NeuroImage (xxxx) xxxx–xxxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

From connectome to cognition: The search for mechanism in human functional brain networks

Ravi D. Mill*, Takuya Ito, Michael W. Cole

Center for Molecular and Behavioral Neuroscience, Rutgers University, 197 University Ave, Newark, NJ 07120, USA

A R T I C L E I N F O

Keywords:
Functional connectivity
Dynamic connectivity
Directed connectivity
MVPA
Multi-modal neuroimaging
Computational modeling

A B S T R A C T

Recent developments in functional connectivity research have expanded the scope of human neuroimaging, from identifying changes in regional activation amplitudes to detailed mapping of large-scale brain networks. However, linking network processes to a clear role in cognition demands advances in the theoretical frameworks, algorithms, and experimental approaches applied. This would help evolve the field from a descriptive to an explanatory state, by targeting network interactions that can mechanistically account for cognitive effects. In the present review, we provide an explicit framework to aid this search for "network mechanisms", which anchors recent methodological advances in functional connectivity estimation to a renewed emphasis on careful experimental design. We emphasize how this framework can address specific questions in network neuroscience. These span ambiguity over the cognitive relevance of resting-state networks, how to characterize task-evoked and spontaneous network dynamics, how to identify directed or "effective" connections, and how to apply multivariate pattern analysis at the network level. In parallel, we apply the framework to highlight the mechanistic interaction of network components that remain "stable" across task domains and more "flexible" components associated with on-task reconfiguration. By emphasizing the need to structure the use of diverse analytic approaches with sound experimentation, our framework promotes an explanatory mapping between the workings of the cognitive mind and the large-scale network mechanisms of the human brain.

A framework for mechanistic discovery in network neuroscience

Since the emergence of human functional neuroimaging, researchers have sought the optimal analytic framework to link non-invasively acquired brain data to cognitive function. An initial focus on changes in regional activation amplitudes (Friston et al., 1994; Kanwisher, 2010) has given way to examination of functional connectivity (FC) between regions and large-scale networks of regions (Biswal et al., 1995; Medaglia et al., 2015; Petersen and Sporns, 2015; Raichle, 2010; Sporns, 2014). This trend provides a macroscopic parallel to the search for the "neural code" in animal neurophysiology, which has also transitioned from analysis of spiking in individual neurons to deciphering patterns of spatiotemporal synchronization in neuronal populations (Fries, 2005; Goldman-Rakic, 1988; Kumar et al., 2010; Laughlin and Sejnowski, 2003; Siegel et al., 2015; Vaadia et al., 1995). Both human and animal literatures have drawn inspiration from earlier connectionist models linking cognition to interactions within simulated networks (Fodor and Pylyshyn, 1988; Rumelhart et al., 1986). Rather than being confined to abstract computational models or animal neurophysiology, recent improvements in technology (e.g. the spatial and temporal resolution of functional magnetic resonance imaging, fMRI; Duyn, 2012; Feinberg et al., 2010; Lewis et al., 2016), methodology (e.g. source modeling of magneto-/electro-encephalography data, MEG/EEG; Brookes et al., 2011; Hipp et al., 2012), and research strategy (e.g. "big data" initiatives such as the Human Connectome Project, HCP; Van Essen et al., 2013) have rendered questions over the network architecture of the human brain more amenable to direct empirical investigation than ever before.

However, whilst current methods allow for the *descriptive* mapping of networks in unprecedented detail and complexity, there remains scope for a clearer *explanatory* understanding of what and how these networks compute. In this review, we outline a framework that targets the discovery of "network mechanisms" to enable this deeper understanding. We operationally define a network mechanism as a set of interactions amongst large-scale neural populations (e.g. cortical regions) that take part in an explanation of a cognitive phenomenon. Concretely, our framework identifies explanatory network mechanisms

* Corresponding author.
E-mail address: rdm146@rutgers.edu (R.D. Mill).

http://dx.doi.org/10.1016/j.neuroimage.2017.01.060
Accepted 25 January 2017

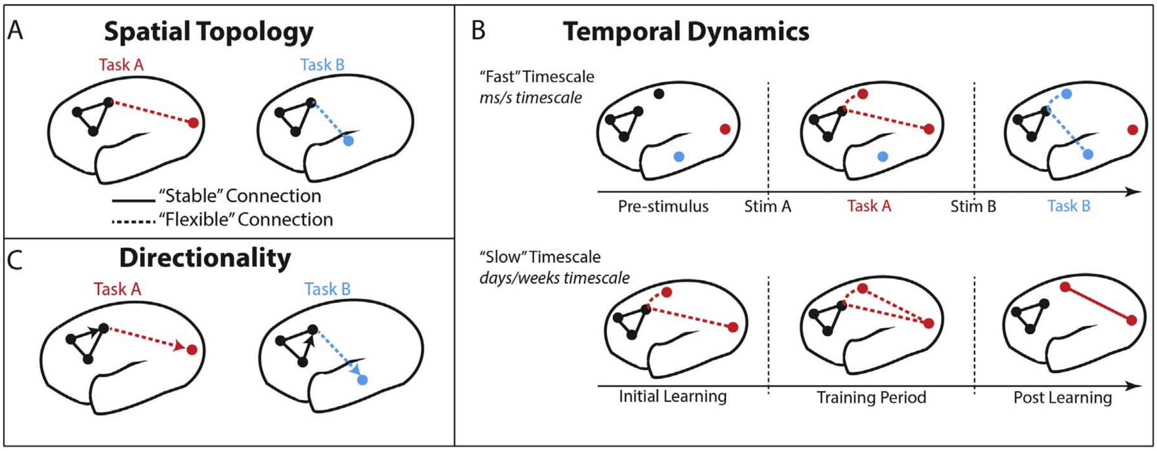

Fig. 1. FC methods provide insight into different functional components to improve the characterization of each network mechanism. All panels depict hypothetical network components for a visuomotor task (Task A) and an audiomotor task (Task B). **A)** Comparing the spatial topology of network connections across different task conditions reveals spatial components of each network mechanism. Solid FC lines here (and in subsequent panels) represent the spatial component that remains "stable" across multiple task domains, whereas dashed FC lines represent components that are more "flexible" across task domains. **B)** Combining well-designed tasks with dynamic FC analyses allows for the temporal components of network organization to be investigated at different timescales. Example network reconfigurations operating on the "fast" scale (associated with stimulus-evoked responding; upper panel) are shown for both visuomotor and audiomotor tasks. Network dynamics operating at the "slow" scale are associated with learning (lower panel), and are visualized for the visuomotor task (Task A) over the course of training. **C)** Establishing whether communication amongst networks occurs in a directed (i.e. lagged, represented by arrows) or undirected fashion serves as another key component, enabling a fuller characterization of activity propagation in the brain.

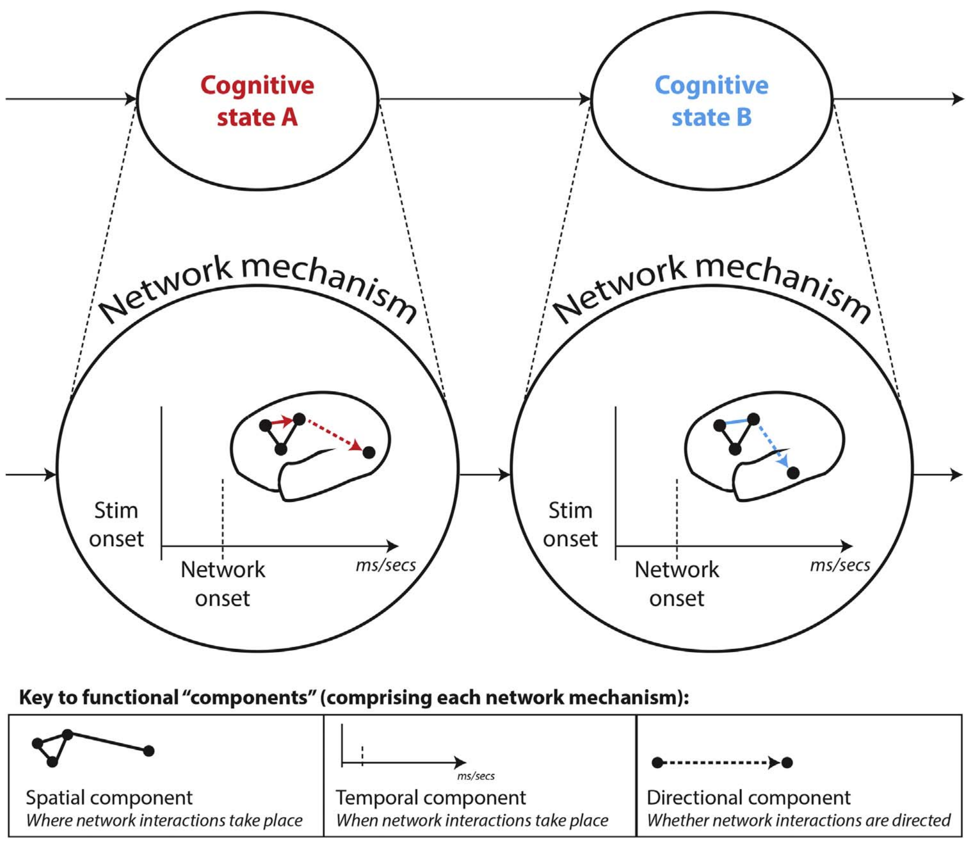

Fig. 2. Depiction of a hypothetical network mechanism comprised of spatial, temporal and directional components. Following from the previous figure, we depict a network mechanism underlying the emergence of two example cognitive states: A (visuomotor task state) and B (audiomotor task state). Colored lines denote connections that are flexible across these cognitive states, whereas black lines denote stable connections. The key in the lower panel distinguishes between each functional component that is superimposed in the full mechanism in the upper panel. This should demonstrate how different functional components combine to enrich the characterization of a given network mechanism. Although the field has primarily focused on describing the spatial topology of brain networks (typically in task-free rest), we argue that combining careful task manipulations with more advanced FC estimation methods can characterize how spatial, temporal and directional components operate collectively within network mechanisms to drive cognition.

via two key research practices: i) careful experimental manipulations of cognitive and neural states, in combination with ii) recently developed FC estimation methods that characterize the operation of a network mechanism via its spatial, temporal and directional "components" (see Figs. 1 and 2). Such network components encompass spatial topology (the spatial configuration of network interactions; see Fig. 1a), temporal properties (the onset, duration and spectral features of these interactions; see Fig. 1b), and directional method of communication (whether interacting regions have consistent asymmetries or lags in how they communicate; see Fig. 1c). To clarify, "components" in our