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Assessing dynamic brain graphs of time-varying connectivity in fMRI data: application to healthy controls and patients with schizophrenia

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Abstract

Graph theory-based analysis has been widely employed in brain imaging studies, and altered topological properties of brain connectivity have emerged as important features of mental diseases such as schizophrenia. However, most previous studies have focused on graph metrics of stationary brain graphs, ignoring that brain connectivity exhibits fluctuations over time. Here we develop a new framework for accessing dynamic graph properties of time-varying functional brain connectivity in resting state fMRI data and apply it to healthy controls (HCs) and patients with schizophrenia (SZs). Specifically, nodes of brain graphs are defined by intrinsic connectivity

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Competing interests

The authors declare that they have no competing financial interests.

networks (ICNs) identified by group independent component analysis (ICA). Dynamic graph metrics of the time-varying brain connectivity estimated by the correlation of sliding time-windowed ICA time courses of ICNs are calculated. First- and second-level connectivity states are detected based on the correlation of nodal connectivity strength between time-varying brain graphs. Our results indicate that SZs show decreased variance in the dynamic graph metrics. Consistent with prior stationary functional brain connectivity works, graph measures of identified first-level connectivity states show lower values in SZs. In addition, more first-level connectivity states are disassociated with the second-level connectivity state which resembles the stationary connectivity pattern computed by the entire scan. Collectively, the findings provide new evidence about altered dynamic brain graphs in schizophrenia which may underscore the abnormal brain performance in this mental illness.

Keywords

R-fMRI; dynamic; time-varying; brain graph; ICA; schizophrenia

1. Introduction

Resting state functional magnetic resonance imaging (R-fMRI) is a powerful technique to characterize functional organization of human brain. A number of resting state brain networks, also called intrinsic connectivity networks (ICNs) such as the default-mode network (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001), motor network (Biswal et al., 1995), ventral and dorsal attention networks (Fox et al., 2006; Ptak, 2012; Vincent et al., 2008; Viviani, 2013), and salience network (Seeley et al., 2007), have been widely recognized by functional connectivity analysis. The main relationship among these networks is that the rest-related default-mode network which is thought to support internally oriented processing is anticorrelated with other task-related networks which act as a generic external attention system (EAS) (Fornito et al., 2012a; Fox et al., 2005). Recently, a more refined and fine-grained parcellation of these large-scale networks into a multitude of smaller constituents (Abou-Elseoud et al., 2010; Allen et al., 2011; Kiviniemi et al., 2009) has been shown by independent component analysis (ICA) (Calhoun et al., 2008; McKeown et al., 1998) in fMRI data. To evaluate the connectivity between multiple brain networks, a method called functional network connectivity (FNC), which examines the temporal relationship among brain components, has been developed (Jafri et al., 2008). Most studies which implement this technique have discovered altered FNC in patients with brain disorder such as schizophrenia (Calhoun and Adali, 2012; Calhoun et al., 2009a; Yu et al., 2012).

Schizophrenia is a severe chronic, mental disease which causes significant social and work problems. Common symptoms include delusion, hallucinations, apathy, and social withdrawal (Marin, 2012). This illness impairs multiple cognitive domains including memory (He et al., 2012), attention and executive function (Heinrichs and Zakzanis, 1998). Although the causes and mechanisms of schizophrenia are still unclear, graph theory-based analysis in brain imaging data suggest that the aberrant topological properties of brain connectivity are important features of this mental disorder (Fornito et al., 2012b; van den Heuvel and Fornito, 2014; Xia and He, 2011).

Graph theory-based analysis has become a powerful technique for analyzing brain imaging data. Particularly, in R-fMRI data, nodes of brain graphs could be voxels, regions of interest (ROIs) parcellated from brain atlas, or spatially independent components (de Reus and van den Heuvel, 2013; Fornito et al., 2013; Yu et al., 2012); edges of brain graphs could be defined based on cross correlation between time series of nodes. Our and others' previous work which implemented graph theory-based analysis in fMRI data have consistently shown disrupted graph metrics of whole brain connectivity in patients with schizophrenia (SZs) (Bassett et al., 2012; Liu et al., 2008; Lynall et al., 2010; Yu et al., 2011a; Yu et al., 2013a; Yu et al., 2013b; Yu et al., 2011b). However, all these studies assessed the graph metrics of stationary functional brain connectivity estimated by the full time series of signals over the entire scan, while brain networks are dynamically connected (Allen et al., 2014) and it has been proposed that quantifying time-varying functional connectivity may provide great insight into fundamental properties of brain networks (Hutchison et al., 2013a).

Dynamics of brain activation and connectivity have long been appreciated in electroencephalograms (EEGs) (Mutlu et al., 2012). Functional micro-states which may correspond to basic building blocks of human information processing have been well-established in EEG data (Hennings et al., 2009; Koenig et al., 2002; Lehmann and Skrandies, 1984; Lehmann et al., 1998; Pascualmarqui et al., 1995). In the last decade, more and more fMRI studies are investigating the temporal dynamics of functional connectivity in the human brain (Hutchison et al., 2013a). Functional brain connectivity has been reported to exhibit changes due to task demands (Esposito et al., 2006; Fornito et al., 2012a; Fransson, 2006), learning (Bassett et al., 2011), maturation (Uddin et al., 2011), and large state transition such as sleep (Horovitz et al., 2009; Horovitz et al., 2008). Brain connectivity under dynamic changes within time scales of seconds to minutes has also been reported in fMRI data (Chang and Glover, 2010; Hutchison et al., 2013b; Kang et al., 2011; Kiviniemi et al., 2011; Li et al., 2013a; Li et al., 2013b; Sakoglu et al., 2010). Most recent time-varying brain connectivity studies with sliding time-windows correlation analysis in R-fMRI data have reported brain connectivity states (patterns) reoccurring over time and subjects identified by a k-means clustering algorithm (Allen et al., 2014), and eigenconnectivities which capture connectivity pairs with similar dynamics identified by principal component analysis (PCA) (Leonardi et al., 2013). However, topological metrics of the time-varying functional brain connectivity which may provide a quantified description of the dynamic mind-brain organization at a system level (Bassett and Gazzaniga, 2011; Fornito et al., 2013; Telesford et al., 2011) have been largely uninvestigated in both healthy controls (HCs) and patients with mental illness such as schizophrenia.

The aim of this study is to develop a framework for assessing dynamic graph properties of time-varying functional brain connectivity in R-fMRI data and apply it to HCs and SZs. This framework combines spatial ICA which is used to define nodes of brain graphs by decomposing the imaging data into functionally homogeneous brain regions (Abou-Elseoud et al., 2010; Kiviniemi et al., 2009; Yu et al., 2011a), sliding time-window correlation analysis which is used to estimate time-varying brain connectivity, and graph theory-based analysis which is used to evaluate dynamic graph metrics. Based on previous studies (Jones et al., 2012; Rottschy et al., 2012; Sakoglu et al., 2010; Wee et al., 2013), we predict that the dynamic properties of the time-varying brain graphs will differ from HCs to SZs. The

findings could provide new insights into the biomarker of schizophrenia about impaired brain performance. The novel framework reported in this study is generalizable to other works of exploring group differences in dynamic brain graphs.

2. Methods

2.1. Participants

82 (19 females) HCs (mean age: 37.7 ± 10.8 ; range: 19 - 62) and 82 (17 females) SZs (mean age: 38.0 ± 14.0 ; range: 18 - 65) participated in this study. Age of the subjects showed no significant group difference (two-sample t-test, $P = 0.87$). All participants provided written, informed consent according to the Mind Research Network institutional guidelines required by the Institutional Review Board at the University of New Mexico and were compensated for their participation. Schizophrenia was diagnosed according to DSM-IV-TR criteria on the basis of a structured clinical interview (First et al., 1995). All patients had chronic schizophrenia [Positive and Negative Syndrome scale, PANSS (Kay et al., 1987); positive score: 15.3 ± 4.8 , range 7-29; negative score: 15.1 ± 5.3 , range 8 - 29] and were prescribed a variety of psychoactive medications, including various combinations of first and second generation antipsychotics, selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors, benzodiazepines and anti-seizure medications. Healthy participants were free of any DSM-IV TR Axis I disorder or psychotropic medication and had no family history of Axis I disorders.

2.2. fMRI data acquisition

Participants were instructed to keep their eyes open during the scan and stare passively at a central fixation cross, and not to fall asleep for five minutes. All images were collected on a single 3-Tesla Siemens Trio scanner with a 12-channel radio frequency coil. T2*-weighted functional images were acquired using a gradient-echo EPI sequence with TE = 29 ms, TR = 2 s, flip angle = 75°, slice thickness = 3.5 mm, slice gap = 1.05 mm, field of view 240 mm, matrix size = 64×64, voxel size = 3.75 mm × 3.75 mm × 4.55 mm. Resting state scans consisted of F = 150 volumes.

2.3. Preprocessing

An automated preprocessing pipeline and neuro-informatics system developed at the Mind Research Network (Bockholt et al., 2010) was used to preprocess the fMRI data. INRIalign (Freire et al., 2002) was used to realign the images. Then the data were spatially normalized to the standard Montreal Neurological Institute (MNI) space, resampled to 3 mm × 3 mm × 3 mm voxels using the nonlinear (affine + low frequency direct cosine transform basis functions) registration implemented in SPM8 toolbox (<http://www.fil.ion.ucl.ac.uk/spm>), and smoothed using a Gaussian kernel with a small full-width at half-maximum of 5 mm to reduce spurious correlations in further analysis (van den Heuvel et al., 2008; Yu et al., 2013a; Zalesky et al., 2012).

2.4. Group ICA and postprocessing

Spatial group ICA (Calhoun and Adali, 2012; Calhoun et al., 2001; Calhoun et al., 2009b; Du and Fan, 2013) was performed on the fMRI data using the GIFT software (<http://>

mialab.mrn.org/software/gift). Subject-specific data reduction by principal component analysis (PCA) retained 120 (Erhardt et al., 2011) principal components (PCs) by preserving the variance higher than 99% using a standard economy-size decomposition (Gene H and Charles F, 1996). Reduced data for all 164 participants were then decomposed into 100 aggregate components. We chose the relatively high model order ICA as previous studies demonstrated that such models yield refined components which correspond to known anatomical and functional segmentations (Abou-Elseoud et al., 2010; Allen et al., 2011; Kiviniemi et al., 2009; Smith et al., 2009; Yu et al., 2011a). Based on the group level ICs, single subject ICs and related time courses were back-reconstructed (Calhoun et al., 2001; Erhardt et al., 2011). The Infomax ICA algorithm (Bell and Sejnowski, 1995) was repeated 10 times in ICASSO (<http://research.ics.aalto.fi/ica/icasso>) to estimate the reliability of the decomposition, and the resulting clusters were found to be compact (Figure S1 in supplementary). 48 independent components (ICs) were characterized as ICNs, as opposed to physiological, movement related, or imaging artifacts (ARTs). The components were evaluated based on expectations that ICNs should exhibit peak activations in grey matter, low spatial overlap with known vascular, ventricular, motion, and susceptibility artifacts, and should have time courses (TCs) dominated by low-frequency fluctuations (Cordes et al., 2000). For an example of the noise components see Figure S2; for an example of ICN components see Figure S3 in Supplementary. Following (Allen et al., 2014), TCs of the 48 ICs underwent additional postprocessing including: 1) detrending linear, quadratic, and cubic trends, 2) multiple regression of the 6 realignment parameters and their temporal derivatives, 3) removal of detected outliers, and 4) band-pass filtering with frequency band [0.01 – 0.10 Hz]. We evaluated whether the regression of head motion should be performed prior to or post ICA. The results showed that doing it post ICA may correct the motion just as well as doing it prior to ICA, while having the benefit of not disrupting the spatial information (Damaraju et al., 2014).

2.5. Stationary and dynamic brain connectivity

For each subject, an $N \times N$ ($N = 48$ ICNs in this study) weighted stationary connectivity brain graph is firstly built using the entire scan time. The weighted network approach allows the connection between two ICNs to be a continuous measure ranging from 0 to 1. The first step is to calculate the Pearson correlation of TCs between all pairs of ICNs, r_{ij} . To distinguish between positive and negative correlations, we do not use the absolute value of the correlation, but compute a signed similarity measure defined as (Mason et al., 2009; Mumford et al., 2010; Yu et al., 2011a)

$$s_{ij} = \frac{r_{ij} + 1}{2}; \quad i=1, 2, \dots, 48; \quad j=1, 2, \dots, 48. \quad (1)$$

Thus a correlation of $r = -1$ has a similarity of $s = 0$, and a correlation of $r = 0$ has a similarity of $s = 0.5$. We do not use any threshold. The fully connected weighted brain graph is represented by the similarity matrix S .

Dynamic connectivity analysis is performed in each subject by applying a sliding time-window (with width of $L = 20$ TR slid in steps of 1 TR) approach. The TCs of the 48 ICNs are divided into temporal segments at each time point by getting $W = F - L + 1 = 131$ time

windows. Then, a $N \times N$ ($N = 48$) weighted brain graph is built using the similarity (**S**) matrix which is converted from correlation (**R**) matrix of time-windowed TCs according to equation (1). Thus, each subject has 131 time-varying brain graphs, $\mathbf{S}^w$, $w = 1, 2, \dots, 131$. Finally, graph metrics including connectivity strength, clustering coefficient, and global efficiency of $\mathbf{S}^w$ are calculated by the brain connectivity toolbox [<http://www.brain-connectivity-toolbox.net/>; for the related equations see (Rubinov and Sporns, 2010)]. To examine if the graph measures are equally dynamic over time in the two groups, Wilcoxon tests are performed to assess the equality of variances of the graph metrics across 131 time-varying brain graphs between 82 HCs and 82 SZs.

Here we use the window width of 20 TRs (40 s) because Shirer et al. reported that cognitive states may be correctly identified on as little as 30 – 60 s of data (Shirer et al., 2012), and another study showed that changes of brain connectivity are not sensitive to the specific time-window length (in the range of 10 – 20 TRs, 20 – 40 s) (Li et al., 2013b). In addition, Allen et al. found that a sliding window size of about 22 TRs (44 s) provided a good trade-off between the ability to resolve dynamics and the quality of connectivity estimation (Allen et al., 2014).

2.6. Connectivity states identification

Recent findings suggest that the variability in functional brain connectivity is hardly random. Fluctuations give rise to highly structured patterns of connectivity that emerge and dissolve over time which are called connectivity states (Allen et al., 2014; Cribben et al., 2012; Yang et al., 2014). Since this study focuses on graph properties of dynamic brain connectivity, we develop a new method to detect connectivity states at individual level and group level base on the graph metric 'connectivity strength'.

First level analysis is performed to identify connectivity states (functional connectivity patterns reoccurring over time) in each individual. Firstly, connectivity strength (cs_{nw}) of each ICN in each time-varying graph, $\mathbf{S}^w$, is computed to get a matrix, $\mathbf{CS}(N \times W)$, $N = 48$; $W = 131$.

$$cs_{nw} = \sum_{i=1}^{48} s_{in}^w; \quad n=1, 2, \dots, 48; \quad w=1, 2, \dots, 131. \quad (2)$$

To estimate how the brain connectivity patterns of different time windows are associated to each other, a new similarity matrix, **Scs**(131 × 131), is then computed based on correlations between each pair of columns of **CS**(48 × 131). Since modules of **Scs**(131 × 131) may correspond to sets of time windows with similar brain connectivity patterns, the modular organization of this similarity matrix, **Scs**(131 × 131), is analyzed with the modularity algorithm of (Newman, 2006) implemented in the brain connectivity toolbox. The number of modules of **Scs**, M , is the number of connectivity states in this subject. To test whether the modularity Q of **Scs** is significantly greater than that expected by chance, a matched random network **Scs_rand** is built using the Brute-Force Mean/Variance Matching algorithm introduced by (Zalesky et al., 2012) for each subject. A paired t-test (164 vs 164) suggests the real network **Scs** has higher ($P < 0.0001$) modularity Q value than the matched

random network **Scs_rand**. Finally, the similarity matrices [**S**(48 × 48)] of the time-windows which belong to the same module of **Scs** are averaged into one graph, **ST^m**(48 × 48) [$m = 1, 2, \dots, M$. M is the number of modules of **Scs**], which is the corresponding connectivity state. See Figure 1 for a pipeline of this analysis. The first level analysis identified $E = 554$ connectivity states in all 164 subjects (a range of 2 to 6 states per subject, totally 276 states in 82 HCs and 278 states in 82 SZs, see Results section).

A second level analysis (which may reveal connectivity patterns reoccurring over subjects) is performed to group the first level connectivity states which showing related connectivity patterns. Firstly, connectivity strength of each IC in each first level connectivity state is computed to get a matrix, **CSST**($N \times E$), $N = 48$, $E = 554$.

$$csst_{ne} = \sum_{i=1}^{48} st_{in}^e; \quad n=1, 2, \dots, 48; \quad e=1, 2, \dots, 554. \quad (3)$$

Then a new similarity matrix, **Scsst**(554 × 554), is computed based on correlations between each pair of columns of **CSST**(48 × 554). Following that, the modular organization of this similarity matrix, **Scsst**(554 × 554), is assessed. Finally, the similarity matrices of the first level connectivity states belonging to the same module are averaged into one graph, **STG**(48 × 48), which is the corresponding second level connectivity state. To test if the modularity Q of **Scsst** is significantly greater than expected by chance, 100 matched random networks **Scsst_rand** are built using the Brute-Force Mean/Variance Matching algorithm introduced by (Zalesky et al., 2012). Q value of the real network **Scsst** is higher than all of the 100 matched random networks **Scsst_rand**, thus the modularity Q value of **Scsst** is significantly higher than random network.

2.7. Graph properties of connectivity states and statistical analysis

Graph metrics including connectivity strength, clustering coefficient, and global efficiency of the brain graphs for connectivity states are calculated using the brain connectivity toolbox [for the related equations see (Rubinov and Sporns, 2010)]. Two sample two-tailed t-tests and permutation tests are performed to test for group differences in the graph measures.

3. Results

3.1. Group ICA and stationary connectivity

Figure 2A displays the spatial maps of the 48 ICNs identified with group ICA. Based on their anatomical and presumed functional properties, 48 ICNs are arranged into groups of auditory (AUD), somatomotor (SM), visual (VIS), cognitive control (CC; referring loosely to the planning, monitoring, and adapting one's behavior), default-mode (DM), and cerebellar (CB) components. ICNs are similar to those observed in previous high model order ICA decompositions (Abou-Elseoud et al., 2010; Allen et al., 2014; Allen et al., 2011; Kiviniemi et al., 2009), and some of them are corresponding to cognitive networks identified by meta-analyses (Amft et al., 2014; Balsters et al., 2013; Kohn et al., 2014; Rottschy et al., 2012). Figure 2B displays the stationary functional connectivity between ICNs, computed over the entire scan and averaged over subjects in each group. Patterns of the brain network

connectivity are consistent with prior literature, showing modular organization within sensory systems and default mode regions, as well as anticorrelation between these domains (Allen et al., 2014; Fox et al., 2005; Yu et al., 2011a). That SZs show lower connectivity is also consistent with previous studies (Liu et al., 2008; Lynall et al., 2010; Yu et al., 2011a; Yu et al., 2013b).

3.2. Dynamic graph properties and connectivity states

Figure S4 in the Supplementary shows the graph metrics including connectivity strength, clustering coefficient, global efficiency of the time varying brain connectivity (131 time windows) in all 164 subjects. Wilcoxon tests of the mean and permutation tests of the median are performed on the variances (across 131 time-windows) of the graph metrics. The results indicate that HCs show higher (all $P < 0.001$) variances in all three measures than SZs (see Figure 3). Figure S5 in the Supplementary shows the variance (across 131 time-windows) of the graph metrics in the number of connectivity states for HCs and SZs respectively.

In the first level analysis, a range of two to six connectivity states are identified in each subject, totaling 276 and 278 states in 82 HCs and 82 SZs respectively. A histogram of states counts (see Figure 4.), listed as the number of states (number of subjects with that number of states) are for HCs: 2(8), 3(43), 4(25), 5(5), 6(1); for SZs: 2(10), 3(34), 4(35), 5(2), 6(1). For the structure of each connectivity state in all subjects see Figure S6 in supplementary. In line with (Allen et al., 2014), one of the features that differs between connectivity states is that the connectivity within and between groups of the ICNs is different between states. For example, connectivity within SM, CC, DM components, between CC and DM is obviously different between state 1 and state 3 for subject HC04 [see Figure S2(B) in supplementary]. For graph properties of the states, HCs show higher (two-sample t-tests of the means and permutation test of the medians, $P < 0.001$) graph metrics (including connectivity strength, clustering coefficient, global efficiency) across the states (see Figure 5).

Only one connectivity state is identified by the second level analysis. For the modular organization of the matrix **Scsst**, see Figure S7 in the supplementary material. 271 first level connectivity states [155 in 75 HCs, 116 in 67 SZs] which are highly correlated to each other are averaged into the second level state. Comparing with HCs, fewer first level connectivity states are associated with the second level connectivity state in SZs. First level connectivity states counts, listed as the number of states (number of subjects with that number of states), are for HCs: 0(7), 1(24), 2(29), 3(16), 4(5), 5(1), mean, 1.8901; for SZs: 0(15), 1(36), 2(17), 3(10), 4(4), mean, 1.4146 (permutation test for a difference in means and medians: $P < 0.005$). HCs still showing higher (two-sample t-tests of the means and permutation tests of medians, $P < 0.01$) graph metrics when comparing the 155 states in HCs with 116 states in SZs. For the structure and graph metrics of the second level connectivity state see Figure 6. It is obvious that the pattern of the second level connectivity state resembles the stationary connectivity pattern by visually comparing Figure 2(B) and Figure 6(B).

4. Discussion

In this study, dynamic graph properties of time-varying functional brain connectivity in HCs and SZs in R-fMRI data are characterized. Nodes of brain graphs are defined with brain ICNs detected by group spatial ICA. Dynamic weighted brain graphs are established by sliding time-window correlation analysis. Graph metrics including connectivity strength, clustering coefficient, and global efficiency of the dynamic brain connectivity are computed. First level and second level connectivity states are detected based on correlation of nodal connectivity strength between dynamic brain graphs. Results demonstrate that dynamic graph metrics showing higher variances in HCs than in SZs; graph metrics of the connectivity states are decreased in SZs; fewer first level connectivity states associated with the second level connectivity state which resemble the stationary connectivity pattern. All findings suggest that the dynamic graph properties of time-varying functional brain connectivity are altered in schizophrenia which provide new potential biomarkers for this mental illness. This work presents a novel framework to assess dynamic brain graphs in R-fMRI data.

Because of the vast amount and small measurement of scale of neurons, it is challenging to construct a whole brain network on the neuronal level (de Reus and van den Heuvel, 2013). Functional brain connectivity networks in fMRI data are often formed on a macroscopic scale based on connections between large-scale brain regions. Parcellation approaches for defining brain network nodes include using predefined anatomical templates such as automated anatomical labeling (AAL) (Liu et al., 2008; Lynall et al., 2010; Tzourio-Mazoyer et al., 2002), randomly generated templates (Fornito et al., 2010; Hagmann et al., 2008) and voxel-based divisions (Buckner et al., 2009; Eguiluz et al., 2005). Quantitative measures of topological properties of brain graphs may be significantly modulated by the approach (de Reus and van den Heuvel, 2013; Fornito et al., 2013). Prior work has shown a detriment to network estimation when using atlas-based regions of interest (ROIs) as graph nodes (Craddock et al., 2012; Shirer et al., 2012; Smith et al., 2011). In addition, the ROIs do not necessarily respect the functional boundaries of the human brain nor do they reflect individual subject differences. In contrast, ICA provides a data-driven, natural approach to construct networks by defining brain components as functionally homogeneous nodes (Calhoun et al., 2012; Sui et al., 2013; Yu et al., 2011a; Yu et al., 2011c). Consistent with previous studies which also define the network nodes using independent spatial brain components (Allen et al., 2014; Allen et al., 2011; Yu et al., 2011a), the stationary brain connectivity of this study is showing modular organization within auditory, somatomotor, visual, cognitive control, and default mode regions, as well as anticorrelation between default mode and task-positive ICNs (see Figure 2B).

Beyond the static functional brain connectivity, we evaluate the dynamic topological metrics of time-varying brain graphs built using sliding time-window correlation analysis which is the most commonly used strategy for examining dynamics of brain connectivity in R-fMRI data (Fu et al., 2013; Hutchison et al., 2013a). Using this approach, recent studies have shown altered temporal dynamics of the brain connectivity in a number of clinical populations. For example, (Jones et al., 2012) investigated dynamic modular architecture of brain networks in Alzheimer's disease. (Sakoglu et al., 2010) studied auditory oddball

(AOD) task-modulation of dynamic FNC in schizophrenia. (Wee et al., 2013) performed this method for early mild cognitive impairment (eMCI) identification. However, these studies do not compute the dynamic graph metrics which quantifiably describe the dynamic whole brain performance. Here we reveal that the variances of the dynamic graph metrics of time-varying brain connectivity are decreased in SZs, suggesting the altered dynamic performance of the brain graphs in schizophrenia. This finding is consistent with a previous study (Rottschy et al., 2012) which found that the connectivity states of HCs switch more often than patients with schizophrenia, suggesting that SZs tend to linger in a state of “weak” and relatively “rigid” connectivity, while HCs dynamically switch between different connectivity states and are therefore probably faster in recruiting necessary resources in the face of changing task demands. Recent works have indeed demonstrated the association between network flexibility and cognitive task performance (Garrett et al., 2013; Madhyastha et al., 2014; Spreng and Schacter, 2012; Thompson et al., 2013a). And other studies show a decrease in task-related changes in brain connectivity [AOD task vs Sternberg working memory task (Calhoun et al., 2006); rest vs AOD task (Yu et al., 2013a)]. To our knowledge, this is the first study to characterize the variance of the dynamic graph measures in time-varying fMRI brain connectivity. The findings provide a new perspective on schizophrenia, showing for the first time about disrupted dynamic graph properties of brain connectivity in schizophrenia which enrich our knowledge about the functional brain dynamics in this disease (van den Heuvel et al., 2013), and underscore the importance of evaluating dynamic changes of brain connectivity.

Prior studies which have questioned the time-varying changes of functional brain connectivity suggest that the variations of the connectivity are not noise but reflect meaningful dynamic properties (Keilholz et al., 2013; Thompson et al., 2013b; Thompson et al., 2014). Particularly, some highly structured, and quasi-stable connectivity patterns reoccurring over time could be assessed as a finite number of so called “connectivity states” (Allen et al., 2014). Recent studies have used k-means clustering (Allen et al., 2014) and hierarchical clustering (Yang et al., 2014) algorithms to detect the connectivity states. Since the aim of the current study is to characterize the graph properties of the time-varying brain connectivity, we implement a new approach with computing the correlation of nodal connectivity strength across 48 nodes between dynamic brain graphs to detect the connectivity states. This technique could identify the connectivity patterns with similar graph organization that reoccurring over time (and subjects) and assemble them into connectivity states. To make sure that the time-varying brain connectivity is distinct from noise, Kwiatkowski-Phillips-Schmidt-Shin (KPSS) tests are performed on the graph metrics of the 554 first level connectivity states. The result that all three P values are less than 0.01 suggesting that the brain connectivity is indeed non-stationary. By comparing the graph metrics of the 276 states in 82 HCs and 278 states in 82 SZs, we also replicate prior findings about decreased graph measures in schizophrenia (Bassett et al., 2012; Liu et al., 2008; Lynall et al., 2010). These findings extend the dysconnectivity hypothesis (Friston and Frith, 1995; Stephan et al., 2006; Volkow et al., 1988; Weinberger et al., 1992) in schizophrenia from stationary connectivity to dynamic connectivity.

Along with the accumulation of dynamic functional connectivity studies, the relationship between the findings of stationary connectivity in previous studies and the findings of

dynamic connectivity in recent studies is an open question. Using a k-means clustering method, (Allen et al., 2014) estimated 7 connectivity states. State 1 which resembles the stationary connectivity pattern emerges most frequently (accounting for > 30%) in the dynamic connectivity and all other states are observed much less frequently (ranging between 7% and 15%). In this study, only one second level connectivity state is established which shows the similar connectivity pattern as the stationary connectivity (see Figure 2B and Figure 6B). $271/554 = 48.9\%$ of first level connectivity states is associated with the second level connectivity state also suggesting that the stationary-connectivity-like pattern emerges most in the dynamic connectivity. When comparing the two groups, it shows that significantly fewer first level connectivity states (emergence in less SZs; $155/276 = 56.16\%$ states emergence in $75/82 = 91.46\%$ HCs VS $116/278 = 41.73\%$ states emergence in $67/82 = 81.70\%$ SZs) are associated with the second level connectivity state, indicating that more dynamic connectivity patterns are not reflected well in the stationary connectivity in SZs. The results imply a disrupted relationship between stationary connectivity and dynamic connectivity in schizophrenia, providing further evidences for the altered dynamic brain graphs in this disease.

A few methodological limitations should be noted in this work. First and foremost, the patients in this study were taking medications, thus drug effects cannot be distinguished from the findings. Recent studies have revealed effects of antipsychotics on both brain structure and function (Fusar-Poli et al., 2013). And the effect of antipsychotics on brain resting cerebral blood flow (rCBF) starts immediately and can be detected after a single dose (Handley et al., 2013), though drug-induced changes in functional brain connectivity have so far only been rudimentarily explored (Nejad et al., 2012). We note that the effects of antipsychotic medication could be computed by antipsychotic dose equivalency measures (Andreasen et al., 2010; Leucht et al., 2014; Patel et al., 2013). Unfortunately, we do not have the full information on medicine dose of the patients in this dataset, so it is not possible to evaluate the relationship between medication and the computed measures. Future studies can control the medication effects by performing the analysis on unaffected first-degree relatives of schizophrenia patients (Meda et al., 2012).

Another concern is that when building brain networks, r values are linearly transformed to s values. The advantage of doing this rather than using absolute of r is that negative r can be separated from positive r (in s values, $0 - 0.5$ vs $0.5 - 1.0$). However there are some potential issues in those values near 0 correlation are upweighted to 0.5 and values near -1 are downweighted to near 0. In order to ensure that the results are not highly sensitive to the r to s transformation, we repeated the analysis using the absolute value of r . Results are highly similar to our reported finding in that HCs show higher variance across 131 time windows for all three graph metrics (Wilcoxon tests: $P < 0.01$). HCs also showing higher values for all three metrics of first level connectivity states (two-sample tests: $P < 0.001$).

When doing group ICA, The number of components 100 is selected based on recent papers showing the benefit of higher model orders approaches which parcellate the brain into finer networks while also preserving the structure that is observed at the lower models (Abou-Elseoud et al., 2010; Abou Elseoud et al., 2011; Allen et al., 2012). However, the concern of sensitive to model order is important. To ensure our results are not highly sensitive to the

specific number of components, we change the number 100 to 90, 110 and re-run the whole analysis. 41 and 53 ICNs are determined from 90 and 110 brain components respectively. We get similar results from both runs. For the structure of stationary functional connectivity of each group see Figures S8, S9 in the supplementary. For dynamic connectivity, HCs showing higher variance across 131 time windows for all three graph metrics (Wilcoxon tests: $P < 0.005$). HCs showing higher values for all three metrics in first level connectivity states (two-sample t-tests: $P < 0.0001$). Only one second level connectivity state is identified (see Figures S10, S11 in supplementary for the modular organization of the matrix Scsst in each run). For the analysis of 90 components, 157 first level states in HCs and 111 first level states in SZs are associated with the second level connectivity state. For the analysis of 110 components, 160 first level states in HCs and 108 first level states in SZs are associated with the second level connectivity state.

We also test the reliability of the analysis using different lengths of time-window. Firstly, we change the time-window length from 5 to 60 TRs (in step of 1 TR) and compute the brain connectivity. Consistent with previous studies (Allen et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013b), shorter time-window results in lower number of significant correlations in brain connectivity matrix (See Figure S12 in supplementary); larger windows reduce variability (See Figure S13 in supplementary). 20 TRs length provides a good trade-off between the ability to resolve dynamics and the quality of correlation matrix estimation (Allen et al., 2014). We also repeat the whole analysis using time-window length with 25 TRs and 30 TRs. We receive similar results in both runs. HCs showing higher variance across time windows for all three graph metrics (Wilcoxon tests: $P < 0.001$). HCs showing higher values for all three metrics of first level connectivity states (two-sample t-tests: $P < 0.0001$). Just one second level connectivity state is identified in each run. For the modular organization of the matrix Scsst for the two analyses see Figures S14, S15 in supplementary. When doing the analysis of 25 TRs length, 147 first level states in HCs and 121 first level states in SZs are associated with the second level connectivity state; when doing the analysis of 30 TRs length, 147 first level states in HCs and 111 first level states in SZs are associated with the second level connectivity state.

Moreover, we note that the second level analysis may also be executed in HCs and SZs separately. We do perform the second level analysis on 276 first level states in HCs and 278 first level states in SZs respectively. The modular organization (see Figure S16 in the supplementary) of the matrix Scsst(276×276) for HCs and Scsst(278×278) for SZs is revealed to be similar to the Scsst(554×554) for the whole sample. The results suggest that the findings of second level analysis are robust.

Similar to (Allen et al., 2014), this study built dynamic brain graphs by time-varying edges (connections) while keeping nodes as static. Spatial ICA is performed based on the assumption that the structure of ICNs remains relatively constant over time. However, a previous work (Kiviniemi et al., 2011) has reported substantial spatial dynamics when doing sliding time window ICA, though that study used low model order ICA decompositions (on average 15 components). In addition, a more recent study (Ma et al., 2014) demonstrated time-varying spatial brain connectivity in HCs and SZs using independent vector analysis (IVA). In contrast with our finding that patients show lower variation of the dynamic graph

metrics, that work found significantly more fluctuations of spatial concordance in schizophrenia. Further studies may develop new approaches to characterize dynamic brain graphs with both time-varying nodes and time-varying edges.

Finally, though altered time-varying brain graphs in schizophrenia are discovered in this work, the biological basis is not clear. Future work may consider multimodal approaches to explore the underlining mechanisms. For example, concurrent EEG-fMRI may provide electrophysiological substrates (Bridwell et al., 2013; Cabral et al., 2013; Mulert, 2013); combination of fMRI and arterial-spin-labeling (ASL) perfusion contrasts data may determine the relationship between dynamic brain connectivity and blood flow supply (Liang et al., 2013); anatomical foundations of dynamic functional connectivity may be observed by combining structural MRI and fMRI (Hermundstad et al., 2013; Rehme et al., 2012; van den Heuvel and Sporns, 2013).

5. Conclusions

In summary, this work develops an approach for computing dynamic graph properties of time-varying functional brain connectivity in which nodes are static ICNs detected by group spatial ICA in HCs and SZs. Patients show lower variances of the graph metrics including connectivity strength, clustering coefficient, and global efficiency over time. The measures of first level connectivity states are decreased in SZs. Second level analysis demonstrates that more connectivity states in SZs are deviate from the pattern of stationary connectivity computed by the whole scan time series. The findings provide insights into the altered dynamic brain graphs in schizophrenia which may underscore the disrupted system-level dynamic brain performance in this disease. Moreover, this study provides a novel framework for characterizing dynamic brain graphs in R-fMRI data which may be employed to detect biomarkers of more mental illnesses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The flowchart of the algorithmic pipeline for the first level connectivity states analysis. Five steps are labeled as follows. ① do group ICA, segment ICA time courses, and calculate the correlation between any pair of ($N = 48$) ICs for each time-window; ② compute nodal connectivity strength of the weighted brain graph for each time-window; ③ calculate the correlation of nodal connectivity strength between any pair of time-windows ($W = 131$) across ($N = 48$) ICs; ④ reorder the time-windows based on the modular organization of the correlation matrix; ⑤ compute the brain connectivity states by averaging the connectivity matrices of the time windows belonging to the same module. (Figure ② used by permission from Allen et al., 2012)

Figure 2.

Spatial maps (A) of 48 ICNs and the stationary functional connectivity (similarity S matrix) between them (B) in HC group and SZ group. ICNs are divided into groups and arranged based on their anatomical and functional properties. Functional connectivity is averaged over all subjects in each group. (AUD: auditory; SM: somatomotor; VIS: visual; CC: cognitive control; DM: default mode; CB: cerebellar)

Figure 3.

Variances of the graph metrics of time-varying brain connectivity (over 131 time-windows). The mean and bootstrapped 95% confidence interval are in red, as well as a boxplot and smoothed density histogram. HCs show higher variances (Wilcoxon and permutation tests, $P < 0.001$ for all three metrics).

Figure 4.
Histogram of first level connectivity states counts: Number of subjects with a certain number of state identified.

Figure 5.

Distribution of Connectivity Strength, Clustering Coefficient, Global Efficiency across first level connectivity states (276 states in HCs and 278 states in SZs). The mean and bootstrapped 95% confidence interval are in red, as well as a boxplot and smoothed density histogram. HCs show higher values of the metrics (two-sample t- and permutation tests, $P < 0.001$ for all three measures).

Figure 6. Schematic connectivity pattern (A; node size indicates nodal connectivity strength; edge threshold = 0.65), structure (B), and distribution of graph metrics (C; mean and bootstrapped 95% confidence interval are in red, as well as a boxplot and smoothed density histogram) for the 155 and 116 first level connectivity states which are associated with the second level connectivity state in HCs and SZs respectively. First level connectivity states showing

higher mean values of the graph measures in HCs (two-sample t-tests and permutation tests, $P < 0.01$).