

MULTIFRAME EVOLVING DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY MOTIFS (EVOdFNCs) FROM CONTINUITY-PRESERVING PLANAR EMBEDDING

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ABSTRACT

The study of brain network connectivity as a time-varying property began relatively recently and to date has remained primarily concerned with capturing a handful of discrete static states that characterize connectivity as measured on a timescale shorter than that of the full scan. Capturing group-level representations of temporally evolving patterns of connectivity is a challenging and important next step in fully leveraging the information available in large resting state functional magnetic resonance imaging (rs-fMRI) studies. We introduce a flexible, extensible data-driven framework for the identification of group-level multiframe (movie-style) dynamic functional network connectivity (dFNC) states. Our approach employs uniform manifold approximation and embedding (UMAP) to produce a planar embedding of the high-dimensional whole-brain connectivity dynamics that preserves important features, such as trajectory continuity, characterizing dynamics in the native high dimensional state space. The method is validated in application to a large rs-fMRI study of schizophrenia where it extracts naturalistic fluidly-varying connectivity motifs that differ between schizophrenia patients (SZs) and healthy controls (HC).

Index Terms— Functional Magnetic Resonance Imaging, Functional Network Connectivity, Dynamic Functional Network Connectivity, Schizophrenia

1. INTRODUCTION

The study of brain network connectivity as a time-varying property began relatively recently and to date has remained primarily concerned with capturing a handful of discrete static states that characterize connectivity as measured on a timescale shorter than that of the full scan. Capturing group-level representations of temporally evolving patterns of connectivity is a challenging and important next step in fully leveraging the information available in large resting state functional magnetic resonance imaging (rs-fMRI) studies. We introduce a flexible, extensible data-driven framework for the identification of group-level multiframe (movie-style) dynamic functional network connectivity (dFNC) states. Our approach employs uniform manifold approximation and embedding (UMAP) to produce a planar embedding of the high-dimensional whole-brain connectivity dynamics that

preserves important from the high dimensional setting such as subject-level trajectory continuity and group-level proximity of subject trajectories. The method is shown to produce naturalistic, interpretable evolving dynamic functional network connectivity trajectory states (EVOdFNCs) whose role in the dynamic SZ vs. HC connectomes differ significantly and interpretably, suggesting the method holds promise for identifying more sophisticated dynamical biomarkers from resting-state fMRI than has thus far been possible.

2. METHODS

2.1 Data

We use data from a large, eyes-open resting-state fMRI study with approximately equal numbers of schizophrenia patients (SZs) and healthy controls (HCs) ($n=311$, $n_{SZ}=150$). Imaging data for six of the seven sites was collected on a 3T Siemens Tim Trio System and on a 3T General Electric Discovery MR750 scanner at one site.. The data was preprocessed with a standard, already published [1, 2], pipeline and decomposed with group independent component analysis (GICA) into 100 group-level functional network spatial maps (SMs) and corresponding subject-specific timecourses (TCs). Through a combination of automated and manual pruning, $N=47$ functionally identifiable networks are retained. Subject specific spatial maps and timecourses were obtained from the group level spatial maps via spatio-temporal regression. The timecourses were detrended, despiked and subjected to some additional postprocessing steps. All subjects in the study signed informed consent forms.

2.2 Dynamic Functional Network Connectivity

Dynamic functional connectivity (*dFNC*) between RSN timecourses was estimated using sliding window correlations. Following protocols from recent studies, dynamic functional network connectivity (*dFNC*) was estimated using pairwise correlations between RSN timecourses on tapered sliding rectangular windows of length 22 TRs (44 seconds), advancing 1 TR at each step [2]. After dropping the first 3 TRs, this procedure yields a $47(47 - 1)/2 = 1081$ -dimensional dFNC measure on each of 136 windows of length 22TRs for each subject.

2.3 Planar Embedding

We apply a Matlab implementation [3, 4] of uniform manifold approximation and embedding (UMAP) to embed all 1081-dimensional dFNCs into the plane. Since dFNCs are computed on sliding windows that advance one TR at a time, they exhibit considerable temporal smoothness in their native high-dimensional space. This within-subject smoothness is an intrinsic feature of the actual dynamics, which we heuristically optimize UMAP's two main parameters (n_neighbors=25; mindist=0.75) toward conserving in the planar embedding. It is worth quickly noting that linear dimension-reduction methods such as PCA or ICA produced

continuous. We collect all continuous trajectory sub-segments (CTSS) $\hat{\alpha}_j(\hat{\gamma}) = \{\hat{\gamma}(t), t \in [t_j, t_j + \tau]\}, j = 1, 2, \dots, T - \tau$ along $\hat{\gamma}(t)$ of temporal duration $\tau = 44$ (twice the windowlength used to estimate the dFNC observations in \mathcal{D}). Each $\hat{\alpha}_j(\hat{\gamma})$ can be approximated by a line L_j , yielding a reduced characterization $(\hat{x}_j, \hat{y}_j, \hat{m}_j, \hat{\ell}_j)$ of $\hat{\alpha}_j(\hat{\gamma})$ in terms of its length $\hat{\ell}_j = \max_{t, t' \in [t_j, t_j + \tau]} \|\hat{\gamma}(t) - \hat{\gamma}(t')\|_2$, its geometric midpoint (\hat{x}_j, \hat{y}_j) and the slope \hat{m}_j of its linearization L_j . The linearized trajectory segment (LTS) triples: $(\hat{x}_j, \hat{y}_j, \hat{m}_j)$ are

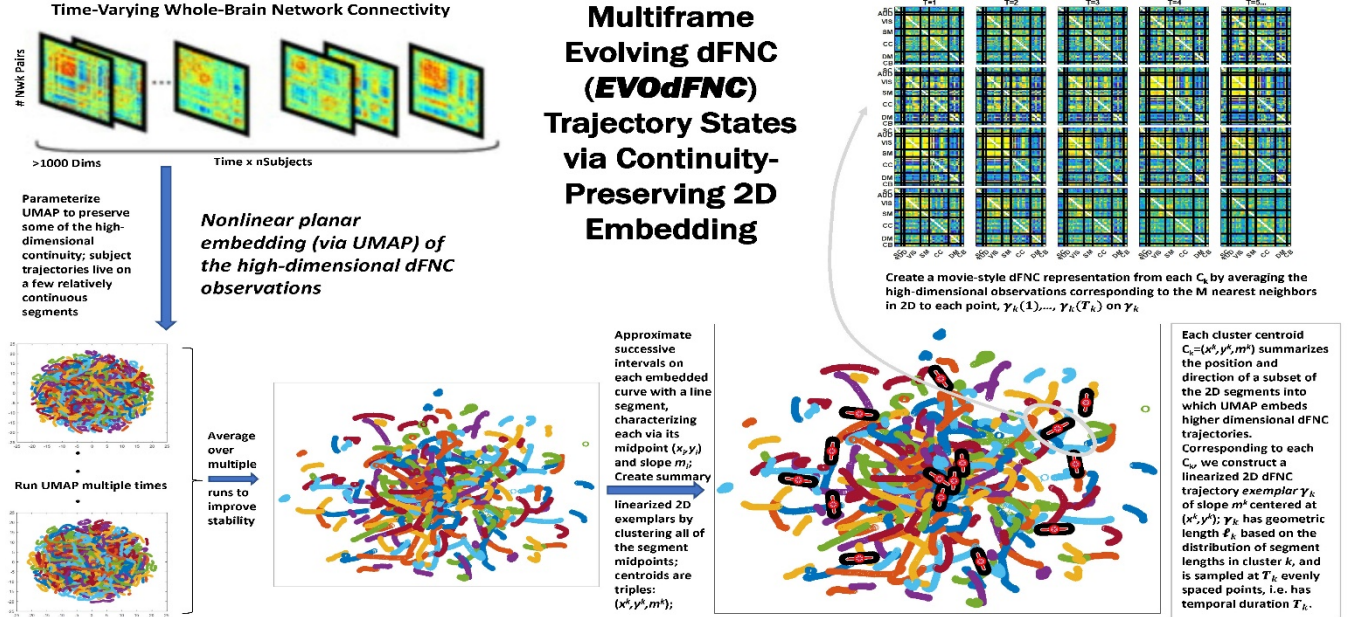


Figure 1 Overview schematic exhibiting the pipeline for producing representative evolving multiframe high-dimensional states of dynamic functional network connectivity (EVOdFNCs). High-dimensional dynamic functional connectivity (HD-dFNC) assessed as pairwise correlations on sliding windows through each subject's GICA network timecourses (top left) are embedded (bottom left) into 2D using uniform manifold approximation and projection (UMAP). Although unsupervised, since it is parameterized to preserve continuity, UMAP embeds subject HD-dFNC observations into contiguous identifiable planar curves. For greater stability we use the average of $R = 25$ embeddings. We replace the curves with a sequence of local linear approximations to segments of duration $\tau = 44$ TRs (twice the window-length on which dFNCs are computed), The linearized segments are parameterized by their position and slope, then clustered to create a set of 2D "linear exemplars" that capture regionally dominant directional trends in the embedded group dynamics (bottom right). Finally, these 2D exemplars are lifted back to high-dimension by averaging the inverse images of the 25 planar nearest neighbors to $\tau = 44$ evenly spaced points along the exemplar. Exemplars are given geometric length equal to the mean length of the segments in their cluster.

diffuse 2D clouds lacking any temporal or intra-subject continuity, while t-SNE performed more than 200-fold more slowly than UMAP on this data, and thus was not practical for achieving a planar embedding of the entire dataset.

2.4 Identification of 2D Linear Trajectory Exemplars

Due to our choice of UMAP parameters within intervals that preserve intra-subject trajectory continuity, the majority of each subject's high-dimensional dFNC trajectory $\Gamma(t) = (v_1(t), v_2(t), \dots, v_{1081}(t))$ embeds, under the r^{th} run of UMAP, into an approximately continuous segment $\gamma_r(t) = (x_r(t), y_r(t))$ in 2D. Continuity is preserved under summation, so the average $\hat{\gamma}(t) = (\hat{x}(t), \hat{y}(t)) = \left(\frac{1}{R} \sum_{r=1}^R x_r(t), \frac{1}{R} \sum_{r=1}^R y_r(t)\right) \in \hat{\mathcal{E}}(\mathcal{D})$ will also be

then clustered with k-means (Matlab implementation, squared Euclidean distance, 2000 iterations, 250 repetitions) where the number of clusters, $K = 10$, was chosen according to the elbow-criterion. From each of the $K = 10$ LTS cluster centroids: $(\hat{x}_j, \hat{y}_j, \hat{m}_j)$ we induce a 2D line segment of length d_i (equal to the mean length of all LTSs in that cluster) and slope \hat{m}_i centered at (\hat{x}_i, \hat{y}_i) . These segments are, roughly speaking, *gradients* of the CTSS, which are in turn averages of continuous embedded segments of the high dimensional dFNC dynamics. The collection of segments induced by LTS cluster centroids will be called *linear trajectory exemplars* or just *exemplars* (see schematic **Figure 1**, top left and bottom).

2.5 High-Dimensional Multiframe Evolving dFNC (EVOdFNC) States from 2D Linear Exemplars

Because UMAP is not straightforwardly invertible, the 2D linear trajectory exemplars cannot be mapped back directly into the high-dimensional dFNC space. To obtain the high dimensional HD-dFNC trajectory segment Y of integer temporal duration τ corresponding to a given 2D linear trajectory exemplar v , (i.e., the “data driven inverse” of v), we average the high-dimensional observations corresponding to the $n = 25$ nearest 2D neighbors of each of τ evenly spaced points along v . The number of 2D neighbors used to invert UMAP, $n = 25$, was chosen to match the number of nearest neighbors parameter in employed in the UMAP embedding. This operation effectively “lifts” a localized 2D linear trajectory exemplar back into high-dimensional dFNC space. The 2D linear trajectory exemplars are, by construction, concentrated in more densely occupied parts of the plane, and the continuity preserving parameterization of UMAP encourages the high-dimensional data-driven inverse of each 2D linear trajectory exemplar to exhibit naturalistic smoothness. These high dimensional inverse images of the 2D linear trajectory exemplars are each multiframe representations of evolving functional network connectivity

Although produced by a clustering step in the 2D segment space, the HD EVOfNCs are more properly viewed as representations of dominant directional trends in the dFNC data than as a hard segmentation of the observed dynamics and we employ them as a parameterization rather than a segmentation of multiframe dynamic evolution in HD dFNC space. Observed dFNC windows of length- τ are expressed in terms of the K length- τ EVOfNCs by weighting each EVOfNC with the proportion in $[0,1]$ of frames in observation that are maximally correlated to the corresponding frame in that EVOfNC).

2.7 Statistical Modeling

Reported SZ effects are from a multiple regression on gender, age, head motion and SZ, and are only reported when significant at the $p < 0.05$ level after correction for multiple comparisons.

3. RESULTS

We find widespread schizophrenia effects on the contributions EVOfNCs make to subject data (**Figure**

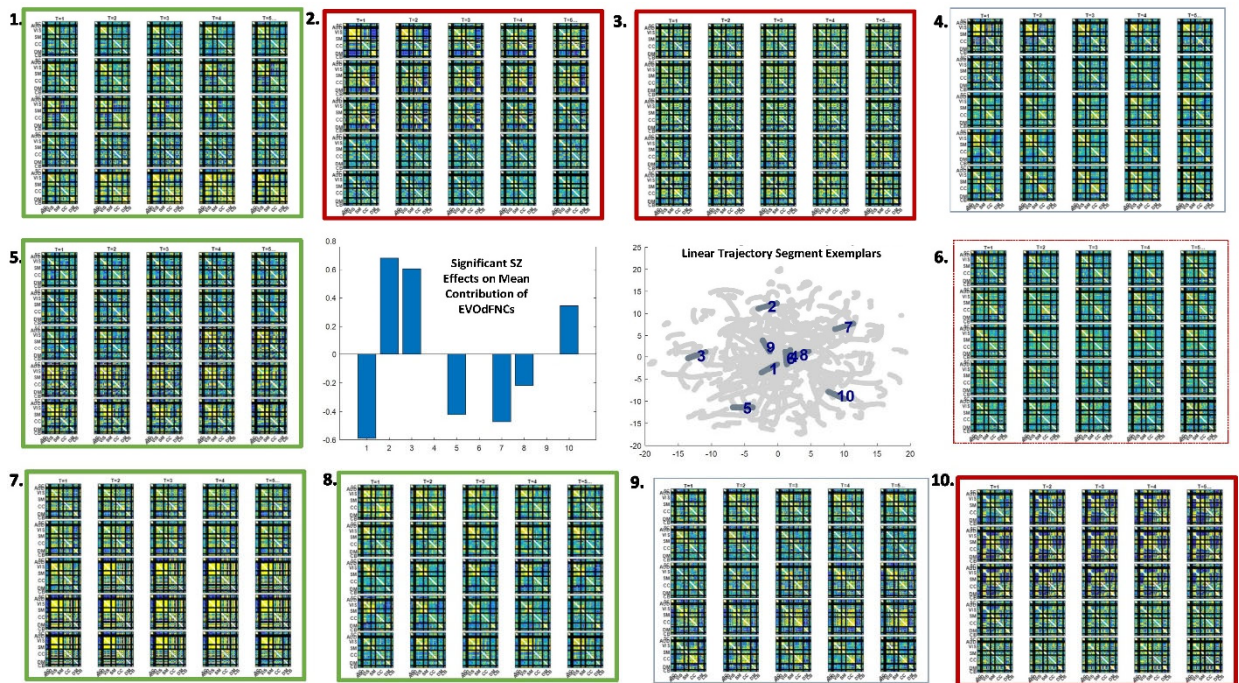


Figure 2 There are pervasive group differences between schizophrenia patients and controls in representational importance of the $K = 10$ EVOfNCs; thick red (resp. thick green) boxes designate significant positive (resp. negative) association with SZ after correction for multiple comparisons; thin dashed red box designates significant ($p < 0.025$) positive association with SZ that is not significant after correction for multiple comparisons. Omitted colorbar is bounded in $[-0.3, 0.3]$.

(EVOfNCs) (see schematic **Figure 1**, top right). Although EVOfNCs have $\tau = 44$ frames, for better visualization we display a subsampled version of the EVOfNCs produced by applying the inversion procedure above to 25 evenly spaced points on the exemplars, yielding a more coarsely sampled version of the EVOfNC that is actually used in the analysis.

2.6 Expressing Observed HD dFNCs Using EVOfNCs

2Error! Reference source not found.) and most importantly this analysis exposes the differences in SZ and HC trajectories that pass through similar patterns of whole-brain resting state connectivity. For example, in the case of subjects lingering in patterns of negative default mode network (DMN) connectivity to other functional domains, the HCs are significantly more likely to arrive there by dissolving some earlier highly modularized structure involving positive

Auditory-Visual-Sensorimotor (AVSM) connectivity and negative AVSM connectivity to Cognitive Control (CC) and DMN, while SZs find their way to the negative DMN-to-Other pattern by modularizing from weaker more diffuse connectivity (**Figure 3**). These findings are consistent with facts about the static connectivity (both full scan, and time resolved) of HCs and SZs but this analysis allows much more refined parsing of *how* certain types of functional integration are achieved or suppressed.

4. DISCUSSION

Characterization and analysis of the time-varying resting state connectome continues to rest heavily on identifying a small number of fixed whole-brain connectivity patterns that manifest on timescales shorter than the full scan duration. The small set of fixed “states” is then then employed to model brain dynamics as a stationary Markov process, with the brain occupying and transitioning between this small set of fixed patterns. More sophisticated analyses of the complex dynamical processes that support human cognitive, emotional, executive and motor functions require frameworks for characterizing and leveraging the fluidly varying high dimensional dynamics of presented by functional imaging modalities such as fMRI. Here we introduce an approach that works from a data-driven inversion of the dynamic gradients in a planar embedding of the high-dimensional dynamics to capture group-level multiframe evolving “movie-style” representations of dynamic functional network connectivity (EVOdFNCs) in a large

schizophrenia imaging study. The method has produced plausible, interpretable, naturalistic high-dimensional EVOdFNC states, whose contributions to HC and SZ dynamic connectivity differ significantly, and which expose how differently the two groups manifest and recede from certain characteristic organizational

states of the connectome, such as the pattern in which DMN is anticorrelated with other networks and non-DMN networks are all lightly intercorrelated with each other. We believe this is an important first step toward more sophisticated analysis of high dimensional functional imaging data, allowing researchers to more finely resolve the relationship of longer dynamic *processes* to human health and performance.

5. ACKNOWLEDGMENTS

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6. REFERENCES

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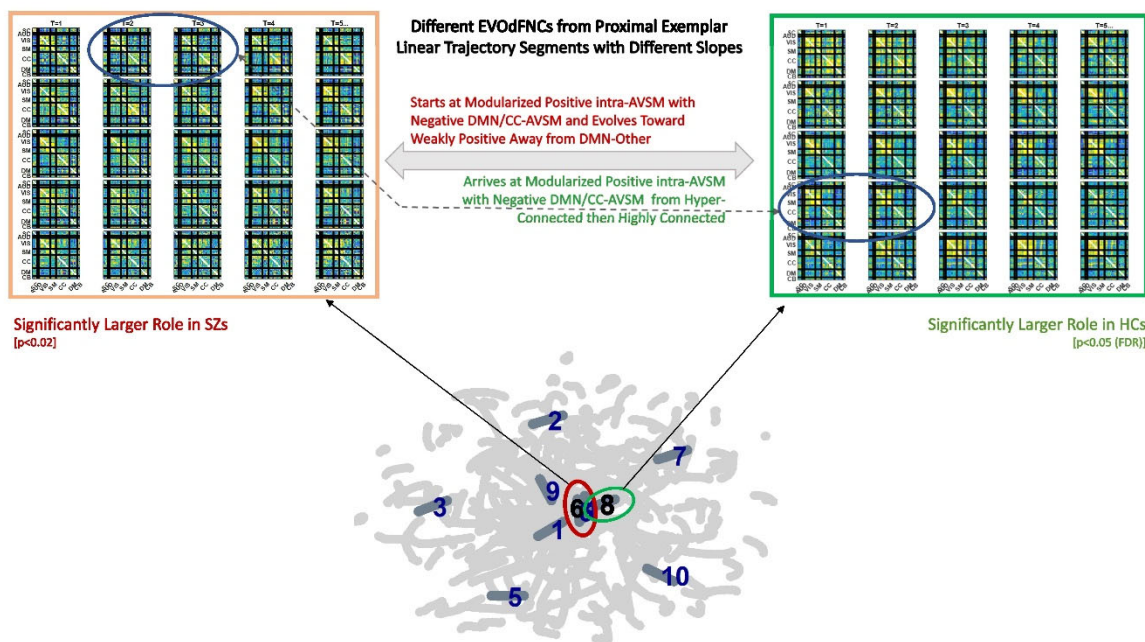


Figure 3 Top row shows two EVOdFNCs (rightmost in green is significantly more important in HCs than SZs; leftmost in red is significantly more important in SZs than HCs). The underlying exemplars (bottom row, in red and green ovals respectively) are proximal but have different slopes, representing different ways of passing through this region of the embedding and sufficiently different trajectories in the high-dimensional source space that one is more characteristic of HCs and the other of SZs.