Graph analysis of the human connectome: Promise, progress, and pitfalls

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Abstract

The human brain is a complex, interconnected network *par excellence*. Accurate and informative mapping of this *human connectome* has become a central goal of neuroscience. At the heart of this endeavor is the notion that the brain connectivity data can be abstracted to a graph of nodes - representing neural elements (e.g., neurons, brain regions), linked by edges - representing some measure of structural, functional or causal interaction between nodes. Such a representation brings connectomic data into the realm of graph theory, affording a rich repertoire of mathematical tools and concepts that can be used to characterize diverse anatomical and dynamical properties of brain networks. Although this approach has tremendous potential – and has seen rapid uptake in the neuroimaging community – it also has a number of pitfalls and unresolved challenges which can, if not approached with due caution, undermine the explanatory potential of the endeavour. We review these pitfalls, the prevailing solutions to overcome them, and the challenges at the forefront of the field.

1. Introduction

The uptake of graph theoretical tools into brain connectivity research has proceeded at such a phenomenal rate that one could gain the impression that graph theory was only very recently developed. Yet graph theory, as a branch of mathematics, dates back over two hundred years, at least as far as Leonhard Euler's thesis on the 'bridges of Königsberg' (Euler 1736). Euler introduced the notion of representing an interconnected system as the edges (bridges) and nodes (locations) of a graph, and showed how their organization could yield complex topological properties with various implications (here, efficiently traversing bridges). Graph theory is generally considered to be a branch of combinatorics - that is, concerned with the study of discrete structures - and has been used to address a broad range of problems from "covering algorithms" (i.e. how to colour maps) to the *Travelling Salesman Problem* (i.e. in which order should a salesman visit a set of multiple cities to minimize his distance traveled). Already we encounter two of the basic elements of graph theory: First, it was born from a real world problem and remains an extraordinarily pragmatic and empirically useful field. Second, it is dependent upon a discretization of the system under study; an important issue when it comes to imaging neuroscience. Importantly, graph theory is ideally suited to study complex systems of interacting elements, the brain being one example.

Several major advances in the 20th century preceded the rapid uptake of graph theory into neuroscience. Chief amongst these was the work on random graphs - pioneered by Erdos and Renyi (Erdos and Renyi, 1959) - and its later extension to random scale-free networks (Barabási and Albert, 1999) - that is, random networks with a power law degree distribution (degree referring to the number of connections possessed by each network node). Another seminal discovery concerned the so-called "small-world" phenomenon; the simultaneous presence of locally clustered connectivity and short path lengths between nodes in many real-

world networks (Watts and Strogatz, 1998a; Stephan, *et al.*, 2000a). This organization provides a topological foundation for the dual notions of functional integration (short path lengths) and functional segregation (high clustering) – key organizational principles of the brain (Tononi, *et al.*, 1994; Friston, *et al.*, 2004). The realization that many complex systems found in nature, ranging from phylogenies, social interactions, electrical and telecommunication grids, transportation systems and metabolic networks, can be characterized by one or multiple non-trivial organizational properties, including power-law scaling, small-worldness and other features, such as modularity (Fortunato, 2010), hierarchy (Ravasz and Barabasi, 2003) and rich-club ordering (Colizza, *et al.*, 2006), pointed to a set of similarities ("universalities") in very diverse systems (Strogatz, 2001; Newman, 2003a) including the brain (Bullmore, *et al.*, 2009).

The connectome, representing the complete set of neural elements and inter-connections comprising the brain (Sporns, Tononi and Kotter, 2005), is a perfect candidate for graph theoretic analysis. Indeed, it was seminal work examining the organization of large-scale connectivity networks in the *Caenorhabditis Elegans* (White, *et al.*, 1986), cat (Scannell and Young, 1993; Scannell, *et al.*, 1999), and non-human primate nervous systems (Felleman and Van Essen, 1991a; Young, 1992; Hilgetag, *et al.*, 1996; Sporns, *et al.*, 2000b), as well as early computational analyses of the principles of cortical organization (Tononi, *et al.*, 1999; Stephan, *et al.*, 2000a), that illustrated the potential neuroscientific applications of graph theory. This research mandated a gold standard in connectivity data and provided an impetus for early connectivity databases in non-human primates, such as "CoCoMac" (ww.cocomac.org), which can be seen as a prelude to *The Human Connectome Project* (Stephan, *et al.*, 2000a; Stephan, *et al.*, 2001; Kötter, 2004; see also Stephan, 2013 in this issue). The parsimonious nature, computational properties and intuitive appeal of small world networks made their uptake

into brain connectivity research - via analyses of CoCoMac - almost immediate (Hilgetag, *et al.*, 2000b; Sporns, *et al.*, 2000d, 2000a, 2000c; Stephan, *et al.*, 2000b; Sporns and Zwi, 2004a) and represents a compelling examples of the confluence of computational and empirical neuroscience. Though much of this early work focused on structural connectivity data in non-human species, the rapidly emerging interest in functional connectivity led to the first demonstrations, obtained from MEG data (Stam, 2004b) then from fMRI data (Eguiluz, *et al.*, 2005; Salvador, *et al.*, 2005; Achard, *et al.*, 2006), of small-world and scale-free properties in human brain functional networks. These analyses where then extended to the first in vivo structural maps of the human connectome generated using diffusion imaging (Hagmann, *et al.*, 2007; Hagmann, *et al.*, 2008; Skudlarski, *et al.*, 2008; Zalesky and Fornito, 2009) and found rapid applications in the clinical neurosciences (Stam, *et al.*, 2007a) (Micheloyannis, *et al.*, 2006; Rubinov, Knock, *et al.*, 2009) (Liu, *et al.*, 2008) (Bassett, *et al.*, 2008; He, *et al.*, 2009; Fornito and Bullmore, 2010; van den Heuvel, *et al.*, 2010; Verstraete, *et al.*, 2011; Xie and He, 2011; Zalesky, *et al.*, 2011; Fornito and Bullmore, 2012; Fornito, Zalesky, *et al.*, 2012).

The exponential growth in brain connectivity research arguably constitutes something akin to a scientific revolution (Kuhn, 1970) either complementing or even subverting the prior prominence of functional specialization in the brain (Friston, 2011b). In this context, graph theory provides a more compelling framework for the analysis of large-scale brain network architecture than traditional, mass univariate neuroimaging and carries the potential to revolutionise our understanding of brain organization (Stam and Reijneveld, 2007; Bullmore and Sporns, 2009; Sporns, 2011b, 2012). However, the extent to which this promise can be realized is critically dependent upon the validity of the graph representation itself. As a branch of combinatorics, graph theory is reliant upon an unambiguous discretization of the brain into distinct nodes and their interconnecting edges, neither of which are trivial.

Moreover, the application of graph theory to neuroscientific data poses several challenges with important implications for how results should be interpreted. Our goal in this article is to highlight these challenges, draw attention to potential pitfalls and discuss progress towards addressing them. Specifically, we do this in relation to the two major steps involved in connectomic analysis: (1) building an accurate map of the connectome; and (2) analyzing and making sense of the resulting data. We focus principally on *in vivo* macro-scale connectomics with MRI, a field that has rapidly adopted many graph theoretic concepts and techniques and which is central to large-scale initiatives such as *The Human Connectome Project* (Van Essen*, et al.*, 2012). We note however, that graph theory can be used to characterize data acquired using other modalities, such as EEG/MEG (Stam, 2004a; Bassett*, et al.*, 2006b; Stam*, et al.*, 2007b; Rubinov, Knock*, et al.*, 2009; Brookes*, et al.*, 2011; Hipp*, et al.*, 2011; Kitzbichler*, et al.*, 2011; Zalesky, Cocchi*, et al.*, 2012), and that many of the issues discussed here also apply to these analyses. Excellent introductions to the basic concepts of graph theory and their application to neuroscience have been provided elsewhere (Albert and Barabasi, 2002; Newman, 2003b; Sporns*, et al.*, 2004; Stam and Reijneveld, 2007; Bullmore and Sporns, 2009; Bullmore and Bassett, 2011; Sporns, 2011b, 2012).

2. Building a connectome

The validity of any graph-based model of a complex system depends on the extent to which its nodes and edges represent true subsystems and their interactions, respectively, of the system under investigation. In some applications, this is straightforward. For example, in social networks, each node represents a person and edges can represent facebook links (Lewis*, et al.*, 2008) email traffic (Barabasi, 2005), co-authored publications (5) or some other measure of social exchange. Such networks are very well defined. Correct identification of nodes and edges in brain networks is more problematic. It could be argued that each node should

represent a neuron and each edge a synaptic contact. Indeed, a comprehensive neuron-level connectome, comprising 302 neurons (nodes) and ~7000 synapses (edges), has been constructed for the nematode worm *C Elegans* (White*, et al.*, 1986) and similar (albeit statistical) approaches are being applied to the fruit fly *Drosophila Melanogaster* ((Chiang*, et al.*, 2011); www.flycircuit.tw) and mouse (www.mouseconnectome.org; see also (Bock*, et al.*, 2011; Briggman*, et al.*, 2011)) brains. Scaling these analyses to account for the billions of neurons and trillions of connections comprising the human brain is likely not feasible in the near future, however (Kasthuri and Lichtman, 2010; Alivisatos*, et al.*, 2012). Moreover, there is no clear evidence that this level of resolution is the most meaningful for understanding brain structure and function, as brain connectivity and its emergent dynamics are organized across multiple spatiotemporal scales (Buzsaki and Draguhn, 2004; Breakspear and Stam, 2005; Bassett*, et al.*, 2006a; Meunier*, et al.*, 2009), each of which can provide information relevant to understanding human behavior and disease. In other words, there are no 'privileged scales' (Jirsa*, et al.*, 2010). In imaging connectomics, analyses are typically performed at macroscopic spatial resolution (mm-cm), and on the temporal order of milliseconds to minutes. These scales render whole-brain connectomics analytically tractable but create ambiguities in precisely how nodes and edges should be defined.

In light of these ambiguities, it is useful to consider the attributes that a macroscopic map should ideally possess, setting aside limitations on current imaging methodologies. In Table 1 we propose some simple criteria for the nodes and edges, respectively, of such a map, and overview progress towards their fulfillment. A schematic depiction of a connectomic map generated according to these criteria is presented in Figure 1. These criteria are not exhaustive, but rather are intended as a list of important properties that are required for a connectomic model to meet basic criteria for valid graph theoretical analysis. Quick inspection

of these ideal properties reveals that most MRI-derived networks fall short of meeting many of these ideal criteria. In part, this reflects a limitation inherent to the resolution of analysis. For example, there are no clear macroscopic criteria for delineating the brain into functionally meaningful and biologically valid nodes, necessitating the use of heuristic criteria. This limitation, in turn, results from the limited spatial and temporal resolution of current imaging technologies, as well as the relatively indirect measures provided by MRI of many of the phenomena of interest. Consequently, there is a gap between what might constitute an "ideal" map of the connectome and what represents best practice within the constraints of available neuroimaging techniques. In the following, we consider progress and pitfalls associated with attempts to bridge this gap.

-----Table 1 about here------

-----Figure 1 about here------

2.1 Defining nodes

Valid node identification is critical for accurate mapping of inter-regional connectivity (Smith*, et al.*, 2011b; Wig*, et al.*, 2011). Table 1 indicates that an ideal node definition for the human connectome should define functionally homogeneous nodes, represent functional heterogeneity across nodes, and account for spatial relationships. The last of these is easily achieved with standard steretotaxic mapping techniques. The second – accounting for inter-nodal heterogeneity – is more challenging and depends on understanding how both the intrinsic properties of a brain region, and its connectivity with other areas, define its function (Passingham*, et al.*, 2002). Recent work suggests that incorporating such information about nodal functional specialization can lead to highly flexible and adaptive computational models

of the brain (Eliasmith, *et al.*, 2012), though a detailed understanding of functional specialization across the entire brain remains an important challenge for cognitive neuroscience.

The first characteristic – parcellating the brain into homogeneous nodes – has been the subject of considerable attention in neuroimaging. At a cellular level, homogeneity in the brain has been defined in terms of function (e.g., common physiological responses) or anatomy (e.g., shared cytoarchitectonic, myeloarchitectonic or receptor distribution properties) (Brodmann, 1909; Mountcastle, 1997). Though convergent in some areas (Fischl, *et al.*, 2008), the borders formed by these microscopic properties often show poor correspondence with the macroscopic (e.g., sulcal and gyral) landmarks visible with MRI (Rademacher, *et al.*, 1993; Amunts, *et al.*, 2000), necessitating the use of heuristic methods for node definition.

The four most common strategies for node definition in imaging connectomics are (1) anatomical, (2) random[1], (3) functional, and (4) voxel-based. A summary of the strengths and limitations of each of these approaches is presented in Table 2. The nodes defined by each of these methods remain approximations at best, and represent an intrinsic constraint on the accuracy of any resulting connectomic map. Inconsistent or imprecise node definitions can have a major impact on subsequent analyses (Wang, *et al.*, 2009; Antiqueira, *et al.*, 2010; Fornito, *et al.*, 2010; Hayasaka and Laurienti, 2010; Zalesky, Fornito, Harding, *et al.*, 2010). For example, a study of variations in the resolution of random parcellations applied to diffusion-

[1] A random parcellation scheme typically involves breaking up a prior scheme into smaller sub-units using a probabilistic scheme: This random sub-parcellation then remains available for repeated use.

imaging data found that standard topological measures of anatomical networks such as small-worldness can vary by ~95% in the same individual when using a low-resolution (90 regions) compared to high-resolution (4000 regions) parcellation (Zalesky, Fornito, Harding, *et al.*, 2010). Similar results have been reported for fMRI data (Fornito, *et al.*, 2010). In the latter case, the differences between parcellations at resolutions of $\sim 10^2$ nodes compared to $\sim 10^3$ nodes were so pronounced that between-subject variations in some topological properties actually became negatively correlated; i.e., individuals who showed a higher clustering coefficient (a measure of the probability that each node's neighbours are also connected to each other) at low resolutions showed lower clustering at higher resolutions.

One approach to dealing with this parcellation-dependent variability in findings has been to repeat analyses using different parcellation schemes and/or different resolutions (Hagmann, *et al.*, 2008). Though such approaches provide confidence when results converge, consistency is not always guaranteed. As such, the results of any connectomic analysis must be interpreted with respect to the strengths and limitations of the approach used to define nodes, and some parcellations may be more suitable for addressing certain questions relative to others. For example, if the aim is to understand interactions within and between specific sub-networks of regions, a functional approach to node definition (see Table 2) may provide a more valid index of underlying network properties than a random or anatomical parcellation strategy. In this case, it does not make sense to try to obtain consistency across techniques as long as the results are reproducible across experiments.

-----Table 2 about here-----

More recently, methods have been proposed that parcellate the brain according to data-driven clustering of resting-state or DWI measures (Johansen-Berg, *et al.*, 2005; Anwander, *et al.*, 2007; Nelson, *et al.*, 2010; Power, *et al.*, 2011; Yeo, *et al.*, 2011), based on the assumption that each brain region has a unique connectional fingerprint (Passingham, *et al.*, 2002). Incorporating spatial information can help these algorithms define spatially contiguous regions (Cohen, *et al.*, 2008; Craddock, *et al.*, 2012). High-dimensional spatial independent component analysis has also been used in this context (Kiviniemi, *et al.*, 2009). Alternative methods involve parcellation based on quantitative, biological imaging signals (Glasser and Van Essen, 2011) or probabilistic mapping of cytoarchitectonic maps into stereotactic space (Eickhoff, Stephan, *et al.*, 2005; Scheperjans, *et al.*, 2008; Caspers, *et al.*, 2013). Preliminary atlases derived using the latter approach are currently available (www.fz-juelich.de/SharedDocs/Downloads/INM/INM-1/DE/Toolbox/Toolbox_18.html) but cover only limited regions of cortex. Extending the approach to cover the entire brain represents an important goal for the field. Analyses of regional myeloarchitecture or receptor density profiles may also provide useful methods for defining nodes (Zilles, *et al.*, 1995; Zilles, *et al.*, 2002; Eickhoff, Walters, *et al.*, 2005) depending on the question asked of the data.

In summary, there is as yet no widely-accepted means for defining network nodes for connectomic analyses. Quantitative analysis of imaging signals (e.g., (Glasser and Van Essen, 2011)) and multi-modal integration of *in* and *ex vivo* data into probabilistic atlases (e.g., (Eickhoff, Stephan, *et al.*, 2005)) may offer a more biologically principled approach to cerebral parcellation than many of the heuristic techniques currently being used, and will be an important avenue of work in coming years. Dealing with individual variability in the location of these regions will be a challenge however.

2.2 Defining edges

There are three broad classes of brain connectivity: Structural, functional and effective (Friston, 1994, 2011a; Sporns, 2011b). The type of connectivity measured, and method used to quantify it, determines the edges of a brain graph. *Structural connectivity* pertains to the anatomical connections between brain regions–the physical (axonal and dendritic) wiring of the brain–as reported through tracing studies in animals or inferred from diffusion imaging in humans. The connectome was first defined as a "complete description of the *structural* [italics added] connectivity of an organism's nervous system" (Sporns, Tononi and Kötter, 2005; Sporns, 2007, 2011a), though the term has since been adapted to refer to comprehensive maps of functional interactions as well (Biswal*, et al.*, 2010; Alivisatos*, et al.*, 2012). *Functional connectivity* refers to statistical dependencies between spatially distinct neurophysiological recordings and can be either directed or undirected *Effective connectivity* denotes the causal influence exerted amongst neural systems. It cannot be directly derived, but rather must be inferred from multivariate data using an inversion scheme that accounts for the measurement function such as neurovascular coupling in fMRI (Friston*, et al.*, 2003). Effective connectivity rests on a dynamic model of causal effects posed at the neuronal level and is directed - and hence asymmetric (Breakspear, 2004). In contrast, directed, asymmetric (conditional) statistical measures of temporal correlations derived directly from imaging data – such as directed coherence measures, Granger causality and Bayes nets – are not measures of effective connectivity as these do not explicitly model BOLD measurement effects and hence remain distant to neuronal causes (David*, et al.*, 2008). They are thus better described as measures of directed functional connectivity. An important goal for imaging connectomics is to leverage these distinct types of connectivity to define edges that are directed, weighted and dynamic, and which represent heterogeneity in the type of connection made (Table 1). We consider progress towards reaching this goal for studies of anatomical, functional and effective connectivity separately.

2.2.1 Structural Connectivity

Whole brain maps of structural connections derive increasingly from diffusion-weighted imaging (DWI). (Cross-subject covariance in regional morphometric parameters, such as grey matter volume and cortical thickness, can also be used as an indirect measure of anatomical "connectivity" (Lerch*, et al.*, 2006; He*, et al.*, 2007).) Notwithstanding variations in acquisition parameters and data quality, the validity of such a map of the connectome will be determined in large part by the tractography algorithm and model of the diffusion signal on which it is based. These algorithms/models can be broadly classified along three dimensions: (1) deterministic or probabilistic; (2) locally greedy or globally optimal; and (3) based on a single- or multi-direction diffusion model (Bastiani*, et al.*, 2012). The details of each of these properties are summarized in Table 3.

-----Table 3 about here----

A recent, comprehensive comparison of some of the most commonly used tractography algorithms found that network properties vary substantially depending on which approach is used (Bastiani*, et al.*, 2012). In general however, globally optimized tracking algorithms out-performed many of the other approaches according to a range of quality-control criteria, even when a relatively simple single-direction diffusion model was fitted to the data. This advantage of global algorithms arises because they are better able to cope with voxels affected by noise or crossing fibers; a locally greedy algorithm will typically terminate or change direction upon encountering such a voxel whereas a global algorithm will be less affected by

outlying measurements within a putative fiber trajectory (Zalesky, 2008; Zalesky and Fornito, 2009).

Once fiber trajectories between regions have been reconstructed, some measure of connectivity strength between regions should ideally be computed. Whilst DWI does allow estimation of connection weights between regions, it is unclear which weighted measure yields the most biologically informative estimate of anatomical connectivity. Historically, two measures have been used to determine connection weights using DWI. One involves inferring connection strength between two regions from the number of reconstructed trajectories that intersect them. The problem with this approach is that such trajectories are an abstraction of the tractography algorithm itself and are not tantamount to individual axons. The second approach has been to integrate some putative voxel-wise index of fiber integrity (e.g., mean/axial/radial diffusivity or fractional anisotropy) over the extent of the reconstructed tract. The assumption here is that variations in these measures index the integrity of the fiber tract, and thus impact the functional capacity of the connection between regions. A problem with this approach is that averaging a measure over an entire fiber trajectory may obscure more localized effects that a simpler measure such as trajectory count may be more sensitive to. More generally, both trajectory counts and tract-averaged approaches can be affected by a low signal-to-noise ratio, crossing fibers, poor fit of the diffusion model and a number of other factors that are not directly related to the extent of inter-regional connectivity (Jones*, et al.*, 2012).

An alternative is to quantify connection weights using multi-modal imaging. For example, magnetization transfer imaging can be used to estimate the myelin content of DWI-defined

fiber tracts, thus providing a biologically informed measure of the information transfer capacity of a tract (van den Heuvel*, et al.*, 2010). Recent developments enabling estimation of axon diameter and density using tailored DWI acquisitions (Alexander*, et al.*, 2010) also provide attractive solutions. Since important properties such as conduction speed are proportional to axon diameter, further development of such methods will provide a quantitative, physiologically meaningful framework for estimating the strength and conduction delay of anatomical connectivity between regions.

No existing tractography algorithm allows differentiation of afferent and efferent anatomical connectivity using diffusion-imaging data; i.e., all DWI-derived edges are undirected. Though diffusion signals can be used to provide super-resolution contrast (Calamante*, et al.*, 2010) and to estimate various microscopic tissue components of a voxel (Assaf*, et al.*, 2008; Alexander*, et al.*, 2010), the ability to pinpoint the origin and termination of an anatomical connection will likely require a major advance in imaging technology. Since a large portion of anatomical connectivity in the brain, particularly at the macroscopic scale, is thought to be reciprocal (Felleman and Van Essen, 1991b), this limitation may not pose a major problem. However, modeling an inherently directed network such as the connectome with undirected edges will limit the accuracy of any resulting graph-based representation. For example, the variety of motifs – small sub-graphs embedded within a larger network – is substantially impoverished in the absence of directionality. Furthermore, there is currently no way of representing heterogeneity in anatomical connections. For example, it is not yet possible to determine whether a given fiber trajectory carries inhibitory projections, excitatory projections, or a combination of both, though it is generally accepted that most inhibitory projections are local and may thus be primarily contained within the network nodes defined with MRI.

In summary, current DWI protocols allow reconstruction of weighted and undirected edges. These edges are not tantamount to actual fiber pathways. Rather, they represent estimates of axonal trajectories that are subject to the limitations of the data acquisition and analysis techniques (Jones, *et al.*, 2012). While accurate estimation of directed connections remains a long-term prospect, short-term gains can be made through the application of multi-direction diffusion models and globally-optimised tractography algorithms to high quality data, in combination with methods for measuring connectivity weights using either multi-modal imaging (van den Heuvel, *et al.*, 2010) or diffusion-based estimates of axonal structure (Assaf, *et al.*, 2008; Alexander, *et al.*, 2010).

2.2.2. Functional connectivity

Functional connectivity is most commonly computed using the Pearson correlation coefficient between regional activity time courses, though alternative measures such as partial correlation (Marrelec, *et al.*, 2009), mutual information (Salvador, *et al.*, 2010), coherence (Bassett, *et al.*, 2011) and others (Smith, *et al.*, 2011b) have also been used. The resulting edge weights are typically scalar, continuous and symmetric and can be used to quantify both positive and negative covariations in regional activity. The result is a static, fully connected, weighted, undirected and signed connectivity matrix. Prior to graph theoretic analysis, this matrix is typically thresholded to remove noisy or spurious associations and emphasise key topological features. Signs (positive versus negative) are often ignored. Finally, connection weights can be removed by binarizing the network. Thus, from a complete, weighted and signed network we end up with a sparse, binary, and unsigned network (e.g., Figure 1). The final result therefore represents a map far removed from the ideal criteria for edge definitions

proposed above (Table 1). In the following, we discuss some of the issues associated with measuring edge weights, directed connections and dynamic variations in functional connectivity.

Weights and signs. Despite the popularity and simplicity of analyzing binary graphs, weighted generalizations for many commonly used graph theoretic metrics now exist and are being used with increasing frequency in imaging connectomics (Brandes and Erlebach, 2005; Rubinov and Sporns, 2011a). Weighted analyses are attractive, as brain network dynamics define an intrinsically weighted system– i.e., regional pairs vary in the extent to which they functionally interact with each other. Dealing signed edge weights in functional data has been more challenging. Many traditional graph theoretic measures assume only positively weighted connections. Consequently, it has been customary to either take the absolute correlation value as the edge weight, or focus only on positively weighted connections. This practice may distort network properties (Figure 2). It also ignores important information encoded by the sign of the weight, as a positive correlation between regional activity time courses suggests cooperation or integration whereas a negative correlation points to competition or segregation (Fox*, et al.*, 2005; Sonuga-Barke and Castellanos, 2007; Rubinov and Sporns, 2011b; Fornito, Harrison*, et al.*, 2012). Though the contributions of pre-processing techniques to the emergence of negative correlations in fMRI data remains a topic of debate (Fox*, et al.*, 2009; Murphy*, et al.*, 2009; Saad*, et al.*, 2012), it is probable that not all negative correlations are artefacts (Chang and Glover, 2009). Accordingly, anticorrelated network dynamics have been shown to play an important role in behaviour (Kelly*, et al.*, 2008; De Pisapia*, et al.*, 2011). Generalizations of existing formulae for graph theoretic measures that can account for signed weights, and which are applicable to unthresholded graphs (Rubinov and Sporns, 2010), will be an important goal for the near future.

-----Figure 2 about here-----

Directed functional connectivity. Functional interactions in the brain are inherently directed: Neuronal populations are subject to inputs from other regions, increasing their firing rate and hence their output to other populations. A variety of time series methods exist for measuring directed functional connectivity using fMRI. These can be grouped into those that depend upon conditional dependences, such as Patel's τ and Bayes nets, and lag based measures, such as Granger causality. It is not uncommon to see these referred to as effective connectivity (because of their directionality). However, unless they in the least include deconvolution – which is rarely performed (David*, et al.*, 2008; Roebroeck*, et al.*, 2011; Valdes-Sosa*, et al.*, 2011)- they are more accurately classified as functional connectivity because they deal exclusively with the statistical properties of remote neurophysiological signals. A systematic analysis using ground-truth established through simulated multi-area BOLD fluctuations suggested that conditional measures were reasonably accurate in establishing the existence of a functional connection, but were less accurate in detecting the true direction of that interaction (Smith*, et al.*, 2011a). Lag-based measures performed poorly, albeit against time series constructed from zero-lag interactions.

Measuring dynamic changes. Connections between brain regions change over time. Anatomical connections (at the macroscopic level) typically change over weeks, months and years, as new connections form, or existing ones strengthen or weaken in accordance with experience-dependent plasticity. In comparison, microscopic synaptic plasticity occurs on faster time scales: Spike-time-dependent plasticity (STDP) for example, has a time scale on

the order of tens of milliseconds (Song and Abbott, 2001). Even in the absence of plasticity, neuronal ensembles may rapidly synchronize and desynchronize due to the dynamic consequences of their intrinsic nonlinear dynamics (Breakspear, 2002; Breakspear*, et al.*, 2004). Although the low-pass filtering properties of the haemodynamic response render sub-second dynamics impervious to measurement with fMRI, recent research has nonetheless suggested that such dynamics may lie at the heart of large-scale resting state fMRI networks across slower time scales (Deco and Jirsa, 2012).

Characterising functional connectivity in fMRI time series with a single scalar measure (e.g., correlation coefficient) ignores such dynamic instabilities, as well as the documented non-stationarities at temporal scales resolvable with fMRI (Kitzbichler*, et al.*, 2009; Chang and Glover, 2010). Recent analyses have shown that it is possible to identify, in a data-driven manner, significant change-points in brain functional network architecture (Cribben*, et al.*, 2012), as well as dynamic reconfigurations of brain network topology that are relevant for understanding individual differences in behavior (Bassett*, et al.*, 2011). Developments in this area will open new windows into the evolution of brain network dynamics across time. In this context, the proliferation of rapid-TR functional imaging protocols (e.g., (Feinberg*, et al.*, 2010)) will enhance statistical power and enable a wider array of spatiotemporal analyses (e.g., (Smith*, et al.*, 2012)).

An alternative approach to studying dynamic changes in brain networks involves studying functional interactions during different psychological states–i.e., task-related modulations of functional connectivity. This work is directly relevant to informing and extending traditional cognitive neuroscientific models and analyses of behavior. As the task drives regional brain

activity in specific ways however, several processes may contribute to a correlation between regional activity time courses, including: (1) task-unrelated functional connectivity, arising from intrinsic or spontaneous dynamics as is putatively captured in resting-state designs; (2) task-related connectivity, reflecting task-evoked, context-dependent changes in functional interactions between regions; (3) co-activation, caused by common activation to a task in the absence of direct communication between regions; and (4) physiological and instrument noise. Simply correlating regional time courses will not disentangle these various contributions, though their separation has been shown to be critical for recovering meaningful associations between network dynamics and behavior as well as for mapping dynamic reconfigurations of brain functional network organization (Fornito, Harrison*, et al.*, 2012). Details of some of the techniques used to examine task-related functional connectivity that are scalable to whole-brain networks are summarized in Table 4.

----Table 4 about here-----

2.2.3. Effective connectivity

A major difficulty associated with inferring directed connectivity from fMRI data is that the technique provides an indirect estimate of neuronal activity through measurement of BOLD signal variations. Regional differences in vasculature, neurovascular coupling and other haemodynamic parameters can alter the temporal relations between regional BOLD signal changes relative to those observed at the neuronal level and thus distort measures of directed connectivity based on BOLD time series alone (David*, et al.*, 2008; Valdes-Sosa*, et al.*, 2011). A solution to this problem mandates the employment of a regionally-specific forward hemodynamic model, together with a model inversion framework such as Dynamic Causal

Modelling (Friston, *et al.*, 2003). DCM traditionally rested upon a simple, low order and deterministic neuronal state equation and was limited to inference on small network motifs: However recent modelling developments, which incorporate stochastic effects at the neuronal level (Li, *et al.*, 2011; Daunizeau, *et al.*, 2012; Freyer, *et al.*, 2012; Friston, *et al.*, 2012), together with model inversion schemes that employ greedy search algorithms (Friston, *et al.*, 2011; Seghier and Friston, 2012) have brought effective connectivity into the realm of research into large-scale (including resting state) networks. Given that, by definition, effective connectivity is dynamic, context specific, directed and weighted, these are very interesting developments, though they have not yet been applied to the study of whole-brain graphs.

3. Analysing the connectome

Once nodes and edges are accurately defined, the tools of graph theory can be used to characterize a wide array of network properties. When used judiciously, these methods can provide novel insights into brain organization. When used carelessly, they may lead to misleading or incorrect conclusions. In the following, we consider several important issues: namely, addressing the multiple comparison problem in connectomics, graph thresholding, the interpretation of topological measures, reference graphs, and generative modeling.

3.1 The multiple comparisons problem

3.1.1. Family-wise error corrections for connectomics

Connectomics involves the comprehensive mapping of pair-wise interactions between brain regions. Given these data, it is often desirable to map various experimental effects (e.g., task or drug effects, case-control differences, etc.) on an edge-wise basis. These analyses pose a

difficult multiple comparisons problem, which scales as a function of network size. For example, most studies investigate networks of ~10^2 regions. In a symmetric, undirected network of 10^2 regions, there are $(N^2-N)/2 = 4950$ connections. Thus, if these comparisons are treated as independent, any experimental effect must be associated with an extremely low probability ($p < 1.01 \times 10^{-5}$, after Bonferroni correction) of rejecting the null hypothesis to be declared statistically significant. The threshold becomes even more stringent for larger networks (e.g., for a network comprising ~10^3 regions, the threshold would be $p < 1.0 \times 10^{-7}$). Though alternative methods for controlling family-wise error rates can boost power (e.g., (Benjamini and Hochberg, 1995)), they still often perform poorly, particularly when such high-dimensional data are collected in small samples (Zalesky, Fornito and Bullmore, 2010).

One recent approach designed to address this problem uses a graph-based analogue of the cluster-based thresholding strategies employed in traditional mass-univariate imaging analyses (Zalesky, Fornito and Bullmore, 2010). With this method, the null hypothesis is evaluated with respect to the size of interconnected components of edges, rather than individually at each connection. In this context, a graph component refers to a collection of nodes that can be linked together to via a set of suprathreshold edges (see Figure 3). The size of these components is determined following application of a primary, component-forming threshold to the data. This network-based statistic (NBS) offers substantially more power than the FDR for identifying sub-networks of edges showing a common effect (Zalesky, Fornito and Bullmore, 2010)(Figure 3) and has been used to successfully map changes in both structural and functional networks of disorders as diverse as schizophrenia (Zalesky, Fornito and Bullmore, 2010; Fornito, Yoon*, et al.*, 2011; Zalesky, Fornito, Egan*, et al.*, 2012), depression (Zhang*, et al.*, 2011; Bai*, et al.*, 2012), autism (Li, Xue*, et al.*, 2012), attention-deficit hyperactivity disorder (Cocchi*, et al.*, 2012), mild cognitive impairment (Wang*, et al.*, 2012),

amyotrophic lateral sclerosis (Verstraete*, et al.*, 2011), multiple sclerosis (Li, Jewells*, et al.*, 2012) and cannabis abuse (Zalesky, Solowij*, et al.*, 2012). It can also be used with other clustering techniques to reduce the dimensionality of very large, voxel-based networks (Zalesky, Cocchi*, et al.*, 2012; Zalesky, Fornito, Egan*, et al.*, 2012).

----Figure 3 about here----

A different approach that has been developed to perform statistical inference on connectome data is called subnetwork-based analysis (SNBA; (Meskaldji*, et al.*, 2011)). SNBA is a hierarchical method, whereby the connectome is first decomposed into a small set of sub-networks (e.g. cortical lobes or some other coarse subdivision) and a meaningful summary statistic is defined to independently test the desired hypothesis for each sub-network as a whole. This decomposition reduces the number of multiple comparisons from thousands of connections to 10 or so sub-networks, albeit at the cost of reducing the resolution at which an effect can be declared to a series of coarse sub-networks. Only sub-networks for which the null hypothesis is rejected are then investigated further with a finer-grained connection-level inference, using the NBS, for example. The difficulty with SNBA is the lack of a principled approach for decomposing the connectome into a meaningful series of sub-networks. The power to detect an effect is compromised for decompositions for which the effect is not wholly enveloped within a single sub-network, but rather spread across a small portion of many sub-networks. In this case, the small portion of connections demonstrating an effect is likely to be diluted when averaging is performed over the whole sub-network to generate a summary statistic. More recently, the concept of statistical parametric networks (SPN; (Ginestet and Simmons, 2011)) was introduced in the context of mapping functional

connectivity dynamics during a working memory task. SPN relies on the methods discussed above (e.g. NBS, FDR, SNBA) to deal with the multiple comparisons problem.

3.1.2. Machine learning and classification

An alternative means to deal with the high dimensionality of connectomic data involves the application of machine learning algorithms, such as support vector machines (SVMs), to identify multivariate feature combinations that best predict an outcome of interest. Though in its early stages, the combination of these techniques with connectomic measures has proven powerful, having been used to distinguish the brains of healthy individuals from patients with an array of distinct disorders, including autism (Anderson*, et al.*, 2011), schizophrenia (Bassett*, et al.*, 2012), major depression (Lord*, et al.*, 2012; Zeng*, et al.*, 2012), attention-deficit hyperactivity disorder (Colby*, et al.*, 2012; Dai*, et al.*, 2012), Alzheimer's disease and mild cognitive impairment (Chen*, et al.*, 2011; Wang*, et al.*, 2012) and epilepsy (Zhang*, et al.*, 2012). In most of these cases, classification accuracy exceeded 75%, with most showing accuracy > 80%.

A particular strength of the machine learning approach is that it allows inferences at the level of individual participants, which has important clinical implications. However, though the research published to date provides an important proof-of-principle, many of the classification problems investigated thus far, such as distinguishing between a given patient group and healthy controls, are practically trivial since most clinicians are able to make this distinction without the aid of sophisticated connectomic measures. In this context, the practical utility of a connectomic classifier will be determined by three factors. First, it must accurately and robustly predict an outcome of interest across different samples and

experimental settings. This is a necessary requirement for routine use in clinical practice. Second, the outcome predicted should be one that is clinically informative and which cannot be predicted using other means. For example, clinicians can typically distinguish a healthy from unwell person, but predicting treatment response or illness course is often challenging. If connectomic measures assist with the prediction of these outcomes, they will add considerable value to clinical decision-making. Finally, the predictive accuracy afforded by connectomic measures must surpass the performance of other, simpler and less expensive measures (e.g., blood- or plasma-based biomarkers), or even simpler imaging phenotypes such as grey matter volume. Given the time and cost involved in generating connectomic data, the resulting measures must add something that could not otherwise be obtained through simpler and less expensive means. In some cases, connectivity measures have shown greater sensitivity than other metrics (Fleisher*, et al.*, 2009). In other cases, it has been found wanting (Bohland*, et al.*, 2012).

3.2 Graph thresholding

The connectome is an intrinsically sparse network. However, many of the imaging measures used to map its structural and functional properties are continuous association metrics. As noted above, it is often desirable to threshold the data in order to differentiate "true" connections from those that are spurious or noisy. Thresholding can be performed either at the individual level or across participants to generate group-level representations using a range of techniques that vary in their complexity, validity and sophistication (van Wijk*, et al.*, 2010; Ginestet*, et al.*, 2011; Simpson*, et al.*, 2012; de Reus and van den Heuvel, 2013). Enforcing some degree of network sparsity also assists in the computation of many of the canonical graph theoretic measures used to characterize network topology.

Intuitively, one could apply a threshold, τ, such that only connections surpassing some level of statistical significance (or some other criterion) are retained (e.g., retaining only correlations with $p <$ some critical value). A problem with this approach is that it will retain different numbers of edges across different individuals. Most graph theoretic measures are contingent on the number of nodes, N, and connection density $0 < \kappa < 1$, of a graph, where κ represents the proportion of supra-threshold connections relative to the total possible number of connections. It is therefore essential to compare networks with equivalent N and κ. As such, a common approach to graph thresholding has involved adaptively varying the τ threshold for each individual to enforce a fixed value of κ across all participants. As the choice of a given value of κ is arbitrary, a range of densities is often analysed to examine the κ –sensitivity of the findings. However, this approach is still associated with biases (Figure 4) and raises questions concerning the appropriate correction for multiple comparisons. In particular, network measures are often calculated for each connectivity threshold, giving rise to a curve characterizing the measure's evolution as a function of connection density. The simplest approach to statistical inference in this case is to independently test the hypothesis of interest at each discrete density along the curve. However, tests conducted at neighboring densities are likely to be strongly dependent, and furthermore, the number of multiple comparisons is dictated by the granularity of the density range. For these reasons, multiple comparisons correction is not typically used across the family of density thresholds. A more principled approach is to numerically integrate the network measure over the density range, using Euler's approximation. This yields an estimate of the area under the curve (AUC). Statistical inference is then performed on the AUC (He*, et al.*, 2009; Ginestet*, et al.*, 2011; Bassett*, et al.*, 2012), which represents a single summary measure across the range of densities and averts the need for multiple comparisons correction. The disadvantage of the AUC is that significant experimental effects present at only a small range of densities can be lost after integrating

over a larger range of non-significant densities. The effect that graph thresholding has on network fragmentation should also be considered as it can confound network comparisons (Fornito, Zalesky, *et al.*, 2012). Specific thresholding methods that ensure connected graphs have been proposed (Alexander-Bloch, *et al.*, 2010).

------Figure 4 about here------

In a systematic analysis, van Wijk et al. (2010) examined the biases associated with a range of thresholding techniques, including τ- and κ-based thresholding, normalization by matched surrogate data, the use of exponential random graph models (Robins, *et al.*, 2007; Simpson, *et al.*, 2011), and less commonly used approaches such as explicit modeling of, and correction for, N- and κ- dependencies in the data. Some methods performed better than others, though all were associated with some degree of bias. These biases must be considered when interpreting graph theoretic data. The continued development of measures suited to unthrehsolded, weighted and signed graphs (Rubinov and Sporns, 2011a) will assist in alleviating dependence on a particular choice of thresholding scheme. If thresholding is used, an integrated analysis attempting to understand how connectivity weights relate to topological measures can yield important insights into the data (e.g., (Lynall, *et al.*, 2010)).

3.3. Reference networks

Making inferences about the topological organization of a connectivity map based on the raw value of a network measure is problematic because this value is influenced by basic low level network properties, such as the number of nodes, connection density and degree distribution.

To facilitate a more meaningful inference, network measures are hence typically benchmarked against, or normalized to, appropriate null or reference networks that share these same basic properties but have other properties destroyed through construction. This is important because classes of random graphs nonetheless have a range of non-trivial properties - such as robustness and efficiency (Callaway, *et al.*, 2000; Newman, *et al.*, 2001; Strogatz, 2001) – that are also found in many complex systems. Understanding random networks thus plays an important role - perhaps more so than is widely recognised - in brain connectomics, providing a means of bench-marking empirically derived graphs (Hilgetag, *et al.*, 2000a; Sporns and Zwi, 2004b) and, possibly, accounting for much of the apparent structure in the human connectome.

The simplest and most prevalent null model is a random network generated with a rewiring algorithm that preserves degree distribution (Maslov and Sneppen, 2002). The algorithm can be generalized to rewire weighted and signed networks (Rubinov and Sporns, 2011a) , but in such cases typically works best when the proportion of positive and negative weights in the graph is approximately equal. This Maslov-Sneppen null model has become pervasive among neuroscientists in establishing the connectome's small-world organization. In accordance with the Watts and Strogatz small-worldness criteria (Watts and Strogatz, 1998b), connectivity maps – structural and functional - have been consistently found to be considerably more clustered than degree-matched random networks, yet approximately equal in terms of characteristic path length. Exactly how much more clustered the connectome should be for it to be declared a small-world network is an inherent ambiguity of the Watts and Strogatz definition.

For this reason, lattice networks have been suggested as a more appropriate null model for the clustering coefficient (Telesford*, et al.*, 2011). Random and lattice networks represent the extreme ends of a continuous topological spectrum ranging from high clustering and long path lengths (lattice networks) to low clustering and short path lengths (random networks). Small-world networks occupy the middle ground. Assuming the extreme ends of this spectrum provide inherent reference points, it follows that degree-matched lattice networks are the most appropriate null model for the clustering coefficient, while degree-distribution matched random networks are most appropriate for the characteristic path length, although these normalized measures still vary with network size (van Wijk*, et al.*, 2010). The choice of null model therefore depends on the network measure. While several novel measures of small-worldness have been developed based on this thinking (Sporns and Zwi, 2004a; Telesford*, et al.*, 2011), the Watts and Strogatz definition and the associated σ-metric (Humphries*, et al.*, 2006) remain pervasive.

In choosing an appropriate null model, consideration should also be given to the connectivity measure used to derive the connectome's edge weights. In particular, edge weights derived from simple pair-wise measures of statistical association give rise to networks that are deficient in their degrees of freedom and thereby exhibit nonrandom topological structure - even if obtained from uncorrelated, random time series - when benchmarked against the null models described above (Bialonski*, et al.*, 2011; Zalesky, Fornito and Bullmore, 2012). For example, edge weights derived from Pearson's correlation coefficient gives rise to networks that are inherently more clustered than degree-matched random networks (Zalesky, Fornito and Bullmore, 2012). This is due to the transitive nature of the correlation coefficient. Appropriate null models for the clustering coefficient in this case should factor out the transitive effect, revealing only the extent of clustering intrinsic to the connectome. On this

account, degree-matched random and lattice networks are inappropriate. They spuriously inflate the true extent to which the connectome is clustered. This feature can be trivially demonstrated by cross-correlating a series of independently generated, random vectors. The correlation matrix that results can be treated as a hypothetical connectivity matrix, for which the clustering coefficient can be calculated as usual after application of a binarization threshold. According to the common literature, this clustering coefficient should be benchmarked against the clustering coefficient in a degree-matched random network, which would typically be generated with the random rewiring algorithm (Maslov and Sneppen, 2002). If random rewiring of the original network did indeed yield an appropriate null model, the clustering coefficient in the original and randomly rewired network should be approximately the same, since they were both generated randomly. However, as shown in Figure 5, clustering is invariably greater in the original network (Zalesky, Fornito and Bullmore, 2012). The partial correlation coefficient can also suffer bias, and results in an under-estimation of the true extent of network clustering (Figure 5) (Zalesky, Fornito and Bullmore, 2012).

-----Figure 5 about here-----

Null models appropriate for the case when edge weights are derived from Pearson's correlation coefficient can be generated with the Hirschberger-Qi-Steuer (H-Q-S) algorithm (Hirschberger, *et al.*, 2004) or simply by sampling from an inverse Wishart distribution. The advantage of the H-Q-S algorithm is that it matches higher moments of the distribution of correlation values. The shortcoming of these approaches is that they do not preserve the node degree distribution. Null models can also be generated by randomizing the phase of the BOLD

time series in the frequency or wavelet domain (Theiler*, et al.*, 1992; Breakspear*, et al.*, 2003) and then cross-correlating the phase randomized time series to yield null correlation matrices. Linear properties of the time series are preserved under phase randomization (e.g. power spectrum, autocorrelation). However, this approach does not allow for any moments of the distribution of correlation values to be matched. Recent work in the network science literature has also focused on developing reference networks that preserve high-order topological properties such as the extent of transitivity and the clustering coefficient (Bansal*, et al.*, 2009; Wang, 2013). This enables better characterization of high-order topological properties by isolating them from first (dyadic; e.g. node degree) and second order (triadic; e.g. transitivity) effects.

An important yet often overlooked property of the brain concerns its spatial embedding, which endows connectivity maps with a distance-dependent effect. An example of the dependence of functional connectivity on inter-node distance is provided in Figure 6A. As explored below, geometric effects can induce non-trivial organizational properties and, depending on the question asked, should arguably be accounted for with appropriate null models. In empirical data this relationship is complicated by the fact that many artifacts of acquisition (e.g. head motion), preprocessing (e.g. spatial smoothing) and analysis (e.g. the accumulation of errors arising from probabilistic tractography) introduce distance dependent errors into connectivity maps (Van Dijk*, et al.*, 2012).

Non-trivial topological properties of networks can arise from a distance-dependent random wiring rule. Suppose that structural connectivity drops off inversely with inter-node distance (Hellwig, 2000; Kaiser and Hilgetag, 2004; Freeman and Breakspear, 2007; Alexander-Bloch,

Vertes, *et al.*, 2012), that is $C \sim 1 / d^{\alpha}$ where α indices the strength of this effect ranging from 0 (no effect) to 1 (a strong effect) or greater. An example connectivity matrix for α=0.2 is shown in Figure 6B: The corresponding (edge weight preserving) topologically random graph is shown in Figure 6C. If this distance dependent effect is parametrically increased from zero (Figure 6D, left to right) the clustering coefficient increases, outstripping the corresponding increase in path length so that the small world index also increases. If this simple network represented the ground truth in a brain network, then it will have inherited a non-trivial topological property from a geometrically constrained random wiring rule. Suppose now that the distance effect resulted purely from the accumulation of tractographic errors and/or spatial smoothing, thus imparting an exponential decline $C \sim e^{-\alpha d}$ where again α parameterizes the strength of the effect (Figure 6E). Once more, the increase in clustering outstrips the increase in path length, resulting in an increase in the small world index. Here, the apparent topological effect is purely an artifact of the measurement process.

----Figure 6 about here-----

These two cases nuance subtle but important differences, which also differ from the artifactual effect that arises when functional networks are measured with the correlation coefficient. In the case of the latter, the apparent increase in clustering is purely an artifact of the measure applied to the time series and can (and should) be controlled for with suitable reference networks as outlined above. Artifactual network properties introduced through preprocessing imaging data may be partly under experimental control and ideally should also be subject to correction. For example, spatial smoothing with a Gaussian kernel, a preprocessing step that is employed to redress misalignment between diffusion and

anatomical images, introduces exponentially-declining spatial correlations whose exact form can be analytically derived from knowledge of the FWHM of the Gaussian kernel. This knowledge could then be used to construct appropriate reference graphs that embody the same effect. If tractographic errors accrue voxel-wise, then their cumulative effect along a tract will also be an exponential function of distance. This function could (in principle) be explored and then controlled for through simulation. However, whilst the effect of head motion is also distance dependent (Van Dijk, *et al.*, 2012), its functional form (linear/exponential etc) has not yet been determined.

True geometrical effects on topology warrant separate consideration. The effects they impart, such as an increase in clustering (shown above) and non-trivial modularity (Henderson and Robinson, 2011) compared to topologically random networks are nonetheless real in the sense that they are the same as if generated with a purely topological rule independent of any geometry - and could hence facilitate functionally segregated information processing in neural populations. Non-trivial graph properties passively inherited from a geometric effect might hence still enter into the economic trade-off between minimizing wiring cost and maximising topological efficiency (Bassett, *et al.*, 2009a; Bassett, *et al.*, 2010a; Fornito, Zalesky, *et al.*, 2011; Bullmore and Sporns, 2012). Put alternatively, the evolutionary pressure to minimise global wiring length, whilst maximising adaptive network topology, could be partly effected through modifying the form of the relationship between connectivity and distance. Recent work, discussed below, has begun to examine this issue in more detail (Alexander-Bloch, Vertes, *et al.*, 2012; Vertes, *et al.*, 2012).

The extent to which high order network properties might arise from a geometrically-constrained probabilistic rule (with no additional topological rule) could be addressed by characterising the spatial dependence of connection strength in empirical graphs, and using this rule to create appropriate reference graphs that are otherwise random. These then represent the null distribution of any graph metric, such as small worldness, efficiency or modularity. Rejection of such a null would hence imply that an additional, specific topological effect was present in the empirical connectomic data. That is, such an approach would allow one to study whether the brain is more or less clustered, or more or less economical, than expected by its spatial embedding. Such an approach would also allow one to exclude between-group differences in such network properties that might only reflect a very simple low order geometrical statistic.

In summary, the choice of null model for benchmarking topological properties of the connectome is critical and should be dictated by both the network measure that is being benchmarked and the connectivity measure used to derive edge weights. For edge weights derived from diffusion tractography, the choice is relatively clear-cut: degree-distribution matched random networks are appropriate for path length, while degree-matched lattice networks may be more appropriate for the clustering coefficient. For edge weights derived from pairwise measures of statistical association, the choice of null model should factor out any nonrandom topological structure inherent to the measure of association (e.g. transitivity). Null models that preserve the distance-dependence of real, spatially embedded networks allow one to characterize additional topological processes that may be superimposed for functional purposes.

3.4. Interpreting graph theoretic measures

Many graph theoretic measures were developed to study complex systems other than the brain and have since been adapted to suit neuroscientific ends. They should thus be used judiciously and interpreted cautiously. For example, many studies summarize the connectome using measures computed on a node-wise basis. These measures are then averaged to compute a scalar summary characteristic of the network. Naturally, care must be taken when using such a coarse description, and it is possible that such averaged metrics may mask more subtle or focal effects occurring in specific sub-sets of nodes. In certain cases however, such summary metrics have shown behavioural and/or clinical significance (Bassett*, et al.*, 2009b; van den Heuvel*, et al.*, 2009; Lynall*, et al.*, 2010; Fornito, Zalesky*, et al.*, 2011; Zalesky*, et al.*, 2011).

The extent to which each measure provides a meaningful representation of brain function should also be considered. A prime example is the use of path-length based measures such as the characteristic path length, L, global efficiency, E_g, and betweeness centrality, BC. These measures are based on finding the shortest possible path between node pairs, defined as the number of connections on the shortest inter-connecting set of edges. Path length is inversely related to the global efficiency of the network (Latora and Marchiori, 2001); i.e., low L is associated with high E_g. Similarly, nodes that are more frequently located on the shortest path between nodes have high BC, based on the assumption that they absorb a heavy proportion of network traffic. Though intuitively appealing, these measures assume that information propagates throughout the brain along the shortest path between regions. This assumption seems unrealistic, as it assumes that each neuron (or collection of neurons) has global knowledge of network topology and is able to efficiently find the shortest path to its target. The vast number of possible paths in a network as complex as the brain renders this

assumption implausible. Rather, alternative routing strategies that require only local knowledge may provide more realistic models of information-processing in the brain (Boguna, *et al.*, 2009; Telesford, *et al.*, 2011; van den Heuvel, Kahn, *et al.*, 2012; Goni, *et al.*, 2013). Despite this ambiguity, path length-based measures have shown replicated associations with cognitive performance (Bassett, *et al.*, 2009b; Li, *et al.*, 2009; van den Heuvel, *et al.*, 2009; Zalesky, *et al.*, 2011), strong heritability (Fornito, Zalesky, *et al.*, 2011; van den Heuvel, van Soelen, *et al.*, 2012), and sensitivity to disease (Rubinov, Knock, *et al.*, 2009; Lynall, *et al.*, 2010), suggesting that they do index functionally relevant properties of connectomic organization. Such measures likely reflect an upper limit on the efficiency with which information may be routed throughout the brain, since this limit is determined by the shortest path between regions. It is nonetheless interesting that individual differences in this putative upper bound show meaningful phenotypic and genetic associations.

The above issues are not unique to path-length based measures. For example, variations in the clustering coefficient are often interpreted as indexing the degree of local information-processing in a network. In spatially embedded networks such as the brain, locality is defined by spatial rather than topological relations between nodes. Thus, any putative measure of "local" information-processing in the brain must account for spatial constraints on connectome architecture. Similarly, many commonly used techniques for mapping the modular architecture of the connectome, such as the popular Newman-Girvan algorithm (Newman and Girvan, 2004), implement a hard segmentation of nodes into unique modules. In reality, brain regions interact with different sub-networks, thus yielding an overlapping modular architecture. Methods for dealing with such architectures have been developed (Palla, *et al.*, 2005). In combination with techniques for dealing with signed weights (Rubinov and Sporns, 2011a) and characterizing multi-scale architecture (Meunier, *et al.*, 2011), these

algorithms will provide more realistic representations of the modular character of the human connectome. The development of novel, neurobiologically principled measures that more accurately capture the dynamics of information propagation throughout the connectome will be an important avenue of future work.

3.5. Generative modeling

Analyses of empirical connectivity data suggest that specific, isolated changes in topological properties due to a disease process - or an experimental manipulation - are the exception rather than the rule. A straightforward interpretation of this effect is that the disease impacts on different topological properties independently. An alternative, more likely proposition is that the observed changes are the final outcome of a single underlying, generative mechanism that is only partially indexed by any single topological metric. A major strength of graph theory is that it is well suited to the generation and evaluation of competing generative models designed to explain the pattern of differences observed between groups.

Growth models are a popular class of generative models for explaining complex network topology. This approach involves growing networks *in silico*, via the addition of nodes and edges – or the rewiring of existing edges - according to specific rules, and then comparing these networks with empirical ones. An examplar of this approach is the preferential attachment model of Albert and Barabasi (Barabási and Albert, 1999), whereby preferentially adding edges to high degree nodes generates scale-free networks. Similarly, the Watts-Strogatz model illustrates how a small-world topology can be obtained by randomly rewiring a varying number of edges in a lattice (Watts and Strogatz, 1998a). Extensions of this work using neurobiologically plausible constraints (Kaiser*, et al.*, 2007; Nisbach and Kaiser, 2007),

or an activity-dependent Hebbian rewiring rule (Gong and Leeuwen, 2004; Rubinov, Sporns*, et al.*, 2009), have been used to generate networks with properties thought to be important for the brain. Recently, it has been demonstrated that growing networks according to relatively simple rules, such as penalizing long-distance connections and favouring connections between nodes with common neighbours, can reproduce empirically observed variations across a range of topological properties of brain functional networks, including modularity, global efficiency and clustering (Alexander-Bloch, Vértes*, et al.*, 2012; Vértes*, et al.*, 2012). Moreover, varying model parameters reproduced the topological disturbances seen in people with schizophrenia. These findings accord with the view that non-trivial network topology can arise from simple low-level geometric effects, and additionally show how these might account for between group differences.

The clinical potential of these models are beginning to be realized. In one study, a biophysical diffusion-model of disease progression for neurodegenerative disease was applied to anatomical connectomes constructed using DWI-tractography (Raj*, et al.*, 2012). The model identified a hypothesized pattern of disease progression that accurately predicted the spatial distribution of atrophy observed in Alzheimer's disease and behavioural variant fronto-temporal dementia. In a separate experiment graph theoretic measures were used to disambiguate competing models of disease progression in neurodegenerative disease (Zhou*, et al.*, 2012). Each model made distinct predictions about which nodes would be most vulnerable to disease effects based on their topological profile within the network. The data supported a model of transneuronal spread, in which nodes with short path lengths to putative epicenters of disease-related pathology were most vulnerable to atrophy. These studies suggest that model-based connectomics can help test between different models of disease pathophysiology and, potentially, predict patterns of illness progression. Dynamical

models, involving the simulation of biophysically plausible neural mass models on empirically derived anatomical connectivity architectures are also proving useful for understanding the relationship between connectome structure and function in health (Honey*, et al.*, 2007; Deco*, et al.*, 2009; Breakspear*, et al.*, 2010; Cabral, Hugues, Sporns*, et al.*, 2011; Deco and Jirsa, 2012) and disease (Honey and Sporns, 2008; Alstott*, et al.*, 2009; Cabral, Hugues and Deco, 2011; van den Berg*, et al.*, 2012).

Discussion

The accumulation of large connectomic datasets across spatial scales, data modalities and clinical populations has ushered in an exciting era of neuroimaging science, while also challenging the field to find meaningful summary statistics of system organization. A graph theoretical approach provides the opportunity to address this challenge, providing a rich repertoire of summary metrics, new means of constructing and testing specific hypotheses, and a conceptual approach that positions brain network science within the broader context of complex systems (Sporns, 2010). Following tremendous progress and interest, we were invited to retrace some of the unresolved challenges that pervade this approach for this Special Issue on the human connectome.

We have reviewed the graph theoretical approach to connectomics from two perspectives, those of constructing and those of analyzing the resulting network. Key challenges related to *constructing* a graph involve developing methods for measuring nodes and edges that represent adequate representations of biological reality (e.g., Table 1 and Figure 1). These challenges arise from the need to represent the brain as a set of spatially discrete, internally homogenous nodes, and of unambiguously assigning edge weights to the connections or

interactions between these. Misspecification of either is a known limitation on inferences that can be hence drawn (Smith*, et al.*, 2011a). Attempts to define valid nodes will no-doubt benefit from developments in quantitative *ex vivo* and *in vivo* techniques, ideally integrating anatomical and functional properties. However, a single universally accepted definition of nodes – valid across functional and anatomical studies, and invariant to context or question – seems unlikely to be achieved in the near future. Edges are typically quantified using grossly simplified measures. For anatomical networks, it is often unclear which DWI-derived measure represents an appropriate, biologically informative index of connection weight, though developments in using more quantitative indices may soon help resolve this problem. Challenges in the definition of functional connectivity include dealing with non-stationarities, incorporating task-dependent changes, and mapping directionality. Advances in effective connectivity centre on methodological challenges associated with inverting models of networks that are sufficiently large to warrant a graph theoretical approach.

Key challenges associated with *analysing* connectomic graphs include developing a rigorous statistical framework for thresholding networks, comparing graphs, and generating group-level representations; defining novel measures of network topology and dynamics that represent appropriate models of brain structure and function; formulating an array of appropriate null models and guidelines for their judicious use; and developing a systematic framework for the development and validation of novel generative models of network growth, dynamics and disease processes. Recent progress has been made on several fronts, particularly as related to dealing with the multiple comparison problem; developing multivariate classifiers with potential clinical relevance; computational modeling of pathophysiological mechanisms causing connectomic disturbances in different brain disorders; specific null models suitable for particular analyses; appropriate interpretation of

graph theoretic metrics; and the development of measures for dealing with unthresholded, weighted and signed graphs (Rubinov and Sporns, 2011a). In the absence of other methodological innovations, care must be taken to understand how variations in connectivity weights impact network topology, and to characterize the effect of different thresholding strategies on study findings.

An interesting remaining question concerns the value of reducing a complex network such as the brain to a small number of summary statistics such as, for example, the small-worldness index (Humphries*, et al.*, 2006). Such measures have played an influential role in brain network science and the characterization of myriad other complex systems. Whilst conceptually enticing however, single summary metrics may be limited in many settings as they do not permit localization of an effect to specific circuits or regions should they occur. Furthermore, group differences in relatively complex topological metrics might be better explained by basic effects involving the integrity of certain connections. In these cases, greater insight may be revealed by identifying the more basic underlying effect, rather than using a higher-order, whole-brain summary measure. However, care should also operate here, as the notion of functional integration in the brain is an important one so that even such simple, low-level effects may be subsequently compensated for by large-scale network reconfiguration. A pragmatic approach is to test hypotheses in a hierarchical manner, starting with low-level features, such as connectivity strength, degree distribution and geometry, before progressing to investigate higher order topological features such as modularity or small-worldness. This can be achieved using suitably constructed reference graphs, where the choice of which properties to preserve and which ones to randomize can be tailored to each specific hypothesis.

In parallel, generative models, preserving important geometrical features of real brain networks may here again play an important role in testing specific hypotheses (Henderson and Robinson, 2011). By simulating the effect of "virtual lesions", generative models also allow the exploration of putative disease mechanisms that impinge upon network structure and function, particularly those that move away from purely theoretical models of network generation towards biophysically derived models of network dynamics and rewiring (Jirsa*, et al.*, 2010). Such an approach could also be used to determine whether different generative models predict distinctly different network properties and hence different data features. This could be exploited, subject to constrained assumptions about the nature of measurement effects, to specify the posterior likelihood of a specific generative network model given an empirical network. Using a variational Bayes approach, such an approach would then permit inversion of generative network models from empirical data and allow investigators to disambiguate between competing hypotheses that each embody - an approach that has been very successfully employed in other neuroimaging areas (Penny*, et al.*, 2003; Kiebel*, et al.*, 2008; Woolrich*, et al.*, 2009). Whilst this approach already underlies the estimation of effective connectivity in DCM (Friston*, et al.*, 2003), the same inferential framework could be employed to study structural networks, for example disambiguating true geometric influences on network topology (by embodying those in a generative model of structural connectivity) from those due to measurement artifacts (by incorporating these into an observation function). This is an intriguing possibility that would herald the maturation of the field from the question "Is the brain a complex network?" to "What kind of complex network best describes the brain?"

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Figure legends

Figure 1. Illustration of desirable attributes of an ideal connectomic map in comparison to the maps currently generated in typical neuroimaging experiments. **A:** Schematic of an "ideal" connectomic map. Node role heterogeneity is represented by different colours. The edges are directed (arrows), weighted (edge thickness) and encode different forms of inter-regional interaction (solid vs broken lines). The maps also vary over time. **B-D:** illustration of the connectomic maps currently generated with functional MRI (fMRI) and diffusion-weighted imaging (DWI). Node heterogeneity is not represented using any approach. Most studies examine static properties of the connectome, focusing on cross-sectional assessment only. fMRI techniques such as DCM allow representation of directed, weighted and heterogeneous (e.g., modulatory) edge types, though only for small networks (**B**). An increasing number of fMRI studies are examining undirected, weighted and heterogeneous edges, where heterogeneity is modeled simply as a distinction between positive and negative functional connectivity (**C**). A large number of both fMRI and DWI studies analyse undirected and weighted edges (**D**). A substantial number of studies focus on undirected and binary networks (**E**).

Figure 2. Illustration of how neglect of signs on edge weights can distort topological inferences. Shown here is an example graph in which the width of each edge is proportional to its weight, positively weighted edges are represented by solid lines and negatively weighted edges are represented by dotted lines. Colours represent the modular identity of each node, as would be revealed using a decomposition algorithm that only uses the absolute values of edge weights (i.e., ignores the signs of the weights). In this case, intra-modular connectivity is stronger that inter-modular connectivity. However, note that edge 3 is negatively weighted. An algorithm that accounts for signed weights would place node B in the red module, as the

total contribution of negative edge weights within a module should be minimized (i.e., negative functional connectivity implies segregation or competition) (Rubinov and Sporns, 2011b). Signs can also affect estimation of shortest paths. Taking only absolute values, the shortest path between nodes A and B involves edges 1, 2 and 3. Accounting for the fact that edge 3 is negative however, and assuming that information should propagate along positively weighted connections, the shortest path would involve edges 1, 2, 4 and 5.

Figure 3. Illustration of the network-based statistic (NBS). **A:** the NBS is analogous to cluster-based thresholding in traditional fMRI activation mapping studies. In this work, a cluster is defined as a set of supra-threshold, spatially contiguous voxels. The statistical significance of the size (or mass) of each cluster is then determined with reference to an appropriate null distribution. **B:** With the NBS, the size (or mass) of graph components–sets of nodes that can be linked via a set of supra-threshold edges–is computed, and its significance is evaluated with reference to an empirically generated null distribution (e.g., via permutation testing). **C-D:** illustration of the superior power of the NBS over traditional thresholding techniques, such as the false discovery rate (FDR) (Benjamini and Hochberg, 1995). Shown here are results for a comparison of resting-state functional connectivity between healthy controls (n = 15) and patients with schizophrenia (n = 12). White elements represent edges in the connectivity matrix showing significant group differences. Even at a lenient FDR threshold of q = .10, only one edge is declared as showing a significant difference (**C**, two non-black elements are shown because the matrix is symmetric). In contrast, the NBS reveals a distributed sub-network showing significantly reduced functional connectivity in patients (**D**), as illustrated using the anatomical overlay in **E.** Images reproduced, with permission, from Zalesky et al. (2010)

Figure 4. Illustration of the relationship between thresholding and connectivity weight. **A**: a representative functional connectivity matrix taken from a single schizophrenia patient (left) and control (right) from the sample analysed in Fornito, *et al.* (2011). The network comprised 78 anatomical nodes interconnected by 3003 edges, defined using a beta series correlation technique. **B**: the distribution of connectivity weights is shifted towards lower values in the patient (red) relative to the control (blue); the area shaded in red highlights the excess number of low weighted values in the patient's connectivity matrix. **C:** the differences between using a weight-based threshold, τ, and a connection density-based threshold, κ; applying the same τ threshold (solid lines) to the patient and control (e.g., $\tau = .20$) results in different connection densities whereas applying the same κ threshold (e.g., κ; broken lines) results in a different minimum correlation weight threshold, τ. **D**: the correlation matrices after τ-matched thresholding. The minimum weight in the matrix for the patient and control is the same and the mean weight is approximately equal, but the connection density is very different. **E**: the connectivity matrices after κ-matched thresholding. The connection densities are equivalent, but the minimum and mean weight for the patient is lower than for the control. Thus, the patient's connectivity matrix will contain more low-value, potentially spurious weights, giving rise to a more random topology. Figure reproduced with permission from Fornito et al. (2012).

Figure 5. Biases associated with using correlation and partial correlation coefficients to estimate functional connectivity. **A:** Schematic illustrating the distinction between direct and indirect connections between regions *u* and *v*, with respect to a third region, *i*. **B:** Black line illustrates the association between the correlation value on the direct and indirect path for a correlation network generated using completely random time series comprising 10 values (similar results were obtained for 64, 128, 256 and 512 time points). Blue line illustrates the

association for a corresponding network that has been topologically randomized using a rewiring algorithm (Maslov and Sneppen, 2002). Red line illustrates the theoretical lower bound. **C:** The association between correlation values on the direct and indirect path for random networks generated using partial correlations. **D:** Normalized clustering (blue line) and path length (red line) for random networks generated using the Pearson correlation coefficient. The values have been normalized relative to the same properties computed in topologically rewired networks. A topologically unbiased connectivity estimate should yield values equal to 1. In this case, the extent of clustering is much greater than expected by chance. **E:** The same topological properties computed for partial correlation networks. In this case, the extent of clustering is much less than expected by chance. Images reproduced, with permission, from Zalesky et al. (2012).

Figure 6. Illustration of the influence of spatial embedding on topological measures. **A:** Examplar single subject of the dependence of functional connectivity on inter-node distance. Red crosses show homologous inter-hemispheric correlations. Blue crosses show all other pair-wise correlations. Black line shows best fitting exponential function. **B:** Random connectivity matrix with hyperbolic distant dependent strength and density with a 15% sparsity. **C:** Corresponding topologically (weight-preserving) random matrix. **D:** Clustering, path length and small world index of random matrix with hyperbolic distance penalty, normalised to a corresponding topologically random matrix. **E**: Same as panel **D**, but with exponential distance penalty.

Table 1. Ideal characteristics of nodes and edges and current progress in meeting these goals.

	Ideal characteristics	*Progress*
Nodes	*Comprised of functionally/anatomically homogeneous units (intra-nodal homogeneity)* The constituent units comprising a given node (e.g., voxels) should be homogeneous according to the anatomical and/or functional criterion used for node definition.	There are no valid macroscopic criteria for aggregating voxels into functionally/anatomically homogeneous nodes, necessitating the use of heuristic criteria. Recent work suggests that definitions based on quantitative analysis of imaging signals (Glasser and Van Essen, 2011) or multi-modal data integration (Eickhoff, Stephan*, et al.*, 2005) are possible.
	Functionally diverse (inter-nodal heterogeneity) Different brain regions are specialized for different types of information-processing and these diverse roles (e.g., sensory, motor, polymodal, etc.) should ideally be represented in a connectomic map.	Accurately modeling functional specialization of the entire brain is difficult in practice and is a major goal of neuroscience. To some extent, such specialization may be contingent on each region's connectivity profile with other areas (Passingham*, et al.*, 2002).
Edges	*Directed* Each anatomical connection emanates from a source region and links to a target; each interaction represents the causal influence of the activity in one region on the activity in another.	It is not currently possible to differentiate afferent from efferent anatomical connections with DWI. Accurately estimating directed and/or effective functional interactions across the entire brain with fMRI is a challenging and burgeoning area of research. Most studies currently use undirected measures.
	Weighted Connections between regions vary (i.e., are weighted) according to the strength of their interaction.	Both fMRI and DWI provide weighted estimates of inter-regional connectivity, though the appropriate weighting scheme is often unclear. Weights are often ignored for analytic simplicity.
	Heterogeneous Regions make different kinds of connections (e.g., excitatory, inhibitory, modulatory) with other parts of the brain.	It is not possible to distinguish different anatomical connection types with DWI. fMRI allows distinction between positive and negative covariations in regional activity (Fox*, et al.*, 2005). Effective connectivity further allows modeling of modulatory connections (Stephan*, et al.*, 2008). These distinctions are often ignored however.
Both	*Spatially embedded* The brain is spatially embedded and its connection topology is to a large extent constrained by spatial relations between nodes (Kaiser and Hilgetag, 2006; Bassett*, et al.*, 2010b; Vertes*, et al.*, 2012).	Spatial relationships between nodes are readily accounted for by standard stereotaxic mapping techniques. In DWI studies, special care must be taken to exclude spurious connections (e.g., trajectories crossing the intra-hemispheric fissure).

Dynamic Both regional boundaries and inter-regional interactions change across multiple time-scales, from transient, stimulus-evoked perturbations of functional dynamics to changes in anatomical pathways associated with development, ageing and experience-dependent plasticity.	Long-term (i.e., days-to-years) changes in anatomical and functional networks can be mapped through longitudinal imaging. fMRI methods for assessing dynamic network changes over tens of seconds, or in response to varying task conditions, are emerging. Resolving sub-second changes is only presently possible with EEG and MEG.

Table 2. Summary of different approaches to node definition in imaging connectomics[a]

Parcellation	Description	Strengths	Limitations
Anatomical	Node definitions based on *a priori* anatomical information, such as sulcal and gyral landmarks (e.g., (Tzourio-Mazoyer, *et al.*, 2002; Desikan, *et al.*, 2006))	Rapid & intuitive parcellation; low computational burden; high reliability	Low resolution; likely low validity; large variations in node size
Random	Randomly parcellates brain into discrete nodes of similar size, and at varying resolutions (e.g., (Hagmann, *et al.*, 2007; Zalesky, Fornito, Harding, *et al.*, 2010))	Minimizes node size variations; multi-resolution	Unclear validity/reliability
Functional	Node definitions based on *a priori* functional information, such as coordinates of peak activations or meta-analytic results (e.g., (Dosenbach, *et al.*, 2010))	Strong validity, given research hypotheses; good reliability; equal node sizes	Definitions are data-specific; difficult to apply to diffusion data; may miss some regions; definitions based on activation criteria may be unrelated to connectivity
Voxel-based	Each image voxel represents a distinct node (e.g., (van den Heuvel, *et al.*, 2008))	Data-driven; good reliability; high resolution	Unclear validity; computationally intensive; risk of spurious short-range connectivity due to partial volume/smoothing effects

[a] References to reliability concern the anatomical consistency of node definitions, not the consistency of measures computed using these approaches over time (e.g., inter-session reliability of specific topological properties).

Table 3. Summary of three major dimensions along which most tractography algorithms can be classified

Dimension	Approach	Description
Probabilistic vs deterministic	Deterministic	Propagates single trajectories in accordance with the principal direction of water diffusion (e.g., (Basser, *et al.*, 2000)). Does not estimate the spatial uncertainty of the trajectory.
	Probabilistic	Samples a direction distribution function at each step to determine the propagation direction. Allows estimation of a probability density of the most likely location of the tract, and thus its spatial uncertainty (e.g., (Behrens, *et al.*, 2003)).
Local vs global	Locally greedy	Trajectories propagate incrementally using a near-sighted, voxel-by-voxel approach (Basser, *et al.*, 2000; Behrens, *et al.*, 2003). Can be affected by noisy voxels.
	Globally optimal	Estimates the globally optimal path between two regions, typically by representing voxel-wise water diffusion as a connected graph and finding the shortest path between seed and target voxels (Iturria-Medina, *et al.*, 2007; Iturria-Medina, *et al.*, 2008; Zalesky, 2008; Zalesky and Fornito, 2009). More robust to noise.
Single vs multi-direction	Single direction	The direction of water diffusion in each voxel is represented using the primary eignvector of the diffusion tensor (Basser, *et al.*, 2000; Behrens, *et al.*, 2003). Does not distinguish crossing fibers.
	Multi-direction	The direction of water diffusion in each voxel is represented using an orientation distribution function (Tournier, *et al.*, 2004; Behrens, *et al.*, 2007). Allows resolution of crossing fibers, but requires good quality, high angular resolution data.

Table 4. Summary of main approaches used to examine task-related functional connectivity in fMRI studies

Approach	Description
Beta series correlation	Estimates inter-regional correlations of trial-to-trial variations in evoked activity to each task event, as modeled using event-specific regressors in a traditional GLM (Rissman, *et al.*, 2004; Fornito, Yoon, *et al.*, 2011). Yields condition-specific measures of functional connectivity but does not completely separate regional co-activation. Standard errors of beta estimates should be accounted for Applicable to event-related designs only.
Mean amplitude correlation	Estimates inter-regional correlations of trial-to-trial variations of event-specific evoked activity as quantified using mean signal amplitude changes time-locked to each event. Yields a condition-specific functional connectivity measure, but does not completely separate regional co-activation and makes strong assumptions concerning haemodynamic delays (Anticevic, *et al.*, 2010). Better suited to event-related designs.
Psychophysiological interaction (PPI)	Regression-based approach to estimate directed, task-related modulations of inter-regional functional connectivity. Isolates task-related interactions as distinct from task-unrelated connectivity and co-activation. Directional inferences are based on a priori designation of regions as either sources or targets (Friston, *et al.*, 1997; Minati, *et al.*, 2012). Applicable to block- and event-related designs.
Correlational psychophysiological interaction (cPPI)	Estimates correlations in task-related modulations of regional activity. Isolates task-related undirected functional connectivity as distinct from task-unrelated connectivity and co-activation (Fornito, Harrison, *et al.*, 2012). Applicable to block- and event-related designs.

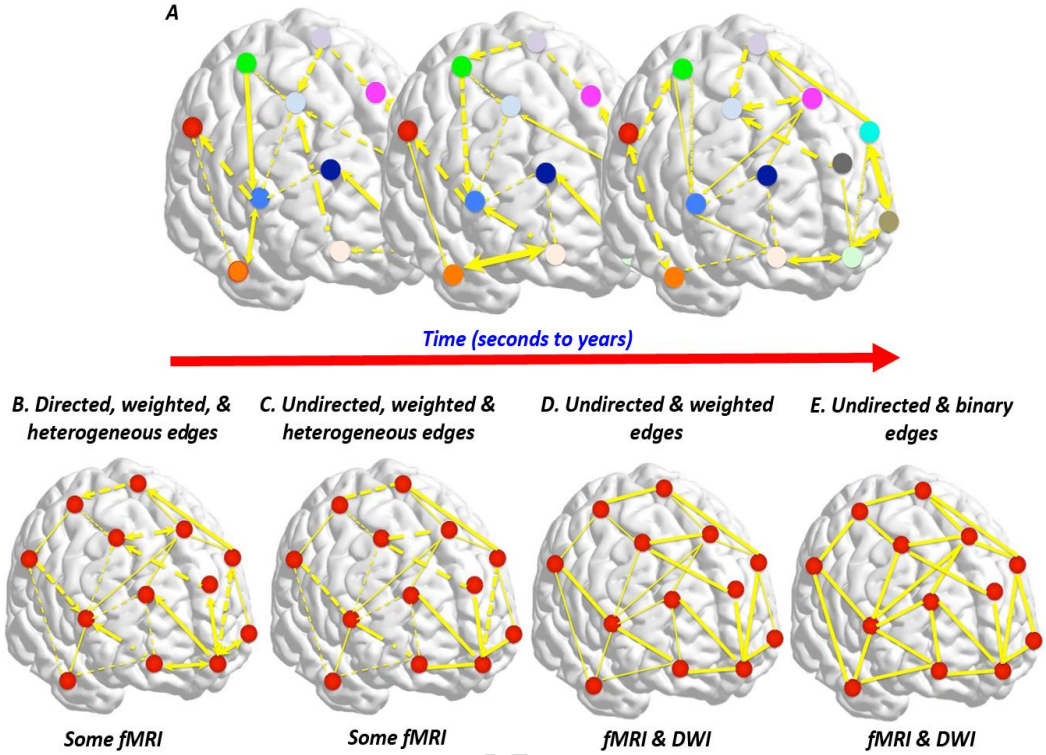


Fig. 1

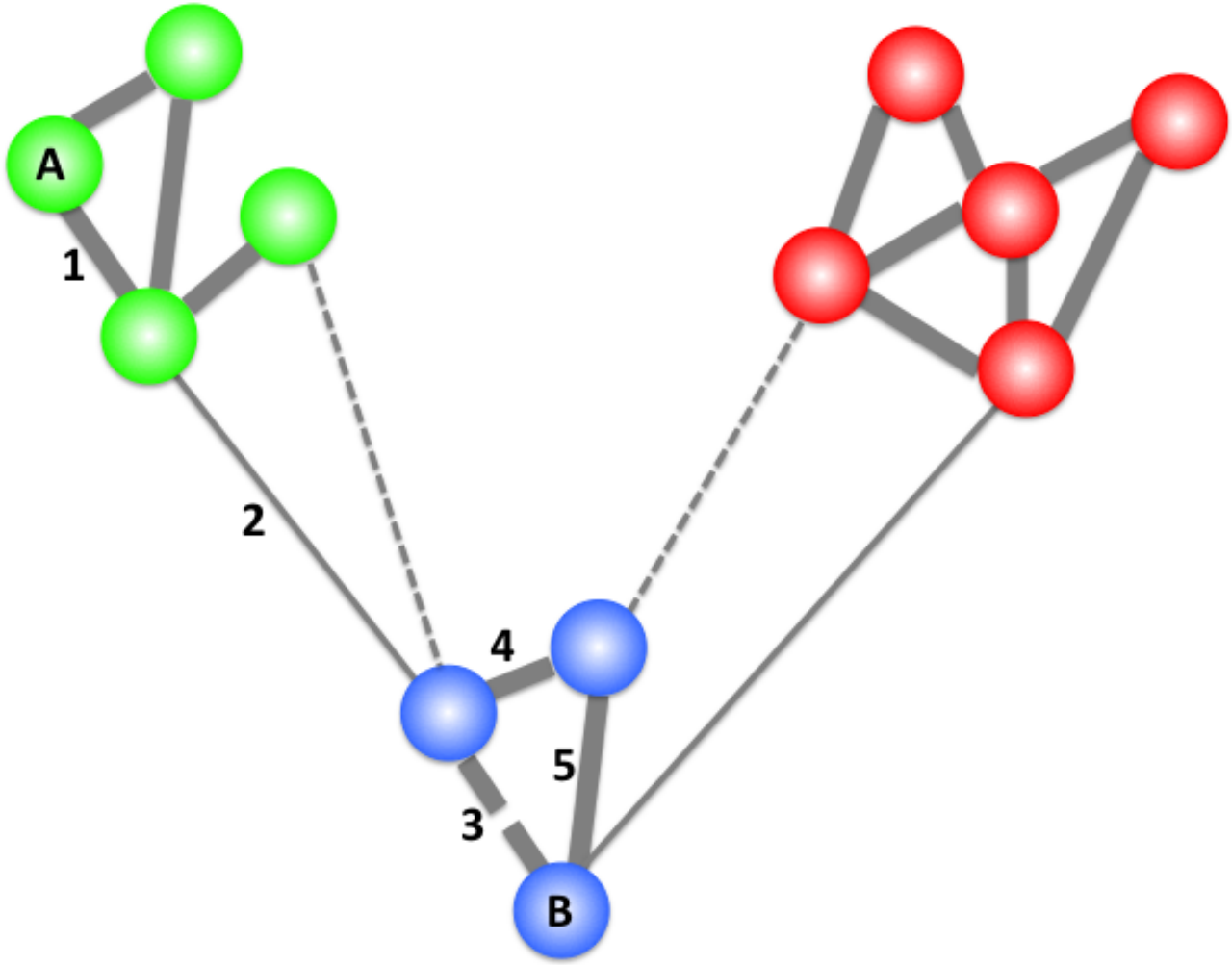
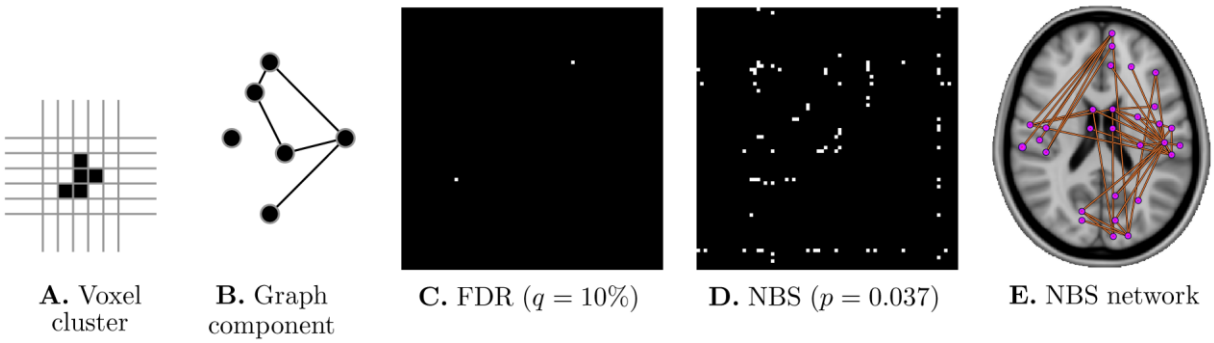


Fig. 2



A. Voxel cluster **B.** Graph component **C.** FDR ($q = 10\%$) **D.** NBS ($p = 0.037$) **E.** NBS network

Fig. 3

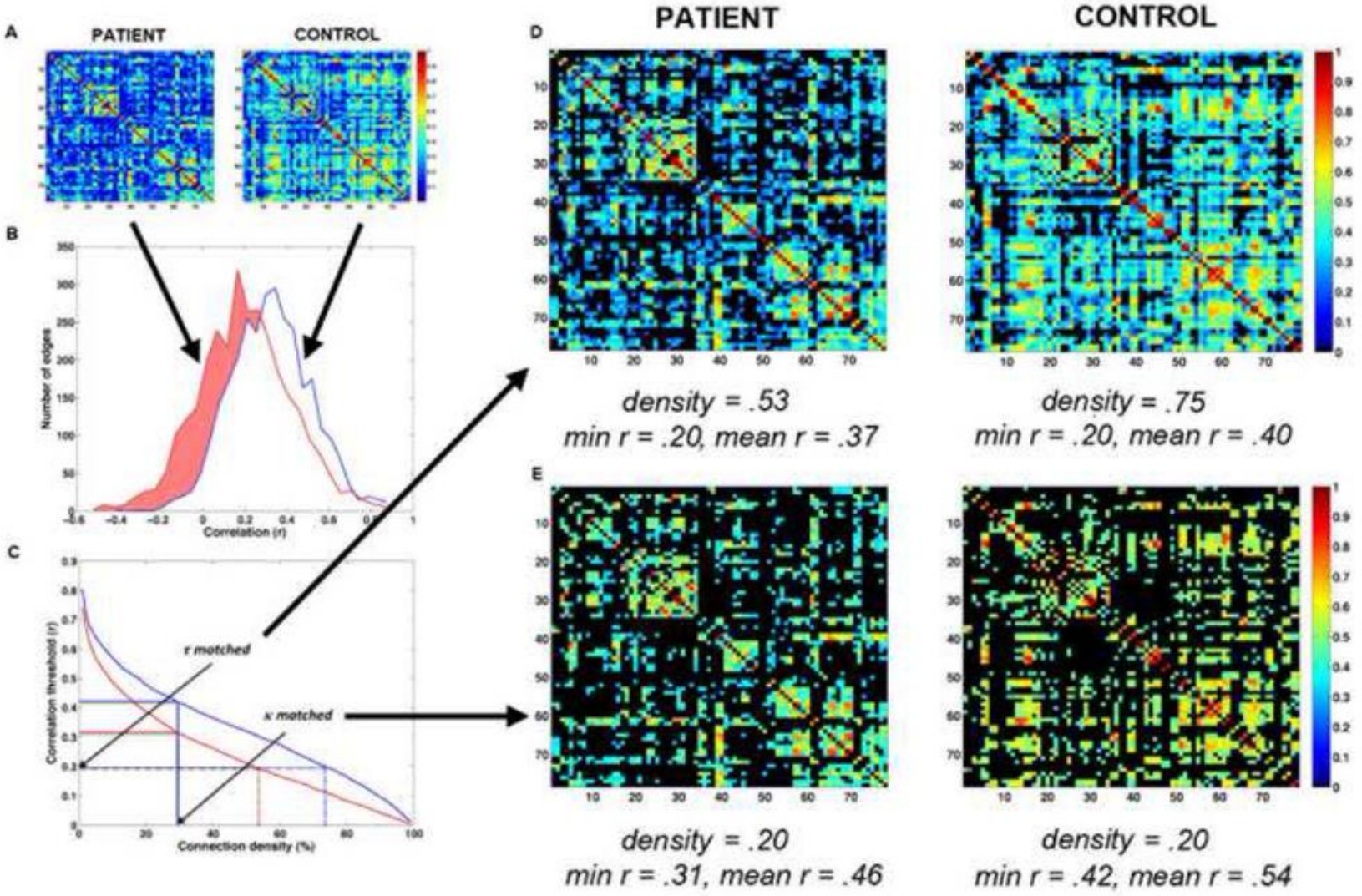


Fig. 4

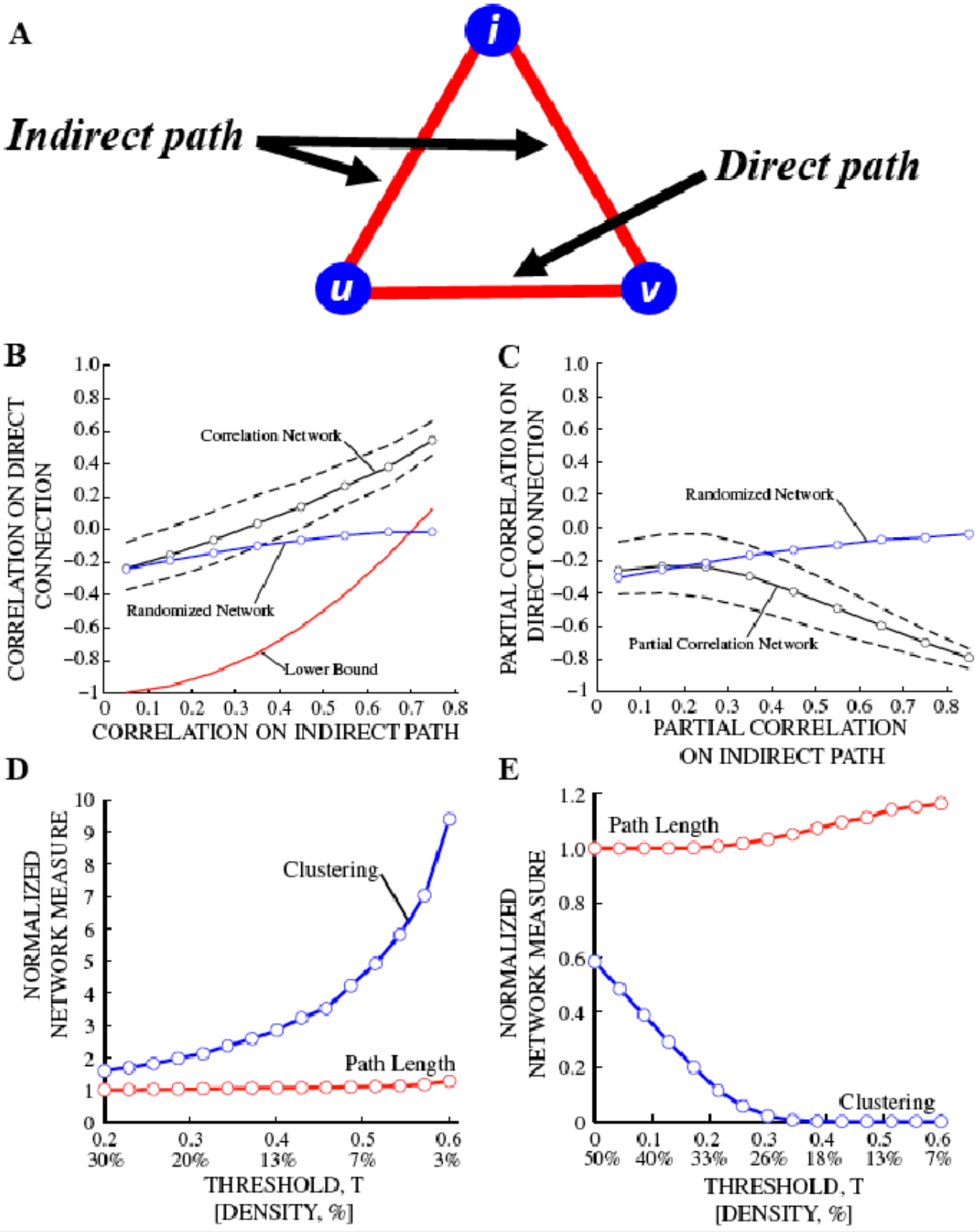


Fig. 5

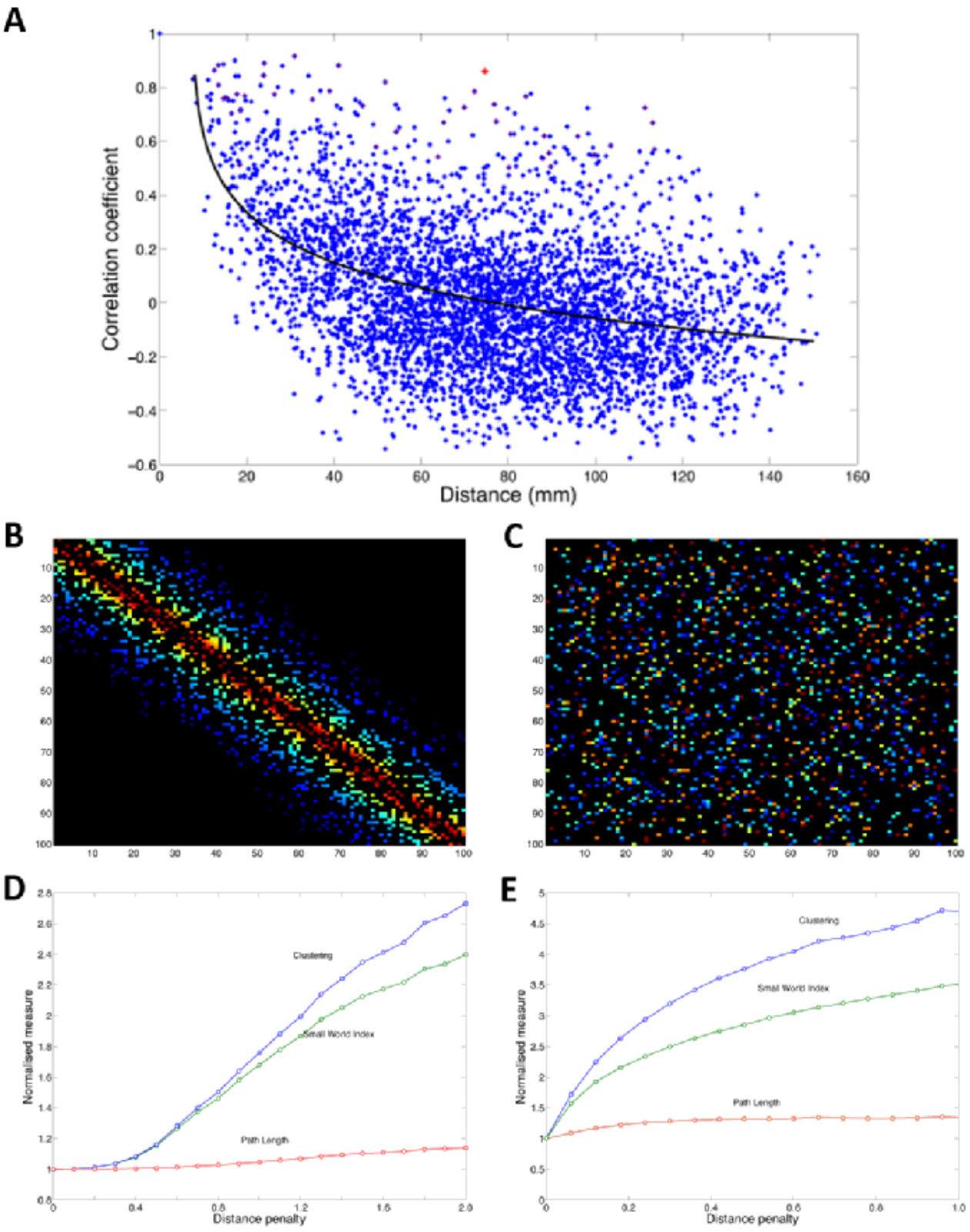


Fig. 6

Highlights

- Reviews progress and pitfalls associated with graph analysis of connectomic data
- Focuses on issues associated with building an analyzing such graphs
- Discusses characteristics of ideal connectomic map
- Considers issue associated with accurate node and edge definition
- Discusses key issues associated with analyzing and interpreting graph models