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Data-driven spatio-temporal dynamic brain connectivity analysis using fALFF: Application to sensorimotor task data

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Abstract—Dynamic functional connectivity (dFC) analysis enables us to capture the time-varying interactions between brain regions and can lead to powerful biomarkers. Most dFC studies are focused on the study of temporal dynamics and require significant postprocessing to summarize the results of the dynamics analysis. In this paper, we introduce an effective framework that makes use of independent vector analysis (IVA) with fractional amplitude of low frequency fluctuation (fALFF) features extracted from task functional magnetic resonance imaging (fMRI) data. Our approach, which is based on IVA with fALFF features as input, (IVA-fALFF) produces an effective summary of the dynamics also greatly facilitating the study of both spatial and temporal dynamics in a more concise manner. IVA-fALFF captures the spatial and temporal dynamics of sensorimotor task data and identifies a component with significant difference in dynamic behavior between healthy controls (HC) and patients with schizophrenia (SZ). Finally, our post analysis using behavioral scores finds significant correlation between brain imaging data and the associated behavioral scores, increasing confidence on our results. Our results are consistent with the previous data-driven dFC analysis as we find similar brain networks showing abnormal behavior in patients with SZ. Moreover, our analysis identifies component behavior in task and rest windows separately and provides additional confirmation of results through correlation with behavioral scores.

Index Terms—Independent vector analysis (IVA), fractional amplitude of low frequency fluctuation (fALFF), sensorimotor (SM) task data, dynamic functional connectivity, behavioral scores

I. INTRODUCTION

The human brain consists of functionally connected regions that interact continuously with each other. Static connectivity analysis cannot capture time-varying interactions across brain networks while dynamic connectivity analysis has been successfully used to capture dynamic patterns from healthy controls and patients with a variety of disorders [1]–[6]. Unusual functional connectivity has helped us to identify various disorders such as schizophrenia [7]–[10], bipolar disorder [11], generalized anxiety disorder [12], attention deficit hyperactivity disorder [13] and mild cognitive impairment [14].

Most dynamic functional connectivity (dFC) investigation procedures only consider the temporal dependence of the

brain regions while overlooking the connectivity of the spatial regions. Few of the studies that analyze changes in spatial networks can be broadly categorized as model or data driven. Model-driven methods make stronger assumptions about the nature of the data, such as in-region of interest (ROI) based methods make use of pre-defined brain networks [15]–[17]. Data-driven methods such as independent component analysis (ICA) can extract brain networks with minimal prior assumptions and have been used to study dynamics [18]–[19]. Independent vector analysis

(IVA) extends ICA to multiple datasets [20]–[21] and can effectively capture the variability in both the spatial and temporal directions. Ma et al., [1] and Bhinge et al., [22]–[23] used resting state fMRI data with IVA to study dynamics using a windowed approach. One issue with the application of IVA for dynamics studies is the fact that as the number of datasets increases, precision of IVA can be compromised [23]–[24]. In addition, study of dynamics primarily consider use of resting state data [1], [22]–[23] while cognitive tasks require responses from participants and a dynamic analysis can show how brain networks evolve with the task [19] and provides synchrony among subjects. The amplitude of low frequency fluctuation (ALFF) approach has been used as an effective summary in a number of studies such as [25]–[26]. In this paper, we introduce the use of fractional ALFF (fALFF) features using task fMRI data for studying spatial and temporal dynamics using IVA. This effectively alleviates the dimensionality issue in IVA and provides another important advantage in summarizing the dynamics. In general, in dynamics studies, following the extraction of spatial and/or temporal maps, summary of dynamics is obtained using a number of post-processing steps [1], [22]–[23], [27]. Our approach based on IVA with fALFF features as input also produces an effective summary of the dynamics also greatly facilitating the study of spatial and temporal dynamics in a more concise manner.

We use a sensorimotor (SM) data collected from 147 healthy controls (HC) and 106 patients with schizophrenia (SZ). We show that the proposed IVA framework with fALFF captures both the spatial and temporal changes successfully. We identify a motor component with significant difference between HC and SZ across the windows. We also perform a post analysis using behavioral scores and identify a number of behavioral

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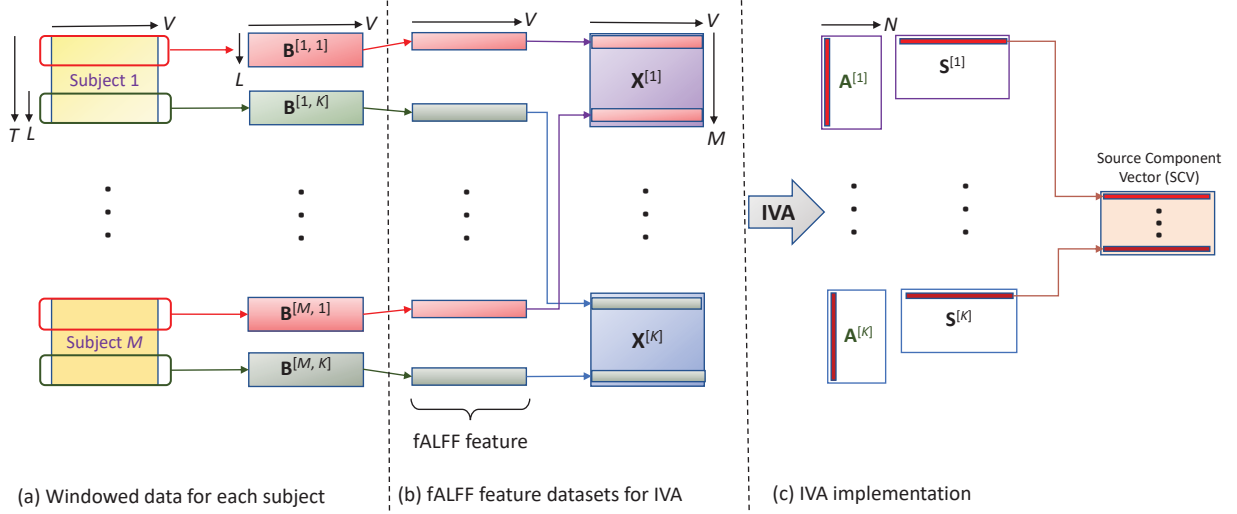


Fig. 1. IVA framework for capturing dynamic brain activity using fALFF features. (a) Windowing fMRI data with no overlap for task-rest blocks. (b) Extracting fALFF features. Each windowed fALFF for all the subjects are concatenated together form one dataset. (c) IVA is used to capture the dynamics.

variables that significantly correlate with the subject variations extracted using IVA, further increasing our confidence on the final results.

The remainder of the paper is organized as follows. Section II presents the fALFF feature extraction and background of IVA. It also shows the proposed IVA framework that we use to capture the dynamics. Section III shows the implementation details and results on the feature data. Section IV provides a discussion of the results and points out future directions.

II. MATERIALS AND METHODS

A. Dataset

We use the MIND Clinical Imaging Consortium (MCIC) dataset (publicly available at <http://coins.trendscenter.org>) comprised of 253 participants: 147 healthy controls (HC) and 106 patients with schizophrenia (SZ) with an age range of 18 to 60 years [28]. The dataset consists of fMRI scans collected from both HC and SZ groups while performing a sensorimotor task from four sites: the University of New Mexico (UNM), the University of Minnesota (UMinn), Massachusetts General Hospital (MGH) and the University of Iowa (UIowa).

The task captures the auditory and somatosensory response with the change of audio tones of different frequencies. Subjects were presented with a sequence of auditory stimuli consisting of 16 different tones each lasting 200 ms and ranging in frequency from 236 Hz to 1,318 Hz with a 500 ms inter-stimulus interval. The first tone presented was set at the lowest pitch and each subsequent tone was higher than the previous one until the highest tone was reached, at which point the order of the tones were reversed. Each tonal change required a button press with the right thumb. A total of 15 increase-and-decrease blocks were alternated with 15 rest (fixation) blocks, with each block lasting 16 seconds in duration.

The fMRI images were collected on a 3-T Siemens Trio scanner in UMinn, UIowa and MGH where UNM used a Siemens 1.5-T Sonata scanner. For all sites prospective acquisition correction (PACE) corrected, whole-brain, single-shot EPI data parallel to the AC-PC line (in-plane resolution 3.4 mm, 27 slices, slice thickness = 4 mm, 1 mm skip, slice order interleaved, TE = 30 ms for 3T, TE = 40 ms for 1.5T, TR = 2 s, FA = 90, FOV = 22 cm, 3DDAs (dummy data acquisition), bandwidth = 3126Hz/pixel) were acquired.

The fMRI data was preprocessed using an automated analysis pipeline [29] carried out in SPM. The pipeline consisted of: 1) aligning all the images with the first image as the reference using INRIalign approach [30] to correct minor motion of the subject; 2) correcting for time differences between the slices using the middle slice as the reference; and 3) spatial normalization to MNI space, including reslicing to $3 \times 3 \times 3 \text{ mm}^3$, resulting in $53 \times 63 \times 46$ voxels. Data were then spatially smoothed with a 10-mm FWHM Gaussian filter. The preprocessed fMRI data is masked to remove the non-brain voxels using the Group ICA of fMRI Toolbox (GIFT) [31]. After masking the dimension of the fMRI data for each subject is $120 \times 67,747$ (number of timepoints(T) \times number of voxels(V)).

B. Data windowing and fALFF feature extraction

We propose a three stage framework to use fALFF features in our dynamic study. The detailed framework is shown in Figure 1. In the first stage, a sliding-window approach is used to divide the data into task and rest windows. Each window is of length $L = 8$ time points (16 seconds) as both task and rest block consists of 8 time points. We exclude the first 5 time points as the first auditory stimulation (task) window starts from $T = 6$. $B^{[m, k]} \in \mathbb{R}^{L \times V}$, denotes the k th window of the m th subject, where M ($m = 1, \dots, 147$ are HC and $m = 148, \dots, 253$ are SZ) is the number of subjects and K

is the number of windows. Windowing the data results in $K = 14$ windows (from $T = 6$ to 117) with no overlap and with alternating task-rest blocks. fALFF maps are computed using the REST software (<http://resting-fmri.sourceforge.net>) on the windowed data. To compute the fALFF features, windowed data is first transformed to the frequency domain and then sum of the frequencies in the low frequency band (0.01 – 0.15 Hz) is obtained. For each voxel, the ratio of the averaged square root of the power spectrum within the 0.01 – 0.15 Hz frequency band to that of the entire detectable frequency range is calculated. In the second stage, the fALFF features computed for all the subjects for one window are concatenated together, yielding $K = 14$ datasets as shown in Figure 1. We perform dimension reduction by applying PCA on the feature dataset and retaining N principal components. We denote the dimension reduced dataset as $\mathbf{X}^{[k]} \in \mathbb{R}^{N \times V}$ and use 90% as the threshold for the variance preserved which gives us order $N = 40$.

C. IVA and the model for dynamics

ICA is a blind source separation technique which decomposes a given set of observations into a mixing matrix and sources by assuming that observed data is generated from a linear mixture of independent sources. It has proven effective in fMRI data analysis [32]-[33], however it is designed for a single dataset. Independent vector analysis (IVA) is an extension of ICA to multiple datasets which enables the use of statistical dependence of latent (independent) sources across datasets by exploiting both second order and higher order statistics [34].

Given K datasets, each consists of V samples, each dataset is a linear mixture of N independent sources,

$$\mathbf{x}^{[k]}(v) = \mathbf{A}^{[k]} \mathbf{s}^{[k]}(v), 1 \leq k \leq K, 1 \leq v \leq V, \quad (1)$$

where, $\mathbf{A}^{[k]} \in \mathbb{R}^{N \times N}$, $k = 1, \dots, K$ denotes the invertible mixing matrix. For a given set of observations, IVA generative model can be written as, $\mathbf{X}^{[k]} = \hat{\mathbf{A}}^{[k]} \mathbf{S}^{[k]}$. $\mathbf{X}^{[k]} \in \mathbb{R}^{N \times V}$ denotes the observations and $\mathbf{S}^{[k]} \in \mathbb{R}^{N \times V}$ are the latent sources. IVA estimates K demixing matrices, $\mathbf{W}^{[k]}, k = 1, \dots, K$ so that the dataset specific sources can be estimated as, $\hat{\mathbf{S}}^{[k]} = \mathbf{W}^{[k]} \mathbf{X}^{[k]}$, using

$$\mathcal{J}_{\text{IVA}} = \sum_{n=1}^N \left[\sum_{k=1}^K \mathcal{H}(\hat{s}_n^{[k]}) - \mathcal{I}(\hat{\mathbf{s}}_n) \right] - \sum_{k=1}^K \log |\det(\mathbf{W}^{[k]})| \quad (2)$$

IVA defines a source component vector (SCV) as, $\hat{\mathbf{s}}_n = [\hat{s}_n^{[1]}, \dots, \hat{s}_n^{[K]}]^T \in \mathbb{R}^K$, where $\hat{s}_n^{[K]}$ is the n th component of the k th dataset. $\mathcal{I}(\hat{\mathbf{s}}_n)$ denotes the mutual information of the n th SCV. The entropy, $\mathcal{H}(\hat{s}_n^{[k]})$ and mutual information term balance the independence within the dataset and dependence across the datasets by minimizing the IVA cost.

Application of IVA on the fALFF feature dataset, $\mathbf{X}^{[k]}, k = 1, \dots, K$, results in maximally independent components (ICs), $\mathbf{S}^{[k]}, k = 1, \dots, K$. We obtain the subject-specific spatial maps,

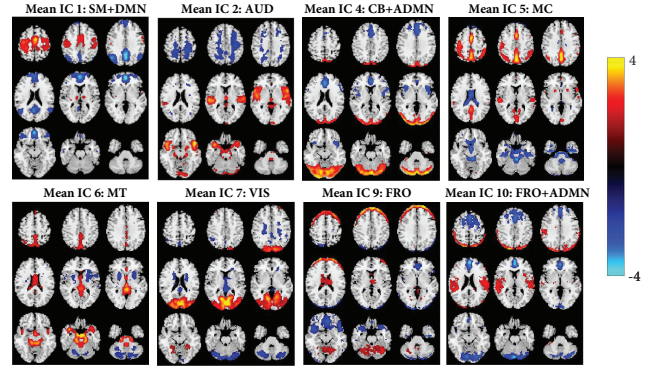


Fig. 2. Spatial maps of the mean ICs are categorized into 9 domains: default mode network (DMN), sensorimotor (SM), auditory (AUD), cerebellum (CB), anterior DMN (ADMN), motor (MC), medial temporal (MT), visual (VIS) and frontal (FRO). Red voxels indicate positive activated and blue voxels indicate negative activated.

using dual regression [31], which are denoted as $\mathbf{s}_n^{[m,k]}$, meaning n th IC of m th subject in k th window. The estimated mixing matrices, $\hat{\mathbf{A}}^{[k]}$, are back reconstructed to obtain dataset-specific mixing matrices, $\mathbf{A}^{[k]} \in \mathbb{R}^{M \times N}$, using, $\mathbf{A}^{[k]} = (\mathbf{D}^{[k]})^{-T} \hat{\mathbf{A}}^{[k]}$, where $\mathbf{D}^{[k]}$ is the data reduction matrix. The reduction matrix, $\mathbf{D}^{[k]}$, comprises of the N eigenvectors, corresponding to the first N largest eigenvalues of the covariance matrix of $\mathbf{X}^{[k]}$. Each column of $\mathbf{A}^{[k]} \in \mathbb{R}^{M \times N}$, indicated as $\mathbf{a}_n^{[k]}, n = 1, \dots, N$, represents the weight of the corresponding source $\mathbf{s}_n^{[k]}$ on each subject. It quantifies each subject's contribution to the ICs and hence is referred to as subject covariations of the ICs.

In this study, we use an IVA implementation which combines two IVA algorithms: IVA-G [20] and IVA-L-SOS [23]. IVA-G takes only second order statistics (SOS) into account by assuming the SCVs are multivariate Gaussian while IVA-L-SOS (IVA-L with SOS) utilizes a multivariate Laplace prior for SCV distribution. IVA-L-SOS takes both SOS and higher order statistics (HOS) into account by calculating the covariance matrix of each SCV and it is a good match for fMRI data. We initialize IVA-L-SOS with a solution from IVA-G to take the advantage of both algorithms.

As IVA is an iterative algorithm, the decomposition results vary from different initialization points. Hence, we use a technique based on cross joint inter-symbol interference (cross-jISI), an extension of the technique proposed in [35] to multiple datasets, in order to select the most consistent IVA run from 30 independent runs with random initializations.

III. RESULTS AND POST-ANALYSIS

A. Experimental results

1) *Estimated ICs*: We obtain $N = 40$ ICs for each of the $K = 14$ windows from IVA. First, we take the Z -score of the ICs which measures the distance of raw scores from population mean in standard deviation units. Then we convert the voxels with Z -score greater than threshold 1.5 ($|Z| \geq 1.5$) from MNI coordinates to Talairach coordinates to assign anatomical and

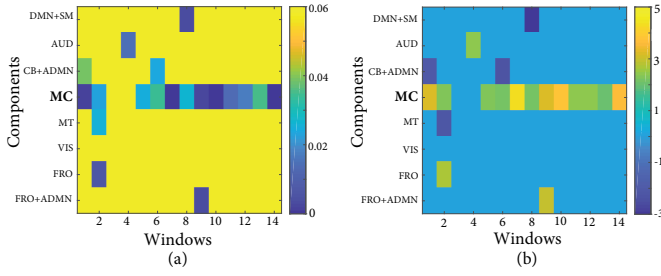


Fig. 3. Dynamic change of group difference for selected ICs. Two sample t -test on the corresponding subject covariations reveals statistically significant difference between the two groups (HC vs. SZ) (a) p -value of components across windows where MC shows group difference in most of the windows. (b) t -value of components across windows where positive t -value means higher activation in HC and negative t -value means higher activation in SZ.

functional labels for the left and right hemispheres. Of the 40 ICs we select 8 task-related ICs for our dynamic study from visual inspection. These networks are labeled based on the following classes: default mode network (DMN), sensorimotor (SM), auditory (AUD), cerebellum (CB), anterior DMN (ADMN), motor (MC), medial temporal (MT), visual (VIS) and frontal (FRO). In an IVA decomposition the corresponding estimated ICs across the windows are maximally dependent and they form a SCV together. For a better visualization, we take the mean of each selected IC across the windows and show the spatial maps of the eight mean ICs (mean SCVs) in Figure 2.

2) *Dynamics of subject covariation*: In order to study the difference in dynamic behavior between healthy controls and patients, we use the subject covariation matrices, $\mathbf{A}^{[k]} \in \mathbb{R}^{M \times N}$, $k = 1, \dots, K$ obtained after back reconstructing the mixing matrices from IVA. The values in each column of subject covariation matrices, $a_{mn}^{[k]}$, $n = 1, \dots, N$, $m = 1, \dots, M$, quantify the contribution of subjects to each IC.

Dynamics of ICs across windows: We perform a two-sample t -test on subject covariations to identify components that show group difference between the HC and SZ group. We summarize the p -values (a) and t -values (b) of the test results for the 8 ICs across 14 windows in Figure 3. A positive t -value indicates higher activation in HC and a negative t -value means higher activation in SZ. All components except VIS show group difference in at least one window where MC shows group difference in most of the windows hence that advocates our component selection for the dynamic study.

Mean subject covariation across windows for HC and patients: We calculate the mean of subject covariation values for the two groups, HC and SZ, separately to compare their contribution in each IC and show the behavior of subject covariation for the two groups in Figure 4. It depicts a clear on-off pattern in most of the windows as the SM task has a paradigm of task-rest blocks. Two ICs, CB+ADMN and MC, are used for example, as CB+ADMN shows higher intensity for SZ in most of windows and MC shows higher intensity for HC in all the windows. The asterisk indicates that the subject covariation yields significant difference between the two groups in that particular window. These plots provide the complementary information of the dynamics of subject covariation.

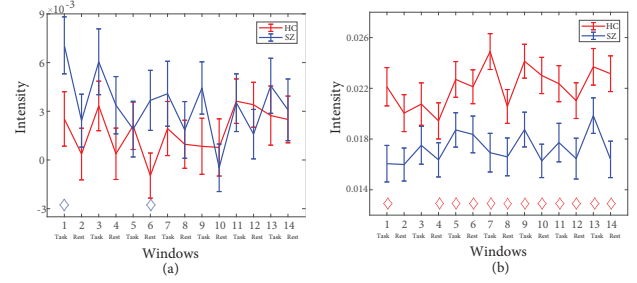


Fig. 4. Mean subject covariation across windows for HC and patients. (a) change of subject covariation in CB+ADMN with time. (b) change of subject covariation in MC with time. Asterisk means group different in a particular window where blue diamond (\diamond) means significantly higher intensity in SZ and red diamond (\diamond) means significantly higher intensity in HC.

ups in that particular window. These plots provide the complementary information of the dynamics of subject covariation.

B. t -maps of the ICs

To summarize the change in spatial maps, we perform both one sample and two sample t -test on the spatial maps of each IC for HCs and SZs either with the task and rest windows. As shown in Figure 5(a), 5(b), both CB+ADNN and VIS yield significant difference between HC and SZ in terms of the number and location of activated voxels. Interestingly, CB+ADNN shows more significant difference in task windows and VIS shows more significant difference in rest windows.

C. Behavioral scores

Along with brain imaging data, behavioral scores have been used recently to study the aberrant behavior in SZ [28], [36]–[37]. A total of 51 behavioral variables (BVs) were available for 253 subjects. We show how our previous results help to identify unique biomedical behaviors in SZ.

First, we consider one BV as a distinct feature, each feature is of length m , the number of subjects for a correlation study between spatial maps and the BVs. Hence, we calculate the Pearson’s correlation coefficient between each feature and average subject covariation across all windows for each of the selected ICs and select 8 features that show the highest correlation. The eight BVs are: Wechsler Adult Intelligence Scale (WAIS-III) [38], Benton Visual Retention Test (BVRT) [39], Wechsler Memory Scale-III (WMS-III) [38], Hopkins Verbal Learning Test-Revised (HVLRT) [40], Grooved Pegboard Test (GP) [41], California Computerized Assessment Package (CalCap) and F-A-S verbal test. We concatenate the behavioral scores as the 15th dataset, yielding $E = 15$ datasets, $\mathbf{X}_{\text{behav}}^{[e]} \in \mathbb{R}^{P \times M}$, $e = 1, \dots, E$, $E = 15$, $P = 8$, $M = 247$. We perform a second level IVA-G on the 15 datasets to validate and interpret our results.

After the decomposition, we check the correlation structure of SCVs where 15th row corresponds to the correlation between features extracted from the behavioral scores and one IC across the windows. We perform a two sample t -test to calculate the group difference between HC and SZ in all the SCVs and only show the results for SCV3 as it yields the high-

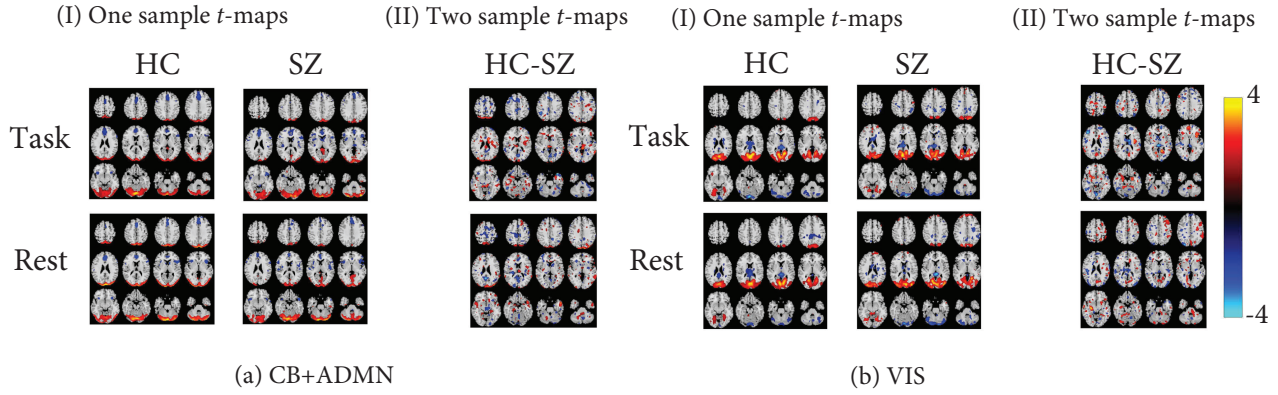


Fig. 5. (a) One sample t -maps and two sample t -maps for CB+ADMN ($p < 0.05$). (I) shows one sample t -maps for HC and SZ both in task and rest. (II) shows two sample t -maps between HC and SZ in task and rest. (b) One sample t -maps and two sample t -maps for VIS ($p < 0.05$). (I) shows one sample t -maps for HC and SZ both in task and rest. (II) shows two sample t -maps between HC and SZ in task and rest.

hest group difference. From 3rd column of the mixing matrix for dataset 15, $[\mathbf{A}_{\text{behav}}^{[e]}]^T \in \mathbb{R}^{P \times P}$, $e = 1, \dots, E$, $E = 15$, $P = 8$ we calculate the contribution of the behavioral scores to SCV3. WMS-3, WMS-3 delay and GP are the most dominant one as shown in Table I where WMS-3, WMS-3 delay are highly associated with working and visual memory and GP is associated with motor functions. Regarding the components, we measured the mean of the 3rd column of $\mathbf{A}_{\text{behav}}$, across dataset= 1,...,14 and see MC, CB+ADMN, FRO+ADMN are the ones contributing most in SCV3 than other ICs. MC is related to motor activity and CB+ADMN, FRO+ADMN are related to motor and memory functions. From these results, the BVs and spatial maps are showing clear correlation as their associated functions overlap. Also, all the contributing components in SCV3 are related to motor activity which validate our previous results.

TABLE I
CONTRIBUTION OF BEHAVIORAL SCORES AND ICs IN SCV3

Contribution of BVs		Contribution of ICs	
BVs	Percentage of contribution	ICs	Percentage of contribution
WMS-3	30	MC	52
WMS-3 delay	25	CB+ADMN	12
GP	20	FRO+ADMN	10
Other BVs	25	Other ICs	26

IV. DISCUSSION

Recently, time-varying spatial and temporal brain networks have been of great interest in neuroimaging studies. IVA captures the spatio-temporal variability with minimal assumptions but has been applied to a small number of subjects due to the decreased precision when working with large number of datasets. Our proposed IVA framework mitigates this issue as we work with extracted fALFF features from the fMRI data.

We use SM task data to identify differences in brain dynamics for SZ patients compared with healthy controls along the time windows. Our framework successfully captures the group difference between HC and SZ without the need for additional post-processing steps. The analysis identifies the networks, SM, MC showing abnormal behavior in SZ as in the previous studies [42]. Correlation study between the brain networks and behavioral scores yields meaningful correlations. There are a number of important future directions. For example, we can study different overlap of windows as well as window sizes and can further study patient subgroups using the behavioral scores.

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