

Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Further Insight into the Brain's Rich-Club Architecture

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Review of Nigam et al.

The pioneering field of connectomics has the ambitious aim of mapping and understanding the connections of the brain. Brain connectivity can be analyzed at several spatial resolutions: macroscopic (whole-brain), mesoscopic (neural populations), and microscopic (single-neuron) scales (Bullmore and Sporns, 2009; Van Essen and Ugurbil, 2012). An important discovery in connectomics at the macroscale is the existence of a rich-club in the brain (van den Heuvel and Sporns, 2011). Members of this club constitute a few “rich” brain regions responsible for distributing a large fraction of the brain's neural communications. Using diffusion magnetic resonance imaging, the rich-club has been shown to include brain areas such as the precuneus, superior frontal/parietal lobules, hippocampus, and thalamostriatal structures in human subjects (van den Heuvel and Sporns, 2011). The implication is a high percentage of intercortical connections travel through these central hubs of information flow. So far, the rich-club has been conceptualized as a large-scale brain network phenomenon in adult humans (van den Heuvel and Sporns,

2011), human newborns (Ball et al., 2014), macaque monkey (Harriger et al., 2012), the nematode worm *Caenorhabditis elegans* (Towlson et al., 2013), and mouse hippocampus (Schroeter et al., 2015).

In a recent study published in *The Journal of Neuroscience*, Nigam et al. (2016) provided new evidence regarding the brain's rich-club architecture. These authors demonstrate that the macroscale rich-club organization of the brain extends to the microscale organization of cortical networks formed by closely spaced neurons. In these neuronal networks, a low percentage (~20%) of the neurons are responsible for a high percentage (~70%) of the incoming and outgoing information flow.

To measure the directional information flow between neurons, Nigam et al. (2016) rigorously analyzed effective connectivity based on *in vitro* (organotypic cultures) and *in vivo* microelectrode recordings in awake behaving mice. Their multistep analysis was designed to minimize spurious neuronal transactions. Transfer entropy, a model-free measure of effective connectivity, was adapted for quantifying single neuronal interactions (Vicente et al., 2011). This allowed the nonlinear and directional relationships of neural firing to be recorded. Using the transfer entropy measure, effective connectivity between hundreds of individual neurons was estimated. This led to an asymmetric weight matrix for each recording. These matrix elements were controlled for three possible factors: (1) the neural firing rate, estimated as spike jitter-

ing at the source neuron; (2) the network drive, which was defined as global effects over the whole network, such as global network synchronization during a burst; and (3) spurious delayed connections between two typical neurons with a similar driver.

Two separate brain graphs were extracted to quantify directed neural network information: a binary graph representing pairwise directional connections between neurons, and its associated weighted graph. Several network measures including information transfer, neuronal diversity, and rich-club coefficient were extracted from the weighted directed graphs. Each of these metrics accounts for a specific aspect of neuronal networks. For instance, the importance of a node or link in the overall dynamical network behavior is quantified by the dynamic importance measure, whereas incoming and outgoing information flow within neuronal interactions is characterized by the neuron diversity measure. All of these measures, however, contribute to detecting possible rich neural populations in cortical networks and understanding their properties.

Given that the rich-club was initially thought to be a macroscale phenomenon observed over a few selected brain regions, the current results obtained by Nigam et al. (2016) challenges our current view about rich brain regions and neurons. These “important” neurons are responsible for the majority of information flow in local neuronal networks. It represents a rich-club structure at the brain's neuronal level with a few nodes experiencing high volume of information traffic, remark-

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ably similar to what is observed in the large-scale networks of the brain (van den Heuvel and Sporns, 2011). In fact, rich neurons in the local cortical networks act as central hubs handling efficient network-wide communications between the nodes. The study also highlights another important signature of rich-club neurons. These neurons have significantly higher firing rates and more diverse outgoing information than “non-rich” neurons. Indeed, the neural firing rate and information transfer values extracted from the pool of rich-club neurons represent lognormal distributions with only a few important nodes generating high rate of neural firing in local cortical networks.

A likely purpose of the brain’s rich-club organization is to ensure efficient neuronal processing at lowest possible cost (van den Heuvel et al., 2012). Although rich brain nodes demand significant metabolic resources, their efficient information processing outweighs this high energy consumption (Towilson et al., 2013). This is a situation that can also be observed in other dynamically efficient systems such as international flight networks. Major airports in cities including London, Frankfurt, and Atlanta are highly costly to run and maintain. However, this cost will be toward their central role in efficiently connecting worldwide flight paths (Guimerà et al., 2005). In analogy, the brain’s dynamical system can be conceived as a collection of interleaved cost-efficient networks where a few nodes (for example, brain regions and/or neurons) are responsible for a disproportionate amount of neural activity (Bullmore and Sporns, 2012). Towilson et al. (2013) suggested that the brain’s rich-club stems from cost-minimization of information processing in scale-invariant neural activities. It is therefore fair to postulate that the brain’s rich-club architecture evolved to meet exhaustive neural demands within the brain’s allocated “energy budget” (Attwell and Laughlin, 2001).

The gap between the brain’s rich-clubs at the macroscale (van den Heuvel and Sporns, 2011) and microscale (Nigam et al., 2016) may be filled by a recently published paper by Fulcher and Fornito (2016). In this study, Fulcher and Fornito (2016) analyzed rich-club properties of a mesoscale mouse connectome, derived from two-photon imaging of whole-brain connectivity at a near-neuronal level (Oh et al., 2014). The results showed a strong presence of rich-club arrangement in the mouse connectome. Additionally, rich-club nodes were strongly associated with genes responsible for metabolic regulation. This provides another piece of convincing evidence for the role of rich-clubs in governing cost-efficient networks.

The brain’s rich-club organization at different spatial scales constitutes a potential ground for characterizing neural network deterioration resulting from disease. Preliminary studies suggest that the brain’s rich-club may be selectively targeted in brain diseases including schizophrenia (van den Heuvel et al., 2013). This hypothesis is also supported by a comprehensive meta-analysis based on the data of more than 15,000 patients with various neurological or psychiatric conditions (Crossley et al., 2014). It shows that nearly all brain diseases are likely to be associated with some form of dysfunction in rich brain areas. These observations are in line with a functional magnetic resonance imaging simulation study showing that virtual resection of rich brain regions cause much more detrimental network effects compared with the damage of non-rich areas (Alstott et al., 2009). In summary, the potential role of the brain’s rich-club at macro-, meso- and micro-scales in neural diseases deserves considerable attention.

From a technical point of view, it would be beneficial to compare and verify the current results by Nigam et al. (2016) using measures of directed neuronal connectivity comparable to that of transfer entropy. For example, measures based on Granger causality (Granger, 1969), a linear representation of directional information flow between signals, can provide a picture of causal interneural interactions that might be different from what the transfer entropy measure provides. As Nigam et al. (2016) pointed out, the “spurious link removal” procedure used here is relatively conservative in the sense that it may ignore partial and indirect relationships between neurons. Also, bivariate (pairwise) comparison between neurons may not provide an accurate picture of the brain neural networks that contains a lot of global interactions. Analysis of neuronal rich-club behavior using multivariate information transfer criteria offers a promising avenue for future research.

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