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Introducing co-activation pattern metrics to quantify spontaneous brain network dynamics

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ABSTRACT

Recently, fMRI researchers have begun to realize that the brain's intrinsic network patterns may undergo substantial changes during a single resting state (RS) scan. However, despite the growing interest in brain dynamics, metrics that can quantify the variability of network patterns are still quite limited. Here, we first introduce various quantification metrics based on the extension of co-activation pattern (CAP) analysis, a recently proposed point-process analysis that tracks state alternations at each individual time frame and relies on very few assumptions; then apply these proposed metrics to quantify changes of brain dynamics during a sustained 2-back working memory (WM) task compared to rest. We focus on the functional connectivity of two prominent RS networks, the default-mode network (DMN) and executive control network (ECN). We first demonstrate less variability of global Pearson correlations with respect to the two chosen networks using a sliding-window approach during WM task compared to rest; then we show that the macroscopic decrease in variations in correlations during a WM task is also well characterized by the combined effect of a reduced number of dominant CAPs, increased spatial consistency across CAPs, and increased fractional contributions of a few dominant CAPs. These CAP metrics may provide alternative and more straightforward quantitative means of characterizing brain network dynamics than time-windowed correlation analyses.

Introduction

Intrinsic networks observed in the resting state (RS) have been intensively explored in the past two decades (for reviews, see Biswal, 2012; van den Heuvel and Hulshoff Pol, 2010), and have contributed enormously to the understanding of brain function. Until recently, all such studies have relied on the key assumption of temporal constancy. However, it was recently observed that RS network patterns may exhibit substantial changes across a single scan (Allen et al., 2014; Chang and Glover, 2010; Smith et al., 2012), and investigations on anesthetized animals (Hutchison et al., 2013b; Keilholz et al., 2013; Majeed et al., 2011) further demonstrated the functional relevance of such phenomena. Complementary to the conventional approaches, which integrate time series signals across the entire scan, the wealth of information carried by widely observed brain dynamics has great potential to unveil new understanding in cognitive and clinical applications (Holtzheimer and Mayberg, 2011; Rubinov and Sporns, 2011; Sakoglu et al., 2010).

Despite the growing interest in resting brain dynamics, analysis strategies and metrics to quantify the temporal variations are still quite limited. The most common approaches focus on the temporal changes of different quantification measures in a sliding sequence of truncated time windows (Chang and Glover, 2010; Handwerker et al., 2012; Hutchison et al., 2013b; Jones et al., 2012). However, sliding window methods always suffer from tradeoffs between the statistical significance achievable in a short duration window (e.g. there are approximately 10 time points in a 20-s window with conventional TR sampling rate) and the reduction in high frequency content obtained as the window duration is increased (for a review, see Hutchison et al., 2013a).

Very recently, some studies looking at resting state functional connectivity have begun to focus on those time frames when the spontaneous BOLD signal in a voxel or region exhibits relatively large amplitude. By deconvolving the task hemodynamic response function from the rest data, Petridou et al. (2013) have identified a series of 'spontaneous events' and demonstrated the contribution of these events to the correlation strength and power spectra of the slow spontaneous fluctuations. Furthermore, Tagliazucchi et al. (2012) have shown that using such spontaneous events allows one to recover those resting-state networks computed with continuous slow fluctuations across the whole scan. Subsequently, Liu and Duyn (2013) proposed co-activation pattern (CAP) analysis, which offers an alternative to the conventional linear correlation analysis and novel insights into the dynamic changes of

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the on-going network patterns. Briefly, the authors noted that conventional linear correlation results (seed-voxel based whole brain correlation) resemble maps obtained by temporally averaging the whole brain spatial maps at a few critical time points when the seed signal intensity surpasses a certain threshold, and demonstrated that multiple stable spatial patterns (referred to as co-activation patterns, or CAPs) can be obtained by temporal decomposition (clustering) of these critical time frames. Compared to the sliding-window approach, CAP analysis promises the examination of state alternations closer to the temporal resolution of individual time frames but relies on very few model assumptions. Furthermore, the variations of different spatial patterns and their associated fractional scan time durations (number of samples of a CAP/total number of TRs), or temporal fractions (Liu et al., 2013) provide richer quantification measures of brain dynamics that are simple to interpret.

Promising as it may seem, several technical concerns potentially prevent CAPs from facilitating routine examination/quantification of brain dynamics: the enormous feature dimension (total number of gray matter voxels) in temporal clustering imposes intensive computational load and may not support data acquisitions at higher temporal/spatial resolutions; the spatial patterns and temporal fractions of the resolved CAPs are sensitive to the choice of temporal clustering numbers.

The primary focus of the current study is therefore to extend and synthesize information inherent in the CAP concepts, and provide a framework to quantify brain dynamics in routine neuroimaging investigations. To demonstrate that the proposed metrics based on CAPs can reveal more elaborate changes in brain repertoire than is shown by sliding-window correlation analysis, we apply both approaches to compare the variability of functional connectivity of two RS networks (the default-mode network (DMN) and executive control network (ECN)) at rest to that of a sustained 2-back working memory (WM) task. As the WM task enforces a control state with more engaged cognitive processing than that of rest, where uncontrolled changes in vigilance may cause significant state fluctuations (Chang et al., 2013; Wong et al., 2013), we anticipate that prominent differences in brain dynamics will be observed between the two mental conditions, thereby affording a means to demonstrate the value of the proposed metrics.

Material and methods

Extension of CAP analysis

A brief introduction of CAP analysis

In conventional seed-based correlation analysis, the network patterns associated with a given seed are typically estimated by the linear correlation between the time series of each gray matter voxel and the referenced seed. The CAP method (Liu and Duyn, 2013) demonstrates that identical network patterns can be obtained by voxel-wise averaging the spatial maps of those time frames when the seed signal intensity surpasses a certain threshold (see Fig. 1A for illustration). Temporal clustering of those extracted time frames based on their spatial similarity can yield multiple spatial patterns (Fig. 1B), which are conjectured to be functionally relevant and reflect co-activation patterns (CAPs) across the whole brain at each individual time frame.

ROI-wise CAPs

The CAPs demonstrated by Liu and Duyn (2013) were obtained from maps based on correlations between a seed and every voxel. However, as shown in Fig.1, those CAPs exhibit identifiable structures that are regionally homogeneous, motivating the use of an "ROI-wise" CAPs analysis, wherein the brain is parcellated into multiple fixed ROIs, and the average signal intensity of all the voxels within each ROI (instead of the raw signal intensity of each voxel) is taken as the feature set for K-means temporal clustering.

In contrast to the original voxel-wise CAPs, ROI-wise CAPs can provide increased spatial signal to noise ratio (SNR) in local brain regions, and more importantly, enhance the overall computational efficiency (the feature size has been reduced from # of whole gray matter voxels to # of ROIs used), which is essential for extension into larger datasets. With a surrogate dataset, we demonstrate that a whole brain ROI-wise CAP analysis provides similar results to a voxel-wise CAP analysis (the CAP analysis section and Supplementary Figs. S1 and S2).

Quantifiable metrics of brain dynamics in CAPs

Information in the spatial patterns of CAPs. The spatial patterns of CAPs explicitly reflect the repertoire of brain states across the whole scan. The spatial similarity between different CAPs and the quantity of CAPs that actually dominate the brain repertoire reflect the extent of network changes incurred by a switch from one state to another, and can therefore be utilized as metrics to quantify brain dynamics.

Unfortunately, in common with other data-driven approaches, e.g. ICA, the derived spatial patterns are dependent on the choice of cluster number k in the CAP analysis. To eliminate the bias from choosing specific k s, we introduce the concept of "overall dominant CAP-set", which is a set of CAPs synthesized across the results from different choices of k s and is representative of brain repertoires across the whole scan.

Specifically, the "overall dominant CAP-set" can be extracted in a two-stage hierarchical procedure. First, the "dominant CAP-set" associated with each cluster number k (see Fig. 2) is generated. Briefly, after re-ranking the CAPs by their temporal fractions (TF) in descending order — CAP^1, CAP^2, … CAP^k, we calculate the series of temporal frame averages $\{S_m\}_{1\leq m\leq k}$ as:

$$S_m = \sum\nolimits_{1\leq i\leq m} SM_i \cdot TF_i \tag{1}$$

where SM_i is the spatial map of CAP^i. The spatial similarity (linear Pearson correlation between the spatial patterns, i.e. the intensity patterns across all the gray matter voxels) of $\{S_m\}_{1\leq m\leq k}$ with the overall time frame average (S_k, i.e. the spatial map generated by averaging all the extracted time frames for CAP analysis) is further calculated as $\{r_m^s\}_{1\leq m\leq k}$. The dominant CAP-set of cluster number k is chosen as the set of CAPs $\{CAP^j\}_{1\leq j\leq n}$ with $\{r_{n-1}^s < r_{thres}^s\} \& \left\{\prod_{p\geq n} \boldsymbol{I}\left\{r_p^s \geq r_{thres}^s\right\}\right\}$ (where r_{thres}^s is a fixed threshold to remove miscellaneous CAPs with relatively low temporal fractions, or signal intensities that do not contribute much to the overall network pattern, and $\boldsymbol{I}$ denotes the indicator function, i.e. $\boldsymbol{I} = 1$ when $r_p^s \geq r_{thres}^s$, 0 otherwise). At the second stage, the most reproducible pattern (the quantity of CAPs and spatial similarity) among all the dominant CAP-sets (for different k s) derived from the first stage is chosen as the "overall dominant CAP-set".

As a synthesized measure, the number of overall dominant CAPs reflects the diversity of network patterns (the fewer number of CAPs, the sparser the dictionary of network patterns), while the spatial consistency across different CAPs indirectly quantifies the uniformity of brain dynamics during CAP alternations (the higher spatial consistency, the less extreme dynamics that state alternations may incur).

Information in the temporal patterns of CAPs. In addition to the spatial patterns, the accompanying temporal information may also quantify the diversity of brain dynamics. A first metric involves the temporal fractions (TF) of different CAPs, which quantify the number of different brain functional modes during the scan. A skewed distribution of CAP TFs, particularly with one (or a few) CAP(s) of overwhelming TF(s), may correspond to a state with more consistent network patterns (less dynamic) compared to those with more equally distributed CAP TFs. A second metric is the frequency of state alternations (FA) in CAPs. Because every abrupt switch of brain state may contribute considerable variation to the observed correlation values, a state with more frequent state alternations may likely be more dynamic compared to those with fewer alternations of states. Thus, FA can also serve as an informative metric to reveal the relative diversity of brain dynamics.