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Dynamics of large-scale fMRI networks: Deconstruct brain activity to build better models of brain function

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Abstract

Ongoing fluctuations of brain activity measured by functional magnetic resonance imaging (fMRI) provide a novel window onto the organizational principles of brain function. Advances in data analysis have focussed on extracting the constituting elements of temporal dynamics in terms of activity or connectivity patterns. Subsequently, brain states can be defined and then be analyzed using temporal features and computational models as to capture subtle interactions between functional networks. These new methodological advances allow to deconstruct the rich spatiotemporal structure of functional components that dynamically assemble into resting-state networks long been observed using conventional measures of functional connectivity. Applications of these emerging methods demonstrate that changes in functional connectivity are indeed driven by complex reorganization of network interactions, and thus provide valuable observations to build better models of brain function and dysfunction. Here, we give an overview of the recent developments in this exciting field, together with main findings and perspectives on future research.

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Introduction

More than two decades ago, the discovery of functional magnetic resonance imaging (fMRI) initiated a rich field of non-invasive human neuroimaging that contributed significantly to our understanding of the brain in health and disorder [1]. Technological advances in MRI scanning have enabled modern fMRI to reach whole-brain coverage at millimeter spatial resolution and sub-second temporal resolution. In addition, fMRI data analysis has always been an active and multidisciplinary research topic which has allowed new paradigms.

In conventional task fMRI, the subject is exposed to a stimulus or is performing a task while the blood oxygenation level dependent (BOLD) signal—a proxy for brain activity—is recorded. Given the experimental timing, a regression model can be built to be fitted to the fMRI timecourses and lead to a statistical parametric map showing where in the brain sufficient evidence for evoked activity is present. While these studies benefit from the spatial coverage and resolution of fMRI, the slowness of the BOLD response is a limiting factor to determine temporal characteristics of brain responses. Mental chronometry using fast advanced event-related designs has been developed to measure small differences in onsets of activity in different regions, but the technique remains limited by the nature of the BOLD signal itself in terms of variability of the signal between brain regions and between subjects [2].

Increasing evidence that spontaneous activity provides information about how distributed brain regions integrate into large-scale functional networks [3], has led to a large interest from the community into "resting-state" studies where subjects can freely engage into a process of mind-wandering [4]. The analysis of these paradigm-free datasets has relied on functional connectivity that is a measure of statistical dependency between a pair of fMRI activity timecourses [5], exploratory multivariate methods such as independent component analysis, as well as graph modeling approaches.

Conventional approaches for resting-state fMRI analysis are driven by average behavior over a whole fMRI run of several minutes leading to dissociated functional networks and, therefore, they will miss important features of dynamics of network interactions [6]. Recent findings reveal that these ongoing interactions, for instance, between high-level networks during mind wandering [7], can be characterized using time-resolved analysis [8,9] based on a different toolset than those of mental chronometry as any timing information is typically ignored (or absent) and network-level interactions are targeted. In this review, we discuss the state-of-the-art in time-resolved fMRI data analysis since the first reports of moment-to-moment fluctuations in functional connectivity [10,11]. While originally designed for exploratory analysis of resting-state fMRI, it is worth mentioning that these methods can be readily applied to task-based fMRI as well; e.g., see Ref. [12] for a more specific overview.

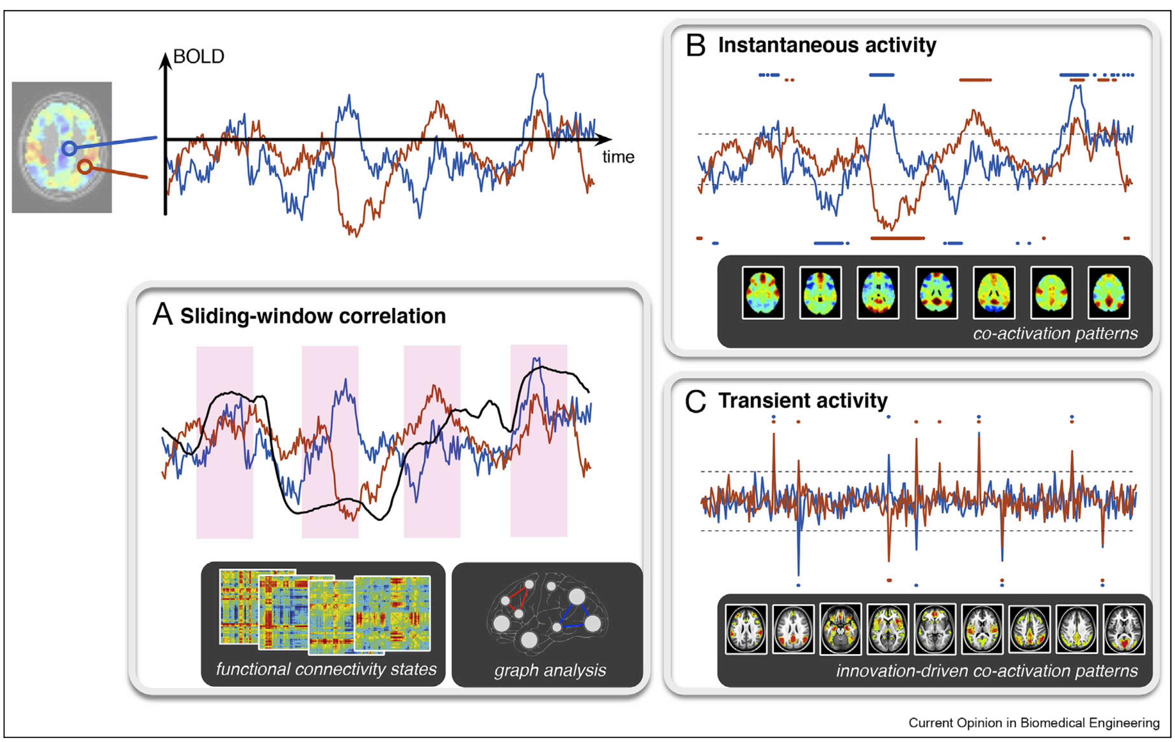
We first briefly discuss different methods to extract dynamic information from fMRI data and then specifically focus on recent methods that encode this dynamic information either through direct observational measures or by establishing brain states that can then be fed into temporal models. We demonstrate how these developments allow managing and summarizing large amounts of information contained by the dynamic characterization of brain activity. Temporal modeling of brain dynamics opens avenues towards more mechanistic models of network interactions, and how they underpin brain function and dysfunction.

Elements of temporal dynamics

From sliding-window correlations to instantaneous activity patterns

The first evidence of functional network organization from resting-state fMRI data was based on functional connectivity as measured by Pearson correlation coefficients between pairs of fMRI timeseries. Computing second-order statistics for the whole brain, considering N_S spatial locations or regions from an atlas, leads to a symmetric connectivity matrix of size $N_S \times N_S$, which was termed as the functional connectome. As the correlational measures reflect the average behavior during the complete fMRI run, we miss moment-to-moment fluctuations in functional connectivity that might be informative about dynamic brain processes. Therefore, functional connectivity was computed over shorter periods of time using sliding-window correlations (SWC) or time-frequency measures [10], as illustrated in Figure 1A. Windowed correlations suffer from a number of methodological issues such as limited statistical power [13] and potential spurious fluctuations

Figure 1



Elements of temporal dynamics (light gray boxes) lead to brain states (dark gray boxes) in different ways. (A) Sliding-window correlation turns functional connectivity in a time-dependent measure. For each window position, all pairwise connections constitute a connectome that can be further analyzed using clustering or decomposition methods. (B) Point process analysis marks timepoints when the activity exceed a predefined threshold. Clustering then identifies different spatial configuration into which the selected regions co-activate. (C) Transient activity obtained using regularized deconvolution. Subsequent thresholding identifies spatial patterns that occur at these critical moments.