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# Instantaneous brain dynamics mapped to a continuous state space

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ABSTRACT

Measures of whole-brain activity, from techniques such as functional Magnetic Resonance Imaging, provide a means to observe the brain's dynamical operations. However, interpretation of whole-brain dynamics has been stymied by the inherently high-dimensional structure of brain activity. The present research addresses this challenge through a series of scale transformations in the spectral, spatial, and relational domains. Instantaneous multispectral dynamics are first developed from input data via a wavelet filter bank. Voxel-level signals are then projected onto a representative set of spatially independent components. The correlation distance over the instantaneous wavelet-ICA state vectors is a graph that may be embedded onto a lower-dimensional space to assist the interpretation of state-space dynamics. Applying this procedure to a large sample of resting-state and task-active data (acquired through the Human Connectome Project), we segment the empirical state space into a continuum of stimulus-dependent brain states. Upon observing the local neighborhood of brain-states adopted subsequent to each stimulus, we may conclude that resting brain activity includes brain states that are, at times, similar to those adopted during tasks, but that are at other times distinct from task-active brain states. As task-active brain states often populate a local neighborhood, back-projection of segments of the dynamical state space onto the brain's surface reveals the patterns of brain activity that support many experimentally-defined states.

## 1. Introduction

The advent of functional Magnetic Resonance Imaging (fMRI) has launched the brain sciences into an exciting frontier by allowing the direct observation of systems-wide activity from healthy human brains (Rosen and Savoy, 2012). The richness of data this technology generates is the subject of cutting-edge research to interpret spontaneous signal fluctuations as indicators of preferential information exchange among the brain's intrinsic networks—i.e., its functional connectivity (FC) (Biswal et al., 1995; Hutchison et al., 2013). Brain FC networks were first defined over relatively long periods of time. Such *static* FC studies reveal that brain FC naturally develops a small-world topology, where densely connected local modules communicate with one another via richly interconnected hubs (Achard et al., 2006; Bullmore and Sporns, 2009). But the brain is not a static system. Rather, differential information exchange among neurons, circuits, and networks enables the brain to deal flexibly with ever-changing environmental stimuli. The availability of rapid (<1s), whole-brain imaging prompted researchers to look for shorter term *dynamics* of brain FC (Deco et al., 2011).

Early efforts to characterize brain dynamics observed that intra-network membership and inter-network communication possessed statistically significant differences when samples were drawn from short time windows during various epochs of an fMRI scan (Chang and Glover, 2010; Keilholz et al., 2013; Smith et al., 2012; Zalesky et al., 2014). While

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these short time window studies confirmed the expectation that the Blood-Oxygen Level Dependent (BOLD) fMRI signal may convey information about short-term brain-state dynamics, the large effect that *a priori* choices in window length had on study results lessened the method's analytic utility (Shakil et al., 2016). The effort to identify rapidly changing dynamics is also hampered by the drop-off in bold SNR at short window lengths.

To avoid the problems inherent in windowed analysis techniques, we present a method that provides a 2D map of the relative similarity of the brain's activity for all time points in the scan. The signal from each voxel first undergoes wavelet decomposition, making use of the BOLD signal's natural spectral scaling to characterize each time point as a summation of activations at multiple frequencies (Billings et al., 2015; Chang and Glover, 2010; Yaesoubi et al., 2015). This multispectral interpretation has been suggested to provide a parsimonious representation of the dynamic properties of complex systems like brains (Bullmore et al., 2004; Ciuciu et al., 2012; Mallat, 1989; Mandelbrot, 1983). To reduce the redundancy of spatial information and improve the SNR, voxel-wise signals are aggregated into a lower-dimensional spatial parcellation using Independent Component Analysis (ICA). In the present study, we treat the collected vectors of multispectral activations from all of the ICA networks at each time point as samples of instantaneous brain states. We then compare each spectrally delimited instantaneous network activation to one another using the Pearson correlation distance.

The dimensionality of the resulting data set is high (equal to the product of the number of functional networks and the number of spectral filters) and difficult to interpret. In order to explore the dynamics of brain activity, we apply t-distributed stochastic neighbor embedding (t-SNE) to represent the data from each time point in a two-dimensional space (van der Maaten and Hinton, 2008). t-SNE is a state of the art data-driven dimensionality reduction algorithm that maintains local distance structure and has found wide application in the data-driven sciences to produce visualizations of *drosophila* behavior, machine learning hidden layers, static functional connectivity networks, and a host of other multidimensional structures (Berman et al., 2014; Mnih et al., 2015; Plis et al., 2014). In comparison to clustering based approaches that segment the time course into a number of predefined states, the map created by t-SNE produces a continuous distribution that can then be segmented empirically (using the watershed algorithm in this study). Information about the timing and the relative similarity of different states is preserved.

Towards the goal of detailing a map of brain-state dynamics, the present study analyzes the wide-ranging states 446 normal volunteers adopt as part of the Human Connectome Project (HCP) (Van Essen et al., 2012b). BOLD fMRI scans from 7 distinct tasks (EMOTION, GAMBLING, LANGUAGE, MOTOR, RELATIONAL, SOCIAL, and WORKING MEMORY (WM)), and from repeated resting conditions (REST1, and REST2) provide a basis to segment a t-SNE embedding of brain-state dynamics across experimentally defined events. We demonstrate the utility of the t-SNE mapping to characterize the human brain's coordination across time, space, and spectra during rest and in the negotiation of changing experimental stimuli.

## 2. Methods

*Data Acquisition and Preprocessing*. The data for this study was obtained from the HCP (Van Essen et al., 2012b). Whole-brain, BOLD--weighted, gradient-echo EPI data were acquired with a $TR = 0.720$ ms, and 2.0 mm isotropic voxels. Volunteers were scanned under 9 conditions, including: REST, EMOTION, GAMBLING, LANGUAGE, MOTOR, RELATIONAL, SOCIAL, and WORKING MEMORY (WM). The SOCIAL scan was examined in more detail during our analysis and is briefly described as follows: volunteers were presented 5 rounds of 20 s movies showing abstract objects making either random motions (*random*) or engaging in socially relevant movements (*mentalizing*). Each movie is followed by a 15 s fixation period where volunteers are asked to look at a '+' symbol. Each scan was performed twice.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.neuroimage.2017.08.042.

A total of 446 volunteer datasets were included in the present study. Minimal data preprocessing was performed by HCP researchers. Steps included: spatial artifact and distortion removal, surface generation, anatomical registration, and alignment to grayordinate space. Voxel time series were normalized to zero mean and unit variance to fit the isotropic noise model expected by the ICA spatial filters. Each volunteer's fMRI data was concatenated, across time, into a single matrix to minimize edge effects from spectral filtering. Scan order was randomized across volunteers.

*Analysis*. Previous studies have suggested that static functional connectivity networks segment into multiple frequency-specific architectures (Billings et al., 2015; Chang and Glover, 2010; Yaesoubi et al., 2015). Therefore, concatenated fMRI datasets were spectrally filtered into an octave of spectral bands, log-spaced over the low-frequency fluctuation range (0.1–0.01 Hz). Using the continuous wavelet transform schema, the filterbank was constructed from a low-order wavelet (Daubechies 4-tap wavelet) to provide optimal segmentation in the time domain with full coverage of the frequency domain (Daubechies, 1992). Brain images from each spectral band were multiplied by a 50 component group ICA spatial decomposition matrix. ICA filters were calculated as part of the HCP beta-release of group-ICA maps (Human Connectome Project, 2014). The number of components was chosen to just exceed the number needed for the eigenvalues of real and randomly shuffled data to be equal (data not shown). Time points were thus modeled as 400-dimensional states (8 spectral bands by 50 functional networks).

The state vectors for each time point were compared, pairwise, using the Pearson correlation distance. This choice highlights coordinated deviations from mean values. The correlation graph was then injected onto a 2-dimensional Euclidean surface using t-SNE. The t-SNE algorithm proceeds in two steps: first, the local neighborhood of each node is emphasized by normalizing inter-node distances via an adaptive Gaussian filter. Second, a 2-dimensional Euclidean version of the graph is constructed by minimizing the KL-divergence between the high-dimensional stochastic distribution and the low-dimensional stochastic distribution. A key innovation to t-SNE is to utilize a heavier tail in the low-dimensional probability distribution—a t-distribution rather than a Gaussian distribution. Doing so causes points that are only moderately far away in the high-dimensional space to be pushed further apart in the low-dimensional representation. This feature allows for naturally affiliative clusters to emerge from an otherwise more compressed state space. Inherent similarities among sequentially sampled points will, none-the-less, cause these points to form their own distinct neighborhood. One way to encourage piecemeal-sequential points to arrive at a group-level neighborhood is to embed points individually onto a group-level training embedding constructed from a sparse subsampling of each individual's scan data. We generated the training embedding in three steps. First, concatenated time series from each volunteer's full set of scans were t-SNE embedded into their own low-dimensional space. Second, ~2% (200 points) were selected from each volunteer's map to construct a group-level subsample. Third, the group-level subsample was t-SNE embedded to construct the training embedding. Subsequently, out-of-sample time points were injected onto the training embedding by satisfying the same symmetrized KL-divergence as used in to generate the training embedding. While removing spurious co-localization imparted by simple co-incidence, this subsampling procedure has the added benefit of reducing the computational load of embedding a large number of data points. (For additional details, please see van der Maaten and Hinton (2008), Berman et al. (2014), and the supplemental materials).

*Quantitative Interpretation Methods.* Density maps were constructed by convolving embedded point distributions by a 2-dimensional Gaussian filter. Density maps were compared using the structural similarity index (SSIM). SSIM is a robust measure of inter-image similarity. It is constructed as the product of three terms that account for differences in