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Incorporating spatial constraint in co-activation pattern analysis to explore the dynamics of resting-state networks: An application to Parkinson's disease

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ABSTRACT

The dynamics of the brain's intrinsic networks have been recently studied using co-activation pattern (CAP) analysis. The CAP method relies on few model assumptions and CAP-based measurements provide quantitative information of network temporal dynamics. One limitation of existing CAP-related methods is that the computed CAPs share considerable spatial overlap that may or may not be functionally distinct relative to specific network dynamics. To more accurately describe network dynamics with spatially distinct CAPs, and to compare network dynamics between different populations, a novel data-driven CAP group analysis method is proposed in this study. In the proposed method, a dominant-CAP (d-CAP) set is synthesized across CAPs from multiple clustering runs for each group with the constraint of low spatial similarities among d-CAPs. Alternating d-CAPs with less overlapping spatial patterns can better capture overall network dynamics. The number of d-CAPs, the temporal fraction and spatial consistency of each d-CAP, and the subject-specific switching probability among all d-CAPs are then calculated for each group and used to compare network dynamics between groups.

The spatial dissimilarities among d-CAPs computed with the proposed method were first demonstrated using simulated data. High consistency between simulated ground-truth and computed d-CAPs was achieved, and detailed comparisons between the proposed method and existing CAP-based methods were conducted using simulated data. In an effort to physiologically validate the proposed technique and investigate network dynamics in a relevant brain network disorder, the proposed method was then applied to data from the Parkinson's Progression Markers Initiative (PPMI) database to compare the network dynamics in Parkinson's disease (PD) and normal control (NC) groups. Fewer d-CAPs, skewed distribution of temporal fractions of d-CAPs, and reduced switching probabilities among final d-CAPs were found in most networks in the PD group, as compared to the NC group. Furthermore, an overall negative association between switching probability among d-CAPs and disease severity was observed in most networks in the PD group as well. These results expand upon previous findings from in vivo electrophysiological recording studies in PD. Importantly, this novel analysis also demonstrates that changes in network dynamics can be measured using resting-state fMRI data from subjects with early stage PD.

Introduction

In the past two decades, brain functional connectivity has been widely studied using resting-state functional magnetic resonance imaging (fMRI). Functional connectivity is most commonly assessed using the Pearson correlation coefficient between fMRI signals from different regions in the brain (Biswal et al., 1995). Several functional connectivity studies have identified sets of spatial patterns that consist of temporally correlated brain regions (Biswal et al., 1995; De Luca et al., 2005; Greicius et al., 2003). These spatial patterns are called resting-state networks. Among the most commonly studied resting-state networks are the default mode network, sensorimotor network, visual network, auditory network

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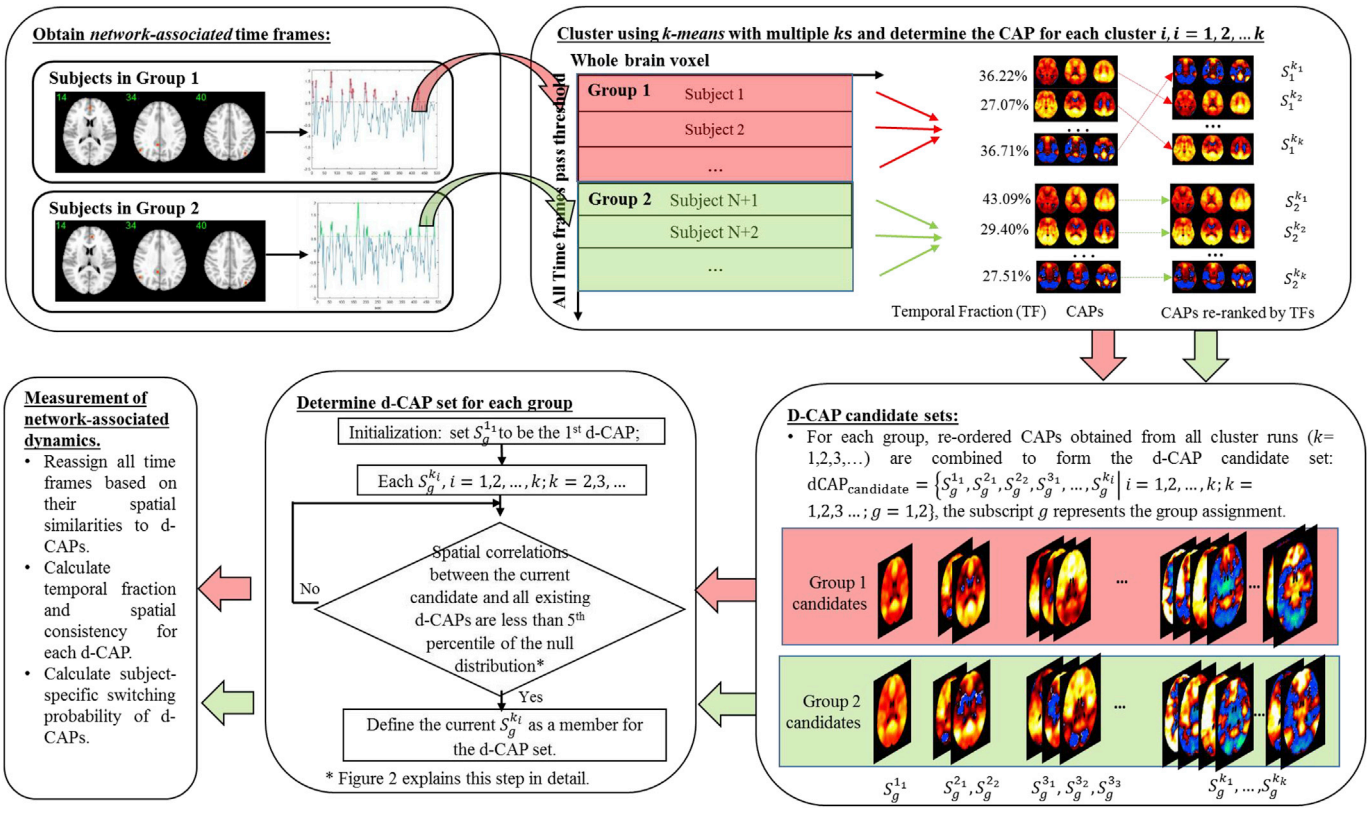

Fig. 1. Group CAP analysis routine.

and executive control network (Beckmann et al., 2005; Damoiseaux et al., 2006; Smith et al., 2009). Investigating resting-state networks has provided fundamental insight into basic neural function (Fox et al., 2005; Smith et al., 2009). Recent studies have shown, however, that the spatial patterns of resting-state networks may change periodically during the epoch of an fMRI scan (Preti et al., 2017). Dynamic functional connectivity analysis has been proposed to identify and investigate these changes in functional connectivity over time (Allen et al., 2014; Hutchison et al., 2013; Preti et al., 2017). Importantly, altered dynamic functional connectivity has recently been reported in neurological disorders such as schizophrenia (Damaraju et al., 2014; Yu et al., 2015), major depression disorder (Holtzheimer and Mayberg, 2011), autism (Price et al., 2014) and Alzheimer's disease (Jones et al., 2012), suggesting that such network changes have pathophysiologic relevance across brain diseases. Investigating dynamic functional connectivity in diseased populations can thus provide vital insight related to poorly understood dynamic brain function in these conditions, and lead to better understanding of disease phenotype, response to therapy, and progression.

Many methods have been proposed for dynamic functional connectivity analysis, such as the sliding-window method (Chang and Glover, 2010), temporal independent component analysis (ICA) (Smith et al., 2012), quasi-periodic pattern method (Majeed et al., 2011; Thompson et al., 2014), and co-activation pattern analysis (Liu and Duyn, 2013). The sliding-window method captures the dynamics of functional connectivity by gathering pairwise linear correlations among brain regions in subsequent temporal windows (Jones et al., 2012; Kucyi and Davis, 2014). Due to its relative simplicity, the sliding-window method is the most widely applied technique in dynamic functional connectivity analysis. One technical challenge of this method, however, is the choice of the window size. Ideally, the window size should be small enough to capture any transients but also large enough to produce stable and statistically powerful results (Hutchison et al., 2013). Temporal ICA decomposes the entire fMRI time series into temporally independent components. Each component is then defined as a distinct temporal functional mode and used to represent the temporal dynamics of functional connectivity (Calhoun et al., 2001; Smith et al., 2012). Temporal ICA is, however, limited by the lack of sample points in conventional resting-state fMRI setting, where approximately 200 time points are typically collected in a 6–10 min acquisition. The Quasi-periodic pattern method identifies a repeated spatiotemporal template within an fMRI scan (Majeed et al., 2011; Thompson et al., 2014). This template is a set of consecutive brain volumes represented throughout the entire scan. Dynamic functional connectivity is then represented by spatiotemporal patterns within this template. This method requires that the spatiotemporal pattern occurs several times during the course of data acquisition, implying that the quasi-periodic pattern method will only capture reproducible dynamic functional connectivity but will miss isolated (yet still potentially important) patterns of dynamic connectivity.

More recently, co-activation pattern (CAP) analysis has been proposed by Liu and Duyn (2013) to track variations of functional connectivity within each individual time frame. Instead of capturing dynamics of whole-brain functional connectivity, the CAP analysis focuses on the temporal dynamics of a specific resting-state network. The basis of CAP analysis is that relevant information of a given resting-state network is expressed by discrete time points where the fMRI signal is large (Chialvo, 2012; Tagliazucchi et al., 2011). Thus in CAP analysis, whole brain fMRI volumes at time points with large fMRI signals are temporally clustered using *k-means* into a predefined number of CAPs to reflect the dynamic behavior of a particular resting-state network.

One advantage of this method is that CAP analysis focuses on individual time frames and therefore does not require a large number of input time points as compared to the analysis methods mentioned above. Furthermore, the CAP method captures a more direct relationship between voxels as compared to the correlation-based sliding window method (Liu and Duyn, 2013). Importantly, the CAP analysis can be extended to whole brain analysis with the entire fMRI volume being input into temporal clustering (Liu et al., 2013). In addition to analysis of basic network dynamics in healthy controls, CAP analysis has also been