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# Spatially Constrained ICA Enables Robust Detection of Schizophrenia from Very Short Resting-state fMRI*

Marlena Duda, Armin Iraji, Vince D. Calhoun, *Member, IEEE*

***Abstract*— Resting-state functional network connectivity (rsFNC) has shown utility for identifying characteristic functional brain patterns in individuals with psychiatric and mood disorders, providing a promising avenue for biomarker development. However, several factors have precluded widespread clinical adoption of rsFNC diagnostics, namely the lack of standardized approaches for capturing comparable and reproducible imaging markers across individuals, as well as the disagreement on the amount of data required to robustly detect intrinsic connectivity networks (ICNs) and diagnostically relevant patterns of rsFNC. Here, we investigate the robustness of (1) subject-specific ICNs standardized to an *a priori* network template via spatially constrained ICA (scICA), and (2) rsFNC differences between schizophrenia and control groups with respect to the length of the fMRI. Our results suggest clinical rsFMRI scans, when decomposed with scICA, could potentially be shortened to just 2-4 minutes without significant loss of individual rsFNC information or classification performance of longer scan lengths.**

***Clinical Relevance*— This work shows diagnostically relevant rsFNC patterns for schizophrenia can be identified from just 2-4 minutes of rsfMRI using an scICA approach. These results can influence future work in neuroimaging biomarker development.**

## I. Introduction

Resting-state functional MRI (rsfMRI) has been a valuable tool for identifying and investigating brain networks and their functional interactions, often referred to as resting-state functional network connectivity (rsFNC), in both typical individuals and those diagnosed with psychiatric and mood disorders. Clinically, rsfMRI offers several benefits, namely that it is non-invasive, it is relatively easy to administer and imposes fewer demands on subjects than other imaging techniques or task-based paradigms, an important consideration for clinical populations that may not be able to perform standardized tasks in the scanner. Studies of rsFNC have also identified characteristic and reproducible connectivity patterns capable of discriminating between various diagnostic groups [1], [2], as well as "fingerprinting" individuals and predicting behavior [3].

While these benefits show promise for rsFNC to serve as a potential biomarker to move towards precision diagnosis in the currently tangled landscape of psychiatric disorders, several factors have prevented widespread clinical adoption of such methods. One challenge is the lack of standardized approaches for capturing imaging markers, in this case individualized intrinsic connectivity networks (ICNs), that are reproducible and readily comparable across individuals. Independent components analysis (ICA) is a widely used data-driven approach for extracting maximally spatially independent components that share co-varying activation patterns from voxel-level fMRI data, and though several group ICA methods have been developed that enforce correspondence between individual-level ICNs in a given group analysis [4]–[6], there is no such guarantee of correspondence across different datasets or analyses. To address this challenge, spatially constrained ICA (scICA) methods have recently been proposed [7] that can extract individualized ICNs guided by the spatial prior of an independently derived and validated network template. The scICA approach is fully automated and ensures the correspondence of ICNs across subjects while maintaining individualized identification of components, suggesting it can be of great use for precision biomarker development.

In addition, there is currently debate in the field surrounding the amount of rsfMRI data needed to generate robust estimates of functional networks and corresponding resting-state functional connectivity (rsFC). Typically, rsfMRI scan lengths range from 5-15 minutes, but recent work has yielded conflicting results, suggesting as little as 5-6 minutes [8]–[10] or as much as 30-40 minutes [11]–[13] of data are necessary to produce sufficiently reliable estimates of individual rsFC. While shorter scanning sessions would be more cost- and resource-efficient for clinical implementation, the ICN and rsFC estimates from shorter time courses can be more susceptible to spurious noise; conversely, while longer scanning sessions have the benefit of averaging across more data, the longer a subject spends in the scanner the more susceptible they are to fatigue, increased head motion, drowsiness, and fluctuations in vigilance [14], which also contribute to noise. Thus, the lack of consensus around an appropriate "minimally sufficient" scan length for clinical applications of rsfMRI has left this an open area of research.

Importantly, existing studies of scan length reliability have focused on atlas- and seed-based approaches; to the best of our knowledge there has been no such examination of reliability using a data-driven ICA approach, specifically scICA. We suggest scan length reliability is dependent, at least in part, on the methodological approach employed. Furthermore, we hypothesize that the regularization provided by the spatial priors in scICA can serve to stabilize the solution even when less data is used, increasing reliability at shorter scan lengths than what is seen in non-ICA approaches.

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M. Duda, A. Iraji, and V.D. Calhoun are with the Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Atlanta, GA 30303, USA (e-mails: mduda@gsu.edu, armin.iraji@gmail.com, vcalhoun@gsu.edu).

Motivated by the lack of consensus in recommended scan lengths for clinical applications, we investigate the robustness of both subject-specific ICNs extracted via scICA and their resultant rsFNC matrices with respect to time series length. We study these in the context of identifying rsFNC differences between schizophrenia and control groups.

## II. Materials and Methods

### A. Data and Preprocessing

We utilized an age- and gender-matched discovery dataset, including 150 schizophrenia (SZ) and 160 control (CON) samples [15]. The rsfMRI data were collected with 3-Tesla MRI scanners with a repetition time (TR) of 2 sec, voxel size of 3.44 × 3.44 × 4 mm, a slice gap of 1 mm, and a total of 157 volumes. We also utilized an independent validation dataset for classification, consisting of 50 SZ and 79 CON samples [16]. The rsfMRI data were collected with 3-Tesla MRI scanners [TR = 2 sec; voxel size: 3.75 × 3.75 × 4.55 mm], for a total of 145 volumes. The experimental procedures involving collection of data from human subjects were approved by the Institutional Review Boards of the participating institutions. Preprocessing for both datasets was done in SPM and included brain extraction, slice-timing, and motion correction steps. Preprocessed data were then registered into structural MNI space, resampled to 3 $mm^3$ isotropic voxels, and spatially smoothed using a Gaussian kernel with a 6 mm full-width at half-maximum on a per-subject basis. Finally, first five timepoints were trimmed and voxel time courses (TCs) were z-scored.

To supplement the relatively short data lengths available from our clinical rsfMRI datasets, we simulated a set of longer fMRI time courses using the SimTB toolbox [17], (https://trendscenter.org/software/simtb/). In our simulation, we set $M$ = 100 subjects and $C$ = 29 components. Simulated spatial maps were 148 × 148 voxels in dimension and TCs were 900 time points in length with a TR = 2 seconds (30 minutes total). We simulated individual variation in ICN spatial maps by randomly varying the size, rotation and translation of template components. The simulation modeled two distinct groups (M = 50/50 subjects) with four engineered group differences: (1) Group A has a larger amplitude for component 7 (C7) than Group B, (2) Groups A and B have different shapes for networks composed of C5 and C10, (3) Groups A and B have different shapes and amplitudes for a network composed of C22 and C23, (4) Group B has stronger FNC between C3 and C4 than Group A. For more details, see the protocol for simulated group differences described in [18].

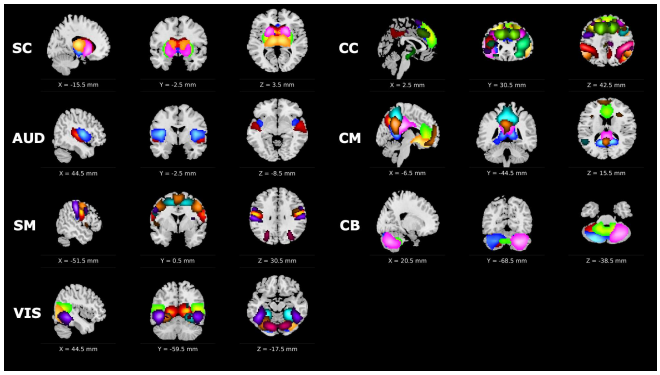


Figure 1. NeuroMark network template used for MOO-ICAR.

### B. Spatially Constrained ICA

We utilized an scICA approach called multivariate-objective optimization ICA with reference (MOO-ICAR), implemented using the GIFT software toolbox (http://trendscenter.org/software/gift) [19]. MOO-ICAR estimates subject-level independent components (ICs) using existing network templates as guides [7]. In this work, we utilized the NeuroMark template (described in [7] and available at https://trendscenter.org/data/) (Figure 1), which consists of N = 53 ICNs categorized into seven functional domains: subcortical (SC), auditory (AUD), sensorimotor (SM), visual (VIS), cognitive-control (CC), default mode (DM) and cerebellar (CB). The following equation represents how the $l^{th}$ network can be estimated for the $k^{th}$ subject using the network template $S_l$ as guidance:

$$max \begin{cases} J(S_l^k) = \{E[G(S_l^k)] - E[G(v)]\}^2 \\ F(S_l^k) = E[S_l S_l^k] \end{cases}$$

$$s.t. \|w_l^k\| = 1$$

In this formulation, $S_l^k = (w_l^k)^T \cdot X^k$ represents the estimated $l^{th}$ network of the $k^{th}$ subject, where $X^k$ is the whitened fMRI data matrix of the kth subject and $w_l^k$ is the unmixing column vector, to be solved in the optimization functions. The function $J(S_l^k)$ serves to optimize the independence of $S_l^k$ via negentropy. Here, v is a Gaussian variable with mean zero and unit variance, G() is a nonquadratic function, and E[] denotes the expectation of the variable. The function $F(S_l^k)$ serves to optimize the correspondence between the template network ($S_l$) and subject network ($S_l^k$). The optimization problem is solved by applying a linear weighted sum to combine the two objective functions, with weights set at 0.5. Applying MOO-ICAR to each subject extracts subject-specific ICNs corresponding to each of the N network templates, as well as the relevant TCs.

### C. Stability Evaluation

We applied scICA via the MOO-ICAR framework to the full reference TC for each subject, and separately to data extracted from just the first 1, 2, 3, … minutes, up to the full-length TC. At each data length, subject-level static functional network connectivity (sFNC) was computed via pairwise Pearson correlation between time courses of all ICNs, resulting in an N × N sFNC matrix. Differences in group-average sFNC between the CON and SZ populations were identified using univariate multiple linear regression including age, gender, scanning site and head motion as covariates (or two-sample t-test in the case of the simulated data). Significant group differences in sFNC were identified as those whose p-values survive FDR correction at $\alpha_{FDR} = 0.05$. We evaluated the stability of both subject-specific measures (ICN spatial maps and sFNC) as well as group differences in sFNC with respect to data length by computing Pearson correlations between measures derived from the partial TCs and the full reference TC. We utilized a robustness threshold of correlation $\geq 0.85$ to the reference, originally proposed in [11], to identify a "minimally sufficient" data length with respect to each metric. This evaluation was applied both to the clinical discovery and simulated datasets.

### D. Group Classification

We further investigated the robustness and clinical utility of scICA-based estimates of rsFNC with a group classification task. Using our discovery rsfMRI dataset as training data, we generated subject-level feature vectors for each data length by extracting the upper triangular of the corresponding scICA-derived sFNC matrix. We fit binary LASSO-regularized linear SVM classification models separately for each data length to classify each subject as SZ/CON. For each model, the lambda parameter was tuned using five-fold cross-validation. After obtaining the optimal lambda value, performance for each of the five models was estimated with 500 rounds of bootstrap resampled five-fold cross-validation. The final five models for each data length were fit using the full training dataset and tested on the independent validation dataset for external evaluation of classification performance and generalizability at each data length.

## III. Results

We evaluated the stability of subject-level estimates of ICN spatial maps and sFNC matrices derived via scICA with respect to the length of rsfMRI data for both clinical (Figure 2A-B) and simulated (Figure 2D-E) datasets. We found no discernible group differences in most subject-level measures, but the CON group exhibited slightly higher stability in sFNC than the SZ group in the clinical data. In the clinical data we found only 3 minutes of rsfMRI data were sufficient to meet the robustness threshold for the subject-specific ICN spatial maps and 3.5 minutes were sufficient for the corresponding subject-level sFNC estimates. Notably, the results from the simulated data with a 30-minute reference TC showed a similar pattern of reliability, surpassing the robustness threshold with just 4 minutes of data for both subject-specific ICN spatial map and rsFNC estimates.

We also evaluated the reliability of group-level sFNC patterns across TC lengths. Results showed the characteristic rsFNC signatures for the SZ and CON groups were highly robust to the length of rsfMRI data used, indicating high group-level rsFNC stability. The mean sFNC matrices derived from even 1 minute of data were highly correlated to the full TC reference for both the SZ (r = 0.94) and CON (r = 0.93) groups, and this relationship continually increased with more of the rsfMRI time course.

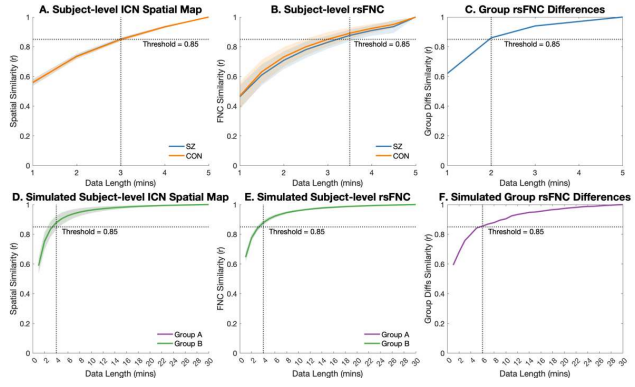


Figure 2. Reliability results for clinical (A-C) and simulated (D-F) datasets. Subject-level measures (A-B, D-E) show mean (solid line) and standard deviation (shaded area) across all subjects. Dotted lines indicate data lengths at which the measures meet or exceed the robustness threshold.

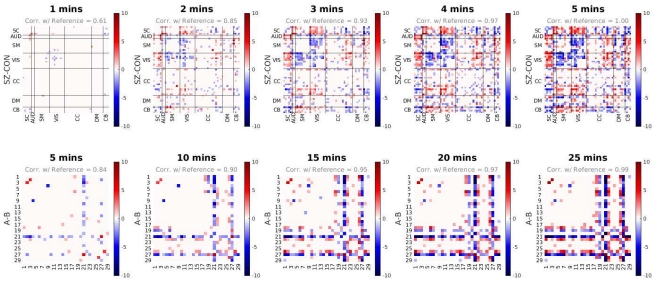


Figure 3. Group differences in rsFNC in clinical (top row; SZ-CON) and simulated (bottom row; Group A-B) datasets. Values are plotted as −log10(p-value) × sign(t-value).

We found significant group differences in sFNC patterns across all experiments (Figure 3). We found 2 minutes of rsfMRI data were sufficient to meet the robustness threshold for group differences in clinical data (Figure 2C), compared to the 6 minutes required in the simulated data (Figure 2F). The differing group-level results between the clinical and simulated experiments could be attributed to the difference in reference scan length (5 vs. 30 minutes), or to the strength of the simulated group differences. In the clinical data the results showed the group differences that were most robust to data length were decreased within-domain connectivity of the VIS domain and increased cross-domain connectivity between SC-SM and SC-VIS domains of the SZ group compared to that of the CON group.

The results from our classification experiments showed highly stable classification accuracy for models fit across the range of 2-5 minutes, with the model trained on 2 minutes of data attaining a relative performance to that of the full TC reference model of 98% in the internal cross-validation (0.73 vs 0.74) and 97% in the external validation (0.68 vs 0.70) (Figure 4A). For each model, we extracted the most influential sFNC edges, defined as the 20% of features with the largest magnitude weights. We found 31 sFNC edges were commonly included among the top feature weights across the five models (Figure 4B) that mainly belonged to the SC, VIS, and SM domains, corresponding with the significant edges identified in the group differences analysis.

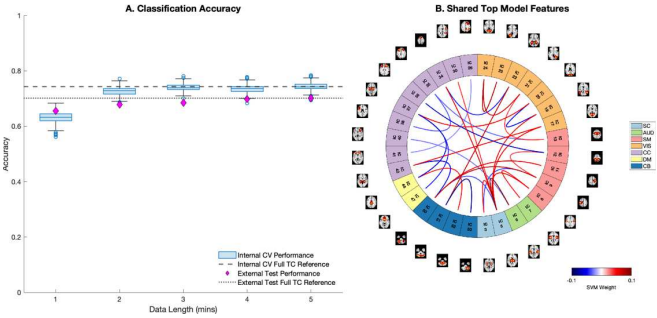


Figure 4. (A) Classification performance of linear SVM models trained at each data length. (B) FNC edges in the top 20% of SVM feature weights shared among all five models.

## IV. Discussion

The aim of this work was to identify a "minimally sufficient" rsfMRI scan length that demonstrates clinical utility, both in producing stable estimates of ICNs and rsFNC

matrices at the single-subject level, as well as capturing diagnostically relevant group differences in rsFNC. Previous work has produced conflicting results, suggesting anywhere from 5-40 minutes as necessary minimum scan lengths to reach adequate reliability, with most recent works advocating for longer acquisitions. One such study suggested that at least 30 minutes of rsfMRI were required to obtain an average subject-level rsFC reliability of $r \geq 0.85$, with respect to a 70 minute reference [11]. In contrast, we found just 3-4 minutes of data can produce an average subject-level rsFNC reliability of $r \geq 0.85$ with respect to both shorter (5 minute) and longer (30 minute) reference TCs (Figure 2B,E). These differing results are likely due to our data-driven scICA approach, in which the spatial priors may serve to help regularize the solution somewhat, leading to increased stability even when analyzing much less data.

Additionally, our classification experiments showed just 2 minutes of data retained 97% of the accuracy of the full-length reference TC, directly demonstrating the utility of shorter TCs in diagnostic predictions. Most existing studies of scan length reliability focus mainly on subject-level measures, namely rsFC, and do not extend the analysis to group-level measures or diagnostic classification tasks. These additional analyses in our study more clearly define the scope of our work in the context of clinical biomarker development and separate the present study from the existing body of work in this area.

This study does have several limitations to consider. Our results are limited by the acquisition protocols of the clinical datasets available to us, which consist of relatively short (5 minute) scans of individuals. We addressed this limitation by simulating longer (30 minute) fMRI time courses, and though the SimTB software has been extensively studied and has shown utility for reliably modeling multi-subject fMRI datasets, the simulations are expectedly limited in both the spatial dimensionality, simulating a single axial slice rather than a three-dimensional full brain, and the ability of the engineered group differences to simulate differences between true clinical populations. Therefore, the conclusions made from our simulated experiments should be tested further in true clinical rsfMRI data of similar scan lengths.

## V. Conclusion

Our results support the idea that when scICA is employed, a "minimally sufficient" scan length may exist in the 2–4-minute range that could be favorable for use in clinical settings, both in maximizing clinical efficiency and patient comfort while retaining diagnostic efficacy. However, more work is still required to validate these results in larger (and longer) data sets, as well as in other diagnoses for which rsFNC biomarkers may be useful. Future work may also include direct comparisons of scICA against other data-driven methods, such as classical group ICA, as well as atlas- and seed-based approaches.

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