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Brain and cognitive reserve: Translation via network control theory

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ABSTRACT

Traditional approaches to understanding the brain's resilience to neuropathology have identified neurophysiological variables, often described as brain or cognitive "reserve," associated with better outcomes. However, mechanisms of function and resilience in large-scale brain networks remain poorly understood. Dynamic network theory may provide a basis for substantive advances in understanding functional resilience in the human brain. In this perspective, we describe recent theoretical approaches from network control theory as a framework for investigating network level mechanisms underlying cognitive function and the dynamics of neuroplasticity in the human brain. We describe the theoretical opportunities offered by the application of network control theory at the level of the human connectome to understand cognitive resilience and inform translational intervention.

Contents

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1. Introduction

The brain is an intricately connected dynamic system that supports substantial information processing capacity underlying human thought (Marois and Ivanoff, 2005). How complex cognitive processes are executed in the brain remains a deeply challenging and unsolved question. Several recent lines of investigation suggest that healthy cognitive function relies on spatiotemporally interdependent (or *networked*) neurophysiological mechanisms: information transmission along white matter tracts, and neural computations within distributed networks of brain areas (cf. Kopell et al., 2014; Medaglia et al., 2015). In kind, abnormal cognitive function may depend on disruptions in networked mechanisms, altering the dynamic propagation of information and the healthy evolution of brain states (Da Silva et al., 2003; Pezard, 1996; Stam, 2014; Van den Heuvel and Sporns, 2013). In the context of these emerging hypotheses, a major challenge remains in the development of generalized theories that account for cognitive function and dysfunction directly from neurophysiological mechanisms that operate at a network level.

Since the pioneering work of Hodgkin and Huxley in the 1940s and 50s, many approaches have been developed to address problems in neural dynamics at cellular and ensemble levels. Yet their implications for cognitive dysfunction in human disease remain largely unknown. Emerging techniques from the mathematical, physical, and engineering sciences may be able to address these challenges when applied to large-scale neuroimaging of the human brain. In particular, dynamic network theory offers an especially useful framework to examine networked mechanisms of brain function and dysfunction as it evolves during cognitive processes.

Dynamic network theory concerns how the time-evolving interactions between many interconnected elements result in complex system behavior. In applications to other real-world systems, techniques from this field have provided fundamental explanations for the emergence of complicated system dynamics from the interactions between system parts (Choi et al., 2001; Yamashita and Tani, 2008; Canard et al., 2012). Moreover, alterations in system function following perturbation or damage have been explained by the spread or diffusion of signals through the system's network (Albert et al., 2000; Boguñá et al., 2003; Buldyrev et al., 2010). While these approaches have been developed in other contexts, the problems that they address are strikingly similar to the problem of explaining healthy and diseased cognitive processes using networked neurophysiological mechanisms. Should this similarity be more than a metaphor, the translation of these approaches to the cognitive and clinical neurosciences may prove crucial to addressing longstanding challenges in the brain and cognitive sciences (see Fig. 1).

Our goal is to understand large-scale functional properties of the human brain, how these properties support cognition, and under what conditions they fail. In clinical presentations, dynamic network theory posits that dysfunction is a result of aberrations in network dynamics. These aberrations can result from the disruption of network structures that support dynamics, the direct disruption of dynamics, or a mixture of the two. Indeed, conceptually, network pathways to disease may occur through structural failures in brain networks (Stam, 2014). These structural alterations may be complemented by alterations in neurophysiological dynamics that support brain function and cognition at multiple spatiotemporal resolutions (Kopell et al., 2014).

Dynamic network techniques offer two powerful advantages in understanding healthy cognition and its alteration in disease or injury. First, dynamic network approaches provide a basis for a formal union between mathematical approaches to complex systems and neurophysiological processes that support cognition. Mathematical axioms and analytic techniques from the emerging field of network science can enter the vocabulary and repertoire of the neurosciences. This affords the ability to conceptualize neuroscientific questions in a robust theoretical framework that has been progressively developing since the 1760s (Euler, 1766). As a result, the cognitive neuroscientist, neuropsychologist, and neurologist can enjoy and benefit from the quantitatively rigorous network representations of neuroimaging data, and directly probe their potential utility in uncovering fundamental insights into cognitive function in health and disease using empirical approaches.

Second, dynamic network approaches can be used to directly inform the manipulation of cognitive outcomes. As system dynamics and their generating network mechanisms are clarified, candidate targets for modification and repair can be proposed. This is particularly crucial to neurological and psychiatric diseases, where impairments in cognitive function are a primary concern in diagnosis and treatment. By drawing on developing methodologies in dynamic network theory, similarities between observed dysfunction in pathological syndromes and features in perturbed dynamic systems can be described. Initial interventions for the brain can be proposed based on the observed dynamic aberrations.

For the purposes of the current paper, we focus on one type of dynamic network analysis and describe its potential to inform theoretical and practical approaches to problems in cognitive dysfunction in neurological syndromes. *Network control theory* is an innovative and leading subfield of dynamic network theory that offers a class of powerful engineering-based conceptual and analytic approaches to examining functional signaling and resilience in networked systems. As a developing subfield, network control theory contains concepts that have been successfully applied to understand, manipulate, and repair complex systems in robotic, technological, and mechanical contexts. We suggest that these conceptual and practical approaches carry distinct advantages in developing brain connectomics into a translationally relevant field of study.

We briefly summarize key principles of network control theory and delineate their implications as an attractive approach to augment those typically taken in clinical neuroscience research, particularly in explaining brain and cognitive "reserve". Namely, we will emphasize the distinct advantage of a control-theoretic perspective on problems in brain structure, function, and cognition in neurological samples. To maintain clarity throughout this review, we consider brain structure and function to be measurable qualities of the brain's morphology and dynamics, respectively. Cognition is represented in the brain's structure and function, and its outputs are measurable in behavioral paradigms in experimental and clinical settings. After providing a basic introduction to reserve and network control theory in this context, we describe the application of network control theory to brain network structure and dynamics in the macro-scale human connectome (cf. Sporns et al., 2005).

We close with a speculative discussion of immediate extensions of network control theory to theoretical and analytic issues in understanding cognitive resilience in neurological diseases and implications for informing treatments. We provide initial hypotheses within this framework. We consider the potential for dynamic network approaches to introduce a conceptual framework for understanding variance in clinical trajectories and to delineate novel features of disease syndromes and targets for translational interventions. Crucially, we suggest that while this area is in its earliest stages, it carries the correct ingredients to promote productive scientific inquiry as the tools from several fields are sufficiently maturing.

2. Definition of reserve

In the clinical cognitive neurosciences, the constructs of "brain reserve" and "cognitive reserve" have been invoked to explain the