Brain Morphological and Functional Networks: Implications for Neurodegeneration

Vesna Vuksanović *

1 Abstract

The highly complex architecture of brain networks has been characterised by modular structures at different levels of its organisation. Here, focus is on modular properties of brain networks from in vivo neuroimaging of cortical morphology (e.g., thickness, surface area) and activity (function). In this chapter I review findings on mapping of these networks, including the time-varying functional networks, and describe some recent advances in mapping the macro- and micro-scales of brain organisation. The aim is to focus on cross-level and cross-modal organisational units of the brain, with reference to their modular topology. I describe recent approaches in network sciences to form bridges across different scales and properties. These approaches raises great expectations that cross-modal neuroimaging and analysis may provide a tool for understanding brain disorders at the system level.

2 Introduction

Traditional approaches to the analysis of experimental recordings of brain activity have focused on the localization of function to specific regions of the brain. While such approaches have enabled progress in understanding neuronal processes in the healthy and diseased human brain, recent work suggests that the description of the brain as a set of independent functional elements is an oversimplification. Each brain region – far from acting in isolation – is functionally connected to other regions through structural white matter connections and through coherent activity [1, 2], creating a complex groups of interconnected functional units. The connectivity architecture of these units exhibits an extraordinary level of complexity, whose properties can be analysed across multiple scales – spatial, temporal or topological. To address these different levels of complexity,

*Vesna Vuksanovic
Email: vesna.vuksanovic@abdn.ac.uk
Aberdeen Biomedical Imaging Centre, University of Aberdeen; Health Data Research, University of Swansea, Swansea, United Kingdom. Preprint chapter to the book *"The Physics of Biological Oscillators"*

significant attention over the past decade has focused on mapping the large-scale networks of the human brain extracted from brain scans using Magnetic Resonance Imaging (MRI) [3, 4, 5]. The aim is to provide a picture of the brain and its connections at the system level.

A common simplified form for brain networks maps is a graph, in which brain regions (nodes) are linked to one another by network connections (edges) [6, 7]. The definition of a node or an edge is of critical importance to the relevance of the resulting brain network models [8, 9, 10]. Inspired by neuroanatomy, the definition of nodes and edges is commonly inferred from diffusion, structural or functional MRIs [9]. For example, nodes are defined by Brodmann areas [11], gross anatomical landmarks [12, 13], or increased functional activation [14]. Likewise, the number of streamlines identified between MRI voxels via diffusion of water along the axons [15], coherent/synchronized activity between voxels time series [16] or correlated morphological characteristics [17] are defined as network edges.

Another level of brain network complexity is the arrangement or nodes and edges, which defines network topology. Evidence has accumulated that large-scale brain networks are characterized by modular topology. This means that they contain communities – groups of nodes that are more densely connected to members of their own group than to members of other groups [18]. Modular architecture, with anatomically segregated and functionally specialised communities, is potentially naturally selected because it reduces metabolic costs [19]. From the graph theory perspective, these networks are preferred since they reduce the wiring cost (the average length and number of connections), which enables more efficient information processing [18]. Moreover, recent findings demonstrate that functional networks are enabled not only by critical modular interactions between brain areas, but also by swiftly reconfiguring patterns of these interactions [20, 21, 22]. Whether the subject is at rest [23], or performing either cognitively demanding or simplistic task, the patterns of functional connections between brain areas change, revealing mutli-layered community structures in time-varying brain activity. Time-varying dynamics of these networks accompany neurological disorders [24], brain injury [25], and psychiatric disease [26, 27].

The estimation of brain structural and functional connections is confounded by experimental limitations of MRI techniques. For example, limitations of diffusion MRIs to accurately reconstruct crossing-fibers within white matter is well documented. More importantly, diffusion MRI, which is predominately used as a surrogate for structural brain connectivity (i.e., physical links between the nodes based on white-matter fiber tracking), lacks tools for reconstruction of axonal connections within gray matter [28]. Given that functional connectivity maps gray matter networks, there is a growing interest in anatomical MRI, (i.e., 3D T1-weighted images) and gross morphological features that can be extracted from both gray and white matter using these images [29]. Anatomical MRIs are simple to acquire and are not limited by artifacts to the same degree as other MRI-based techniques.

To bridge the above experimental limitations, and provide a new insight into macroscale brain connectivity and its advantages, my focus in this review is on corticocortical

networks extracted from anatomical and functional MRI, namely morphological and functional networks. Corticocortical morphological networks are extracted using T1-weighted anatomical MRI, which is a non-invasive assessment of brain's structures at a sub-millimeter spatial resolution. Likewise, corticocortical functional networks are extracted using functional MRI (fMRI), which records brain activity via Blood-Oxygen-Level-Dependent (BOLD) signal as a proxy of neural activity at the whole brain level. For the purpose of this article, I will review evidences of (i) the corticocortical connections that are mediated by similarities in the cortical morphology (i.e., cytoarchitecture) (ii) the relationship between functionally relevant regional co-activity and underlying cytoarchitecture that may induce synchronized plastic changes among related brain areas (i.e., activity-dependent plasticity) and (iii) implications of this relationship to neurodegenerative syndromes. From the graph theory perspective, my focus is (i) on the modular organisation of brain functional and anatomical (morphological) networks, (ii) the time-varying modular topology of functional interactions and (iii) on describing the potential of modular interactions to inform theoretical and practical approaches to problems in neurodegenerative syndromes.

3 Graph Theory and the Brain

One of the mathematical frameworks for studying the human brain structural (and functional) organisation is graph theory. The brain network (graph) is modeled as a set of nodes and edges. Nodes and edges are elementary building blocks of networks and the definition of a node or an edge is of critical importance to the resulting brain network models [30, 31]. The arrangement of nodes and edges defines the organisation of the network, whose topology is quantified using statistical tools of graph theory. Another major property of brain networks is the discovery that they are modular by their topological organisation – they can be decomposed into groups of nodes that are more densely connected to each other than with the rest of the network. In what follows, I will describe in greater details these critical brain network elements and their topological properties, with reference to the two brain networks in focus.

3.1 Brain Network Node

A challenging question in the field of large-scale MRI-based brain network analysis is: how to define meaningful nodes for a brain network? The solutions range from defining nodes using the native resolution of the MRI technique (i.e., voxel-wise resolution) [32], validated parcellations of the cortex based on anatomical or functional landmarks [12, 13] to using random parcellation to ensure equal size for each node [33, 34]. More data-driven approaches include connectivity-defined nodes [14], multivariate decomposition of MRI signal (using statistical techniques such as independent component analysis) [35, 16] or a priory definition of nodes based on meta-analysis [36].

Most of studies on anatomical and functional MRI networks use validated parcellations (brain atlases) to define nodes. The advantage of these methods is that they

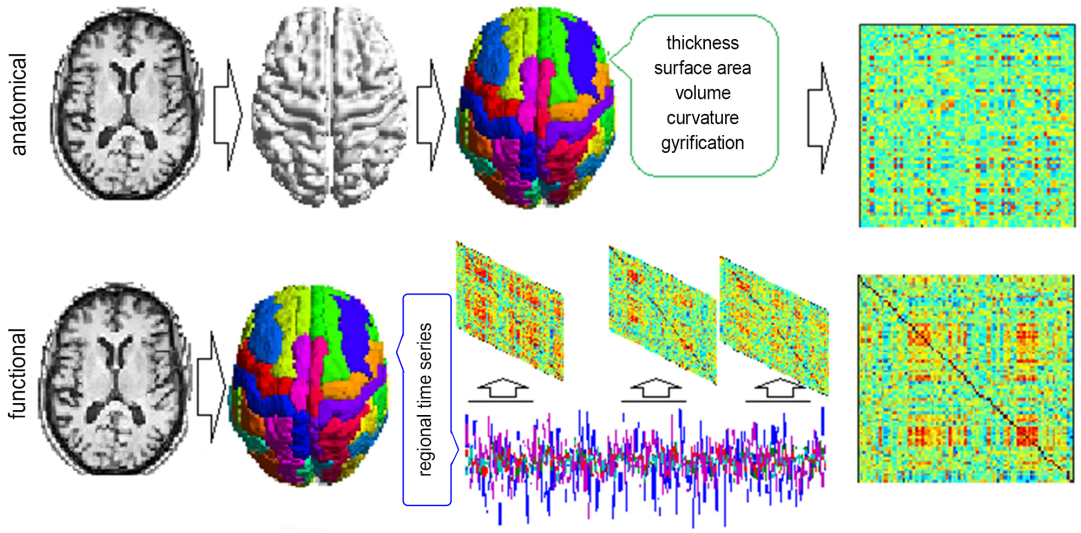

Figure 1: Brain networks from Magnetic Resonance Images (MRI). (Top Panel) Creating the structural correlation matrix on morphological features measured at different brain regions. From left to right: anatomical MRI, reconstruction of cortical anatomy from images and atlas-based parcellation of the cortex (regions are colour-coded), extraction of the morphological features (thickness, surface area etc.) and creation of the correlation matrix (colour-coded are edge weights). (Bottom Panel) Creating the functional correlation matrix on regional time series. From left to right: functional MRI, atlas-based parcellation of the cortex (regions are colour-coded), extraction of the regional time series and creation of the correlation matrix from pair-wise correlations between them (color-coded are edge weights). Time-varying functional correlation matrices are shown in the middle panel – each matrix is calculated as explained using sliding window approach.

are informed by measures of brain function and anatomy and tailored to test specific hypothesis about brain networks of interest. The limitation is that they are not always transferable across different imaging modalities. Nevertheless, findings show consistency in measures of network topology across different parcellation schemes and MRI modalities. Also, the basic estimates of brain networks organization such as node degree (number of nodal edges), clustering (number of triangles in the network) or path length (average number of edges between two nodes) are consistent across different parcellations with the same number of nodes. Modular organization, which is of interest here, is also consistent across anatomical and functional parcellations and modalities [37, 38, 39]. Future work could corroborate these findings by utilizing available random parcellations of the cortex and multimodal MRI techniques.

3.2 Brain Network Edge

In functional and morphological brain networks, edges are defined through an association matrix that captures relations (e.g. cross-correlation, mutual information etc.) between nodal features. The matrix maps all possible pair-wise statistical associations between either regional morphological features or time series of their activity. For the purpose of estimation of network topological organization, these matrices can be binarised – mapping presence (and absence) of associations (edges); or weighted – mapping strengths of association (edge strengths). There are differences in approaches to analyse these networks. Binarised networks are analysed over a range of binarisation thresholds to control for robustness and consistency of topological properties [40] and also for spurious/weak associations or noise [41]. Although arbitrary by its nature, threshold is usually determined by network's deviation from random, null-model topology [42] and the presence of small-world and scale-free topological properties [8]. Network edges can be weighted by the level (i.e., strength) of association between nodal interactions. In functional networks, edges are weighted by pair-wise temporal interactions, which are quantified either by correlation, coherence or synchronicity between time series [16]. In anatomical networks, the edges are weighted by statistical associations (e.g., correlations) between different regional features: thickness, surface area, volume or curvature [43, 44, 45], usually across groups of individuals.

Although neither functional nor morphological correlation are constructed on direct neural (axonal) connections between the regions involved, both networks are largely constrained by underlying structural network [46]. For that reason, numerous studies have been focused on functional interactions that mirror the local (segregated) brain anatomy and axonal links between such interactions [46]. However, the deviations between the these two suggest complex, many-to-one function-structure mapping [47, 48]. Here, focus is on how the brain cytoarchtecture underpins these patterns of structural-functional network associations. The relation between morphological and functional corticocortical connections, which are mapped by cytoarchitectonic and functional networks is discussed in the Section 4.

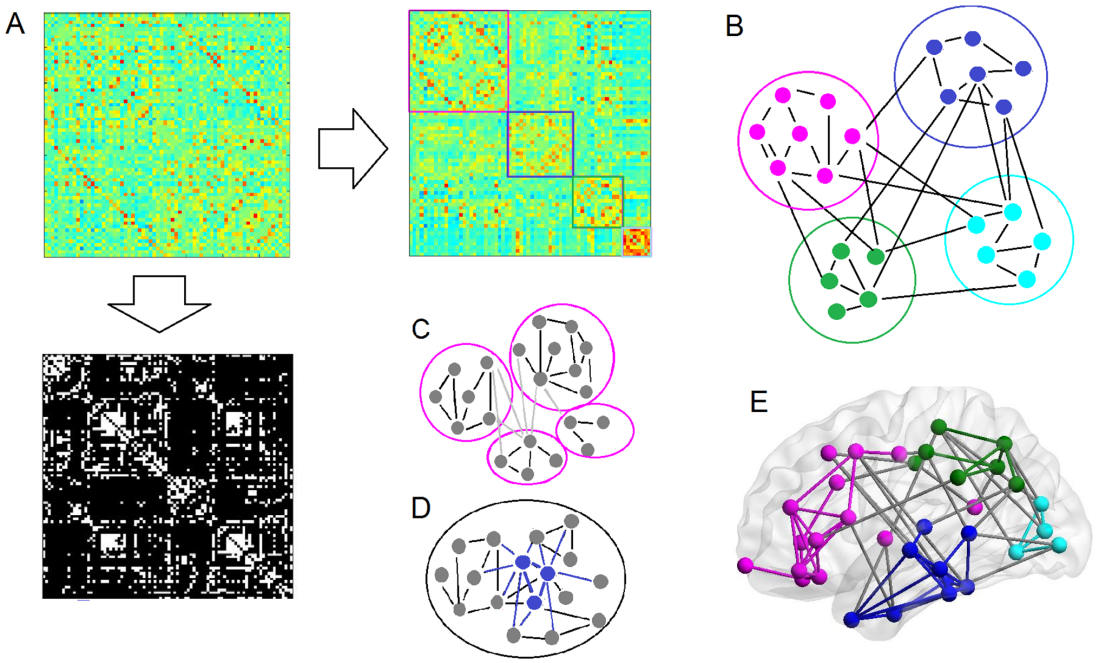

Figure 2: Characterizing the way that different brain region connect to each other. A brain network can be depicted using association matrix or graphs where the nodes are the brain regions and the edges are statistical associations (connections) between regions. Arrangement of nodes in the network defines its topology. (A) The example of an association matrix with the weighted edges (represented by heat-map colours) between brain regions. This matrix can be binarized at a given threshold (black-white matrix) and/or reordered according to modular connections between the nodes (as in the matrix indicated by right arrow). In this example network has four modules (colored in magenta, green, blue and cyan). (B) Another way to visualize this same network is in form of a graph. Nodes within one module are colored with different colours (same as in the matrix). In more general representation, topology of the network can be separated into segregated modules (magenta) (C) and integrative nodes and interactions (blue) (D). (E) Brain view (sagittal) of the network. In this example nodes and edges, that connect nodes within the same module, are visuilised using same colour, grays are edges that connect nodes across different modules.

3.3 Brain Network Modules

Modular topology is one ubiquitous characteristic of complex networks (including the human brain). Networks can be divided into modules by grouping the densely intra-connected sub-sets of nodes into a single sub-group (i.e., module). Algorithms for the division of a (real-world) network into modules are usually optimized to allow for sparse connections between groups (i.e., detection of overlapping communities) [49, 50]. Furthermore, detecting modules in the network may help to identify those nodes and their connections that may perform different functions with some degree of independence. At the same time, detecting modular structures that underpin specific function can be identified by characterizing interactions between those nodes that show relatively similar activity/dynamics [50]. Likewise, meta-analysis on more than 1000 fMRI has shown the existence of functional modules specialized for specific cognitive processes [51].

The brain appears to be divided into 'functional modules' whose intra-modular connectivity reflects the underlying structural (axonal) connections [46]. However, although functional modules usually mirror local brain anatomy, they also incorporate long-range interactions (i.e., those between spatially distant brain areas) [52, 53, 54]. More pertinent to this paper, the modular topology of brain functional (MRI) networks is documented across different parcellations of the cortex (i.e., brain atlases) [39, 55, 37]. Modularity as a property of morphology has been widely studied in the context of evolution and development [56]. Recent neuroimaging studies suggest modular organization of cortical morphology across regional thickness [44, 37], surface area [57] or volume [45]. There is consistency in the organisation of these networks whether they are based on correlating these features across individuals within one group [37, 57, 58] or correlating regional features of an individual brain [43]. The brain modular, yet integrated, functional organisation lowers the wiring cost (i.e., the average length and number of connections) of the network [59], thus potentially lowering metabolic costs [60] while providing more efficient information processing [18]. More importantly, modularity is also cognitively and behaviorally relevant; for example, it correlates with variations in working memory [61].

3.4 Dynamical Functional Networks

An additional 'layer' to modular organisation of brain networks is the notion of dynamical functional networks. In this context, the focus is on how likely regions are to change their "module allegiance" and synchronize their activity with a different set of nodes. The analysis of changes in network interactions over time utilises non-stationary, time-varying dynamics of neuro-imaging recordings. Up to this point, I have reviewed some of methods to map functional connections which predominantly utilize static network approaches (in which network edges remain constant throughout time) derived from graph theory [6, 62]. However, such approaches are unable to characterize or identify *changes* in regional interactions over time. Furthermore, the emergence of dynamic functional networks from static structural connections may resolve a fundamental understanding of how structure and function map onto each other.

A promising way to obtain a fundamental understanding of how patterns of functional connectivity change over time is the simulation of brain dynamics using a sophisticated modeling framework that implements nonlinear Kuramoto like dynamics on a physical network backbone informed by both structural (white matter) and functional (fMRI) connectivity maps [63, 53, 64]. At the same time, the computational models represent a powerful approach to bridge microscale and macroscale brain organization by simulation of large-scale biophysical models of coupled brain regions. Drawing on the same inspiration as the Virtual Brain Project [65], this approach builds on prior work with nonlinear models of neuronal activity (e.g., of Wilson-Cowan oscillators [66] or neural mass models [67]) by placing oscillators on an empirically-derived anatomical connection network, thereby directly accounting for heterogeneous connectivity between cortical and subcortical areas. The resulting large-scale circuit models can be used to simulate complex neural dynamics that are transformed into realistic resting-state fMRI (rs-fMRI) signals via an additional biophysical hemodynamic model [68].

4 Morphology and Function

Corticocortical interactions form a communication system which underpins sensory and higher cognitive and behavioural processes in the brain. It is important to identify specific network properties and how they facilitate this communication; are there general rules that govern organisation of these interactions? In this context, the hierarchical, modular organization is a widely documented across neural systems. A well studied example at the micro-level is modular columnar organisation of the neocortex (i.e., microscale of brain organisation that is related to functionally divided vertical formations of the cortical surface or cortical columns representing the basic functional units of the cortex). Although spatially distant, columns in cytoarchitectural areas usually share some common properties, which are repeated iteratively within each area, and are most commonly grouped into entities by sets of dominating long-range, intracortical connection [69]. While cortical microstructure is mostly used to describe local properties of individual areas, studies investigating cortical connections focus on the relationship between areas (i.e., their structural – morphological – features). Organization of long-range cortical connections across different brain areas can inform our understanding of how the cortical function emerges from structural constraints [70]. MRI studies take a simplified view of cortical morphology by reducing it to a single measure: the mean volume, cortical thickness, surface area, gyrification index or curvature. In contrast to functional networks, computed on correlations of regional fMRI across time within an individual brain, morphological networks are computed on correlations among regional morphological properties across subjects. Only recently, morphometric similarity networks were extracted on an individual brain [43]. The connectivity architecture of these networks is shaped by genetic and environmental factors (that are variable across individuals) [71, 70] and is related to human cognitive performances (e.g, general intelligence) [43].

Mapping a cross-scale organisation at micro- (cytoarchitectonic) and macro- (regional) levels, has shown evidence of a significant association between cytoarchitectonic

features of human cortical organization and whole-brain corticocortical connectivity [72, 73]. Findings suggest that aspects of microscale cytoarchitectonics and macroscale connectomics are related and may have the potential to reveal more about the etiology of neuropathological processes in the diseased brain (see Section 5). There is a number of studies regarding genetic influences upon the coordinated growth of spatially segregated areas during development (see for example [74]) or longitudinal (although) focal changes in morphology following training and learning new skills [75, 76]. With the exceptions of two recent studies [77, 37], comparative studies of whole-brain functional and morphological networks are lacking. Recent findings from fMRI studies, suggest that interindividual variability in functional connectivity is not uniformly distributed across the cortex: the association regions, including language, executive control, and attention networks, are likely more variable than the unimodal regions, such as the visual and sensorimotor cortices [78]. It is known that these cortices share similar morphology and projecting neural connections, which may pave the way to cross-analysis of these networks. Precisely because they cannot be reduced to spatially close regions, functional modules contain information about non-structural level of neural organisation, which can only be investigated via analysis of time series of neural function. An additional dimension to this investigation are temporal fluctuations in functional networks characterized by striking differences in network organization, in particular nodal affiliations with different modules. Understanding whether these time-varying behaviour of functional networks reflects a discrete cytoarchitecture organisation, may encourage a shift from from descriptive correlations to predictive mechanisms. If the later is true, each cytoarchitecture components and switching modules should exhibit similar spatial organisation.

5 Implications for Neurodegeneration

MRI studies assessing correlated changes in anatomical or functional regional properties have argued that neurodegeneration targets those networks that are highly correlated in healthy individuals [79], leading to a so called "disconnected network syndrome" hypothesis [80]. Moreover, recent findings on cross-correlated micro- and macro-architectures, in particular the size of layer 3 neurons (known to be affected in Alzheimer's disease) [72], may inform new approaches in studying neurodegenerative syndromes. Similar approaches have been successful in revealing patterns of distinct involvement of the two cortical features (thickness and surface area) in Alzheimer's disease and behavioral variant FrontoTemporal Dementia (bvFTD) [44]. However, more work is needed for these approaches to be validated in clinical settings. I suggest that for initial application of these methods, in line with [44], the connectome can be sampled at the resolution of anatomical landmarks to examine macro-scale organisational units of the cortex and the role of each units in the neurodegeneration. By formulating the problem of vulnerability to neurodegeneration as a problem of network topology, one can investigate how different regional morphological features contribute to this vulnerability. When nature of this vulnerability is clarified, the cross-scale networks could be studied [72]

to evaluate micro-scale connectivity. Finally, the roles in network vulnerability can be validated against functional and anatomical networks examined across range of parcellations schemes, including random parcellation. Thus, the joint properties of functional and morphological brain networks may offer better estimates of vulnerability to neurodegenerative syndromes. The examination of these networks across multiple temporal and spatial scales would represent dynamic network mechanisms underlying not-so-easily differentiated clinical states in these syndromes. These dynamic network interactions and their underpinning morphological properties could inform treatments in these diseases and may mediate treatments outcome.

6 Conclusion

Large-scale brain networks provide mathematical tools to assess functional and structural brain organisation upon simple network parcellation schemes and simplified network dynamics. This approach has been successful at providing the different functional and structural topologies of healthy and diseased brain [79]. Here I have provided a support for studies of cross-modal functional and anatomical (morphological) networks, which provide the opportunity to promote a basis for applying a unified network approach that can be extended beyond current approaches. Implementation of the network strategies suggested here will test: (i) how modular architecture of functional network is mediated by structural configuration at the meso- and micro-scales, (ii) that is possible to provide the link of functional network organisation with the cytoarchitecture and (iii) that research in these network properties will inform neurodegenerative models and treatments.

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