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An approach to directly link ICA and seed-based functional connectivity: application to schizophrenia

Lei Wu^{1,2}, Arvind Caprihan¹, Juan Bustillo³, Andrew Mayer¹, and Vince Calhoun^{1,2,3}

¹The Mind Research Network, Albuquerque, New Mexico 87106

²Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, New Mexico 87131

³Department of Psychiatry, University of New Mexico, Albuquerque, New Mexico 87131

Abstract

Independent component analysis (ICA) and seed-based analyses are widely used techniques for studying intrinsic neuronal activity in task-based or resting scans. In this work, we show there is a direct link between the two, and show that there are some important differences between the two approaches in terms of what information they capture. We developed an enhanced connectivity-matrix independent component analysis (cmICA) for calculating whole brain voxel maps of functional connectivity, which reduces the computational complexity of voxel-based connectivity analysis on performing many temporal correlations. We also show there is a mathematical equivalency between parcellations on voxel-to-voxel functional connectivity and simplified cmICA. Next, we used this cost-efficient data-driven method to examine the resting state fMRI connectivity in schizophrenia patients (SZ) and healthy controls (HC) on a whole brain scale and further quantified the relationship between brain functional connectivity and cognitive performances measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery. Current results suggest that SZ exhibit a wide-range abnormality, primarily a decrease, in functional connectivity both between networks and within different network hubs. Specific functional connectivity decreases were associated with MATRICS performance deficits. In addition, we found that resting state functional connectivity decreases was extensively associated with aging regardless of groups. In contrast, there was no relationship between positive and negative symptoms in the patients and functional connectivity. In sum, we have developed a novel mathematical relationship between ICA and seed-based connectivity that reduces computational complexity, which has broad applicability, and showed a specific application of this approach to characterize connectivity changes associated with cognitive scores in SZ.

*Correspondence: Lei Wu, Image Analysis and MR Research Core, The Mind Research Network, 1101 Yale Blvd NE, Albuquerque, NM 87106, Tel: 505-369-9631, lwu@mrn.org.

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Keywords

Schizophrenia; Functional connectivity; ICA; Cognitive scores; MATRICS

Introduction

The diagnosis of schizophrenia has been traditionally made based on symptoms, e.g., hallucinations, delusions etc. However the schizophrenic phenotype varies drastically in terms of patterns and severities across individual cases (Jablensky 2010), and could be significantly suppressed by antipsychotic treatments and other factors (Lui, et al. 2010). Researchers have been searching for neurophysiologically specific biomarkers/causes. Among numerous techniques and findings, resting state functional connectivity from neuroimaging has emerged as a promising candidate (Arbabshirani, et al. 2017; Friston 2011; Sheffield and Barch 2016).

Functional connectivity during the resting state provides a novel and complementary tool to explore brain organization (Biswal, et al. 2010; Fox, et al. 2005; Fox, et al. 2007) as well as the mechanics of brain function and behavior (Baird, et al. 2005; Van Dijk, et al. 2010). It reveals more reliable “intrinsic” diagrams of brain neuronal communications, compared to task-based analysis given that the latter induces less than 5% energy changes (Raichle and Gusnard 2002). This intrinsic functional connectivity has shown increasing evidence in capturing the variability associated with neuropsychiatric illnesses, e.g., schizophrenia (Camchong, et al. 2011; Fitzsimmons, et al. 2013; Garrity, et al. 2007; Lynall, et al. 2010; Skudlarski, et al. 2010). Resting state data collection also reduced performance confounds in SZ with cognitive deficits (Friston 2011). Because of this, resting state functional connectivity has been widely studied to predict disease states (Arbabshirani, et al. 2013; Arbabshirani, et al. 2017; Craddock, et al. 2009; Du, et al. 2012; Krishnadas, et al. 2014; Shen, et al. 2010; Silva, et al. 2014; Venkataraman, et al. 2012).

The disconnection/dysconnectivity hypothesis of schizophrenia has been considered for over 20 years (Friston 1998; Friston and Frith 1995; Pettersson-Yeo, et al. 2011; Stephan, et al. 2006; Stephan, et al. 2009) where the term “dysconnectivity” refers to either abnormal reductions in functional interactions or to abnormal increases (Stephan, et al. 2009). Although functional dysconnectivity has been found in many studies, the revealed patterns show a great deal of inconsistency across studies (Sheffield and Barch 2016). Alterations between cortical and subcortical regions have been reported (Cetin, et al. 2014; Cheng, et al. 2015; Damaraju, et al. 2014; Sui, et al. 2015; Woodward, et al. 2012; Zhou, et al. 2010). Other frequent findings are hyper- or hypo-connectivity associated with default mode networks (DMN), with both intra-DMN and inter-DMN-nonDMN connectivity (Karbasforoushan and Woodward 2012; Moran, et al. 2013; Unschuld, et al. 2014). Changes in global (whole brain) functional connectivity have also been found in some studies (Bassett, et al. 2012; Cole, et al. 2011; Lynall, et al. 2010). One suggestion to address this heterogeneity in findings is that cognitive dysfunction may contribute to functional connectivity (Sheffield and Barch 2016). Detecting links between cognitive impairments, a core feature of schizophrenia, and aberrant functional connectivity may better help

understand the neurobiological mechanism underlying disconnection and perhaps help clarify the diagnostic boundaries of the syndrome.

Methodologically speaking, it is helpful to consider two types of functional connectivity methods primarily used at present – seed-based temporal correlation analysis and spatial independent component analysis (ICA) (Beckmann, et al. 2005; Buckner and Vincent 2007; Calhoun and Adali 2012; Calhoun, et al. 2001a; Calhoun, et al. 2009b; Cole, et al. 2010; Joel, et al. 2011; Van Den Heuvel and Pol 2010). Seed-based approaches find the connectivity of a seed to the rest of the brain. The seed can be a collection of points based on prior functional magnetic resonance imaging (fMRI) studies or be based on an atlas, in which case it is a seed with a larger region-of-interest (ROI). The advantage of this method lies in its simplicity, which pinpoints directly the voxel regions to which the seed region is connected. However, seed-based methods are hypothesis driven which requires prior knowledge of seeds or ROIs whose representativeness is not always reliable (Cole, et al. 2010; Sohn, et al. 2015). The information of a functional connectivity map from this type of method is restricted and biased to a selected seed region, leaving undetermined the connectivity patterns on a whole-brain scale (Van Den Heuvel and Pol 2010). ICA on the other hand is data driven and computationally efficient in examining general connectivity patterns from whole brain. ICA yields brain voxel regions with strong temporal coherence, seen as intra-connected maps. However, the spatial network/connectivity maps identified by ICA are derived by maximizing statistical independence from each other, and its interpretation in terms of connectivity coherence may not be as straight-forward as seed-based results (Sheffield and Barch 2016). The ICA approach may in some cases only detect localized synchronous voxels in a partial intrinsic network (e.g., the split regions of default mode network) especially when using high model orders (Calhoun and de Lacy 2017). To study connectivity across different networks, ICA is usually employed in a component/regional macroscopic scale often with a focus on inter-network connectivity, called functional network connectivity or FNC (Allen, et al. 2012a; Jafri, et al. 2008). It would be very useful to be able to utilize the computationally efficient and other benefits of ICA in the context of a whole-brain seed-based approach.

One goal of this paper is to develop an efficient data-driven method to examine resting state functional connectivity in SZ on a whole brain scale, and quantify the relationship between brain functional dysconnectivity with both cognitive deficits and symptomatology. Voxel-based connectivity maps have been studied to look for brain connectivity differences in schizophrenia with diffusion imaging and with resting-state fMRI data (Cheng, et al. 2015; Skudlarski, et al. 2010; Wu, et al. 2015). These voxel-based connectivity maps have high dimension ($N \times N$), where N is the number of brain voxels. This is not only computationally expensive, but a direct comparison of these connectivity maps across groups can lead to underestimation of important differences after correcting for multiple comparisons. The cmICA method (Wu, et al. 2015) was developed as one way to address this problem, and it has been previously applied to parcellate whole brain diffusion imaging data (Wu, et al. 2015; Wu, et al. 2013). In that paper, we show that cmICA can be used for dual parcellation of the brain connectivity (regardless of it being structural or functional). The dual parcellation consists of a set of spatially independent maps S and a corresponding dual set of spatial maps R , such that R defines the brain connectivity magnitudes from independent

sources S to the whole brain (see Discussion). Here we propose a computationally optimized cmICA for functional connectivity data. We apply the enhanced cmICA to resting state fMRI data collected from 60 SZ and 61 HC. The new method increases sensitivity to subtle connectivity changes across subjects (Allen, et al. 2011; Koch, et al. 2010; Wu, et al. 2015). Moreover, our approach increases longer-ranged inter-regional connectivity sensitivity and spatial localization compared to conventional ICA connectivity methods (Wu, et al. 2015), both of which may facilitate the detection of relationships between abnormal connectivity and cognitive deficits in schizophrenia.

Methods

1. Theory

We present a novel simplification of cmICA that is specifically applicable to fMRI data sets, when connectivity between two voxels is defined as the temporal cross-correlation between them. This simplification arises because the first step of ICA is principle component analysis (PCA), and we show that PCA of a voxel-based connectivity map can be done directly based on the BOLD signal, without first calculating individual connectivity maps.

Some of the advantages of cmICA and its meaning have been discussed previously in the context of diffusion imaging data (Wu, et al. 2015), and these ideas apply here as well. Specifically, we will decompose each subject's voxel-wise brain connectivity matrix ($C = \sum S_k R_k$) into a sum of source regions (S_k), and their respective connectivity maps (R_k) to the whole brain with that source. One limitation of the original cmICA algorithm is the high computational burden if employed on a voxel-wise basis for the whole brain, as it requires generating the entire connectivity matrix prior to the ICA decomposition as well as data reduction on a fairly large adjacency matrix for each subject (Wu, et al. 2015). To calculate functional connectivity (temporal correlation) per voxel pairs from a standard 3mm³ fMRI and store whole brain connectivity matrices would require $1 \times 10^9 \sim 2 \times 10^9$ times of correlation calculations and 18~26GB of memory per subject, depending on the mask size (Cheng, et al. 2015). In practice, it is critical to optimize the algorithm in terms of calculation speed and memory cost.

1) Single subject optimization—The original cmICA performed PCA/ICA directly on the brain connectivity matrix C , and parcellated it into spatially independent source maps S and corresponding connectivity profile maps R that define the connectivity of each source S to the whole brain, i.e., $C = RS$.

In the case of functional connectivity, each connectivity element in matrix C is carried out as a standard Pearson's correlation coefficient on temporal courses per voxel pair in fMRI BOLD signal. The connectivity matrix C (voxel×voxel) from BOLD data X (time×voxel) is

$$C = \text{corr}(X) = \frac{\tilde{X}^T \tilde{X}}{n-1}, \quad \tilde{X} = \frac{X - \mu_X}{\sigma_X} \quad [1]$$

where $\tilde{X}$ is the temporally normalized X for each voxel, where μ_x is the mean and σ_x is the standard deviation.

A standard SVD/PCA analysis of $\tilde{X}$ gives $\tilde{X} = V\Sigma U^T$ (where U and V are the unitary matrices and Σ is the eigenvalue diagonal matrix), which implies that $C = \frac{U\Sigma^2U^T}{n-1}$. In other words PCA decomposition of C can be calculated from PCA of $\tilde{X}$, importantly without calculating the connectivity matrix C .

If W is ICA demixing matrix after ICA on the reduced dimension PCA output $\tilde{U}$ corresponding to U , then with $C = RS$, we have

$$S = W\tilde{U}^T, \quad R = \frac{\tilde{U}\tilde{\Sigma}^2W^{-1}}{n-1} \quad [2]$$

This clearly shows that an ICA decomposition of C can simply be derived from the PCA/ICA decomposition of $\tilde{X}$ without prior computation of functional connectivity matrix C (see in Appendix 1).

2) Group level derivation—The group-level cmICA adapts the same 2-step PCA procedure as is typically used in group ICA (Calhoun, et al. 2001a; Erhardt, et al. 2011; Wu, et al. 2015), where it runs the standard 1st PCA on individual subject, and concatenates the PCA results per subject to run the 2nd PCA and ICA to compute the group maps. However, since the connectivity matrix C is not computed; the original group level cmICA's back-reconstruction has no individual input to project from. Therefore, it needs a new derivation accordingly. Here, we applied the similar GICA principle from previous work (Erhardt, et al. 2011; Wu, et al. 2015) complemented by matching each subjects loadings/contributions to the final PCA/ICA, where it yielded.

$$R_k = \tilde{u}_k \tilde{\sigma}_k^2 \tilde{v}_k \tilde{\Sigma} W^{-1}, \quad S_k = W \tilde{\Sigma}^{-1} \tilde{v}_k^{-1} \tilde{u}_k^T \quad [3]$$

where $(\tilde{u}_k \tilde{\sigma}_k^2 \tilde{v}_k)$ is the reduced SVD/PCA result from single subject k , and $(\tilde{U} \tilde{\Sigma} \tilde{V})$ is the reduced SVD/PCA result at concatenated group level where $\tilde{v}_k$ is the partition of $\tilde{V}$ for the subject k , and W is the demixing matrix in ICA decomposition. We chose GICA for back-reconstruction instead of other approaches, e.g., dual regression, because it filters out the artifact (low PCA variance) contribution to the R maps (Erhardt, et al. 2011)

Using this approach, cmICA for functional connectivity is now optimized to be to an execution of spatial ICA on normalized BOLD data, rather than on the original voxel-wise connectivity matrix. This eliminates the original limitation of high memory and computation costs.

3) cmICA maps as seeds for seed-based connectivity—Seed-based approach for functional connectivity analysis requires creating seed regions first. The (average) time series of BOLD signal is extracted from the seed and the connectivity map is then computed by temporal correlating this reference time series with the time courses of all other brain voxels (Cole, et al. 2010; Fox, et al. 2009; Joel, et al. 2011). However, there is no golden standard for seed selection and there are numerous options available (Sohn, et al. 2015). One option is to use the ICA source maps S as seeding regions (Cole, et al. 2010) or to use seed regions as constraints in a spatial ICA analysis (Lin, et al. 2010).

In optimized cmICA for functional connectivity analysis, the derived source maps S can be interpreted as “seed” regions. Since in spatial ICA $\tilde{X} = TS$, the temporal component T represents each S map’s common time course, the connectivity map for each seed region S can be computed as the temporal correlation between the representative time course T and all brain BOLD time series.

$$\begin{aligned} \text{corr}(X, T) &= \frac{\tilde{X}^T T}{(n-1)\sigma_T} \quad [4] \\ RS = C &= \frac{\tilde{X}^T \tilde{X}}{n-1} = \frac{\tilde{X}^T TS}{n-1}, R = \frac{\tilde{X}^T T}{n-1} \\ \therefore \text{corr}(X, T) &= \frac{R}{\sigma_T} \end{aligned}$$

i.e., a seed-based correlation map is equivalent to a (normalized) connectivity map R in cmICA, using an ICA-defined source as seed. We revisit this topic in the Discussion.

In cmICA, S and R maps represent two different spatial components, which has been interpreted in (Wu, et al. 2015) extensively. S maps define the spatial segregations of connectivity restricted by statistical independence, whose distributions are relatively sparse, (i.e., super-Gaussian). S are also more consistent across different individuals (Allen, et al. 2012b), mental status (task/rest) (Joel, et al. 2011) and disease states (Wu, et al. 2015). R maps, the loadings in ICA, define the shared connectivity maps using the corresponding S regions as “seeds”, without spatial independence or stationary constraints. Therefore, R maps are less sparse and may capture more inter-subject variability (Joel, et al. 2011; Wu, et al. 2015). An inter-subject variability test of S and R was conducted in Appendix 2.

2. Subjects

Subjects were recruited via a Center of Biomedical Research Excellence (COBRE, <http://cobre.mrn.org>) program at the Mind Research Network (Aine, et al. 2017). In this paper, we used fMRI data from the same group of SZ subjects ($n = 60$, age = 38.6 ± 3.4 years) and HC subjects ($n = 61$, age = 35.0 ± 10.5 years) that we previously studied for diffusion imaging (Wu, et al. 2015). Four SZ and three HC subjects were excluded (5 without fMRI collections and 2 with excessive motions - maximum translation above 3mm or maximum rotation above 3°). COBRE data is also shared via the COINS data exchange (<http://coins.mrn.org/dx>) (Scott, et al. 2011; Wood, et al. 2015). Each subject provided written

informed consent according to guidelines at the University of New Mexico and compensated for their participation. Prior to inclusion in the study, all healthy subjects were screened to ensure they were free from neurological or psychiatric diseases (DSM-IV Axis I) as well as active substance use disorders (except for nicotine). Structural clinical interviews for DSM-IV (SCID) and case file reviews confirmed diagnosis of schizophrenia for the patients. The specific clinical screening protocol can be referred to our recent work (Cetin, et al. 2014; Sui, et al. 2015), SZ and HC subject groups did not differ in age ($p=0.11$), gender ($p=0.24$), race ($p=0.61$) and parental socioeconomic status ($p=0.22$), a less biased premorbid intelligence estimate (Saykin, et al. 1991; Yeo, et al. 2014). Table 1 provides demographic and clinical data.

3. Cognitive and clinical assessment

All assessments were performed within 1 week of the scan date. Three cognitive assessments were collected in all subjects. 1) The WTAR was conducted to provide a measure of premorbid intelligence for neuropsychological evaluation (Holdnack 2001). The age-standardized score was used for this study. 2) WASI-II battery was chosen for intelligence evaluation. The standardized full scale IQ, calculated from four subtests (vocabulary, similarities, block design and matrix reasoning), was used for this current study (McCrimmon and Smith 2013). 3) MATRICS is a cognition measure specifically designed for patients diagnosed with schizophrenia and related disorders (Green, et al. 2014). The composite T-score, summarized from seven cognitive domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition) were used. All sub-category scores are provided in the Supplemental A. In addition, the Positive and Negative Syndrome Scale (PANSS) (Kay, et al. 1987) was collected for all SZ, with the positive, negative and general psychopathology subscales used in the current study.

4. Data acquisition and preprocessing

All participants were scanned on a 3Tesla Siemens TIM trio equipped with 12-channel radio frequency coil at MRN. Subjects were instructed to fixate on a central cross hair presented with eyes open at rest. Resting state functional scans were collected by means of T2*-weighted gradient echo planar imaging sequences at 5 minutes long, 150 volumes with the following parameters: repeat time (TR) = 2s, echo time (TE) = 29ms, field of view = 240mm, acquisition matrix = 64×64 , flip angle = 75° , voxel size = $3.75 \times 3.75 \times 4.55 \text{ mm}^3$, gap = 1.05mm, 33 slices, ascending acquisition. A high-resolution structural anatomy was also acquired via a 3D MPRAGE T1 sequence (sagittal; matrix, 256×256 ; FOV, 256 mm; slice thickness, 1 mm; no gap; in-plane voxel size, 1 mm $\times$ 1 mm; flip angle, 7° ; TR, 2.53 s; TE, 1.64 ms) to provide the anatomical reference for the functional scan.

FMRI data were preprocessed using the software package SPM8. The first five image volumes were removed to avoid T1 equilibration effects. Images were then realigned using INRI align – a motion correction algorithm unbiased by local signal changes (Freire and Mangin 2001). Slice timing was corrected using the middle slice as the reference frame. Next, data were spatially normalized into standard Montreal Neurological Institute space

(Friston, et al. 1995), spatially smoothed with a 5mm full width at half-maximum Gaussian kernel and sub-sampled to $3 \times 3 \times 3$ mm, resulting in a total of $53 \times 63 \times 46$ voxels.

The data were also detrended and temporal band-pass filtered from 0.001 to 0.15 Hz to remove non-spontaneous artefacts (scanner drift, slow vascular/metabolic oscillation) and other high frequency noises (motion, breathing, heartbeat) (Allen, et al. 2011; Cordes, et al. 2000), and to be as close to the resting-state “low frequency fluctuation” (Biswal, et al. 1995; Biswal, et al. 1997; Cordes, et al. 2000; Lowe, et al. 2000; Lowe, et al. 1998; Van Den Heuvel and Pol 2010). The potential impact of temporal filtering on ICA results were investigated (see Supplemental B). Last, voxel time courses were normalized for the purpose of the cmICA optimization. As temporal variance normalization minimizes the possible bias in subsequent data reduction, it is usually preferred for connectivity and/or temporal modulation analysis (Allen, et al. 2012a).

5. cmICA model order selection

In our original cmICA paper for diffusion connectivity, we explored both low ($N_c = 30$) and high ($N_c = 100$) model order, and found the low model order matched better with the JHU tract atlas. In this study, we chose a medium model order ($N_c = 50$) for cmICA after multiple tests and comparisons for the following reasons. First, functional data contains larger variance than structural data, in both noise level and physiological signal level. Second, structural connectivity from diffusion imaging (a very sparse matrix) is much more localized than functional connectivity (a non-sparse matrix). Third, high/medium model order provides a finer-grained regional separation of sources in the cortical and subcortical compartments (Abou-Elseoud, et al. 2010; Kiviniemi, et al. 2009; Wu, et al. 2010). We chose medium order over high order, 70-100 typically used in fMRI spatial ICA literatures (Allen, et al. 2012a; Allen, et al. 2011; Wu, et al. 2010), because temporal filtering in the initial preprocessing removes considerable variance associated with the non-“low-frequency fluctuation” (LFF) artefacts (see detailed model order estimation in Appendix 3).

To ensure the validity of model order selection on our dataset, ICASSO (Himberg, et al. 2004) with 20 re-runs and random initial conditions, was used to test the convergence during ICA training and the stability and the “best run” was selected to provide a robust and replicable result using a minimum spanning tree (MST) method introduced in (Du, et al. 2014) and implemented in the GIFT toolbox. After cmICA, data was decomposed into functional source maps S and corresponding connectivity maps R . The resulting 50 independent source maps were manually evaluated using existing procedures (Allen, et al. 2011; Calhoun, et al. 2010; Wu, et al. 2010) with motion, imaging and physiological artefact removal (including mixed components consisting of artifact and RSN sources, see Supplemental F for details), yielding 28 resting state network (RSN) components (Allen, et al. 2011; Mantini, et al. 2009) for further study.

6. Connectivity group difference analysis

As in Wu et al. 2015, we observed that the cmICA back-reconstructed source S maps - the “seeds” - were fairly stable among individuals while the dual connectivity R maps maintained more variability. This is mainly because of the spatial *stationarity* assumption on

S across subjects on spatial ICA (Calhoun, et al. 2001a; Calhoun, et al. 2001b), whereas *R* maps, i.e., the mixing matrix in ICA, have no explicit statistical/mathematical restrictions (Joel, et al. 2011). Prior to statistical analysis, the normality tests (see Supplemental C) were performed on back-reconstructed maps to ensure the Student t-tests and/or linear regressions were the suitable statistical approach. We then examined *S* and *R* maps' group differences between SZ and HC separately via simple two sample T-tests as a pre-screening step. We found that the *S* maps did not show any statistically significant differences at p^* smaller than 0.05 with FDR multiple comparison correction at whole brain level and cluster extent larger than 20 voxels, while a greater proportion of cells in the *R* maps showed group differences. It is important to notice that the inter-subject variability on source maps *S* may still be detectable in many cases which have been explored extensively in (Allen, et al. 2012b), but in this study it didn't pass the significance test. Therefore, the following (demographic/cognitive/clinical) multivariate regression analyses were conducted on connectivity *R* maps (per voxel) only. This agrees with previous findings from Joel et al., 2011, that independent *S* maps partial out the variances across subjects (or task conditions) significantly, whereas *R* maps (or seed based maps) would keep those variances. This results in *S* maps being less dependent on individual variabilities and external-induced co-activations (see Appendix 2).

Next, different demographic factors were investigated as covariates on functional connectivity *R*. Previous studies have indicated effects of age and gender on resting state functional connectivity (Allen, et al. 2011; Geerligs, et al. 2015; Meunier, et al. 2009). Age effects were also found in same set of subjects from our previous work in structural connectivity (Wu, et al. 2015). In this study, we first used a backward multivariate model selection procedure (Allen, et al. 2011) to check the impact of different demographic factors by performing a multivariate analysis of covariance (MANCOVAN, <http://www.mathworks.com/matlabcentral/fileexchange/27014-mancovan>) on effects of age, gender (male 0, female 1), social economic status (SES, education, and parental education) and group label (SZ 1 HC 0), as well as their interactions to detect which predictor(s) in the design matrix showed variabilities in the response. In addition, potential motion effects on functional connectivity were also examined by including motion nuisance parameters (x, y, and z translations and pitch, roll, and yaw rotations) from SPM INRIalign motion estimations and by adding additional motion cleaning, e.g. data despiking. No significant motion effect was found in either case (see Supplemental D). This is likely because the motion residuals are reduced via the initial temporal filtering and the removal of motion-related artifacts via spatial ICA, and because of the low correlations between motion parameters and regressors in design matrix. The final regressions were only performed on retained regressor(s) in order to decrease the degrees of freedom used in the MANCOVAN computation (Allen, et al. 2011).

7. Multivariate analysis on cognition and clinical assessment

During the regression analysis on various cognitive performances, we noticed a high multicollinearity (Tolerance < 0.2, variance inflation factor > 5) among WTAR, WASI and MATRICS due to the high correlations ($r = 0.59\sim 0.7$) among these three variables. Without proper model selection, this may lead to invalid estimation in individual responses (Belsley, et al. 1980; Tabachnick, et al. 2001). To ensure prediction accuracy, we first tested effects on

three cognitive scores without differentiating group types, searching for significant effects associated with function connectivity. We also tested effects on three group interaction terms (group×WTAR, group×WASI, and group×MATRICS) looking for disease-related regressor(s) associated with functional connectivity changes. The final regression was only performed on the most significant covariates and collinearity safe model (Variance inflation factor (VIF) <5) $M = (\text{group, age, WTAR, WASI, and MATRICS})$, OZP was removed due to no significant effects and no significant impacts on WTAR/WASI/MATRICS' responses. Similarly, in symptom-based analysis, PANSS general psychopathology score were correlated with positive and negative scores ($r = 0.51, 0.35$). The general score was removed in regression model due to the high multicollinearity (VIF>5), and the final regression model was $M = [\text{group, age, PANSS POS, PANSS NEG, and OZP}]$. All tests are attached in Supplemental E. The detected regions were adjusted using the same significance test as before.

In addition, we examined the impact of patients' medication usage (using total OZP dose equivalence) on MATRICS and PANSS performances as well as on functional connectivity, since it has been reported that medications have large impact on symptoms and/or cognitions (Gimpel, et al. 2005; Green, et al. 2004; Lui, et al. 2010; Millan, et al. 2014), which may potentially affect functional dysconnectivity associations.

Results

1. Spatial components and Connectivity components

The cmICA analysis resulted in 28 components (out of 50, the other 22 components are provided in Supplemental F). All the components were consistent with and extended previous ICA findings (Allen, et al. 2012a; Allen, et al. 2011) and survived the stability tests (See ICASSO and inter-subject stability in Appendix 2 and 3).

Figure 1 shows the aggregate S and R maps for all 28 selected components. The maps are sorted in seven groups for display convenience, which include subcortical (3), somatomotor (6), occipital (6), temporal (3), attentional network (4), default mode network (DMN, 4), and cerebellum (CBM, 2) regions. The source maps S , shown in 3-dimensional plots in Figure 1, were thresholded ($t > \mu + 4\sigma$) using t-statistics for visualization and also identified strongest and most representative voxels across subjects (Allen, et al. 2011). Also a high-level rendering of S is used for presentation clarity, as S maps are considered to be 'seeds' and the R maps to be the resulting connectivity. Detailed S are provided in Table 2 (Talairach labels) and Supplemental F, and S and R side-by-side in Supplemental L.

Figure 1 also shows connectivity maps R (orange color) corresponding to their sources S . The R maps are converted to correlations using Equation [4] so that it is comparable across different components for the whole brain, and thresholded using t-statistics on correlation significance (two-tailed $p < 0.05$). The high spatial overlapping between S and its corresponding R indicated high intra-source connectivity in all components. Sources of precentral (S7), occipital (S4), temporal (S30) and mid cingulate cortex (S44) also showed relatively large inter-regional connectivity beyond source-defined area in their R maps, e.g., R4 and R30 double-confirmed high temporal-occipital/lingual/cuneus connectivity. The

ventral temporal cortex is involved in high-level visual process, object perception and recognition (Schacter, et al. 2010). The striatum putamen (S/R31), caudate (S/R14) and cerebellum (S/R23, S/R29) had least extra-source connectivity. Beyond these source-isolated components, we also noticed a distinct network-isolated group, DMN. The original “split” DMN components of S50 (L angular), S8 (R angular) and S21 (PCC/precuneus), due to the high model order (Abou-Elseoud, et al. 2010; Kiviniemi, et al. 2009), show inter-DMN connectivity in R21, R50, and R8, but not to the rest of the brain, suggesting its high “isolation” may serve different cognition from other brain functional networks. Last, the results from *R* maps pointed out strong lateral connectivity. Some lateral pairs originally separated in *S* distributions (S35/S2 and S50/S8) showed high lateral connectivity in *R*.

To examine the numerical differences between *S* and *R*, spatial distribution and similarity were calculated. Figure 2 (A) shows *S* and *R*’s marginal histograms for the least correlated component #4 (top left) and the highest correlated component #8 (top right) and their corresponding 2-dimensional joint histogram (bottom) respectively. As expected by the theory, *R* maps’ intensities were much more spread-out (less super Gaussian) than their matching independent *S* maps. Figure 2 (B) shows the spatial correlation between *S* and *R* maps without voxel thresholding. All pairs are highly correlated ($r > 0.55$), indicating that, though distributed differently, intra-network connectivity still dominates in both connectivity representations.

2. Functional connectivity group differences

Thresholding was only used for spatial pattern visualization for each component above, and it was not applied during group difference analysis or for multivariate statistical analysis done later. The analysis was done with the full brain mask to include effects on whole brain connectivity, rather than restricting to local and/or intra-network connectivity. In Figures 3 and 4 the significant regions of functional connectivity (*R* maps) are shown with the results grouped based on the categories of the corresponding *S* maps (obtained by cmICA).

After regression analysis on demographic inputs, we found that (similar to our last finding on structural connectivity (Wu, et al. 2015)), out of all the covariates (age, gender and SES) tested, only age predicted a significant variability whereas the age’s interaction with groups or any other factors in the design matrix did not indicate a significant variability. Gender, one commonly examined variable, had significantly smaller associations with functional connectivity than that for group and age. In addition, adding gender into design matrix had little effect on the group and age effects and did not alter the resulting conclusion. (see ‘gender’s response in Supplemental G). Large functional connectivity decreases ($p^* < 0.05$ FDR corrected, cluster extent > 20 voxels) associated with aging are shown in Figure 3. We then only removed age effect on between-group comparison by testing the statistical differences with age as a covariate. Age effect was removed in following clinical data regression analysis as well.

Figure 4 shows group differences between SZ and HC on resting state functional connectivity ($p^* < 0.05$ FDR, cluster > 20). Since connectivity difference analysis of *R* maps was conducted on whole brain volume without restriction to seed *S* defined regions, we found significant group differences in both intra-*S* connectivity and long-range inter-regional

connectivity for most components. For instance, functional connectivity from sources S39 (lingual) and S37 (cuneus/precuneus) both showed decreased intra-source connectivity as well as decreased connectivity towards parietal lobe and temporal lobe, but showed increased connectivity towards subcortical region in SZ. Overall, the results indicated a broad range of significantly decreased connectivity in SZ. However many cortical sources, S35, S2, S9, S7, S39, S37, S11, S30, S42, and S5 showed increased inter-regional connectivity to regions which included subcortical area, thalamus and caudate. On the other hand, caudate (S14) had increased inter-regional connectivity towards temporal, occipital and frontal areas. This abnormality of increased inter-subcortical-cortical connectivity is consistent with previous findings (Cetin, et al. 2014; Cheng, et al. 2015; Damaraju, et al. 2014; Sui, et al. 2015). The MNI table of detected regions is provided in the Supplemental H.

3. Multivariate analysis on cognitive performance

In this study, all SZ were treated with antipsychotic drugs, and the total OZP dose equivalent (Table 1) and MATRICS score was moderately correlated ($r = -0.31$). However, we did not find any significant effect of OZP on functional connectivity, and therefore it was excluded from the regression model.

Our model was chosen to identify the cognitive test that was most sensitive to schizophrenia related connectivity differences. We found that out of three different cognition tests, MATRICS has strong associations with functional connectivity than did the WTAR and WASI results. The MATRICS' results are presented and discussed here, and WTAR and WASI results are provided in Supplemental I. In addition, in this study we are mainly interested in schizophrenic-related connectivity abnormality, therefore, we conducted a whole-brain regression analysis on cognitive scores and multiple comparison correction first (to avoid 'double dipping'), and then overlapped these significant affected areas with areas indicating group differences in functional connectivity (Figure 4). The remaining areas were further examined in terms of cognitive association.

Figure 5 showed the effects of MATRICS on functional connectivity with corresponding *S* seeds ($p < 0.05$ FDR, cluster > 20), with detailed MNI information provided in Table 3. A separate *S* and *R* correspondence was provided in Supplemental M. As expected, MATRICS effects were mostly positive (top row, orange-colored), i.e., cognitive performance improved with functional connectivity increasing and deteriorated with connectivity decreasing. However, we found one case of negative effect on functional connectivity from source S14 (caudate) towards frontal area in its connectivity map R14 (top left, blue-colored). All the corresponding sources were indicated in Figure 5 (bottom middle). Out of all the component pairs, the "occipital" source group was the most MATRICS associated area, including S39, S37, S11 and S4 (bottom middle, red-colored). The S11 (cuneus/lingual) showed the largest and strongest connectivity affected areas, mostly towards parietal lobe. We also noticed that, most MATRICS captured dysconnected areas were cross-regional (i.e., the affected area in *R* was not in the *S* defined area). The scatter plots (bottom left and right) showed the effects for the peak values in R14 and R11, indicated by asterisks in the maps. The rest were attached in the Appendix 4. In all positive effects, SZ's functional connectivity were significantly

lower than HC's and both positively correlated with MATRICS scores; whereas in negative case of R14, SZ's functional connectivity were significantly higher than HC's and both negatively correlated with MATRICS scores; but there were no significant slope differences between SZ and HC in all examined components (see Appendix 4).

4. Multivariate analysis on PANSS

The multivariate analysis of functional connectivity on both PANSS positive and negative covariates from patients showed no significant effects. In addition, we did not find correlations in both PANSS scores with antipsychotic dose equivalents (see the Supplemental J), nor did the latter change the covariance between symptom scores and functional connectivity significantly in this study.

Discussion

1. cmICA and its connectivity maps

Originally we developed cmICA method for segregating brain structures (i.e., S) using their connectivity properties (Wu, et al. 2015). Similar types of connectivity-based clustering/parcellation methods have been widely used in cortex parcellations and other sub-region parcellations (Anwander, et al. 2007; Cloutman and Ralph 2012; Klein, et al. 2007; O'Muircheartaigh, et al. 2011; Saygin, et al. 2011). Previously, we used whole brain structural connectivity matrix derived from diffusion weighted imaging (DWI) and found the brain maps blindly separated by cmICA were graphically aligned with the established atlas of white matter axon tracts (see the cover illustration for HBM vol. 36 issue 11 and details in (Wu, et al. 2015)). In addition, cmICA generates the dual connectivity map R , which represents the connectivity profile of its structure S across the whole brain without spatial independence restriction. We found that connectivity-based cmICA in both brain structural and functional studies captured more details in group differences between SZ and HC compared to non-connectivity based methods, e.g., FA maps or BOLD fALFF maps, providing evidence to support schizophrenia as a dysconnectivity-related disease (Caprihan, et al. 2011; Sui, et al. 2015).

The results show that the functional connectivity R maps from cmICA capture more variability than the conventional independent S maps in group analysis. The 'stationarity' in the group-level may somewhat restrict 'variability' across subjects along S . This is because the standard Group-ICA is primarily seeking a group 'common' map in the first place, while it does allow for cross-subject variability (Allen, et al. 2012b), more variability is captured in the timecourses, i.e. the loadings (Allen, et al. 2011). The R maps, the loadings as well, are not restricted by the mathematical model either.

The mathematical optimization of cmICA from this work eliminated the original memory limit and made it feasible for whole brain fMRI without subsampling. The cmICA is now essentially a spatial ICA on BOLD time series instead of on a connectivity matrix. S maps in cmICA, which are connectivity-based segregating sources, become virtually the same parcellations from BOLD data. R , the connectivity profiles of its corresponding S sources, are equivalent to correlation map of its ICA time course T to the original BOLD. R

represents the functional connectivity between independent “clusters” and the entire brain, which can also be seen as seed-based connectivity. This method provides a convenient way to oversee different brain networks’ functional connectivity in the whole brain, intra and inter-regionally.

2. cmICA and seed-based functional connectivity

Traditionally, ICA-based connectivity (S map only) and seed-based (or ROI-based) connectivity represent different functional connectivity information (Damoiseaux and Greicius 2009; Rosazza, et al. 2012; Sohn, et al. 2015; Zuo, et al. 2010). Joel et al., 2011 described mathematically the relationship between these two methods, with ICA derived S maps as intra-network (or within-network connectivity) that involve very distinct functions from each other, whereas seed-based connectivity maps are a summation of intra-network and inter-network (or between-network connectivity). The cmICA provides a common framework to efficiently compute and compare results from both methods. While S maps remain the same as intra-network connectivity in cmICA, R maps are essentially a summation of intra and inter-network connectivity using S as seeds.

The relationship between S and R can also be interpreted from a linear regression perspective. The difference lies in the covariate(s)/regressor(s) in the design model. Using BOLD time series as dependent variables when choosing all the ICA time courses as predictors in a single regression model, the resulting regression coefficients (effects) would be roughly equivalent to S maps corresponding to each predictor loadings. When choosing a single ICA time course as a predictor for regression separately, the resulting regression coefficient would be an R map responding to that time course. Intuitively, S maps are more “isolated”/independent/sparser than R maps, because each S map has removed connectivity effects from each other and only reflects intra-network/source connectivity, whereas R maps will capture global connectivity (intra and extra-network) towards each particular network. The connectivity captured from R is also a finer grained (voxel scale) extension of our previous work on functional network connectivity (FNC) that describes inter-network connectivity (component scale) (Jafri, et al. 2008).

3. cmICA-based functional connectivity vs. node-based functional connectome

In addition to the connectivity methods mentioned in this article, e.g., seed-based correlations or cmICA-based loadings, the node-based “functional connectome” methods are also widely used for functional connectivity analysis. The node-based methods include the atlas-defined functional connectivity matrix developed within the Human Connectome Project (Craddock, et al. 2013; Hagmann, et al. 2012; Van Essen, et al. 2013), as well as the ICA-defined FNC matrix, i.e., temporal correlations across ICA timecourses (Allen, et al. 2012a; Allen, et al. 2011; Calhoun, et al. 2009a; Jafri, et al. 2008). The node-based methods shifts the emphasis from large-scale brain maps into a node+edge matrix or graph network (Smith, et al. 2013). The node-based functional connectome matrix provides a macroscopic view of brain connectivity diagram, while cmICA-based and seed-based functional connectivity provides connectivity down to regions or voxels. These two methods are complementary to each other. One way to look at the relationship between these two methods is that the functional connectome matrix is a “summary” of all the R maps into a

single value, whereas R maps are the “details” of the former at a voxel scale. FNC assumes that all voxels associated with the S map have one shared time course, therefore forcing intra-network/node connectivity to be 1 always (i.e. the FNC matrix’s diagonal line), regardless of specific voxel locations or time window. Whereas the proposed R map eliminates this limitation providing a method to examine within-node connectivity. An extension of cmICA is to examine the temporal dynamics of intra-network connectivity in addition to spatial inter-network connectivity dynamics. Functional connectome based methods do not explicitly provide information about spatial dynamics as they fix the within-node connectivity.

4. Dysconnectivity in schizophrenia

In this study, we found extensive functional connectivity abnormalities in SZ, which strongly supported the theory of using functional dysconnectivity from neuroimaging as a biomarker for diagnosis (Friston 2002; Friston 2011; Stephan, et al. 2006; Stephan, et al. 2009). Interestingly, we also found significant structural connectivity difference between SZ and HC using diffusion imaging in the same group of subjects (Wu, et al. 2015). However, a more detailed understanding of the connection between structural connectivity and functional connectivity will require further studies.

As mentioned in the introduction, the patterns of abnormal functional connectivity established in previous studies have a large inconsistency (Sheffield and Barch 2016) with both regional dysconnectivity and global dysconnectivity findings. The advantage of our approach is that cmICA can parse the ultra-large and ultra-complex whole-brain functional connectivity (Cheng, et al. 2015) into a few sources and connectivity maps, which not only reduces the search extent and multiple comparisons significantly without losing generalization, but can also enable testing of loadings, for example patients and controls cognitive performance. In this study, we found a global functional dysconnectivity (mostly decreasing) in SZ, whereas only certain region-linked dysconnectivity was associated with MATRICS-measured cognition deficiency. Other work using overlapping COBRE fMRI data only found abnormal increases in the thalamus (Sui, et al. 2015). An increase of thalamus-related connectivity in patients was also found in our study (see Result 2).

5. Cognition-based analysis versus symptom-based analysis with dysconnectivity

The HC performed better than the SZ on both WTAR and WASI tests. The MATRICS battery, a NIMH/FDA endorsed validation test specifically designed for schizophrenia, provides excellent psychometric properties and normalization for demographics (August, et al. 2012; Buchanan, et al. 2011; Keefe, et al. 2011; Nuechterlein, et al. 2008). In this study, we found evidence in support of MATRICS’ sensitivity in schizophrenia-related cognitive impairment that is highly associated with BOLD functional dysconnectivity. Whereas, WTAR and WASI scores, though correlated with MATRICS (see Supplemental E), had much less or no differences in functional connectivity between two groups (see Supplemental I).

Still, it is crucial to examine the brain-behavior relationship carefully such that the observed functional system may underlie the “actual” mechanisms of the cognition deficits, instead of

a “generalized” disturbance (Sheffield and Barch 2016). Our results showed only small brain areas of abnormal functional connectivity associated with cognitive performance. The majority of the cmlCA connectivity maps that were different in SZ and HC groups were directly (positively) correlated with cognitive performance. These included cuneus/lingual and parietal/temporal networks, which could be associated with visual memory encoding, word recognition, and/or visual processing/learning skill impairment in patients (Landgraf and Osterheider 2012; Mechelli, et al. 2000; Saykin, et al. 1994; Silverstein, et al. 2009; Tohid, et al. 2015). An exception was the caudate-to-frontal network (S14/R14), which had inverse relationship to cognition. This network was also different in the connectivity as it was higher in the SZ group. There is growing evidence that shows the linkage between caudate and frontal area that plays a fundamental role in executive functioning and cognitive flexibility, and is related to reward/goal-related decision-making (Balleine, et al. 2007; Eslinger and Grattan 1993). This different behavior of the caudate-to-frontal network might be less clear. We speculate that caudate aberrantly interferes with frontal functions in SZ patients actively, resulting in an overcompensating effort related with cognition (Cole, et al. 2010; Cole, et al. 2011). Further assessment and validation are required on aberrant cognitive control neural circuitry in schizophrenia (Eisenberg and Berman 2009).

In this study, we also used PANSS to examine schizophrenia symptom severity, and it showed virtually no relationship with functional connectivity. Previous studies suggested that neuro-cognitive impairment is a key factor underlying functional disability and related outcomes in schizophrenia (Green 1996), and is independent of psychotic symptoms (Keefe and Harvey 2008). For instance, many patients exhibit clear cognitive deficits before the onset of psychotic symptoms. As expected, the positive symptoms score in this work was neither correlated with MATRICS score nor with BOLD functional dysconnectivity, which confirmed positive symptoms are not the sole source of cognitive impairment in schizophrenia (Keefe, et al. 2006). However, the negative symptom scale from our data was moderately correlated with MATRICS composite T score ($r = -0.27$, $p = 0.046$), which is consistent with earlier findings (Green, et al. 2004; Patterson, et al. 2001; Sui, et al. 2015). This is not surprising, as negative symptoms in schizophrenia share numerous characteristics with cognitive deficits and functional behavior (Harvey, et al. 2006; Millan, et al. 2014); but the observed correlation between negative symptom and cognitive deficits is eliminable with some effort (Harvey, et al. 2006).

Substantial evidence showed that cognitive-based measurement serves as a good predictor of performance improvement in social/community functional outcome of SZ, whereas symptom-based measurement did not or is less of a predictor (Bell and Bryson 2001; Bryson and Bell 2003; Carrión, et al. 2013). This makes cognition-enhancing agents in schizophrenia as rationale for psychopharmacological intervention and early prevention (Carrión, et al. 2013; Green, et al. 2004). Overall, our work and others mentioned above suggests that cognitive based analysis is a better candidate for validating “dysconnection” theory in schizophrenia than symptom based analyses.

6. Limitation

In order to make the R maps in our algorithm be similar to resting state (i.e., low frequency fluctuation) functional connectivity directly after one-step back-reconstruction (without post-processing), we conducted temporal filtering 0.001 to 0.15Hz prior to running PCA/ICA. This step makes the artifact detection algorithms (especially for artifacts mixed with RSN sources), that primarily use frequency information/ratio, less accurate; as the higher portion of the frequency has been removed. In this study, we mainly relied on visual inspection of spatial source patterns and prior experiences, while only using the high/low ratio artefact detection (Allen, et al. 2011) as a reference (see Supplemental K).

While R maps indeed capture more inter-subject variability than S maps do (Appendix 2), R will contain relatively more noise residuals than S will in the current algorithm. R maps are less independent from the other components' in the current framework, as it captures its sources' connections with other components (including some degree of noise components) as well. However, these maps are also less sensitive to noise/artefacts than standard seed-based connectivity methods because R maps also benefit from the spatial filtering that ICA provides and are primarily driven by a given component. Mathematically speaking, the influences from other sources (to the current source S) in the R maps rely on the strength of inter-component connectivity, i.e., the correlations between ICA time courses, and the noise/nuisance components tend to be poorly correlated with (biological meaningful) RSN sources. The other aspect is that, S though much more constrained across subject, was restricted by spatial independence and stationary, which in reality may not be necessarily true always. For instance, we found that the original three "split" DMN S maps of left angular, right angular and PCC/precuneus (due to the high model order) show inter-DMN connectivity in all three corresponding R maps, but not to the rest of the brain, suggesting its high "isolation" from other brain functional networks. Also, some R maps pointed out strong bilateral connectivity versus spatially independent unilateral S maps. Last, we would like to point out again that the advantages of our algorithm is that we have both R and S maps for exploration, which can directly relate a seed-like approach with an ICA-like approach. Granted there may be residuals contained in the current algorithm. We are working on improving the algorithm by embedding artefact removal in generating R maps in a relatively automated manner.

Conclusion

A computationally efficient algorithm for cmICA to analyze functional connectivity is proposed. The cmICA generates a connectivity-based brain parcellation and their corresponding voxel-wise connectivity profiles. The novel data driven cmICA enables us to do a high dimensional (whole-brain) functional connectivity analysis. The connectivity patterns indicated a large-scale brain functional dysconnectivity in schizophrenia, as well as strong interactions with cognitive performance. Our study supports the theory of schizophrenia as a disorder of "connectivity" (Friston 1998; Friston 2002; Garrity, et al. 2007; Stephan, et al. 2006; Stephan, et al. 2009) and identified relationships of connectivity with cognition which may help to better understand schizophrenia and its diagnosis. Future work lies in improving connectivity-based biomarker by enhancing fMRI temporal

acquisition (Feinberg and Setsompop 2013; Posse, et al. 2012), integrating with other neuroimaging modalities, e.g., DWI, EEG (Sui, et al. 2015; Wu, et al. 2015; Wu, et al. 2010) and network graph theory (Yu, et al. 2016). Longitudinal connectivity studies combined with cognition assessments will be useful for monitoring disease progression (Green, et al. 2004).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

1. Equivalence test

The mathematical equivalency between proposed cmICA (on temporal normalized fMRI $\tilde{X}$ directly) and standard cmICA (on connectivity matrix C of temporal correlations) is due to the equivalency between PCA decomposition of C and PCA of $\tilde{X}$ as we showed in the manuscript. To validate the equivalency of our simplified version of cmICA on functional connectivity, we tested our theory on real fMRI data. We used group-averaged BOLD signal as our testing input. Then we conducted both the simplified cmICA on temporal normalized BOLD signal and a direct standard cmICA on the entire functional connectivity matrix. The model order was 50.

The results are shown in Figure A1 (independent sources shown in peak-valued slice per component, bottom row), and standard cmICA's components from ultra-large connectivity matrix (top right) are sorted by matching the components derived from simplified cmICA from temporal normalized BOLD (top left). As we can see, PCA decompositions (middle row) between standard cmICA and proposed simplified cmICA were either identical or only directionally flipped, which do not impact ICA results. And (bottom row) the independent components S on both sides are mostly identical, except small contrast differences in some components (row 1 column 6, row 3 column 8, row 5 column 7, row 6 column 5, row 7 column 2). This was due to preprocessing procedure and infomax ICA convergence in real data. In order to maintain the connectivity relationship (in R), we did not remove the global mean prior to PCA in this study, which may impact slightly on the ICA yields due to subtle infomax convergence differences. However, note that this problem could significantly cut down at group level, as long as the component's variance dominates in the entire group.

Figure A1.
Simplified cmICA vs Standard cmICA

Although computation demands were not the primary topic of our work, our proposed method has the additional advantage of reducing the computation significantly while producing nearly identical results in real data tests. See the ‘cmICA computation comparison table’ below.

Table A1

cmICA Computation Comparison Table

Methods	Running time (seconds)	Memory cost (Gigabytes)
<i>Standard ‘connectivity-based’ ICA</i> * (on connectivity matrix 57285×57285)		
Full EVD/SVD+Infomax	22617.4	24.6
ARPACK+Infomax	124.6	
EM+Infomax	2373.7	
<i>Proposed cmICA</i> *		
Full EVD/SVD+Infomax	25.0	~0.1
ARPACK+Infomax	24.0	
EM+Infomax	42.1	

* Infomax used for ICA (~23-26s per run)

2. Inter-subject variability/stability

We conducted a general stability/variability visualization of both *S* and *R* individual maps via t-distributed stochastic neighbor embedding (t-SNE) (Maaten and Hinton 2008). As expected (Figure A2 and A3), *S* maps across all subjects are much more stable than *R* maps.

Fig. A2.
t-SNE similarity of *S* maps.

Fig. A3.
t-SNE similarity of R maps

We mentioned briefly in the manuscript (Methods “1. Theory-3) cmICA maps as seeds for seed-based connectivity” and “6. Connectivity group difference analysis”) that it was because of the spatial “stationarity” assumption of (temporal-concatenated) group ICA. We added more theoretical background from previous elaborations (Allen, et al. 2012b; Erhardt, et al. 2011) as suggested.

The proposed cmICA adopted group spatial ICA using temporal concatenation (Allen, et al. 2012b; Calhoun, et al. 2001a; Erhardt, et al. 2011), which was found to work better for fMRI based data compared to the methods using spatial concatenation (Erhardt, et al. 2011; Schmithorst and Holland 2004) and widely used in GIFT (Calhoun, et al. 2004)(<http://icatb.sourceforge.net/>), MELODIC (<http://www.fmrib.ox.ac.uk/fsl/>) and many other fMRI based analysis. The temporal concatenation approach assumes *common* aggregate spatial maps S across subjects but allows for unique time courses T for each subject. This assumption (stationary on S but nonstationary on T) makes the variabilities on time courses T are much larger than on spatial maps S (Erhardt, et al. 2011). Although spatial ICA decomposition of functional connectivity matrix in cmICA does not naturally contain time courses, mathematically they are equivalent to separate input data into two parts, *loadings* by *independent spatial maps*. In fMRI data, it yields *time courses* T and *spatial maps* S ; in functional connectivity matrix data, spatial ICA yields *connectivity maps* R and *spatial maps*

S. Hereditarily, in cmICA the *loadings R* across subjects carry much larger variabilities than the *spatial maps S* do.

3. Model order selection

In addition to referring to our previous experiences in fMRI model order selection, the model order was validated by the following procedure in this particularly study. We tested group ICA on model order 30, 50, 60, 70 and 100 with 10 repeated runs in this study, and conducted stability tests on the components from these five model orders separately. We intended to use a relatively higher model order in order to capture more detailed anatomical structures (Allen, et al. 2011) meanwhile we noticed that the components' stability is very consistent at 30 and 50, but started to drop after model order 60 (see clustering and stability test results below). Therefore, we used the model order 50 in this study.

(a) Model order 30

(b) Model Order 50

(c) Model order 60

(d) Model order 70

(e) Model order 100

Fig. A4.
Cluster similarity test.

(a) Model order 30

(c) Model order 60

(d) Model order 70

(e) Model order 100

Fig. A5.
Stability test

4. MATRICS effects on functional connectivity and peak regressions

Fig. A6.
MATRICS effects on functional connectivity and peak regressions

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Fig. 1.

The S maps for the 28 selected cmICA components with dual parcellation of functional connectivity are shown rendered on 3D brains at the top of each category. The components have been divided into 7 groups consisting of subcortical, somatomotor, occipital, temporal, attentional network, default mode network (DMN) and cerebellum areas. The corresponding R maps after being converted to correlations are plotted separately for each component at the bottom of each category.

Fig. 2.

A) The marginal histogram of the component with least correlation (Number 4) is shown on the left, and the marginal histogram of the component with highest correlation (Number 8) is shown on the right. Their joint histograms are shown below. B) The spatial correlation between all the pair S-R maps is shown. All pairs are highly correlated ($r > 0.55$).

Fig. 3.

The surface map shows regions of functional connectivity (R map) significantly correlated with age (displayed as the $-\text{sign}(t)\log_{10}(p)$ to reflect both the intensity and direction of the effect). Effects are considered significant if test statistics exceeded the FDR threshold ($\alpha = 0.05$) with a cluster extent of at least 20 contiguous voxels. The major effect seen is that functional connectivity decreases with age (blue regions).

Fig. 4.

Functional connectivity group differences between SZ and HC are shown (hot color: SZ > HC; cold color: SZ < HC). Large differences are observed in both intra-*S* connectivity and long-range inter-regional connectivity for most components. The results indicate a significantly decreased global connectivity in schizophrenia whereas an increased inter-regional connectivity towards all subcortical area, particularly to the thalamus and caudate. The same color map is used as in Figure 3.

Fig. 5.

Multivariate analysis results of the relationship between MATRICS cognitive scores and functional connectivity are shown. Top left) A significant negative correlation between MATRICS score and functional connectivity was observed only in component R14 in regions between caudate and frontal lobe. Top right) Nine components had significant positive correlation between MATRICS score and functional connectivity Bottom middle) All 10 source *S* maps associated with MATRICS are shown. Subcortical maps are in violet shades, DMN in grey, somatomotor in green, temporal in turquoise and occipital in red. Bottom left and right) Scatter plots with regression between MATRICS score and functional connectivity at the voxel with maximum correlation (R14 and R11). These plots are for qualitative visualization of the relationship between MATRICS score and functional connectivity at voxels with maximum positive (R11) or negative (R14) correlation.

Table 1

Demographics, behaviour and medication history of subjects.

	Schizophrenia Patients (n=60)	Healthy Controls (n=61)	p-value
Age (Years)	38.6±13.4	35.0±10.5	0.11
Gender (Male:Female)	47:13	42:19	0.24
Race *	2:2:4:1:51	2:0:5:0:54	0.61
Socioeconomic Status			
Highest Level of Education *	3.8±1.4	4.6±1.3	2.6e-3
Parental Education Level *	4.2±2.1	4.7±1.9	0.22
Family Psychosis History *	15 (25%)	1 (1.6%)	7.5e-5
Illness Duration * (Years)	16.4±12.2		
WTAR *	99.8±15.3	109.4±12.7	3.8e-4
WASI *	98.7±17.2	110.2±11.9	5.9e-5
MATRICES *	31.6±13.2	50.3±8.3	6.2e-14
PANSS *			
Positive	15.0±4.6		
Negative	14.9±4.9		
General	29.5±8.4		
Medication			
OZP * dose equivalent (mg/day)	16.5±11.4		

Notation:

* Race - American Indian (or Alaska native) : Asian : black (or African American) : native Hawaiian (or other pacific islander) : white

* Highest level of education/parental education level - “1” grade 6 or less, “2” grade 7 - 12 (without graduating high school), “3” graduated high school or high school equivalent, “4” part college, “5” graduated 2 yr college, “6” graduated 4 yr college, “7” part graduate/professional school, “8” completed graduate/professional

* Family psychosis history - having first degree relative with psychosis

* Illness duration – counted from the age at first diagnoses of schizophrenia or schizoaffective disorder

* WTAR - Wechsler Test of Adult Reading

* WASI - Wechsler Abbreviated Scale of Intelligence

* MATRICES - Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus cognitive battery

* PANSS - Positive and Negative Syndrome Scale

* OZP – Olanzapine

Table 2

MINI table of cmlICA sources *S*.

INDEX	LABEL	BA	VOL (cc)	Zmax	MINI (x, y, z)
Subcortical					
S31	Putamen (L/R)	*	18.3/18.0	34.2/34.1	(-27, 3, 3)/(27, 9, 0)
S14	Caudate (L/R)	*	20.6/21.1	26.0/25.6	(-9, 6, 15)/(9, 9, 12)
S36	Thalamus (L/R)	*	14.0/16.7	20.2/20.8	(-9, -21, 3)/(9, -21, 0)
Somatomotor					
S35	Postcentral (L)	1-3, 5, 7, 40, 43	30.8/*	23.7/*	(-42, -30, 48)/*
S2	Postcentral (R)	1-3, 5, 7, 40, 43	*/3 3.5	*/18.9	*/(42, -30, 54)
S9	Supplementary motor (L/R)	6, 32	22.41/23.4	24.5/24.6	(0, -27, 66)/(6, -21, 69)
S7	Precentral (L/R)	3, 4, 6, 9, 13, 43, 44	15.0/17.5	33.9/35.1	(-54, -9, 30)/(57, -6, 27)
S49	Supplementary motor (L/R)	6, 8, 32	23.6/22.5	18.5/17.9	(-15, 3, 60)/(15, 3, 60)
S19	Superior parietal (L/R)	5, 7	21.2/22.9	18.1/17.9	(-12, -60, 60)/(15, -57, 63)
Occipital					
S39	Lingual (L/R)	17-19, 30	18.9/23.3	19.5/20.4	(-24, -69, -9)/(24, -72, -6)
S37	Cuneus/Precuneus (L/R)	7, 17-19, 23, 30	23.2/26.0	20.5/21.3	(-18, -84, 27)/(12, -84, 27)
S3	Calcarine (L/R)	7, 17-19, 23, 30	23.6/23.2	21.4/21.0	(0, -87, 3)/(3, -87, 3)
S11	Cuneus/Lingual (L/R)	17-19, 30	23.2/23.6	18.9/18.3	(-15, -69, 6)/(15, -69, 9)
S4	Superior occipital (L/R)	13, 21, 22, 38-42	17.9/13.8	16.5/14.8	(-57, -57, -3)/(57, -57, -3)
S45	Middle/inferior occipital (L/R)	18, 19, 37	19.7/19.6	26.3/27.7	(-30, -96, 0)/(36, -90, -3)
Temporal					
S30	Superior temporal (L/R)	13, 21, 22, 38-42	24.1/19.4	18.7/16.8	(-48, -30, 6)/(48, -18, 3)
S1	Middle temporal (L)	19-22, 37-39	23.8/*	15.5/*	(-54, -39, -3)/*
	Inferior frontal/precentral(L)	9, 13, 44-47	15.1/*	13.2/*	(-54, 18, 9)/*
S42	Middle/superior temporal (R)	13, 21, 22, 38-42	*/33.3	*/15.1	*/(48, -27, -9)
Attentional network					
S44	Middle cingulate (L/R)	9, 23, 24, 31, 32	12.1/11/5	17.4/16.5	(-3, 30, 33)/(3, 27, 33)
S5	Middle/inferior frontal (L/R)	6, 8-11, 46, 47	15.9/22.7	15.9/17.2	(-45, 21, 21)/(51, 33, 15)
S18	Insula/precentral (L/R)	13, 22, 40, 41, 45, 47	12.8/15.2	15.7/15.6	(-45, -6, 9)/(45, 3, 6)
S15	Superior parietal (L/R)	7	16.1/15.5	14.3/14.5	(-24, -63, 39)/(30, -63, 42)

INDEX	LABEL	BA	VOL (cc)	Zmax	MNI (x, y, z)
Default mode network					
S21	Posterior cingulate (L/R)	23, 29-31	22.1/24.5	22.2/21.3	(-3, -42, 24)/(6, -42, 24)
S50	Angular (L)	39, 40	19.7/*	18.1/*	(-42, -63, 48)/*
S8	Angular (R)	39, 40	*18.2	*18.5	*/(51, -51, 45)
S12	Anterior cingulate (L/R)	10, 24, 25, 32	24.1/23.5	17.9/17.8	(-3, 39, -6)/(3, 39, -9)
Cerebellum					
S23	Posterior cerebellum (L/R)	*	25.1/27.8	22.4/22.5	(-24, -72, -33)/(30, -69, -33)
S29	Anterior cerebellum (L/R)	*	17.3/19.7	30.3/30.3	(-6, -54, -18)/(6, -54, -18)

Table 3

Cognitive scores association with functional connectivity.

SOURCE	LABEL	BA	VOL(cc)	Zmax	MNI(x, y, z)
<i>NEGATIVE</i>					
Subcortical					
S14	Inferior frontal gyrus	9, 44, 45, 46	1.1/0.7	-4.0/-4.2	(-57, 12, 12)/(54, 30, 15)
Caudate	Middle frontal gyrus	9, 46	0.1/0.8	-4.0/-4.0	(-51, 15, 30)/(48, 30, 21)
	Insula	13	*/1.0	*/-4.0	*/(39, 0, 9)
	Precentral gyrus	6, 44	0.3/*	-4.1/*	(-54, 12, 9)/*
POSITIVE					
Subcortical					
S36	Cingulate gyrus	23, 24, 31, 32	1.5/2.1	7.4/78	(0, -27, 33)/(6, -27, 33)
Thalamus	Anterior cingulate	24, 32	0.7/0.2	6.7/4.7	(-3, 39, 12)/(3, 39, 12)
	Precuneus	7, 31	0.1/1.4	4.5/58	(0, -75, 45)/(12, -63, 33)
Default mode network					
S21	Thalamus	*	1.5/1.0	6.5/5.4	(-15, -21, 3)/(15, -18, 9)
Posterior cingulate	Lentiform nucleus	*	0.1/0.1	5.1/4.5	(-21, -9, 3)/(12, -6, -3)
Somatomotor					
S2	Superior temporal gyrus	21, 22, 38, 41, 42	1.1/0.6	6.9/6.2	(-54, -9, -6)/(54, -30, 9)
Postcentral	Transverse temporal gyrus	41, 42	0.1/0.3	6.7/6.3	(-57, -15, 9)/(48, -30, 9)
	Middle temporal gyrus	21, 22	1.0/0.1	6.2/4.5	(-57, -9, -6)/(57, -36, 6)
	Inferior temporal gyrus	20	0.2/*	5.4/*	(-48, -6, -24)/*
S7	Fusiform gyrus	19, 37	*0.5	*/4.8	*/(36, -69, -12)
Precentral	Lingual gyrus	18, 19	*0.2	*/4.8	*/(30, -75, -9)
	Inferior Occipital Gyrus	19	*0.1	*/4.7	*/(42, -75, -12)
Temporal					
S30	Cuneus	7, 18, 19, 23	5.0/0.8	8.1/5.3	(-3, -78, 30)/(3, -78, 30)
Superior temporal	Precuneus	7, 19, 23, 31, 39	3.4/1.3	7.2/5.2	(-3, -78, 33)/(30, -75, 42)
	Precentral gyrus	4, 6	1.9/1.0	67/57	(-30, -30, 57)/(42, -9, 54)
	Superior occipital gyrus	19	0.4/*	6.1/*	(-30, -87, 27)/*
	Postcentral gyrus	2, 3, 5, 40	2.4/2.2	6.0/5.5	(-42, -27, 60)/(36, -39, 57)

SOURCE	LABEL	BA	VOL(cc)	Zmax	MNI(x, y, z)
	Superior parietal lobule	5, 7	0.1/0.9	4.2/6.0	(-24, -78, 45)/(27, -51, 60)
	Posterior Cingulate	23, 30, 31	0.4/0.2	5.6/4.5	(-12, -57, 21)/(6, -60, 24)
	Angular gyrus	39	0.3/*	5.2/*	(-33, -78, 30)/*
	Middle temporal gyrus	19, 39	0.4/*	5.2/*	(-33, -84, 24)/*
	Cingulate gyrus	31	0.5/0.1	4.8/4.5	(-18, -60, 24)/(3, -63, 27)
	Inferior parietal lobule	39, 40	0.2/0.3	4.5/4.7	(-27, -42, 57)/(39, -42, 57)
	Inferior parietal lobule	39, 40	0.2/0.3	4.5/4.7	(-27, -42, 57)/(39, -42, 57)
Occipital					
S39	Postcentral gyrus	1, 2, 3, 5, 40	1.6/2.3	6.2/7.1	(-54, -18, 48)/(36, -45, 63)
	Precentral gyrus	4, 6	0.4/2.6	5.2/6.5	(-42, -18, 51)/(48, -12, 45)
	Inferior frontal gyrus	9, 44, 45, 46	0.8/*	6.1/*	(-45, 12, 24)/*
	Paracentral lobule	5, 6, 31	0.2/0.1	5.5/5.3	(0, -30, 54)/(3, -27, 51)
	Inferior parietal lobule	40	0.6/0.4	5.1/5.5	(-57, -27, 36)/(36, -42, 60)
	Medial frontal gyrus	6	0.4/0.5	5.2/5.3	(0, -27, 54)/(3, -24, 54)
	Middle frontal gyrus	46	0.3/*	5.1/*	(-45, 18, 24)/*
S37	Superior temporal gyrus	22, 41, 42	*1.2	*7.2	*/(57, -30, 15)
	Postcentral gyrus	40	*0.3	*6.5	*/(57, -27, 15)
	Transverse temporal gyrus	41, 42	*0.3	*5.9	*/(57, -24, 12)
S11	Postcentral gyrus	1, 2, 3, 5, 40, 43	5.1/5.3	7.5/8.3	(-45, -36, 54)/(51, -24, 42)
	Inferior parietal lobule	40	1.0/0.4	8.6/5.2	(-45, -39, 57)/(48, -36, 60)
	Superior temporal gyrus	21, 22, 41, 42	*1.6	*7.7	*/(63, -24, -3)
	Precentral gyrus	3, 4, 6, 13, 43	2.5/3.7	7.4/7.7	(-48, -9, 48)/(45, -15, 45)
	Middle temporal gyrus	21, 22	*1.6	*6.8	*/(60, -27, -3)
	Medial frontal gyrus	6, 32	0.9/1.1	6.3/6.2	(0, -21, 57)/(3, -24, 57)
	Paracentral lobule	4, 5, 6, 31	1.4/1.1	6.0/5.6	(-3, -30, 54)/(6, -21, 51)
	Insula	13, 40	0.5/0.8	5.4/5.6	(-45, -15, 15)/(39, -21, 21)
	Cingulate gyrus	24, 32	0.1/0.8	4.5/5.4	(-3, 15, 45)/(12, 18, 33)
	Middle temporal gyrus	21, 38	*0.4	*5.5	*/(42, 6, -27)
S4	Superior occipital	38	*0.4	*5.5	*/(39, 12, -39)
	Superior occipital	38	*0.4	*5.5	*/(39, 12, -39)