Syllabus contribution ISMRM Workshop

Title
How to Analyze a Network? Graph theoretical analysis of connectome maps

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The connectome

The (human) brain describes a complex system of anatomically interlinked and functionally interacting elements. If we examine the brain at the micro cellular scale, neurons are connected to other neurons by means of dendrites, axons and synapses. If we study the brain at the meso- or macroscale -like we mostly do with Magnetic Resonance Imaging (MRI) -, neural columns and large-scale brain regions are anatomically interconnected by long-range axonal projections, facilitating neural communication and functional interaction. The 'connectome' describes a comprehensive map of the connections of an organism's nervous system, and is believed to act as an anatomical basis for functional dynamics and functional interactions between brain regions to occur, and thus to be a requisite for brain function to emerge (Sporns, 2011; Sporns, et al., 2005). The field of 'connectomics' includes that part of neuroscience that is involved in the detailed mapping/reconstruction of the neural connections of the nervous systems of species, combined with the extensive studying of the structure of the derived brain wiring maps. In animals, Electron Microscopy (e.g. (Helmstaedter, et al., 2013) and tract-tracing approaches (e.g (Bota, et al., 2012; Markov, et al., 2013; Modha and Singh, 2010; Oh, et al., 2014; Scannell, et al., 1995; Van Essen, 2012)) have enabled the reconstruction of detailed (partial) connectome maps of the nervous systems of several animal species. In humans -in which invasive approaches are highly limited-, advances in diffusion-weighted, functional MRI and EEG/MEG have led the way to the *in vivo* mapping of structural and functional brain connections, and therewith the first reconstructions of the macroscale human connectome (e.g. (Hagmann, et al.; Hagmann, et al., 2008; Iturria-Medina, et al., 2008; Salvador, et al., 2005a; van den Heuvel and Sporns, 2011; Van den Heuvel, et al., 2008)).

Once a connectome map is reconstructed, the next frontier is the examination of its structure. What are the topological features that describe the complex organization of the system as a whole? The second part of the field of connectomics thus has the aim to elucidate key architectural features of

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the brain's connectome and study how these features may play a role in brain functioning (see for review (Bullmore and Sporns, 2012b; Sporns, 2011; Sporns, 2012; Stam and Reijneveld, 2007; van den Heuvel and Hulshoff Pol, 2010)). In the last decade, 'graph theory' (or 'network science') has become a more and more popular framework to study the organizational structure of reconstructed brain networks (Bullmore and Sporns, 2009). The goal of this morning workshop is to provide an -introductory- course on the topic of 'How brain networks can be analyzed using graph theory'.

Graph theory as a tool to extract key organizational features of brain networks

One way to approach the brain as a system is by describing it as a 'network' or 'graph'. Within this mathematical framework, the structure of a neural system is described as a collection of 'nodes' (which can be neurons, neural columns and/or large-scale brain regions) and 'edges' describing the connections interlinking these nodes (which can be axons, white matter bundles, functional interactions). [Figure 1 provides a schematic overview of the extraction of structural and functional brain networks from MRI data (Filippi, et al., 2013; van den Heuvel and Fornito, 2014)].

Once such a formal, mathematical description is established, graph theory can be used to describe the overall topological architecture of the network, allowing for the investigation of organizational features that would otherwise remain hidden when we would exclusively focus on information form single brain regions and/or single connections. One appealing aspect of the use of network science to describe and examine brain networks is that graph theory provides a vast array of data-driven metrics to describe the topology of networks (Bullmore and Sporns, 2009; van den Heuvel and Sporns, 2013). A number of such graph theoretical attributes have been shown to be particular useful in describing the organization of neural networks (Rubinov and Sporns, 2010). In what follows, a short introduction on a number of graph theoretical attributes commonly used in the field of MRI connectomics and their interpretation in context of the organization of neural systems is given [see Figure 2 for schematic illustration].

'Clustering' describes the tendency of nodes to locally link together, describing a high level of connectivity in the direct surrounding of a node. In brain networks, high levels of clustering (or its cousins 'local efficiency' and 'transitivity') and 'modular organization' -the tendency of groups of nodes to form densely connected subclusters or communities within the overall network- are thought to reflect functionally linked neuronal assembles, and thus to form an anatomical substrate for local information processing and functional segregation of brain systems (Sporns, 2013). Providing insight into the more global organization of a network, the 'characteristic path length' (or its inverse cousin 'global efficiency') reflects the ease of to which information can be transported across the network, summarizing the number of steps that -on average- have to be taken to travel from one node to another node in the network. Short path lengths (or high global network efficiency levels) in brain networks have been suggested to reflect high levels of communication efficiency between neural regions (Sporns, 2013). Networks with a high level of clustering (thus reflecting a high level of local organization), but still with a relative short average path length (thus reflecting high levels of global communication capacity) are referred to as 'small-world networks' (Watts and Strogatz, 1998), a class of networks known to exhibit properties of an efficient topological structure.

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Evaluating the above described graph theoretical metrics, network studies of the human, but also of the macaque, cat, mouse and rat brain, have shown evidence of brain connectomes to show an efficient small-world modular architecture, with high levels of clustering, short communication pathways, a pronounced functional and structural community structure (indicating the formation of locally segregated functional subdomains) (e.g. (Bassett and Bullmore, 2006; Hagmann, et al., 2008; Iturria-Medina, et al., 2008; Salvador, et al., 2005b; Stam, 2004; Van den Heuvel, et al., 2008)). Converging evidence suggests that these network attributes play a role in cognitive brain functioning (Bassett, et al., 2009; Li, et al., 2009; van den Heuvel, et al., 2009) and importantly, a growing number of patient-control studies tend to show that disruptions in graph theoretical attributes like clustering, path length and small-world and/or modular structure may play a role in the etiology and/or disease course of neurological and psychiatric disorders (see for review for example (Bassett and Bullmore, 2009; Crossley, et al., 2014; Filippi, et al., 2013; Fornito, et al., 2012; Pievani, et al., 2014; Seeley, et al., 2009; Stam and van Straaten, 2012; van den Heuvel and Fornito, 2014; van den Heuvel and Kahn, 2012)).

In addition to metrics describing the global structure of a network, graph theory also provides the opportunity to describe and examine the role of individual nodes in the overall network structure (describing a 'node-centric' analysis of networks). In this respect, 'degree' and 'centrality' graph metrics provide insight into the role of a node in the overall architecture of the network, for example elucidating nodes that show high connectivity and a central role in for example the communication paths across the network. Network studies of the brain have shown evidence of a heavy-right-tailed distribution of nodal connectivity (e.g.(Cole, et al., 2009; Sporns, et al., 2007; Tomasi and Volkow, 2010; van den Heuvel, et al., 2010)), suggesting a potential 'scale-free'-like (Barabasi and Bonabeau, 2003) type of organization (Bassett, et al., 2008; Eguiluz, et al., 2005; Van den Heuvel, et al., 2008), suggesting the formation of a small, but prominent present, group of highly connected 'brain hubs'. Recent connectome studies have suggested that these putative brain hubs show a tendency of densely connecting to each other, reflecting a potential 'rich club organization' of neural systems, indicating that the 'rich' nodes of the network form a mutually connected collective or 'club' in the overall network (Bullmore and Sporns, 2012a; Harriger, et al., 2012; Senden, et al., 2014; Shanahan, 2012; Towlson, et al., 2013; van den Heuvel, et al., 2012; van den Heuvel and Sporns, 2011; Zamora-Lopez, et al., 2009). Due to their high-degree and central embedding in the overall network, rich club regions and their connections have been hypothesized to form a backbone for neural communication and to thus form an anatomical substrate for neural integration between otherwise segregated functional systems (van den Heuvel and Sporns, 2013).

Shifting gear from a 'node-perspective' to a more 'edge-perspective' view of networks, graph theory also provides the opportunity to provide more insight into the role of the *edges* in the overall network architecture. Examples of edge-centric approaches include the evaluation of the contribution of edges to the communication capacity of networks (de Reus and van den Heuvel, 2013), the examination of recurrent classes of communication paths in networks (called 'path motifs') (van den Heuvel, et al., 2012), and approaches that compute the formation of so-called 'edge communities', being subsets of edges that play a similar role in the network (de Reus, et al., 2014). Furthermore, new, potentially powerful approaches in the examination of graph theoretical aspects of neural networks and their behavior over time include 'spectral graph theory'

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examinations (de Lange, et al., 2014), the examination of dynamical networks (Bassett, et al., 2013) and the use of dynamic simulation models (Deco and Kringelbach, 2014; Deco, et al., 2012). The use and understanding of these graph attributes with respect to brain networks and brain function is still in its infancy, but include highly promising new ways to get a better understanding of the structure and dynamics of brain networks. They underscore an ongoing expansion of the field of brain connectomics.

In this workshop we will discuss the use and application of standard graph theoretical metrics (e.g. degree, clustering, path length, modules) in the field of brain networks, talk about different types of global networks organization (e.g. small-world, scale-free, rich club organization) and their interpretation and implication in context of neural networks and brain function. In addition, we will also briefly discuss theoretical metrics such as edge based graph metrics (e.g. edge-classes, rich clubs, (path) motifs) and their potential application in the examination of brain networks.
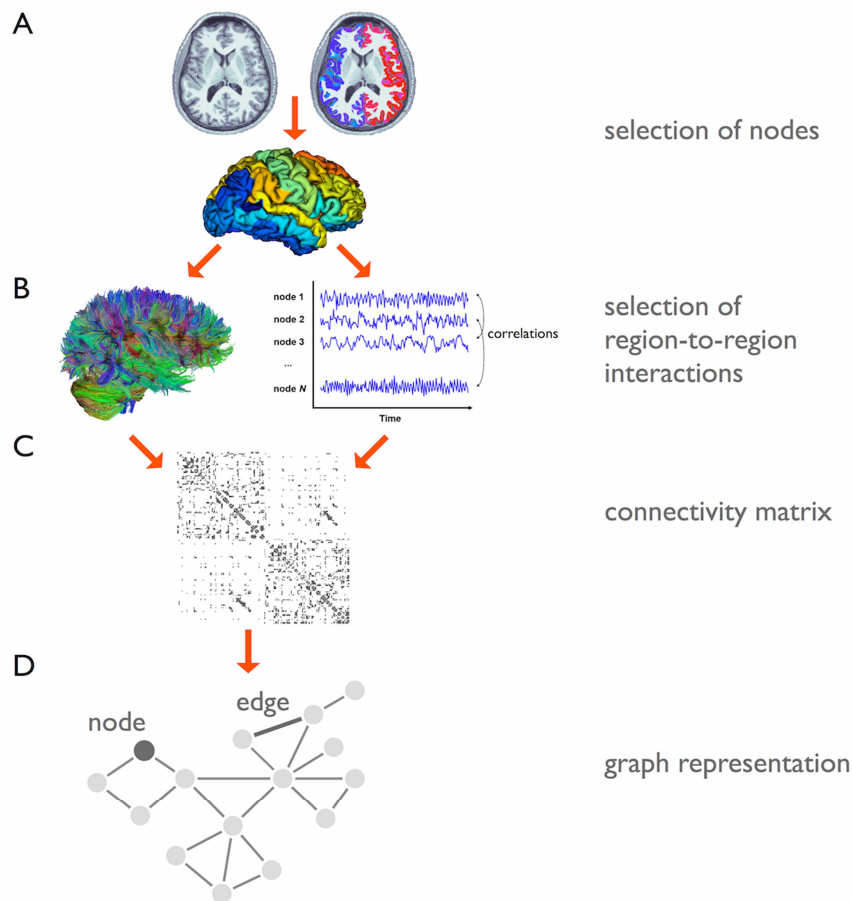
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Figure 1. Figure schematically illustrates how a brain network and graph can be derived from MRI data. **A.** Brain regions can be defined on the basis of segmentation and parcellation of grey matter of a T1 anatomical image or by selecting regions from a predefined brain atlas (e.g. the AAL template, Brodmann regions etc.). The segmented regions form the 'nodes' of the to-be-reconstructed graph. **B.** After the selection of the nodes, the 'edges' of the network are defined, reflecting the (level of) interaction between each of the brain regions. Examples of types of interaction include reconstructions of physical white matter pathways and their strength by means of Diffusion-Weighted MRI (DWI) or functional interactions by means of computation of the level of interaction (e.g. correlation) between resting-state fMRI/EEG/MEG time-series of brain regions. **C.** Region-to-region connectivity (i.e. the reconstructed DWI pathways or functional connectivity measurement) is computed for all region pairs (i.e. region 1 to region 2, region 1 to region 3, region 2 to region 3 etcetera) and stored in a so-called connectivity matrix. The connectivity matrix is of size N x N, with N being the total set of brain regions depicting the level of connectivity between each pair of regions. Cell entries of the connectivity matrix can include information on the presence/absence of connections (i.e. 1 or 0), but may also hold information on the strength of a connection (i.e. number of reconstructed streamlines, fractional anisotropy of the tracts or level of functional coupling), in which case we refer to the matrix as a 'weighted connectivity matrix'. **D.** The connectivity matrix describes a mathematical 'graph' with the columns and rows of the matrix describing the 'nodes' of the graph (i.e. the selected brain regions from A) and the cell-entries describing the (binary or weighted) interactions between the nodes referred to as graph 'edges'. Figure is adapted from (Filippi, et al., 2013; van den Heuvel and Fornito, 2014).
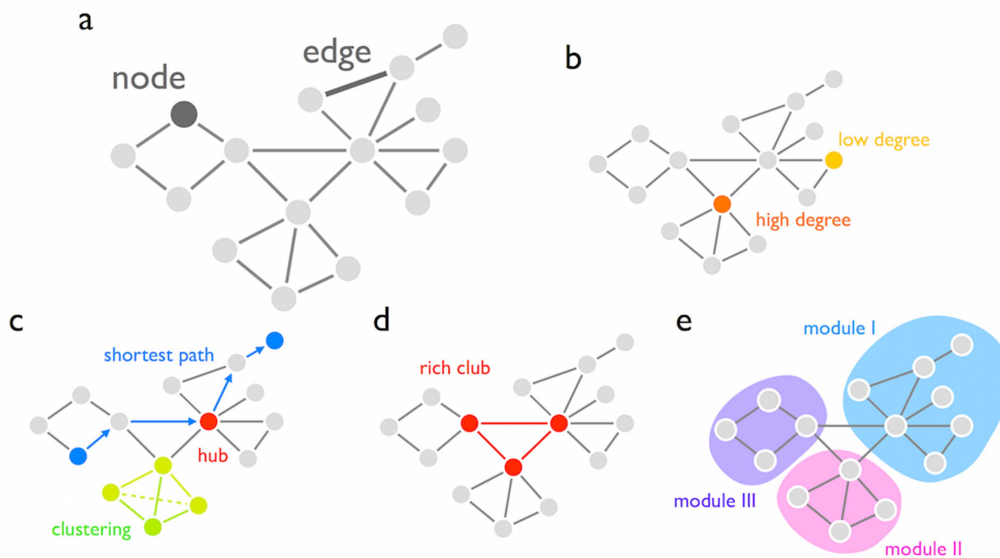
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Figure 2. Figure illustrates a number of graph metrics commonly used in MRI connectomics. **A.** A graph consists of a collection of 'nodes' and a collection of 'edges' describing the interactions between nodes. **B**. The graph metric degree expresses the number of graph edges per node. **C.** The (binary) clustering of a node reflects the level of connectivity between the direct neighbors of a node, computed as the ratio between the number of closed and possible triangles around a node. High levels of clustering are believed to reflect a high level of local organization and information segregation. The distance (or path length) between two nodes in the network describes the minimal number of edges that have to be passed when traveling from a node to another node in the network (blue arrows). In brain networks, relative short communication pathways are believed to reflect high levels of communication efficiency. A node with high level of connectivity and a central position in the network (for example hosting a large number of all shortest paths) is often referred to as a 'hub' (red node). **D.** A dense level of mutual connectivity (more than chance level) of connectivity between high degree hub nodes illustrates the formation of a 'rich club' in a network (red nodes and edges). **E.** Communities (blue, purple and pink) reflect groups of nodes that are relative densely connected to nodes within the same community, but relatively sparsely connected to the rest of the network. Figure is adapted from (van den Heuvel and Fornito, 2014).

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