Higher Dimensional Analysis Shows Reduced Dynamism of Time-Varying Network Connectivity in Schizophrenia Patients

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Abstract— **Assessments of functional connectivity between brain networks is a fixture of resting state fMRI research. Until very recently most of this work proceeded from an assumption of stationarity in resting state network connectivity. In the last few years however, interest in moving beyond this simplifying assumption has grown considerably. Applying group temporal independent component analysis (tICA) to a set of time-varying functional network connectivity (FNC) matrices derived from a large multi-site fMRI dataset (N=314; 163 healthy, 151 schizophrenia patients), we obtain a set of five basic correlation patterns (component spatial maps (SMs)) from which observed FNCs can be expressed as mutually independent linear combinations, i.e., the coefficient on each SM in the linear combination is maximally independent of the others. We study dynamic properties of network connectivity as they are reflected in this five-dimensional space, and report stark differences in connectivity dynamics between schizophrenia patients and healthy controls. We also find that the most important global differences in FNC dynamism between patient and control groups are replicated when the same dynamical analysis is performed on sets of correlation patterns obtained from either PCA or spatial ICA, giving us additional confidence in the results.**

I. Introduction

Connectivity between the functional networks obtained from fMRI data by various methods, including blind source separation techniques such as independent component analysis (ICA), continues to be a central focus of much resting-state fMRI research. Until very recently, most of these studies have worked from a simplifying assumption that functional network connectivity (FNC) is a stationary characteristic of the brain at rest, at least on the time scale of a typical fMRI scan. Interest is emerging [1,2,3] however in the dynamical properties of network connectivity. One approach [1,3] seeks to characterize time-varying dynamic FNCs (dFNCs) in terms of a small set of prototype connectivity states that emerge from K-means clustering of observed dFNCs. In this framework, individual dFNCs are replaced by the prototype state they most resemble. A subject is in exactly one state at any given time. Our approach models the dFNCs as weighted sums of maximally statistically independent connectivity patterns (Fig. 1 (A)) called "states". Weights can be positive or negative (Fig. 1 (B), Fig. 2 (boxed)), indicating additive contribution of either the connectivity pattern itself, its so-called *pro-state*, or the connectivity pattern in its *anti-state* form, with signs flipped: correlations become anti-correlations and vice-versa. In this framework a subject is in all states to some degree at all times. Weights do not sum to one - otherwise they would not be independent - and it is possible to simultaneously have same-sign high magnitude contributions from more than one state. This approach was motivated by a desire to understand network connectivity dynamics in terms of (not necessarily observable) patterns, possibly clusters, of signed network pair correlations that "pipe in" and fade out of observed time-varying FNCs in a relatively independent manner. While our main interest was in studying FNC dynamics as reflected in temporally independent correlation patterns drawn from the observed data, one could ask similar questions about how connectivity dynamics project onto data-driven collections of correlation patterns optimized differently. The main point is to have a set of correlation space *basis patterns* around which to organize and analyze complex dynamical variations in network connectivity. For example, the collection could maximize pairwise spatial independence between the correlation patterns (using spatial ICA), or could produce mutually orthogonal correlation patterns presented in order of maximal variance retention (using PCA). The basis pattern sets produced by tools optimizing different objectives will naturally present different individual and relative features. We focus here on dynamical properties that are sufficiently generic to allow for an interesting side-by-side comparison of tICA, sICA and PCA results. Interesting group differences in dynamical behavior of particular tICA correlation patterns, interpretable with greater focus on specific network-pair correlations are reported in [4].

II. Matrials and MEthods

A. Participants, Preprocessing, Network Identification and Dynamic Functional Connectivity

Some basic information about data collection, preprocessing, network identification and computation of dynamic functional connectivity are summarized in this section. Details are available in [1]. Resting state functional magnetic resonance imaging data (162 volumes of echo planar imaging BOLD fMRI , TR = 2 sec.) was collected from 163 healthy controls (117 males, 46 females; mean age 36.9) and 151 age and gender matched patients with schizophrenia (114 males, 37 females; mean age 37.8) during eyes closed condition at 7 different sites across United States. After standard preprocessing, the fMRI data from all subjects was decomposed using group ICA into 47 functionally meaningful network spatial maps (http://icatb.sourceforge.net) of which 47 were identified as functionally meaningful resting state networks (RSNs).

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Subject specific spatial maps (SMs) and timecourses (TCs) were obtained from the group level spatial maps via spatio-temporal regression. The timecourses were detrended, despiked and subjected to some additional postprocessing steps. Dynamic functional connectivity (dFNC) between RSN timecourses was estimated using a sliding window approach. Following protocols from recent studies on dynamic connectivity [1, 2], we use a tapered rectangular window length of 22 TRs (44 seconds), slid 1 TR at each step, and computed pairwise correlations between RSN time courses within these windows.

B. Temporally Independent Connectivity Patterns

Recent work [1, 2] on functional network connectivity dynamics has used clustering algorithms to identify a small set of prototype connectivity "states." Observed dFNCs are replaced by the prototype states they most resemble, allowing connectivity dynamics to be described as a process of moving from one to another of these summary states. In this work, we further develop the higher-dimensional framework introduced in [5] for studying network connectivity dynamics. The objective here is to express time-varying FNCs as weighted sums of correlation patterns whose contributions change independently of each other in time (Figs. 1 and 2), allowing us to develop a richer picture of the interplay between connectivity patterns that are strongly present in the data but:

- The patterns can contain common sets of network-pairs with given correlation strengths.
- The patterns themselves may not strongly resemble empirically observed FNCs.

To achieve this goal we apply group temporal independent component analysis (tICA) to dFNC matrices concatenated along the subject x time dimension, decomposing this concatenated structure into five maximally mutually independent timecourses (because we are performing this analysis at the group level, these are in fact subject x time "courses"), each with an associated connectivity pattern or spatial map that is shared across subjects (Fig. 2). Abusing language a bit, we will refer to the connectivity patterns (spatial maps) as components even though it is the subject x timecourses that are being estimated by tICA.

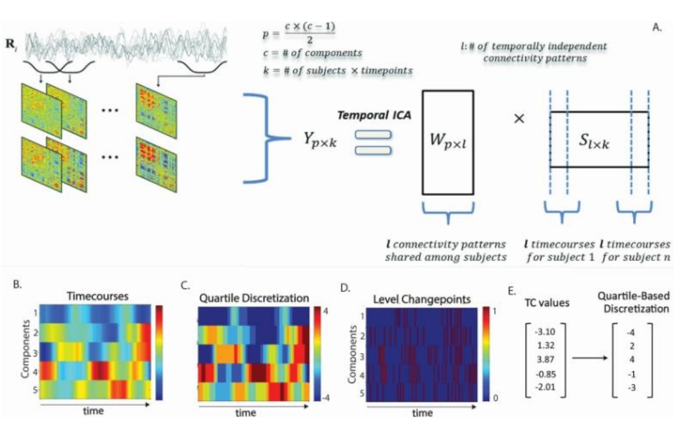

Fig. 1 (A) Schematic outline of group temporal ICA (tICA). (adapted from [1]); (B) Subject's component TCs, (C) transformed to signed quartile discretization, (D) with level changes marked in red; (E) Example of converting vector of TC values to "meta-state" of the discretized levels.

C. Spatially Independent Connectivity Patterns and dFNC Principal Components

We perform a group (spatial) independent component analysis (GICA) on the dFNC data using protocols directly analogous those employed for higher-dimensional fMRI data [1, 2]. The model order of five, used in all decompositions presented here, was chosen in an effort to balance tractability of complex linearly additive effects with a desire for richly featured basis pattern collections. The basis patterns (Fig. 3 (top)) obtained by group sICA are maximally spatially (cell-wise) independent, but neither mutually orthogonal nor informative about the way dFNC variance is organized. For a set of mutually orthogonal basis patterns whose structure explicitly reflects dominant directions of data' variance, we use the first five components of a PCA along the subject x time dimension of the concatenated dFNC data.

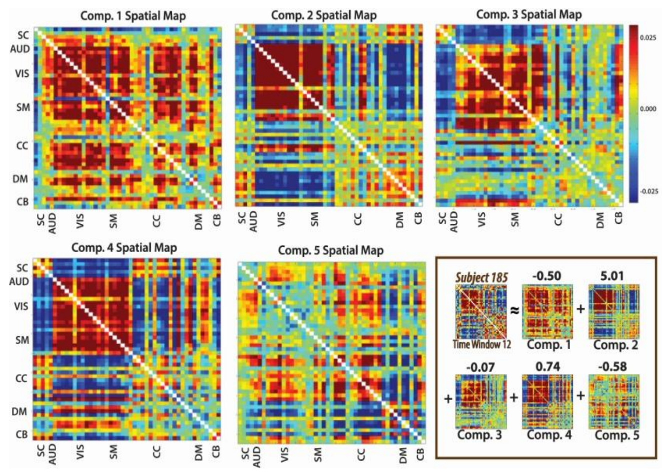

Fig. 2 (Non-boxed) The tICA component spatial maps (basis patterns) with functional modules labeled: subbcortical (SC), auditory (AUD), visual (VIS), sensorimotor (SM), attentional/cognitive control (CC), default mode (DM), cerebellar (CB); (Boxed) One dFNC expressed as weighted combination of the basis patterns.

C. Timecourse Discretization

To work over a more tractable state space, we discretize the timecourses (Fig. 1 (B), (C), (E)) according to their signed quartile: the vector $[w_1^{(k)}(t), w_2^{(k)}(t), w_3^{(k)}(t), w_4^{(k)}(t), w_5^{(k)}(t)]$ of subject k's time t component weights is converted to $[\lambda_1^{(k)}(t), \lambda_2^{(k)}(t), \lambda_3^{(k)}(t), \lambda_4^{(k)}(t), \lambda_5^{(k)}(t)]$ where $\lambda_i \in \{\pm1, \pm2, \pm3, \pm4\}$ indicating the quartile of the (same-sign) weights each $w_i^{(k)}$ falls into. When $\lambda_i^{(k)}(t) = \ell \in \{\pm1, \pm2, \pm3, \pm4\}$, component i is said to be *occupied* at level ℓ. When ℓ is positive, it is *state i* (or *pro-state i*) is occupied; when ℓ is negative, *anti-state i* is occupied. The length-five vectors to $[\lambda_1^{(k)}(t), \lambda_2^{(k)}(t), \lambda_3^{(k)}(t), \lambda_4^{(k)}(t), \lambda_5^{(k)}(t)]$ are referred to as *meta-states*. The timecourses for sICA (resp. PCA) correlation patterns are obtained by regressing each subject's dFNC data at each time window on the set of sICA (resp. PCA) correlation patterns. Discretization of sICA timecourses and principal component timecourses follows the tICA procedure exactly.

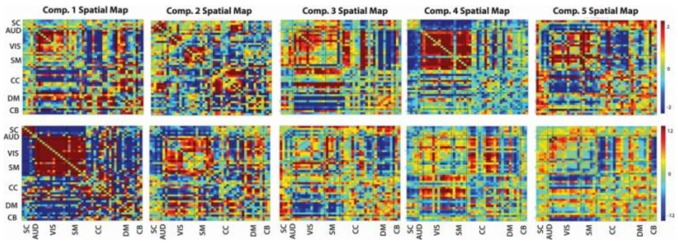

Fig. 3 (Top) Spatial ICA basis patterns; (Bottom) PCA basis patterns, all with functional modules labeled: subbcortical (SC), auditory (AUD), visual (VIS), sensorimotor (SM), attentional/cognitive control (CC), default mode (DM), cerebellar (CB)

D. *Diagnosis Effects*

We employ a simple linear model, $y = \beta_0 + \beta_{gender}X_{gender} + \beta_{age}X_{age} + \beta_{diagnosis}X_{diagnosis} + \varepsilon$ to estimate the effect of diagnosis on the various measures investigated here. The diagnosis variable is binary, with SZ coded as '1' and HC as '0', so $\beta_{diagnosis} > 0$ indicates a positive correlation with SZ and $\beta_{diagnosis} < 0$ shows a negative correlation with SZ. We generally report or display the value of $\beta_{diagnosis}$ when its false discovery rate (FDR) corrected p-value is less than 0.05.

III. Results

In preliminary work with tICA connectivity patterns, we investigated many features of the time-varying weighted contributions made by tICA-derived correlation patterns to observed dFNCs. Diagnostic status (schizophrenia patient (SZ) or healthy control (HC)) had highly significant effects on most of our dynamical measures. We focus here however on four global metrics of connectivity dynamism:

1) The number of times that subjects *switch* from one meta-state to another (denoted by ***s***)
2) The *number* of distinct meta-states subjects occupy during their scans (denoted by ***n***)
3) The *range* of meta-states subjects occupy, ie., the largest L^2 distance between occupied meta-states (denoted by ***r***)
4) The overall *distance* traveled by each subject through the state space (the sum of the L^2 distances between successive meta-states, denoted by ***d***)

The first measure captures how often a subject switches between meta-states, without accounting for how many or how divergent the meta-states are (one could switch between two very similar states in rapid succession). The second records the number distinct meta-states are passed through. A very high ratio of n to the number of time points implies high s; a very high ratio of n to the number of possible meta-states implies high r. The third measure indicates how divergent the meta-states occupied are. The value of r, except when identically zero, need not imply anything about s or n. It is a lower bound for d. The final measure, d, incorporates information from the other three without being fully determined by them. It is maximized when a subject switches frequently between two meta-states at distal boundaries of the state space.

A. *General Reduction of Dynamic Range and Fluidity in Schizophrenia Patients*

We find consistent evidence of reduced FNC dynamism among schizophrenia patients.

1. SZ exhibit diminished *dynamic fluidity*:
   a. SZ switch less frequently between five-dimensional meta-states (Fig. 4)
   b. SZ occupy a smaller number of distinct meta-states during their scans (Fig. 5).
2. SZ operate over a restricted in *dynamic range*:
   a. SZ remain trapped in a smaller radius hypersphere of the state space (Fig. 6)
   b. SZs cover less distance as they move through the state space (Fig. 7).

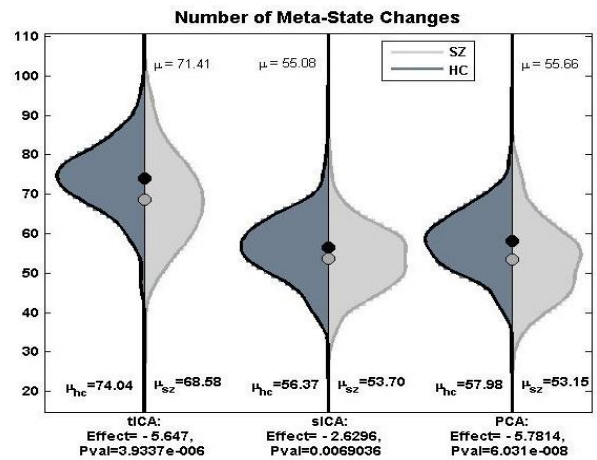

Fig. 4 Diagnosis effect on *s*, the number of meta-state changes (along vertical axis), evaluated for basis patterns generated by tICA (left), sICA (middle) and PCA (right).

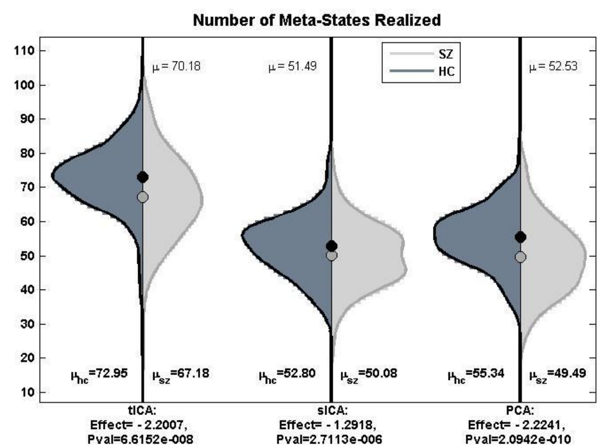

Fig. 5 Diagnosis effect on *n*, the number of meta-states realized (along vertical axis), evaluated for basis patterns generated by tICA (left), sICA (middle) and PCA (right).

As there are many ways to approach multivariate connectivity and dynamics, we evaluated several approaches to see how sensitive the main findings were to the underlying analytic pathway (specifically the method of decomposing dynamic FNC data). Encouragingly, these findings hold regardless of how the basis correlation patterns were generated (tICA, sICA or PCA). In light of emerging evidence for greater high frequency content in SZ network timecourses [6], the overwhelmingly suppressive effect of SZ diagnosis on global measures of connectivity dynamism suggests a complicated picture with respect to SZ and functional networks. Somewhat paradoxically, although SZ network timecourses carry more rapidly fluctuating content than those of healthy controls, the overall structure of pairwise network correlative relationships (as projected onto tICA, sICA or PCA-produced basis patterns) is evidently more static for SZ than HC.

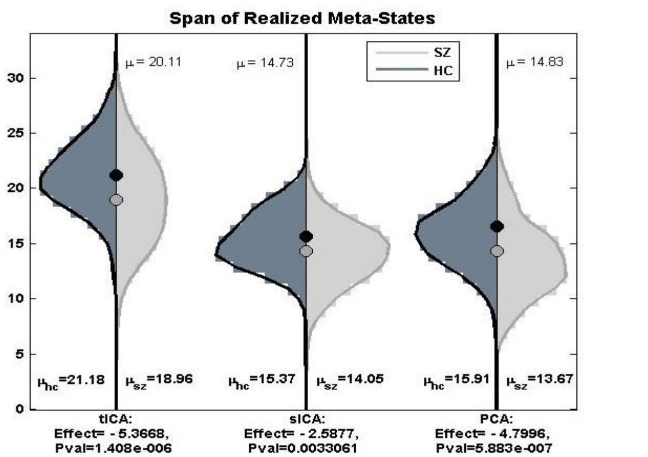

Fig. 6 Diagnosis effect on the span (maximum L2 distance), *r*, between realized meta-states (along vertical axis), evaluated for basis patterns generated by tICA (left), sICA (middle) and PCA (right).

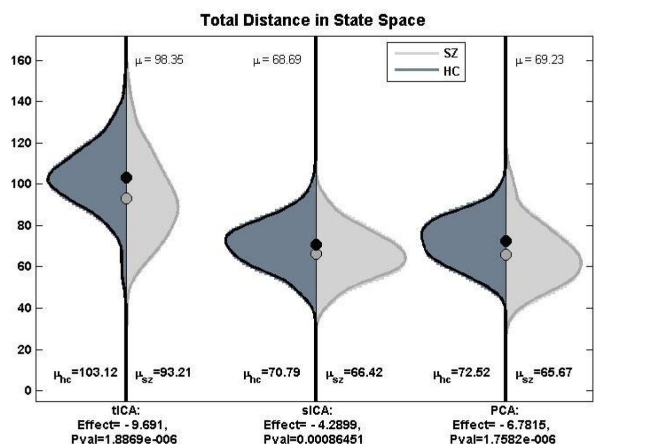

Fig. 7 Diagnosis effect on the total distance (summed L2 distances between successive meta-states), *d*, traveled through the state space (along vertical axis), evaluated for basis patterns generated by tICA (left), sICA (middle) and PCA (right).

IV. Discussion

We extended a framework introduced in [5] for analyzing dynamic network connectivity in terms of small sets of correlation patterns that combine additively to form (or approximate) observed time-varying dFNCs. Our main interest has been in patterns whose simultaneous contributions (obtained using group temporal ICA) are, in magnitude and direction, maximally mutually independent. The general framework we develop for higher-dimensional analysis of connectivity dynamics should carry over easily however to settings with different goals and assumptions. To probe the role of decomposition algorithm on results, we repeated our analysis for basis patterns produced using two other common data-driven methods (group spatial ICA and principal component analysis). The power of this higher-dimensional data-driven approach is demonstrated by the strong statistical evidence it provides for diminished dynamic fluidity (Figs. 4 and 5) and restricted dynamic range (Figs. 6 and 7) of network connectivity in schizophrenia patients vs. healthy controls. Additional confidence in the robustness of the tICA-based results is provided by their replicability, with respect to both direction and statistical power, when the analysis is performed on correlation patterns obtained using spatial ICA and PCA.

References

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