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Graphs of Brain Networks

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Abstract

Background: This commentary discusses the study by Telesford and colleagues in which they use network science to analyze resting state functional magnetic resonance imaging (rsfMRI) data collected in nonhuman primates.

Methods: Their findings using a network science approach in nonhuman primates are considered in the context of results from human studies.

Results: The network science approach to analyzing rsfMRI data from nonhuman primates yields results that are, for the most part, similar to results using alternative analyses methods in human studies.

Conclusions: Network science to analyze rsfMRI may promote a better understanding of the brain as a complex system.

Keywords

Graph Theory; Nonhuman Primate; Resting State; fMRI; Network Science.

IN “THE EFFECTS OF ALCOHOL on the Nonhuman Primate Brain: A Network Science Approach to Neuroimaging,” Telesford and colleagues (2013) use network science, previously used to analyze human data, to analyze functional magnetic resonance imaging (fMRI) data from nonhuman primates “at rest” for the first time. The network science approach models the relations between different brain regions by constructing a graph (e.g., Fig. 1). Brain graphs, made up of *nodes* (i.e., brain regions) and *edges* (i.e., physical or functional connections between brain regions), demonstrate properties such as small-worldness (a balance between network segregation and integration), modularity (decomposability of the system into smaller subsystems), and heterogeneous degree distributions (the likely presence of highly connected nodes or “hubs”). This approach models the brain as a system with multiple interacting regions that produce complex behaviors (cf., Bullmore and Bassett, 2011). In this study, graph analysis of resting state fMRI (rsfMRI) data from anesthetized monkeys (1 Rhesus macaque and 10 Vervet monkeys) revealed in both species overlapping hubs that included the medial prefrontal cortex, cingulate cortex, temporal lobes, and visual cortex. The Vervet monkeys additionally showed hubs specific to anterior cingulate and parietal lobe regions. These hubs were categorized as belonging to the “default mode network.”

Based on brain regions with highly synchronous blood-oxygen-level-dependent (BOLD) activity, analyses of human fMRI data collected during resting state (i.e., without task demands or at “rest”) have identified multiple “intrinsic functional connectivity networks (IFCNs)” (for review, see Sporns, 2010). Two popular methods of processing rsfMRI data are region of interest (ROI) and independent component analysis (ICA). The ROI analysis uses signals from seed regions (i.e., clusters of voxels delineating a known ROI) chosen a priori to seek significant correlations with synchronous activities of every other voxel of the brain, thereby providing a hypothesis-driven approach to identifying functional networks (Margulies et al., 2007; Van Dijk et al., 2010). ICA, a highly data-driven statistical approach requiring few a priori assumptions, separates BOLD signals into maximally independent, nonoverlapping spatial and time components before extraction of networks (Beckmann et al., 2005).

Correlated BOLD activity in the resting condition is believed to reflect intrinsic neural connectivity representing functional anatomical networks, the nodes of which are not necessarily connected structurally or that have connections yet to be identified (Beckmann et al., 2005; Buckner et al., 2008; Damoiseaux and Greicius, 2009; Krienen and Buckner, 2009; Raichle, 2009; Seeley et al., 2007). The first IFCN identified in humans was the “default mode network” (Raichle et al., 2001), comprising medial frontal, cingulate, and inferior parietal regions, as well as the precuneus (Greicius et al., 2003; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997); other studies include regions of the temporal lobe (Andrews-Hanna et al., 2010; Greicius et al., 2004; Minoshima et al., 1997) and lobules of the cerebellum (Habas et al., 2009). Functions ascribed to the default mode network include homeostatic and personal awareness, as well as readiness for impending action (Buckner et al., 2008; Raichle et al., 2001). Other IFCNs, considered pertinent to specific sensory or cognitive functions include the auditory, executive control, or salience detection networks (Greicius et al., 2003; Raichle et al., 2001; Seeley et al., 2007; Yeo et al., 2011).

Graph theory, although similar to ICA, “places less emphasis on specific brain regions and focuses on global interactions across the brain” (Telesford et al., 2013). Whereas ICA focuses on a particular group of brain areas, graph theory measures the functional integration (ability to rapidly combine information from distributed brain areas) and segregation (ability to process information within densely interconnected groups of brain areas) of all areas as a whole (global level) and the role of a given area within the whole-brain network (regional level). In addition to permitting estimates of stable, static resting state, intrinsic functional connectivity, graph theory is able to uncover dynamic and mutable connectivity patterns that likely occur to enable the brain to flexibly and rapidly shift between intrinsic networks to facilitate complex behavior (Cole et al., 2013).

As the main goal of the Telesford and colleagues (2013) study was to demonstrate the ability of graph theory to construct IFCNs, the question is whether their analysis successfully reproduced previous rsfMRI findings. The inclusion of frontal, cingulate, and parietal cortices in the default mode network seems robust across a number of both human (Greicius et al., 2003; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997) and nonhuman primate (Hutchison et al., 2011; Mantini et al., 2011; Margulies et al., 2009; Rilling et al.,

2007; Vincent et al., 2007) studies as well as in the current experiment (with the exception of parietal region which was not included in the network constructed from analysis of the single Rhesus monkey). However, although human studies and 3 previous studies in nonhuman primates (i.e., Hutchison et al., 2011; Margulies et al., 2009; Vincent et al., 2007) include the precuneus in the default mode network, and although the single Rhesus monkey analyzed by graph theory in the current study had a hub encompassing the precuneus, the precuneus was notably absent from network identified in the Vervet monkeys. Also notable in this study was the inclusion of the visual cortex in the default mode network, which comports with previous monkey results (Hutchison et al., 2011; Margulies et al., 2009), but is in contrast with the human literature. It is unclear whether these discrepant findings are due to species differences, anesthesia used in the monkey studies (whereas humans are typically awake), or the method of analysis.

Indeed, a recurring and much debated problem is that of the appropriate method to use in analyzing fMRI data: there is no “gold standard,” approaches are heterogeneous, and false positives often emerge (Duncan and Northoff, 2013; Eklund et al., 2012). Is it reasonable, however, to expect a consensus? Telesford and colleagues (2011) argue in favor of the network science approach suggesting that the complex system that is the brain must be understood by depicting its organization as a whole rather than by representing the system as independent elements or by explaining only its constituent parts. To move forward, however, investigators must understand complex systems analyses and apply them correctly.

Another application of network science investigation involves identification of spatial and temporal changes in brain function in response to pharmacological stimulation, a method commonly referred to as pharmacological MRI. Identifying how centrally active molecules may alter IFCNs could enhance understanding of normal brain organization. Telesford and colleagues (2013) use graph theory to analyze fMRI data following acute (1 g/kg) alcohol administration to the Rhesus monkey. They demonstrate that acute alcohol increases the randomness of the default mode network, or in other words, decreases its integration. This is in contrast to human studies that have explored the effects of acute alcohol administration on IFCNs: none have reported effects on the default mode network (Esposito et al., 2010; Khalili-Mahani et al., 2012; Spagnolli et al., 2013). Instead, all 3 studies thus far conducted in healthy human volunteers demonstrate that acute alcohol affects the IFCN related to the visual system (Esposito et al., 2010; Khalili-Mahani et al., 2012; Spagnolli et al., 2013). That Telesford and colleagues (2013) did not show effects on the visual network could be due either to the lack of statistical power (i.e., $n = 1$) or because the default mode network they identify in their Rhesus and Vervet monkeys includes the visual cortex.

The Telesford and colleagues (2013) study highlights the importance of careful consideration of the kind of analyses methods to be applied to fMRI data and offers network science as an appealing method to promote accurate understanding of the brain as a complex system. Although preliminary, the study also provides support for the use of pharmacological MRI to gain a better understanding of the brain in health and disease.

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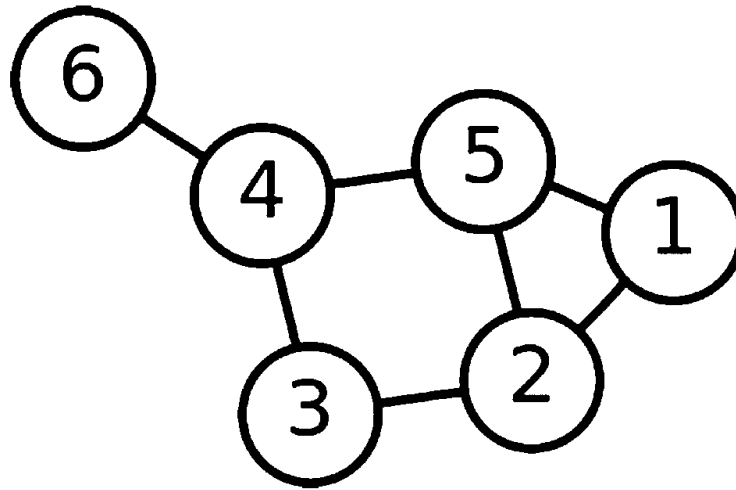


Fig. 1.
An exemplary graph where the numbered circles represent nodes and the lines connecting them represent edges.