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Co-activation patterns in resting-state fMRI signals

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ABSTRACT

The brain is a complex system that integrates and processes information across multiple time scales by dynamically coordinating activities over brain regions and circuits. Correlations in resting-state functional magnetic resonance imaging (rsfMRI) signals have been widely used to infer functional connectivity of the brain, providing a metric of functional associations that reflects a temporal average over an entire scan (typically several minutes or longer). Not until recently was the study of dynamic brain interactions at much shorter time scales (seconds to minutes) considered for inference of functional connectivity. One method proposed for this objective seeks to identify and extract recurring co-activation patterns (CAPs) that represent instantaneous brain configurations at single time points. Here, we review the development and recent advancement of CAP methodology and other closely related approaches, as well as their applications and associated findings. We also discuss the potential neural origins and behavioral relevance of CAPs, along with methodological issues and future research directions in the analysis of fMRI co-activation patterns.

Introduction

The advent of resting-state functional magnetic resonance imaging (rsfMRI) has significantly improved our understanding of the organization of large-scale brain networks in health and disease (Biswal et al., 1995; Fox and Raichle, 2007; Zhang and Raichle, 2010). The rapid growth of resting-state research stemmed from the observation that temporal correlations between spontaneous fMRI signals of different brain regions correspond well with known functional connections and networks. Resting-state connectivity is conventionally assessed by computing temporal correlations over an entire scan, which is typically several (and possibly tens of) minutes long. While this "static" connectivity analysis reveals core functional systems and shows similar information as structural brain connectivity (Greicius et al., 2009; Honey et al., 2009), it neglects time-varying information in resting-state fMRI signals that may provide further information about brain function (Hutchison et al., 2013).

Efforts to extract and quantify time-varying information in resting-state fMRI data have opened up a new area of research on "dynamic" resting-state functional connectivity (DFC) and accompanying methodology. Among the existing set of DFC methods, one approach deviates from conventional time-domain approaches by regarding single fMRI volumes at individual time points, instead of fMRI time courses, as basic units of analysis, and focusing on recurring co-activation patterns (CAPs) of the brain and their variability over time. Whereas several excellent reviews describe DFC methods and their applications more generally (Hutchison et al., 2013; Preti et al., 2017), a dedicated survey of CAP analysis is absent to date. Here, we aim to fill this gap by 1) elucidating the basic rationale behind the CAP analysis and its relation to rsfMRI connectivity, 2) surveying variants of CAP analysis methods and their applications, focusing particularly on the aim of understanding global signal variations, 3) examining similarities and dissimilarities between the CAP method and other related DFC approaches, 4) discussing potential neuronal correlates of transient CAP events, 5) identifying issues and limitations of the CAP method that researchers should be cautious about, and 6) proposing potential directions for future research in this area. These topics will be organized into separate sections below.

Temporal decomposition of resting-state data into co-activation patterns

Early explorations of the time-varying nature of rsfMRI connectivity

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applied sliding-window and time-frequency coherence analyses (Chang and Glover, 2010; Hutchison et al., 2012; Sakoğlu et al., 2010). These and related approaches examine rsfMRI correlation/coherence within time windows (often 1–2 min) much shorter than a typical scanning session, aiming at uncovering more transient interactions between brain areas. However, most approaches for such "dynamic" connectivity analyses are still based on pairwise relationships between fMRI time series. Though very straightforward, these time-domain methods have limitations for quantifying fMRI data, which typically has orders of magnitude more voxels (N) than time points (T). If pairwise correlations were calculated for all possible voxel pairs, the resulting cross-correlation matrix would have orders of magnitude more elements ($N \times (N-1)/2$, considering its symmetry) than actual measurements $N \times T$, with a maximal rank $T-1$ much lower than its size N. This rank-deficit matrix would represent a very redundant quantification of data covariance. Likewise, resting-state networks (RSNs) typically comprise *thousands of* brain voxels but are derived from correlations computed over [often] only *hundreds of* time points. The discordance between spatial and temporal dimensions simply suggests that the pairwise correlations between two voxels is actually accompanied by co-variation of a much larger number of brain voxels. The presence of covariation across large sets of voxels is the rationale behind the practice of using much larger brain

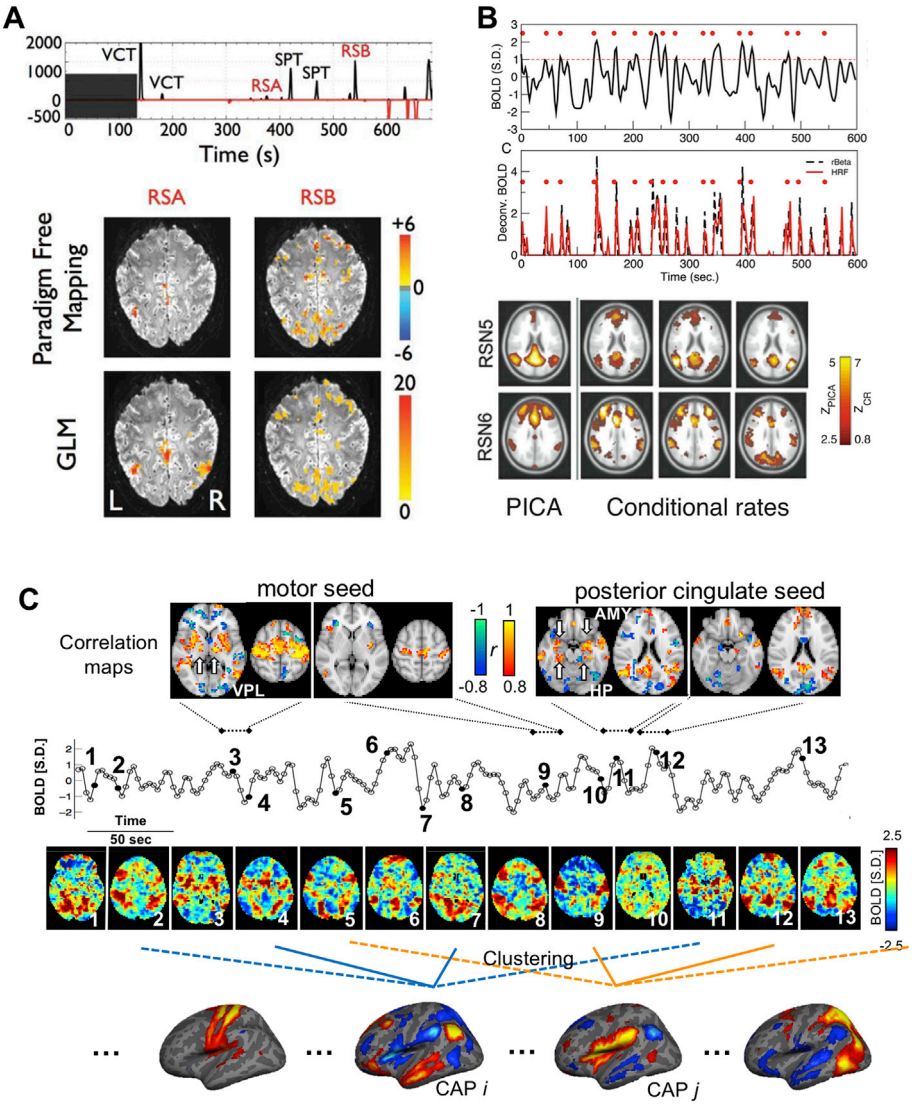

Fig. 1. Three major methods that focus on co-activation events in resting-state fMRI. (A) Two task-unrelated activation events detected by the parameter free mapping (PFM) and their spatial patterns. The activation and deactivation events are detected from fMRI signals of a representative subject as spikes in activation time series (ACT) derived using the PFM (black and red traces in the top panel). In addition to those evoked by visually cued tapping (VCT) and self-paced tapping (SPT) tasks, there were also two task-unrelated activation events (RSA and RSB) were detected in the positive ACT. The spatial activation patterns of the RSA and RSB are derived using the PFM and general linear modal (GLM) and shown in the bottom panel. All panels in (A) are adapted from (Gaudes et al., 2011). (B) Point process analysis (PPA) identifies supra-threshold events in fMRI signals. The point process events (red dots in the top panel) were defined as time points where the normalized fMRI signals cross a threshold of 1 (red dashed line in the first row) from below. These events coincide well with the peaks of de-convolved fMRI signals derived using either the hemodynamic response function (HRF) or the rBeta function (the second row of the top panel). Conditional rate maps of these events (the right three columns of the bottom panel), which indicate the probability of seeing such events at different brain regions conditional on seeing one at a given seed, show very similar network patterns as those derived by probabilistic ICA (the left column of the bottom row). All panels in (B) are adapted from (Tagliazucchi et al., 2012a). (C) Co-activation patterns (CAPs) and dynamic resting-state fMRI connectivity. Thirteen examples of single fMRI volumes show clear instantaneous patterns of brain co-activations that even include thalamic nuclei and hippocampus (the third row). They are corresponding to black solid circles shown in the normalized fMRI signal from the posterior cingulate cortex (PCC) region (the second row with a unit of standard deviation (S.D.)). Seed-based correlation maps (the top row) within four short time windows (16.1 s, 7 fMRI volumes) are largely determined by instantaneous brain co-activation patterns of included time points. For example, the presence of ventral posterolateral nucleus (VPL) in one of the sensorimotor maps is attributed to the co-activation at the time point 3, and the presence of the amygdala (AMY) and hippocampus (HP) in one of the PCC maps can be explained by the instantaneous pattern at time point 11. CAPs were derived by grouping all time points into subgroups using clustering and then taking the means (centroids) of these subgroups (the bottom row).