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Dynamic functional connectivity: Promise, issues, and interpretations

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ABSTRACT

The brain must dynamically integrate, coordinate, and respond to internal and external stimuli across multiple time scales. Non-invasive measurements of brain activity with fMRI have greatly advanced our understanding of the large-scale functional organization supporting these fundamental features of brain function. Conclusions from previous resting-state fMRI investigations were based upon static descriptions of functional connectivity (FC), and only recently studies have begun to capitalize on the wealth of information contained within the temporal features of spontaneous BOLD FC. Emerging evidence suggests that dynamic FC metrics may index changes in macroscopic neural activity patterns underlying critical aspects of cognition and behavior, though limitations with regard to analysis and interpretation remain. Here, we review recent findings, methodological considerations, neural and behavioral correlates, and future directions in the emerging field of dynamic FC investigations.

Introduction

Until recently, most fMRI studies have implicitly assumed that the statistical interdependence of signals between distinct brain regions (*functional connectivity*, FC, Friston, 2011; for all abbreviations, see Table 1) is constant throughout recording periods of task-free experiments, as reflected in the analysis tools and metrics that are commonly applied to the data. While studies operating under this assumption have afforded exceptional developments in understanding large-scale properties of brain function, the resulting characterization ultimately represents an average across complex spatio-temporal phenomena. Accordingly, it has been proposed that quantifying changes in functional connectivity metrics over time may provide greater insight into fundamental properties of brain networks. Here, we discuss recent studies examining dynamic properties of resting-state FC. We consider the existing techniques for their evaluation, challenges and limitations with regard to methodology and interpretation, the electrophysiological basis of such dynamics, and

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information that these investigations could potentially reveal about brain organization and cognition that may fundamentally change the way we examine neuroimaging data.

Resting-state connectivity and static characterizations

The so-called "resting state" has received considerable attention in recent years and has been investigated with multiple modalities, including positron emission tomography (PET), magnetoencephalography (MEG), and electroencephalography (EEG), though the dominant approach is presently functional magnetic resonance imaging (fMRI). Resting-state fMRI (RS-fMRI) is a non-invasive method in which the FC and other properties of blood–oxygen-level-dependent (BOLD) signals are examined from scans acquired with no explicit task (Biswal et al., 1995; reviewed in Fox and Raichle, 2007). FC is quantified with metrics such as correlation, covariance, and mutual information between the time series of different regions, wherein the temporal and spatial scales examined are determined by the question of interest (Bressler and Menon, 2010; Bullmore and Sporns, 2009; Friston, 2011). It therefore represents an empirical characterization of the temporal relationship between regions, without indicating how the temporal covariation is mediated (Friston, 2011; Friston and Buchel, 2007). Various techniques for FC analysis have revealed sets of spatially distributed, temporally correlated brain regions ("intrinsic connectivity networks", ICNs; also referred to as "resting-state networks"; Beckmann et al., 2005; Damoiseaux et al., 2006; Power et al., 2011; Yeo et al., 2011). While the neural underpinnings and functional role of spontaneous fluctuations and correlations remain unresolved (reviewed in Leopold and Maier, 2012), evidence suggests that ICNs relate to underlying neural activity (Britz et al., 2010; Brookes et al., 2011a,b; de Pasquale et al., 2010, 2012; Fox and Raichle, 2007; He et al., 2008; Laufs, 2008, 2010; Liu et al., 2011; Mantini et al., 2007; Musso et al., 2010; Nir et al., 2007, 2008; Shmuel and Leopold, 2008) and are likely shaped, but not fully determined, by structural connectivity (SC; for review, see Damoiseaux and Greicius, 2009). Patterns of FC observed at rest have also been shown to resemble those elicited by more traditional task-based paradigms or derived directly from task-data (Biswal et al., 1995; Calhoun et al., 2008; Fox et al., 2006; Laird et al., 2011; Smith et al., 2009; Vincent et al., 2007).

The duration and number of scans used for computing ICNs of a given subject vary considerably between studies. Presently, a typical acquisition in humans includes a single scan of approximately 5–10 min using a repetition time (TR) in the range of 2–3 s that allows for whole-brain coverage with standard imaging sequences. It has been suggested that correlation values within and between ICNs stabilize within 4–5 min of data (van Dijk et al., 2010), implying that most studies are adequately sampling the network activity despite relatively few data points. Indeed, most studies do converge on similar network patterns even across a variety of behavioral states (e.g. eyes closed, open, or open and fixating; Bianciardi et al., 2009; but see McAvoy et al., 2012) though there are also subtle, but important, differences in the patterns across both normal and diseased states (for reviews, see Greicius, 2008; Heine et al., 2012; Menon, 2011). The univariate and multivariate approaches typically applied to resting-state data (for review, see Cole et al., 2010) assume that the strength of interactions between regions is constant over time. For example, seed-based correlation approaches represent the relationship between two regions of interest as a single correlation coefficient that is calculated from the time series of the entire scan; temporal variations in this value will not be captured (see Fig. 1 for illustration). Another common technique, spatial independent component analysis, decomposes the fMRI data into a pre-specified number of components with maximal spatial independence. While this strategy removes the need for explicitly defining seed regions, it does not (without additional processing) account for changes in the strength of inter-regional interactions over time.

Examining the dynamics of functional connectivity

The assumption of stationarity provides a convenient framework in which to examine and interpret results. Approaches built upon these assumptions have produced a wealth of literature expanding our knowledge of large-scale brain networks. Yet, given the known dynamic, condition-dependent nature of brain activity (Rabinovich et al., 2012; von der Malsburg et al., 2010), it is natural to expect that FC metrics computed on fMRI data will exhibit variation over time. Indeed, FC has been demonstrated to exhibit changes due to task demands (Esposito et al., 2006; Fornito et al., 2012; Fransson, 2006; Sun et al., 2007), learning (Albert et al., 2009; Bassett et al., 2011; Lewis et al., 2009; Tambini et al., 2010), and large state transitions such as sleep (Horovitz et al., 2008, 2009), sedation (Greicius et al., 2008), and anesthesia (Boveroux et al., 2010; Peltier et al., 2005). Further, while between-subject variation is to be expected given its reported correlation with a variety of individual measures (IQ, personality, etc.; Adelstein et al., 2011; Song et al., 2008; van den Heuvel et al., 2009; Wei et al., 2011), within-subject FC has also been shown to vary considerably, even between different scans within the same imaging session (Honey et al., 2009; Liu et al., 2009; Meindl et al., 2010; Shehzad et al., 2009; Van Dijk et al., 2010). In fact, changes in both the strength and directionality of functional connections appear to vary not only between runs, but also at much faster time-scales (seconds–minutes) (Allen et al., in press; Chang and Glover, 2010; Handwerker et al., 2012; Jones et al., 2012; Kiviniemi et al., 2011; Sakoglu et al., 2010), a property that is not exclusive to humans (Hutchison et al., in press; Keilholz et al., 2013; Majeed et al., 2011).

Interpreting temporal variations in FC metrics (such as correlation) that are computed from fMRI time series is not necessarily straightforward. Low signal-to-noise ratio (SNR), changing levels of non-neural noise (e.g. from cardiac and respiratory processes and hardware instability), as well as variations in the BOLD signal mean and variance over time, can induce variations in FC metrics (see Issues and limitations section below). In addition, since functional networks can be spatially overlapping (i.e., the time series of a single node may have partial correlations with that of multiple networks), the FC between two regions that is attributed to their involvement in one particular network can appear to change if the time series of overlapping networks are not appropriately separated (Smith et al., 2012). It is also unclear the extent to which dynamic FC is best conceptualized as a multistable state space wherein multiple discrete patterns recur, akin to fixed points of a dynamic system, or whether it simply varies along a continuous state space. At present, studies have begun to identify discrete, reproducible patterns of FC and of the multivariate time series (refer to Reproducible patterns of sliding-window correlations, Single-volume co-activation patterns, and Repeating sequences of BOLD activity sections below), indicating some degree of multistability.

To gain insight into whether FC fluctuations can be attributed to neural activity or simply noise, it is necessary to compare changes in FC metrics to simultaneous measurement of neural or physiological processes and further, to examine whether the degree or pattern of variability can significantly differentiate between individuals or populations (refer to Interpreting fluctuations in BOLD functional connectivity section below). For example, studies are beginning to identify potential correlates of variations in resting-state FC in simultaneously recorded electrophysiological data (Allen et al., 2013; Chang et al., 2013b; Tagliazucchi et al., 2012b) as well as behavior (Thompson et al., in press), suggesting that variations in FC are to some degree of neuronal origin and perhaps linked with changes in cognitive or vigilance state. Disease-related alterations in the dynamic properties