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A Network Neuroscience of Neurofeedback for Clinical Translation

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Abstract

In the emerging field of network neuroscience, the brain is represented as a network of discrete yet functionally and structurally interconnected areas. Mathematical and computational tools to characterize the organization of this network can provide insights into the principles guiding brain structure and function, and can pinpoint differences between healthy individuals and individuals suffering from psychiatric disease or neurological disorders. The field is now faced with the question of how to devise clinical interventions that target these network alterations. Potential solutions to this question include the combination of emerging theories of network control with cutting-edge interventions such as neurofeedback. Each of these techniques may now be mature enough to combine to obtain a theoretically-motivated framework informing viable neuropsychiatric therapies.

Keywords

graph theory; network science; neuroimaging; neurofeedback; control theory; clinical therapies

Introduction

The human brain is fundamentally a network, or a system of interconnected functional units [1]. Such a network can be formulated as a graph, a mathematically well-defined object that is amenable to empirical study. A brain graph represents areas or regions as network nodes, and it represents connections between those areas as network edges (Fig. 1) [2]. The graph representation of the human brain is conceptually flexible: inter-regional connections can either be structural in nature – for example, estimating the number or volume of white matter tracts between areas – or they can be functional in nature – for example, estimating the degree of functional influence that one area has on another. In the context of both structure

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and function, network representations have proven particularly useful in deriving organizational principles at a systems level [3].

Importantly, the network approach can also be used to better understand when these organizational principles are altered, or when the normative generative mechanisms supporting those principles go awry [4]. Indeed, by facilitating a comparison of healthy and diseased brains, the network approach has led to the discovery of characteristic differences underlying many neuropsychiatric diseases and neurological disorders [5], which may be responsible for the observed clinical symptoms. Despite these successes, it is not yet common practice to exploit network differences to devise viable clinical therapies. Establishing such a framework would offer a bottom-up approach, informing the development of neuromodulation therapies directly with features of the interconnected brain itself, to address the network-level functional alterations that characterize diseased brains.

The development of such a framework is challenging on many levels. For example, while it is often clear how a diseased brain network functionally differs from a healthy brain network, it is not well understood what functional alterations must be induced in the diseased network in order to reconfigure it into the healthy state [6]. To address this challenge, we must have a mechanistic, dynamic understanding of how the network functions. With such an understanding, we may be able to determine how a given functional alteration to the network impacts its function in the future, for example by bringing a diseased brain network back in line with how it is configured in healthy brains. This dynamic, mechanistic view of networks, known as network control theory (Fig. 2), is an established framework in other areas of network science and engineering [7], and is primed for extension into neuroengineering more generally and network neuroscience specifically [8]. Technical challenges must be addressed before clinically applying control theory, but those are not discussed here.

Moreover, once the necessary network alteration is understood, there must exist a means with which to induce such a change. In the context of neuropsychiatric disorders, this network alteration may be altered (higher or lower) functional connectivity between particular brain regions, the specifics of which may be disorder-dependent. To address this challenge, we consider the viability of neurofeedback as a mechanism to provide therapeutic brain network alterations [9]. Neurofeedback is a type of biofeedback wherein the subject is presented, in real time, with information derived from brain signals. The signals, which originate from electroencephalographic (EEG), functional magnetic resonance imaging (fMRI), or others imaging modalities, are presented directly to the subject, typically in audio or video format. This forms a closed loop system that enables the subject to regulate their own brain activity (Fig. 3). Using neurofeedback, a subject may be taught to stimulate a specific area or connection in their brain [10] that is thought, based on a mechanistic dynamic model, to be likely to create alterations in their brain network that may attenuate symptomatology.

In this brief article, we discuss the current state of the field supporting the development of neuromodulation therapies informed by brain network structure and function. We begin with a brief account of the application of tools from network science to neuroimaging data to

better understand the brain from a systems perspective. We recount seminal studies revealing network-level alterations in brain connectivity in disease states, and then we describe engineering-based theories of driving a network from an altered state to a healthy state via targeted interventions. We focus on findings from the past decade, with an emphasis on results from the past 2 years. We consider how this control framework might lead to the principled development of therapeutic interventions that capitalize on neurofeedback. Finally, we suggest that such a mechanistically motivated, bottom-up approach to neurotherapy has significant clinical advantages over the current manner in which therapeutic neuromodulation is delivered.

Network neuroscience

Essential to any therapeutic methodology is the correct identification of the target on which to intervene. In clinical scenarios when the target is a pattern of distributed changes in the structure or function of neural circuits, the tools of network neuroscience may be particularly useful. The unique contribution of the network approach lies in its ability to identify potentially complex patterns of functional differences in the brains of a healthy versus target population, rather than narrowly searching for univariate discriminative features. Capitalizing on this sensitivity to distributed features could enable the development of a therapy to correct those differences.

Network neuroscience is a mathematical, computational, and theoretical framework with which to understand the structure and function of the brain, and the interactions of its component parts [11, 12]. At the most basic level, network neuroscience views the brain as a system of nodes connected by edges. Traditionally, nodes are areas or regions of interest, often selected by parcelling the brain into a set of discrete non-overlapping volumes. Edges connecting nodes can represent structural relationships [2], for example defined by the number or strength of white matter tracts linking two brain areas [13]. Alternatively, edges can represent functional relationships, for example defined by the magnitude of temporal correlation between the activity of two brain areas [14]. The network approach breaks from the classical univariate view of brain activity by placing emphasis on the patterns of interactions between brain areas, rather than on regional activity alone. In this way, we study functional connectivity patterns in isolation, without considering regional activation, structural connectivity, or other types of information.

Interaction patterns can be quantitatively characterized using topological statistics to summarize networks in many different ways [15]. Arguably the simplest such statistic is node degree, which equals the number of other nodes to which a node connects (Fig. 1A). Network hubs are thought to have disproportional influence on brain function. Topologically, these are often high degree nodes, and are anatomically located in areas that are active in the brain’s default or baseline mode [16]. Complementing the notion of hubs, topological statistics can also be used to probe segregation versus integration of nodes or groups of nodes within the network. A characteristic marker of segregated network structure is modularity, or the presence of groups of densely interconnected nodes, which often perform similar functions [17] (Fig. 1C–D). Conversely, integration within the network can be captured by the characteristic path length, which reflects the average number of edges

that must be traversed to get from any node in the network to any other node in the network (Fig. 1B). In the human brain, longer path lengths are thought to be detrimental to efficient information transmission, and indeed evidence suggests that individual differences in IQ are correlated with individual differences in the lengths of paths through structural brain networks [18].

Using these statistics and the larger toolbox from which they come, network neuroscience can offer quantitative characterizations of brain networks and, significantly, uncover novel biomarkers in disease that could be used to inform clinical interventions. However, this approach has yet to be implemented.

Abnormal networks and disease

In recent years, network neuroscience in conjunction with fMRI has lead to the discovery of network discrepancies in many different neuropsychiatric diseases relative to the healthy population [19]. Specifically, topological statistics have proven to be useful biomarkers of schizophrenia [20, 21, 22, 23, 24], epilepsy [25], Alzheimer's disease [26, 27, 28], and autism [29, 30, 31, 32].

Many of these studies detail changes in interregional connectivity levels within individuals who have a clinical condition. For example, a large number of studies investigating autism spectrum disorder have revealed a complicated pattern suggesting global hyperconnectivity [33, 34], global hypoconnectivity [35], or, more likely, a complicated pattern involving both [36, 37, 5]. Additionally, fMRI studies of individuals with schizophrenia describe patterns of decreased striatal-prefrontal and striatal- limbic connectivity [38], as well as decreased connectivity from the ventral tegmental area and midbrain to several cortical and subcortical regions [39]. More recently, topological statistics have been included as features in a classifier to identify individuals with mild cognitive impairment with 93.3% accuracy [27].

Together, these studies – and many others like them – support the utility of network neuroscience as a mathematically rigorous framework in which to describe alterations in the brains of individuals with neuropsychiatric disorders. That is, with this set of tools, we are able to establish what state the brain is in, and how that state differs from the state of a healthy brain. Therapeutically, we would like to devise a way to bring the state of a diseased brain in line with that of a healthy brain, thus correcting for the disease. The traditional (time-invariant) network toolbox, being solely descriptive in nature, can not answer this question for us. Instead, we must seek tools that will give us insight into how to alter, or perturb, a network in order to reach a particular end state. This framework is particularly useful for neuropsychiatric disorders resulting from distributed pathology (pervasive developmental disorders, depression, etc.). This would be less appropriate for diseases of focal etiologies, such as epilepsy, stroke, Parkinson's disease, or multiple sclerosis. These disorders do not result from differences in functional connectivities, but rather from very localized pathology.

Control of networks

While topological statistics allow for the identification of functional differences in brain networks that correlate with disease, the tools cannot provide us with ways to therapeutically invoke that information. From a theoretical perspective, this critical gap is addressed by network control theory (NCT), a mechanistic - rather than descriptive -mathematical framework [40, 7]. Whereas network science can be used to establish which state the brain is in, NCT can in principle be used to predict (pending clinical validation) which targeted interventions will be most effective in bringing the functional connectivity of a diseased brain back in line with that of healthy brains via modulation of regional activity.

NCT is based on the notion that a change in the activity level of a given node will have rippling effects throughout the network [7]. Moreover, some nodes will have a different impact on the network than others, based on their specific location within the global topology. Intuitively, a high-degree hub could affect quite a different change on the network than a low-degree node. Nodes that can have a large influence (of any sort) over the network are referred to as control points [6]. NCT posits that with the identification of the correct set of control points for a given type of influence (Fig. 2a), and the identification of the correct way in which to modulate their activity (Fig. 2b), the brain can be driven from some arbitrary initial state (Fig. 2c) to some arbitrary target state (Fig. 2d), by inputting the correct energy pattern to the correct nodes (Fig. 2e) [8, 41].

As detailed above, many of the abnormalities that occur in neuropsychiatric diseases tend to be functional changes in the strength of connectivity between certain regions. Therefore, it would be useful to identify those control points that mediate the amount of connectivity between brain areas. From a theoretical perspective, control nodes that modulate connectivity between two different areas of the brain are called boundary control nodes [6]. There exists a set of boundary control nodes for every pair of modules within the brain network, and these nodes are theoretically predicted to govern the amount of functional connectivity between the modules. The theory predicts (although the predictions needs to be clinically validated), that with the correct boundary control nodes identified, the brain can be driven to an arbitrary state by interventions that modulate the activity of boundary nodes.

Boundary nodes possess the ability to control inter-regional synchronization, however, this is not the only tool available to us. Modal control nodes are able to steer the brain into difficult to reach states [6]. Manipulation of these particular nodes, for example, may help individuals achieve better task switching. Furthermore, average control nodes steer the brain into easy to reach states [6]. Manipulation of these nodes could allow the brain to relax to the default mode, and could perhaps assist individuals to reach a meditative state. Regardless of the choice of node, we must be able to modulate their activity level in order to steer the brain. In the next section, we propose that neurofeedback is natural way in which to change nodal activity in both healthy and diseased networks, and may prove useful as an effector of network control.

Neurofeedback in disease

Neurofeedback, a subset of biofeedback in which the subject is presented with feedback derived from their own brain signals in real time, is an established method with which to reconfigure brain networks. In neurofeedback, a subject is presented with features typically derived from a specific region of interest, and is asked to modulate the amplitude of those features (Fig. 3). For example, a specific frequency band of an EEG recording could be extracted from the electrode overlying a particular brain region, and the power of that signal could be displayed to the subject as a level on a thermometer or bar graph (Fig. 3c). Typically, the most frequently used neurofeedback modality has been EEG, however other modalities such as fMRI are recently beginning to be investigated due to their increased spatial resolution [9, 42].

Leveraging neurofeedback via fMRI to treat neuropsychiatric diseases has a rich recent history and touches a wide variety of clinical symptoms [9, 43, 44]. For example, by learning to voluntarily suppression activity in dorsolateral prefrontal cortex (responsible for engagement) and the right insula (responsible for regulation), participants can successfully suppress a specific phobia of spiders [45]. Furthermore, learned voluntary control in order to increase regional activity in the supplementary motor area and the parahippocampal cortex (responsible for memory), lead to a decrease in motor reaction times and a decrease in memory for specific words, respectively [46].

More clinically, neurofeedback has been used to teach war veterans suffering from post-traumatic stress disorder (PTSD) to regulate activity in their amygdala (responsible for emotion) to produce a meaningful decrease in clinical symptomatology [47]. Additionally, a set of patients with post-herpetic neuralgia (chronic nerve pain) were taught via neurofeedback to regulate the regional activity of the rostral anterior cingulate cortex (thought to be involved in pain perception), to successfully decrease their level of perceived pain [48]. While many of these techniques have produced meaningful results, the current state of therapeutic neurofeedback mediated neuromodulation has focused on regional activity while remaining relatively agnostic to interregional connectivity. This focus places the field at a disadvantage because neuropsychiatric diseases are thought to be disorders of connectivity [49, 50, 51]. Furthermore, those studies that do target inter-regional connectivity ([10, 52, 53] and [54] for a broad overview) do not establish mechanistically how the network changed to produce the observed results.

Historically, the decision of what exactly to feed back to the patient has largely been informed by results from behavioral neuroscience. For example, to treat depression, allow the subject to regulate the level of activity of areas associated with positive emotions [55]. To treat obesity, allow the subject to control the level of activity of areas associated with gustatory functions [56]. While this reasoning is intuitive, it lacks a mechanistic understanding of how neurofeedback is affecting the brain as a whole, challenging the optimization of delivery [57]. Without a mechanistic understanding of how the network needs to be altered to obtain a particular result, it remains challenging to knowingly limit the effects of the neurofeedback to the symptomatology being targeted, thereby minimizing undesired effects. Faced with the need to develop such an understanding, it is useful to turn

to recent advances in other fields like network neuroscience and control theory, for a holistic, mechanistic, and dynamical view of the brain that can inform the optimization of these clinical interventions.

Methodological Considerations

While above the argument that network science and network control theory are well poised for application to therapeutic neurofeedback is made, several considerations must be addressed. First, graphs must be considered within the context in which they were created, and studied accordingly. For example, a functional connectivity graph encoding the Pearson correlation coefficient of pairwise regional correlations makes the assumption that the data are normally distributed. Thus, the accuracy of the resulting graph depends on the validity of this assumption. As such, the distribution and character of the underlying data must be taken into consideration when performing any network analysis.

A central component of the above arguments is the notion of comparing the brain networks derived from healthy individuals with the networks derived from unhealthy individuals. Inherent in this process is the actual comparison of networks with each other. This can be a non-trivial exercise, especially when dealing with groups of healthy and diseased individuals. Exactly how to compare groups of graphs can be complicated: one can average each group, and compare two single statistics, or one can compute a statistic for each individual and compare two vectors of statistics. Generally, it is thought that averaging networks destroys information, and should be avoided [24, 58, 59, 60]. Comparison becomes more complicated when graphs are of different sizes or contain different weight distributions [61].

Modern network neuroscience generally involves the application of some parcellation to the brain, where signal is averaged within each parcel. The selection of parcellation scheme will, by construction, have an impact on the results of the study. However, without applying a parcellation to the brain, and performing analysis on a voxel-by-voxel basis, is computationally intensive and generally is avoided. One common way to mitigate the influence of specific choice of parcellation on results is to apply several different parcellations to the data and analyze the resulting timeseries through a common pipeline. In this way, it is possible to show that the main conclusion of the results is invariant with respect to the particular choice of the parcellation.

The above neurofeedback therapy synthesizes information from both functional and structural brain networks. While this approach explicitly accounts for the dynamic nature of functional connectivity within the construct of NCT, it is important to acknowledge that structural brain networks are dynamic as well, although on much larger timescales. The method presented here makes a simplifying assumption that the structural brain network is static, which imposes a temporal constraint on the usability of this therapeutic methodology. Specifically, the duration between structural mapping, and neurofeedback delivery must be short compared to the timescale of structural reorganization, as the neurofeedback is specific to the structural network mapped.

The therapeutic paradigm proposed here is entirely dependent on the data used to inform it. That is, specifics of the therapy emerge from both the structural and functional connectivity networks of an individual or group. These networks themselves, and any statistic or quantity derived from the networks, is a product of the method of data collection. Results will be dependent on the specifics of the imaging, as well as the pre-processing, which both require making assumptions about the data. Each assumption may trim information and narrow the field of view. Therefore, choices surrounding methods of imaging and preprocessing must be considered at length.

Lastly, the bulk of this methodology has yet to be experimentally validated. As such, the arguments presented here must be taken in context. Neurofeedback with the goal of modulating the activity of a specific brain area is difficult. Furthermore, network control theory as applied to brain networks has only been validated in simulation thus far. However, experimental validation is possible and likely is shortly forthcoming, as there presently are no significant methodological or technological boundaries.

Conclusions

Neurofeedback as a therapy has been successful in treating a wide array of neuropsychiatric diseases and their accompanying symptoms. However, a mechanistic understanding of how neurofeedback impacts whole-brain networks has remained elusive. Here, we describe network neuroscience and principles of network control that could prove useful in establishing a theoretically principled paradigm in which to deliver neurofeedback. Beyond clinical implications, developing a mechanistic model for neurofeedback opens a window through which to establish a deeper understanding of the diseases being treated.

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- Network neuroscience and its application to neuropsychiatric disorders is discussed
- Network control theory may fortify our mechanistic understanding of these disorders
- Neurofeedback is presented as a therapeutic tool for these disorders
- We discuss a framework to leverage these three methods for clinical therapy

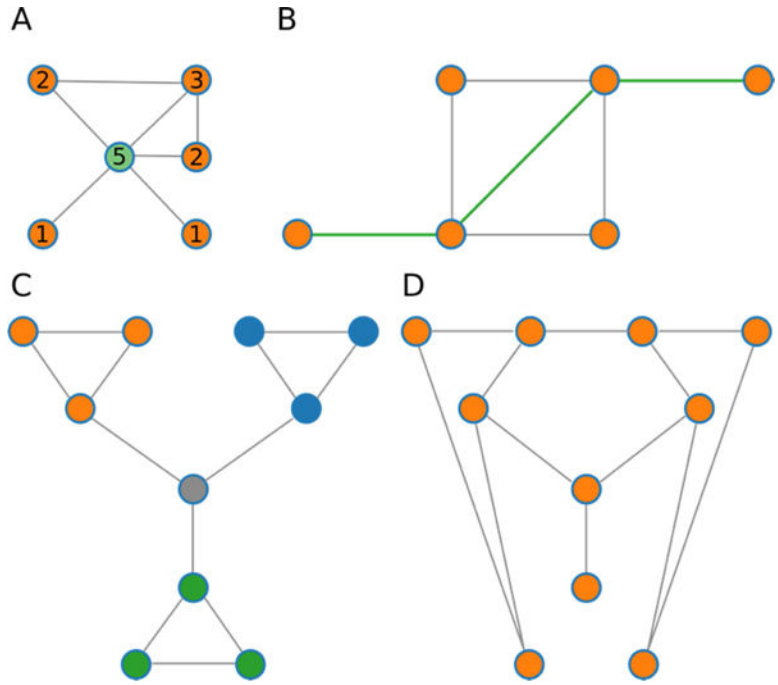

Figure 1.

Statistics to quantitatively characterize network organization in the human brain. (A) A schematic of node degree. The degree of each node is indicated by a number superimposed on top of it; the strongest hub node is located in the center of the graph, with degree 5, highlighted in green. (B) The shortest path length between two nodes is the path that traverses the fewest intervening nodes. In this schematic, the shortest path between the two outer nodes is highlighted in green. (C) An example of a modular network in which there are three groups of densely interconnected nodes. One module contains the orange nodes, another the blue nodes, and a third the green nodes; they grey node is not part of a module. (D) A non-modular network, to offer a contrast to the graph in panel (C).

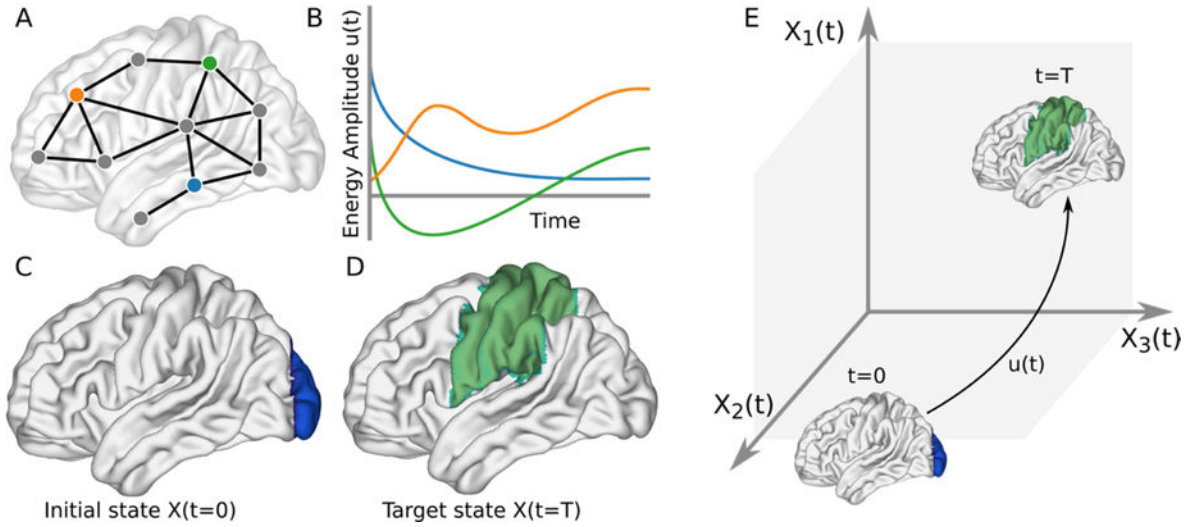

Figure 2.

Control of brain networks. By the identification of the correct control points (A), and the identification of the correct energy modulation function over time (B), a brain can be brought from an arbitrary initial state (C) to an arbitrary target state (D), by steering the brain state along a desired trajectory in regional activity space (E).

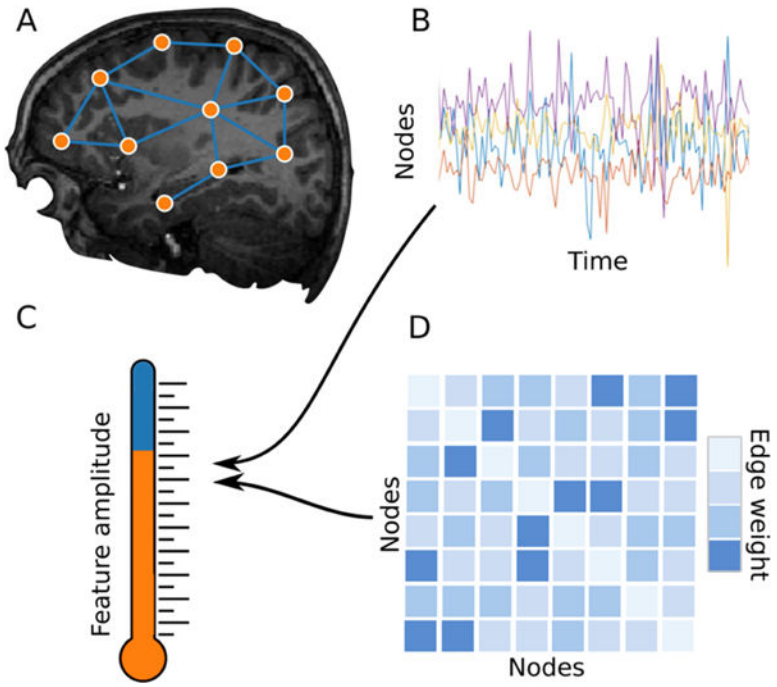

Figure 3.

Neurofeedback paradigms. (A) fMRI captures the activity level of brain areas over time. (B) Activity over time of specific pre-defined regions is extracted from the fMRI. Features can be extracted from these activity levels and displayed back to the subject via visual or auditory methods. (C) Alternatively, regional functional connectivity can be calculated from the regional time series, and information extracted from this data can be given to the subject. (D) The feature to be given back to the subject can be displayed via a visual thermometer, which the subject is observing, in order to construct a closed-loop system.