-sub-modules, and so on. A hierarchical structure has been shown to be a fundamental characteristic of many complex systems (Ravasz and Barabási 2003).

17.2.3 Small World (SW) Property

The small world phenomenon (Milgram 1967) refers to the property that two nodes in complex networks often are separated by much fewer edges than what one would expect. Small-world networks can be assessed using two network features (Watts and Strogatz 1998). First, the clustering coefficient describes how well neighbours of a node are connected where neighbours are all nodes that are directly connected to a node. For small-world networks, this proportion of links between neighbours is much higher than for randomly connected networks. Another more recent measure for this local connectivity is local efficiency (Latora and Marchiori 2001). Second, the characteristic path length describes the average number of connections one has to cross to go from one node to another node following the shortest possible path (the one with the lowest number of connections). This measure is only slightly higher than for a randomly organised network. Another more recent measure for this global feature is global efficiency (Latora and Marchiori 2001). For a small-world network, the clustering coefficient is thus much higher while the characteristic path length is comparable to that of a randomly connected network.

To ensure a comparable characteristic path length, small-world networks contain ‘short-cuts’ that directly link different parts of the network. Using these long-range connections, one can quickly reach different parts of the network over few intermediate links.

Most complex networks are also small-world networks. One main advantage of small-world networks is that they incorporate fast communication within functional modules (i.e., high clustering coefficient), and still allow for reliable and efficient signal propagation to nodes in different modules (i.e. short minimal path length). They also enable easier synchronisation of network activity (Masuda and Aihara 2004).

17.2.4 Scale-Freeness

Many complex networks have been shown to be scale-free or scale-invariant, a property of how the values for the number of connections of a node, its degree, are distributed. For randomly connected networks, the degree of a node will be close to the average degree of all nodes in the network, which means that the degree will be on the same characteristic scale: if the average degree is 10, all network degrees may be in the range of 0–99. On the other hand, scale-free networks do not show a characteristic scale: even if the average degree is 10, some nodes may have a degree of 100, 1000, or higher, thus reaching different orders of magnitude. For scale-free networks, the degree distribution follows the form $P(k) \sim k^{-\gamma}$, where $P(k)$ denotes the probability that a node is linked to k other nodes, and γ is the exponent of this power law. The seminal work of Barabási and Albert (Barabási and Albert 1999) has proposed an abstract model for the growth of such scale-free networks. Since then, many artificial networks and some biological ones have been demonstrated to be scale-free (Jeong et al. 2000). However, for structural neural networks usually only aggregate networks with connections between brain regions rather than between individual neurons have been reconstructed. The only organism for which the complete neuronal network structure is known is the roundworm *Caenorhabditis elegans* (White et al. 1986; Achacoso and Yamamoto 1992). However, a scale-free distribution is not supported in this case (Amaral et al. 2000). It therefore remains to be clarified whether whole-brain structural connectomes are scale-free or not.

17.2.5 Hubs

Scale-free and also other complex networks can have ‘hubs,’ nodes that participate in many more connections than one would expect. Because of their structural significance, hubs are usually also interesting from a functional point of view (Jeong et al. 2001; Goymer 2008). Studies show that such networks are very robust against random lesions, while being vulnerable towards removal or knockout of hubs (Newman 2003; Warren et al. 2014). This resilience is believed to be advantageous from an evolutionary point of view, which is in accordance with the finding that hubs have been observed in most biological networks.

17.2.6 Rich-Club Organization

Networks with hubs often incorporate rich-club organization, a bias for hubs to connect with one another, rather than with other nodes. It has been suggested that evolution favours both (hubs and rich-club organization) properties because they increase the robustness of networks to random breakdowns (McAuley et al. 2007). Along these lines, rich-club organization supports versatile information processing, allows for the dynamic resource allocation in a context-dependent manner and the collaborative integration of multisensory information (Zamora-Lopez et al. 2010; Collin et al. 2013; Senden et al. 2014).

17.3 Developmental and Evolutionary Patterns

As for other aspects of biology, it is useful to look at connectomes in terms of their evolutionary origins and developmental trajectories. Indeed, evolutionary mechanisms have been linked to topological network properties (Ebbesson 1980, 1984), and a number of complex network growth models have been proposed (Barabási and Albert 1999; Ravasz and Barabási 2003; Louf et al. 2013). Such models are usually framed on a rather abstract level, and it is ongoing work to elucidate how certain complex network properties arise using growth mechanisms based on local information exchange only (Sporns et al. 2004). Along these lines, Kaiser and Hilgetag (2004a, b) and Nisbach and Kaiser (2007) propose a local, spatial growth rule for the self-organization of network topologies with similar clustering coefficients and characteristic path lengths as for structural brain connectivity.

Advances in computing performance have led to the generation of novel research tools (Stanley and Miikkulainen 2002; Torben-Nielsen and De Schutter 2014; Zubler and Douglas 2009; Koene et al. 2009), paving the way for detailed computational models of neural network evolution (Verbancsics and Stanley 2011;

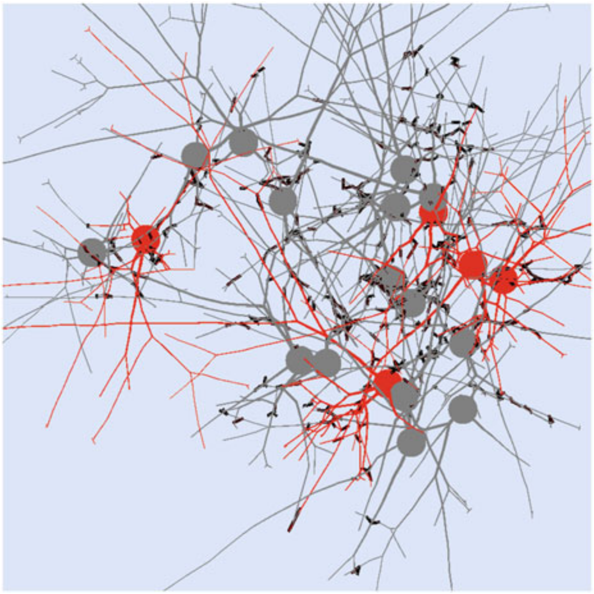


Fig. 17.2 Neuronal network morphology after simulated development (Bauer et al. 2014). The network is composed of differentiated neurons (*grey*). For better visualization, examples of neurons are coloured in *red*. Synapses (*black rectangles*) form at appositions between axons and dendrites

Gauci and Stanley 2010) and development (Bauer et al. 2012, 2014) (Fig. 17.2). In the future, such models will likely allow for a more extensive comparison to biological data across different spatial scales and developmental stages.

In the following, we give a short review of connectome patterns observed across different species and developmental stages.

One of the simplest species possessing a neural network is *Cnidaria*. These animals show a diffuse two-dimensional nerve net for the polyp stage, which, in terms of network science, is called a regular or lattice network (Fig. 17.3a). In such networks, neighbours are well connected (high clustering coefficient) but there are no long-distance connections. We therefore do *not* have a small-world network yet. Such lattice networks are an important part of neural systems such as the retina, as well as some cortical and subcortical layered structures.

For functionally specialized circuits, however, a regular organization is unsuitable. The connectomes of evolutionary higher progressed species therefore have modular topology (Kaiser 2015). Starting with the formation of sensory organs and motor units, neurons aggregate in ganglia. Such ganglia are often not only spatially clustered but also are modular in terms of connectivity (Fig. 17.3b). In this way, ganglia can process one modality without interference from neurons processing different kinds of information. A well-studied example of a modular network is the neuronal network of *C. elegans* (White et al. 1986; Achacoso and Yamamoto 1992), the first organism in which the complete set of neural connections or ‘connectome’

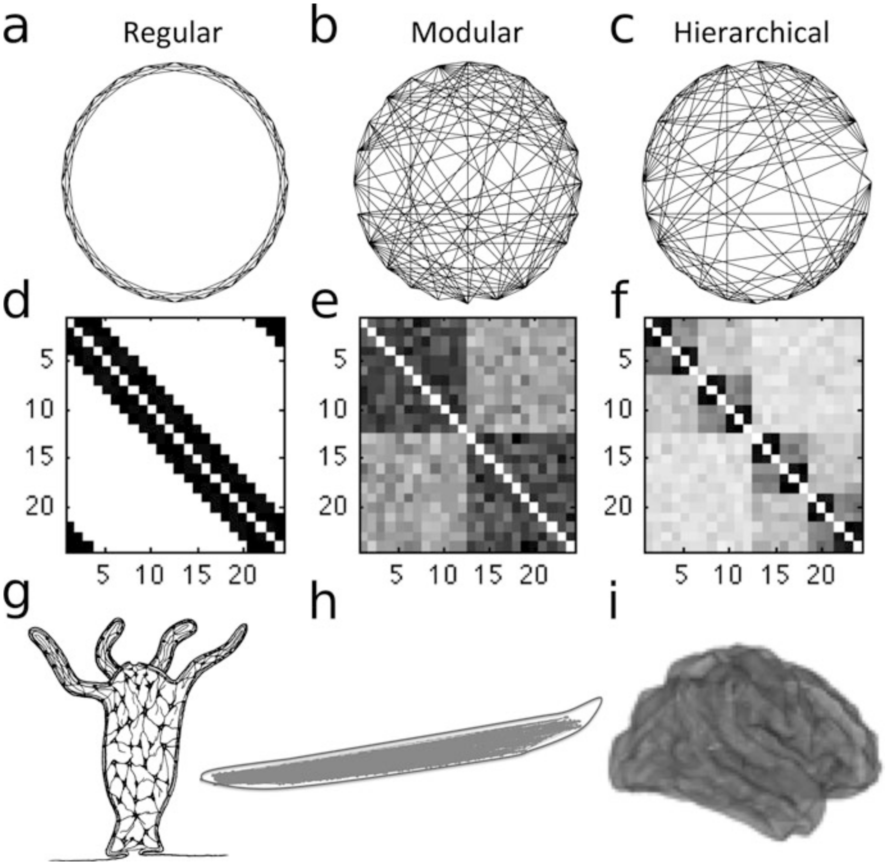


Fig. 17.3 Examples of different types of neural networks (From Kaiser and Varier 2011). (**a**) Regular or lattice network. (**b**) Modular network with two modules. (**c**) Hierarchical network with two modules consisting of two sub-modules each. (**d–f**) Matrices represent the circular network topologies. (**g–i**) Species possessing the afore detailed network architectures. (**g**) Polyp stage of *Hydra* (phylum Cnidaria) shows a nerve net. (**h**) Nematode *C. elegans* shows a modular network. (**i**) Global human neural network traced by diffusion tensor imaging

(Sporns et al. 2005) is known. In addition, the connectome of the fruit fly *Drosophila melanogaster* has been investigated in this respect (Cardona et al. 2010; Ito et al. 2013). Indeed, a high modularity in terms of both spatial proximity as well as topology are observed. However, with increasing complexity of neural processing, a single module for one modality or function is not sufficient; an example is the visual system in the rhesus monkey (macaque) where the visual module consists of two network components: the dorsal pathway for processing object movement and the ventral pathway for processing object features such as colour and form (Young 1992). These networks are hierarchical, because smaller sub-modules are nested within modules (Fig. 17.3c). A hierarchical structure has been observed in most modular brain connectomes (Chatterjee and Sinha 2008; Bassett et al. 2008; Felleman and van Essen 1991; Hilgetag et al. 2000). It has been argued that hierarchical topology embeds a rich dynamic and functional repertoire based on an economical wiring diagram (Meunier et al. 2010; Kaiser et al. 2010; Hilgetag and Hutt 2014).

From a developmental perspective, it is notable that certain poly-sensory and high-order association areas of cortex, which are the most complex areas in terms of their laminar architecture, also exhibit the most complex developmental trajectories (Shaw et al. 2008). Hence, structural and functional hierarchy is reflected also developmentally during brain ontogenesis.

Although there is a trend for spatial neighbours to be in the same module, it is not necessarily always true (da Fontoura et al. 2007). For the visual cortex in primates, for example, the frontal eye field is most closely linked to the topological module related to vision while being in the frontal lobe it is spatially distant from the other visual regions that are part of the occipital lobe.

On a smaller scale, a connectivity pattern composed of modules is the superficial patch system or daisy architecture, a patchy motive of clustered axonal projections in the superficial layers of cortex (Rockland and Lund 1983, 1982; Gilbert and Wiesel 1983). Interestingly, this connectivity pattern has been observed in mammalian species except rodents (Van Hooser et al. 2006). Different hypotheses exist for how it arises during development (Mitchison and Crick 1982; Buzas et al. 2006; Bauer et al. 2012). On the macroscale, modularity has been shown to develop early on during human development (van den Heuvel et al. 2014).

Modular systems (Fig. 17.4) usually have, in addition to the strong intramodular connectivity, sparse links between modules. These intermodular connections can

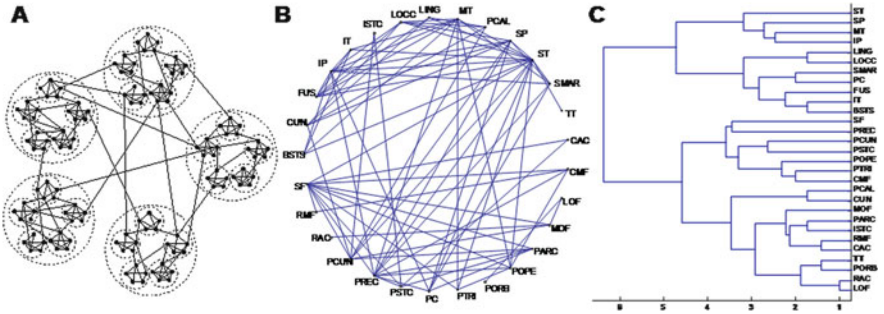


Fig. 17.4 Modules. (a) Schematic hierarchical modular network with modules at two levels, cortical regions (*large circles*) including columns (*smaller circles*) that include individual neurons. For modules, there are more connections within the same module than to other modules. (b) Modular organization of human corticocortical connectivity (Hagmann et al. 2008). Cortical areas were arranged around a circle by evolutionary optimization so that highly interlinked areas were placed close to each other. Note that nodes in the same cluster, having a high structural similarity, also have a similar function. (c) Dendrogram of the same network using hierarchical clustering. A dendrogram running from the root to the leaves (here, from *left* to *right*) consists of branches connecting objects in the tree. The distance of the branching point on the x-axis is the rescaled distance when clusters are combined

serve as shortcuts, hence rendering the average path length between any two to be short. A short path length supports global brain functions, as the distributed entities can efficiently be integrated (Sporns and Zwi 2004). Commonly, it has been shown that many neural networks possess a small-world organization, as, for example, *C. elegans* (Watts and Strogatz 1998), *Drosophila* (Ito et al. 2013), the fibre tract networks between brain regions in the cat (Scannell et al. 1995), the macaque (Hilgetag and Kaiser 2004; Sporns and Zwi 2004), and human brain (He et al. 2007; Hagmann et al. 2008). Recent work using injections of an anterograde tracer yielded the mouse connectome at the mesoscale resolution (between single-neuron and whole-brain imaging resolution) (Oh et al. 2014). Also in this case, a high clustering coefficient and the presence of hubs indicate small-world topology (Sporns and Bullmore 2014). The incorporation of the small-world property across many different species underlines its significance in promoting efficient and fast communication between any two nodes, while keeping the total wiring length comparably small (Karbowski 2001). However, these shortcuts come at rather high metabolic costs, as they require the development of (spatial) long-range connections. Interestingly, (Varier and Kaiser 2011) found that in *C. elegans* the majority of nodes connected via long-range connections are born around the same time. This finding suggests that developmental trajectories could allow for the efficient establishment of neuronal connections, by forming these long-range projections early during development, without the need for energetically expensive guidance cues. Related to this, a recent study on the *C. elegans* and human connectome found that the characteristic path length is longer than what one would expect based on the modularity alone (Kim and Kaiser 2014). Entropy-based considerations indicate that this discrepancy originates from evolutionary pressure towards efficient encoding of developmental processes.

Overall, in modular networks there is a multidimensional trade-off between saving axons, communication costs, and genetic efficacy. As for modularity, small-world organization has been shown to arise early during human brain development (van den Heuvel et al. 2014), and remain stable during brain maturation (Lim et al. 2013).

A further common hallmark of brain networks is the presence of hubs. For mammals such as macaques, subcortical regions such as the hippocampus and amygdala are the most highly connected nodes (Kaiser et al. 2007). The structural centrality of these nodes goes usually hand in hand with functional significance. Additionally, computational studies demonstrate that networks with hubs are more resilient towards random node removal or knockout (Kaiser et al. 2007; Newman 2003; Warren et al. 2014). It is therefore not surprising that many brain diseases usually involve malfunction of hub brain regions (Crossley et al. 2014). Interestingly, hubs are usually in the centre of the brain, forming early during development (Hwang et al. 2012; Varier and Kaiser 2011), and presumably originating earlier during evolution. It has been suggested that the time that is available for connection establishment, from node formation to brain maturation, has a crucial role in the developmentally efficient establishment of hubs in vertebrates as well as in *C. elegans* (Varier and Kaiser 2011).

Interestingly, most brain networks with hubs have been shown to exhibit a rich-club connectivity, for example, in the *C. elegans* (Towlson et al. 2013), cat (de Reus and van den Heuvel 2013), macaque (Harriger et al. 2012), and human brain (van den Heuvel and Sporns 2011). As for hubs, rich-club organization has been shown to arise early during development (Ball et al. 2014; van den Heuvel et al. 2014). Such a developmental priority points towards this connectivity pattern to serve as a developmental scaffold, and to confer several advantages to the network as a whole (Collin et al. 2013; van den Heuvel et al. 2012). This central role in the network is in accordance with pathological rich-club organization observed in neurodevelopmental and other brain diseases (Grayson et al. 2014; Ray et al. 2014; Daianu et al. 2013).

17.4 Conclusion

In summary, complex neural networks become less homogeneous during evolution in line with their increasingly varied functional tasks. Neural systems in species above a certain evolutionary stage show a modular, hierarchical and typically small-world topology with rich-club organization. This shift in structural complexity goes hand in hand with the (functional) specialization of the tasks that the organism performs. This relationship between structure and function is reflected in evolution (Sherwood et al. 2008; Semendeferi et al. 2011), as well as development (Hill et al. 2010). In addition to this functional perspective, certain network features emerged as a consequence of the network topology itself: as brain networks evolved to become more complex, there was the inherent pressure for greater resilience in the face of injury. For example, although hubs and rich-club organization entail the formation of additional axons, they are evolutionarily beneficial as they support such improved resilience towards lesions. Simpler, regular networks seen in primitive life forms have a higher degree of redundancy and are therefore less sensitive (Kaiser and Varier 2011).

Multiple studies have shown that the topology of biological neural networks satisfies a nontrivial ‘fitness function,’ that is, a combination of multiple natural requirements. Aspects such as wiring economy, fast information flow, richness of dynamics, functional specialization, integrative communication, robustness, and developmental efficiency (Bullmore and Sporns 2012; Kim and Kaiser 2014) influence connectome topologies. Hence, network science serves as a way of understanding the structure and function of neural networks in light of evolutionary pressure. Knowledge of how such multidimensional trade-offs can be satisfied will also likely help in the improved design and planning of many artificial networks.

The early (temporal) formation of many complex network properties underlines their significance and points to a genetically encoded blueprint. Possibly, these initial properties support the reliable unfolding of the developmental process. Interestingly, such characteristic network features are often disrupted in neurodevelopmental and neurodegenerative brain diseases, suggesting a better understanding of the connectome to be valuable from a clinical perspective (Stam 2014; Collin and van den Heuvel 2013). State-of-the-art computational models have been proposed to account for many real-world network characteristics (Barabási and Albert 1999; Ravasz and Barabási 2003). However, these models are usually phrased on a rather abstract level, and not directly relatable to biological mechanisms. The detailed modelling of connectome development will have a major part in the better understanding of the connectomes themselves.

Finally, elucidating the link between topological characteristics and functional processing (e.g., does consciousness structurally correlate with the top level of a hierarchical neural network and where is this 'top' level?) remains one of the main challenges of the field. Because the structure and function of neural networks are mutually influencing each other, insights into their dynamic interaction will constitute a crucial part of this endeavour.

Acknowledgments This work was supported by the Engineering and Physical Sciences Research Council of the United Kingdom (EP/K026992/1) as part of the Human Brain Development Project (http://www.greenbrainproject.org). R.B. was also supported by the Medical Research Council of the United Kingdom (MR/N015037/1).

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