



## Technical Note

# Mutually temporally independent connectivity patterns: A new framework to study the dynamics of brain connectivity at rest with application to explain group difference based on gender



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## ABSTRACT

Functional connectivity analysis of the human brain is an active area in fMRI research. It focuses on identifying meaningful brain networks that have coherent activity either during a task or in the resting state. These networks are generally identified either as collections of voxels whose time series correlate strongly with a pre-selected region or voxel, or using data-driven methodologies such as independent component analysis (ICA) that compute sets of maximally spatially independent voxel weightings (component spatial maps (SMs)), each associated with a single time course (TC). Studies have shown that regardless of the way these networks are defined, the activity coherence among them has a dynamic nature which is hard to estimate with global coherence analysis such as correlation or mutual information. Sliding window analyses in which functional network connectivity (FNC) is estimated separately at each time window is one of the more widely employed approaches to studying the dynamic nature of functional network connectivity (dFNC). Observed FNC patterns are summarized and replaced with a smaller set of prototype connectivity patterns (“states” or “components”), and then a dynamical analysis is applied to the resulting sequences of prototype states.

In this work we are looking for a small set of connectivity patterns whose weighted contributions to the dynamically changing dFNCs are independent of each other in time. We discuss our motivation for this work and how it differs from existing approaches. Also, in a group analysis based on gender we show that males significantly differ from females by occupying significantly more combinations of these connectivity patterns over the course of the scan.

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## Introduction

## Functional connectivity and dynamic functional connectivity

The functional magnetic resonance imaging (fMRI) research community is often focused on identification of functionally meaningful networks that exhibit coherent activity over time. In seed based approaches these networks are typically defined as a collection of voxels whose fMRI time series correlate strongly with the time series of a seed voxel or seed region (Bressler and Menon, 2010; Bullmore and Sporns, 2009). The identified networks with these approaches are generally referred to as functional connectivity (FC). In contrast to this, independent component analysis (ICA) as a data-driven approach identifies

maximally spatially independent configurations of voxel weightings (referred to as ICA components). Each component is characterized by a single time course (called the mixing coefficients) (Beckmann et al., 2005; Calhoun et al., 2001b; Damoiseaux et al., 2006).

Networks (Erhardt et al., 2011a) obtained in these ways have been shown to track closely with previously identified functional domains. In the case of ICA, it is also common to evaluate temporal coherence among network time courses, typically measured by correlation or mutual information, as evidence of functional connectivity among the networks, called functional network connectivity (FNC) (Allen et al., 2011; Jafri et al., 2008).

A key feature of most connectivity analyses (FC or FNC) is that the temporal coherence is evaluated *globally*, as a property characterizing network pairs over the entire duration of a study. More recent work has indicated however that these patterns of connectivity are highly dynamic (Calhoun et al., 2014; Hutchison et al., 2013) with key features obscured by averaging over whole experiments. To date, investigations of so-called dynamic FNC (dFNC) have largely been based on computing correlations over sliding windows through the original time courses (Allen et al., 2012; Kiviniemi et al., 2011; Rashid et al., 2014; Sakoğlu

Abbreviations: independent component analysis, (ICA); functional connectivity, (FC); functional network connectivity, (FNC)

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et al., 2010) though other approaches have also been tried (Chang and Glover, 2010).

#### *Functional network connectivity and dynamic functional network connectivity for explaining differences between different demographics groups*

Significant evidence (Fox and Greicius, 2010; Jafri et al., 2008; Kilpatrick et al., 2006; Lynall et al., 2010; Rashid et al., 2014) for differences in connectivity between different groups of subjects such as male/female (Kilpatrick et al., 2006) or schizophrenia/healthy controls (Jafri et al., 2008; Lynall et al., 2010) has emerged from both static and dynamic connectivity analyses. Schizophrenia patients, for example, have been found in static FNC to have stronger connectivity between certain resting state networks than healthy controls (more specifically, connectivity between relatively less connected networks increases in the patients) (Jafri et al., 2008). More recently, a dynamic analysis (Sakoğlu et al., 2010) of task-modulated FNC evaluated on sliding time course windows concluded that task-modulation of motor–frontal, RLFP–medial temporal and posterior default mode (pDM)–parietal connections was significantly greater in schizophrenia patients, while task modulation of orbitofrontal–pDM and medial temporal–frontal connections was significantly greater in healthy controls. A recent study by Rashid et al. (2014) observed that schizophrenia and bipolar patients make fewer transition to certain states and they spend less time in highly intercorrelated states which could only be observed in a brain dynamics study. In another recent study (Damaraju et al., 2014) it has been shown that dwell times of dynamic connectivity states are significantly different in schizophrenia patients vs. healthy controls.

#### *Contribution*

Sliding-window analyses generally seek to characterize each subject's connectivity patterns at each time window in terms of a limited collection of prototype patterns. This can either involve matching each time-windowed connectivity to one element in a finite set of connectivity patterns obtained by clustering (Allen et al., 2012; Majeed et al., 2011), or as proposed by Leonardi et al. (2013) connectivity patterns can be decomposed into a linear combination of mutually orthogonal PCA components. Both approaches have limitations: Clustering techniques cannot be easily adjusted to recognize observations that are linear combinations of certain basic patterns. On the other hand, mutual spatial orthogonal components estimated by PCA cannot be interpreted independently, and by design, successive PCA components, explain smaller and smaller proportions of the variance in the data. Furthermore, the spatial orthogonality assumption of PCA is independent of temporal behavior of connectivity patterns.

In this paper we introduce the concept of mutually temporally independent dynamic connectivity patterns. While in conventional clustering approaches one and only one connectivity pattern (cluster centroid) is occupied at a time and in PCA-based approaches, components do not have a clear temporal dynamic interpretability, in this paper, we look for patterns of connectivity with mutually independent temporal behavior. The temporal behavior of these patterns is defined as a weighted contribution to the observed dFNC at each time point.

#### **Materials and methods**

The closest work to the present study is Allen et al. (2012) and our pipeline is similar up to the computation of sliding-window dFNCs. However, as mentioned in the Contribution section, we are seeking correlation patterns that make maximally temporally independent additive weighted contributions to observed dFNCs rather than a set of summary patterns reflecting cluster means within the observed data. To support comparisons with earlier work, we used the same data and followed relevant stages of the preprocessing pipeline from Allen et al.

(2012). In Fig. 1 we present the overall procedure for computing temporally independent connectivity patterns.

Data consisted of 405 healthy participants (200 females) collected from a 3 T Siemens TIM Trio at the Mind Research Network (TR = 2 s, TE = 29 ms, flip angle = 75°, voxel size = 3.75 × 3.75 × 4.55 mm) and were preprocessed through a standard SPM pipeline including timing and motion correction, spatial normalization, and mild spatial smoothing (see Allen et al., (2012) and Allen et al. (2011) for more details on data collection and preprocessing). Data was originally anonymized, and included a narrow range of ages (mean age: 21.0 and range: 12–35).

#### *Group spatial ICA*

Following Calhoun and Adali (2012) and Calhoun et al. (2001a) group spatial ICA (GICA) was used to find functional networks of the input data. GICA is implemented in several stages: First, a subject-level principal component analysis (PCA) reduces the subject data temporal dimension to 120 principal components (PCs). This is followed by a group-level PCA on concatenated subject principal components, from which 100 PCs are retained. A set of maximally spatially independent group-level spatial maps (SMs) are obtained from this reduced group-level data using an Infomax-based algorithm. To find the most stable SMs, Infomax was repeated ten times and clustered via ICASSO (Himberg and Hyvarinen, 2003). The aggregate spatial maps that emerge from this process are the modes of component clusters.

After removing components corresponding to movement, imaging artifacts or components that were contaminated with white matter, fifty components were left to study.

Subject specific spatial maps and time courses were estimated using the GICA1 (Allen et al., 2011; Erhardt et al., 2011b) algorithm. Some additional postprocessing of time courses were also performed, including detrending, multiple regression of the size realignment parameters and their temporal derivatives and outlier removal.

#### *Dynamic FNC estimation*

A set of 116 dFNCs was computed for each subject on successive sliding windows (length = 32, step size = 1 TR = 2 s), tapered by convolving with a Gaussian of sigma 1 TR. Time courses are cropped with the size of our window radius (16) at each end. Functional network connectivity in a given window is estimated by calculating a  $C \times C$  correlation matrix (where  $C = \#$  of components). Window length in sliding-window analyses must be chosen carefully. Short windows can lead to poor correlation estimates, while long windows can blur out the temporal resolution necessary to study dynamics. Through experimentation we found that a window of length 32 provided a good tradeoff between temporal resolution and reliability of FNC estimation and regardless small changes in the window size did not dramatically impact the results. We further refined the covariance matrix estimates at each time window by applying a sparsity constraint with a regularizing parameter ( $\lambda$ ), optimized for each subject, to the precision matrix (the inverse of the correlation matrix) (Friedman et al., 2008).

#### *Estimation of temporally independent patterns of connectivity*

The approach presented in Allen et al. (2012) was focused on identifying recurring connectivity patterns in subject dFNCs, for which clustering algorithms would be an obvious choice (i.e. K-means clustering). However, these patterns need not be temporally independent, and the centroids produced by clustering simultaneously observed dFNCs diminish the odds that these centroids represent patterns that tend to occur. In this study, however, we want to identify co-occurring patterns of functional network connectivity whose relative contributions change independently of one and other in time. To achieve this goal we concatenate dFNC matrices along the time dimension and use temporal ICA

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