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Review

# The behavioral and cognitive relevance of time-varying, dynamic changes in functional connectivity

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ABSTRACT

Recent advances in neuroimaging methods and analysis have led to an expanding body of research that investigates how large-scale brain network organization dynamically adapts to changes in one's environment, including both internal state changes and external stimulation. It is now possible to detect changes in functional connectivity that occur on the order of seconds, both during an unconstrained resting state and during the performance of constrained cognitive tasks. It is thought that these dynamic, time-varying changes in functional connectivity, often referred to as dynamic functional connectivity (dFC), include features that are relevant to behavior and cognition. This review summarizes four aspects of the nascent literature directly testing that assumption: 1) how changes in functional network organization on the order of task blocks relate to differences in task demands and to cognitive ability; 2) how differences in dFC variability between different contexts relate to cognitive demands and behavioral performance; 3) how ongoing fluctuations in dFC impact perception and attention; and 4) how different patterns of dFC correspond to individual differences in cognition. The review ends by discussing promising directions for future research in this field. First, it comments on how dFC analyses can help to elucidate the mechanisms of healthy cognition. Next, it describes how dFC processes may be disrupted in disease, and how probing such dysfunction can increase understanding of neural etiology, as well as behavioral and cognitive impairments, observed in psychiatric and neurologic populations. Last, it considers the potential for computational models to uncover neuronal mechanisms of dFC, and how both healthy cognition and disease emerge from network dynamics.

## 1. Introduction

The brain has an incredible ability to dynamically adjust to a constantly changing environment. This ability enables adaptive changes in cognition and behavior that allow humans and animals to successfully navigate a complex and inconstant world. An appreciation of the role of dynamic neuronal signaling in adaptive cognition and behavior is not new (e.g., Hebb, 1949). What is new is the ability to measure large-scale neural functioning across the entire brain at high enough temporal and spatial resolution to detect these dynamic changes while individuals are engaging in complex cognition. A growing body of research, predominantly – but not exclusively – using functional magnetic resonance imaging (fMRI), indicates that brain network organization dynamically changes when a constrained cognitive context changes. This could be, for example, a change from an intrinsic, resting state to the performance of a cognitive task; or between pairs of tasks that have different cognitive demands (for a review, see: Medaglia et al., 2015). This literature estimates what has been termed the "functional connectome", or a complete description of the functional connections between regions distributed throughout the entire brain (Bullmore and Bassett, 2011). Pairwise estimates of the functional connectivity (FC) between brain regions are combined to form a description of whole-brain FC patterns, in which distinct functional networks that interact with each other can be detected. This literature largely assumes that FC remains constant across a block of rest or a cognitive task and assesses changes in FC patterns across those blocks, on the order of minutes. As an example, it was recently demonstrated that whole-brain functional network organization changed systematically during both a task probing motor execution and a task probing working memory as compared to rest, with increased network segregation underlying successful motor execution and increased network integration underlying successful working memory (Cohen and D'Esposito, 2016). With recent advances in analysis techniques, it is now possible to detect time-varying changes in FC measurements on the order of seconds. This rapid time-varying FC is often

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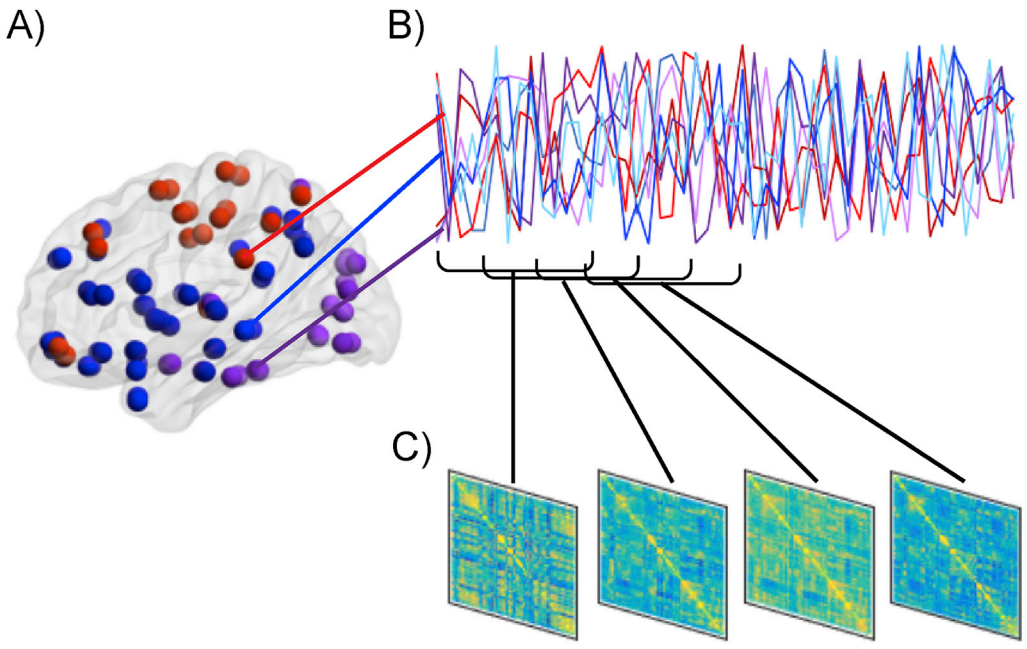


**Fig. 1. Steps to conduct a dFC analysis.** A) First, the brain is parcellated into nodes, which can consist of anatomical or functional regions of interest, or components derived from a data-driven method such as independent component analysis. B) Second, the time-series across all pairs of nodes are related to each other, often by computing correlations or coherence, but other methods such as co-activation patterns or temporal derivatives can be used as well. Commonly, this is repeated within pre-specified and overlapping "windows" of fixed length (as pictured), but novel methods that do not require the assumptions of sliding window approaches can also be utilized, such as dynamical conditional correlations (Lindquist et al., 2014), multiplication of temporal derivatives (Shine et al., 2015) or co-activation patterns (Liu and Duyn, 2013). C) Last, individual connectivity matrices are computed for each window. Once multiple FC matrices are computed for each time-series, dFC analyses quantifying how the matrices differ from each other can be conducted.

referred to as dynamic FC (dFC). Much dFC research to date has focused on three aspects of time-varying FC patterns. First, on characterizing dFC within resting state scans, both within and across populations (i.e., across development or diagnoses). Second, on assessing the validity of dFC as measured with fMRI and on improving dFC estimation techniques to minimize artifacts and spurious findings. And third, on relating fMRI estimates of dFC to those acquired via electrophysiological methods to determine the neuronal source of these dynamic fluctuations in FC patterns. Informative reviews of this literature have already been written (Calhoun et al., 2014; Hutchison et al., 2013; Preti et al., 2016). The current review takes a novel approach and highlights progress to date regarding how these dFC measurements, during both rest and cognitive tasks, relate to behavior and cognitive ability. With proper methodological implementation, if characteristics of these measurements are reliably related to behavioral and cognitive outcomes it indicates that there are aspects that are likely neural in origin.

### 1.1. Introduction to common dFC estimation methods

Optimal methods for estimating dFC are still being developed (for reviews, see: Hutchison et al., 2013; Preti et al., 2016). This section summarizes existing methods to provide context for the following discussion of the literature. Pre-processing of raw fMRI data for a dFC analysis requires the same steps as static FC analyses, which have been discussed in detail elsewhere (for a recent review, see: Ciric et al., 2017). Just as with static FC analyses, the brain is then parcellated into regions of interest, or nodes (Fig. 1A). This is often executed using structural or functional brain atlases, or via data-driven approaches such as independent component analysis. Once data has been sufficiently processed, there are two main categories of methods that can be used to quantify what is referred to as dFC. First, and more common, are various approaches to estimating short segments of static FC that, when combined, allow for the investigation of time-varying dynamics in FC across those segments. Second are approaches that estimate activity patterns at individual data acquisition timepoints, or changes in activity patterns, and how those fluctuate across time.

The most commonly used method for quantifying dFC is the sliding window approach. Here, FC connectivity matrices are computed over fixed-length segments ("windows") of the fMRI time-series. There are limits regarding how short that length should be to minimize spurious dynamics. Suggestions range from 40 to 100 s depending on features of the collected data as well as processing steps implemented (Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015). The sliding window approach allows for multiple connectivity matrices to be computed for each fMRI run. Typically, separate windows overlap substantially (Fig. 1B). Connectivity matrices can then be compared across windows to assess how FC dynamically varies from one window to the next (Fig. 1C). Observations within a window can be given equal weight or, alternatively be down-weighted at the beginning and end of the window. This latter method is termed a tapered sliding window. Within each window, FC is computed as it would be in a standard, static FC analysis. With fMRI data, this is often achieved via calculating the correlation or coherence amongst all pairs of nodes.

An emerging method to calculate a series of FC matrices throughout the scan is the dynamic conditional correlation (DCC) approach (Choe et al., 2017; Lindquist et al., 2014). This is a model-based approach that accounts for certain aspects of fMRI data that traditional sliding window approaches cannot account for. For example, window lengths do not have to be set in advance or equal across the length of the scan, allowing for greater flexibility to detect non-regular changes in FC. Further, past timepoints can be taken into account and appropriately weighted. The DCC method has been show to improve reliability and to better fit fMRI data than sliding window approaches (Choe et al., 2017; Lindquist et al., 2014).

Once multiple FC matrices are constructed, there are two common methods to quantify dynamic changes in FC. First, all connectivity matrices across all windows and participants can be clustered into groups of similar matrices. This can be accomplished using a clustering method