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# Altered spatial and temporal concordance among intrinsic brain activity measures in schizophrenia

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ABSTRACT

Various data-driven voxel-wise measures derived from resting-state functional magnetic resonance imaging (rs-fMRI) have been developed to characterize spontaneous brain activity. These measures have been widely applied to explore brain functional changes in schizophrenia and have enjoyed significant success in unraveling the neural mechanisms of this disorder. However, their spatial and temporal coupling alterations in schizophrenia remain largely unknown. To address this issue, 88 schizophrenia patients and 116 gender- and age-matched healthy controls underwent rs-fMRI examinations. Kendall's W was used to calculate volume-wise (across voxels) and voxel-wise (across time windows) concordance among multiple commonly used measures, including fractional amplitude of low frequency fluctuations, regional homogeneity, voxel-mirrored homotopic connectivity, degree centrality and global signal connectivity. Inter-group differences in the concordance were investigated. Results revealed that whole gray matter volume-wise concordance was reduced in schizophrenia patients relative to healthy controls. Although two groups showed similar spatial distributions of the voxel-wise concordance, quantitative comparison analysis revealed that schizophrenia patients exhibited decreased voxel-wise concordance in gray matter areas spanning the bilateral frontal, parietal, occipital, temporal and insular cortices. In addition, these concordance changes were negatively correlated with onset age in schizophrenia patients. Our findings suggest that the concordance approaches may provide new insights into the neural mechanisms of schizophrenia and have the potential to be extended to neuropsychiatric disorders.

## 1. Introduction

The human brain is a complex and dynamic system, the basal metabolism of which accounts for nearly 20% of the total body energy consumption, highlighting the importance of characterizing resting-state spontaneous brain activity (Raichle, 2006; Raichle and Mintun, 2006). Brain function can be examined *in vivo* by using a variety of non-invasive neuroimaging techniques. Among them, resting-state functional magnetic resonance imaging (rs-fMRI) has shed lights on the spatiotemporal organization of spontaneous brain activity by measuring the blood-oxygen-level-dependent (BOLD) contrast in the absence of a task or stimulus (Biswal et al., 1995; Fox and Raichle, 2007). Currently rs-fMRI still serves as a brain mapping approach with the best trade-off between temporal (seconds) and spatial (millimeters) resolutions to delineate the human neural functional architecture. Two fundamental approaches to analyzing rs-fMRI data have been widely used to study the rich structure of intrinsic brain activity from the perspective of functional connectivity: seed-based correlation analysis and independent component analysis (Cole et al., 2010). The former estimates the correlation between activity in an *a priori* seed region and that in other regions (Biswal et al., 1995; Fox et al., 2005; Greicius et al., 2003); the latter identifies the spatial distribution of distinct functional connectivity networks based on statistical patterns in their dynamic time series (Damoiseaux et al., 2006; van de Ven et al., 2004). In addition, the application of graph theoretical approaches has provided a powerful tool to characterize topological properties of complex brain networks on a whole brain scale (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011; He and Evans, 2010), and human brain networks have been found to have an optimum small-world topology (a high local specialization and a high global integration) through these approaches (Watts and Strogatz, 1998).

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Despite different definitions, various data-driven voxel-wise measures based on rs-fMRI have been proposed to reveal distinct aspects of spontaneous brain activity (Margulies et al., 2010; Zuo and Xing, 2014). To describe the local characteristics of a single voxel, a measure of amplitude of low-frequency fluctuation (ALFF) (Zang et al., 2007) that calculates the voxel-wise magnitude of specific frequency bands in the frequency domain and its normalized version, fractional ALFF (fALFF) (Zou et al., 2008), have been developed; by virtue of the assumption that neighboring voxels within a functional brain region synchronize their metabolic activity under certain conditions, Zang proposed regional homogeneity (ReHo) to measure the functional coherence of a given voxel with its nearest neighbours (Zang et al., 2004). These local measures are conceptually and practically straightforward, and have been widely employed to explore brain functional changes in schizophrenia (Chen et al., 2013; He et al., 2013; Hoptman et al., 2010; Huang et al., 2010; Liu et al., 2006; Ren et al., 2013; Turner et al., 2013; Xu et al., 2015; Yu et al., 2013, 2014). To depict the relational characteristics among multiple voxels, graph theory-based degree centrality (DC) is receiving substantial attention and this measure reflects the centrality or functional importance of a given voxel by assessing its relationship with the entire functional network, allowing researchers to capture the complexity of the functional connectome as a whole (Buckner et al., 2009; Tomasi and Volkow, 2010; Zuo et al., 2012); the emergence of voxel-mirrored homotopic connectivity (VMHC) has made it feasible to quantify the functional connectivity between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere (Anderson et al., 2011; Zuo et al., 2010b); since global signal has been shown to be a source of neural information (Power et al., 2017; Scholvinck et al., 2010; Yang et al., 2014; Zhu et al., 2018), global signal connectivity (GSC), computed as the voxel-wise functional connectivity of the global signal, may be of functional relevance and serve as a tool for studying clinical population (Hahamy et al., 2014). These relatively complex measures have also been broadly applied to the study of schizophrenia and have enjoyed significant success in unraveling the neural mechanisms of this disorder (Chen et al., 2015; Guo et al., 2014, 2015; Hahamy et al., 2014; Hoptman et al., 2012; Li et al., 2015; Tomasi and Volkow, 2014; Wang et al., 2014, 2017; Zhu et al., 2017; Zhuo et al., 2014).

Given that spontaneous fluctuations are a hallmark of neural signals, it is natural to expect that human brain will dynamically integrate, coordinate and respond to internal and external stimuli across multiple time scales. Therefore, rs-fMRI measurements assuming spatial and temporal stationarity throughout the whole resting-state scan period cannot capture the full extent of spontaneous brain activity. Since the initial work focused on dynamic functional connectivity analysis (Chang and Glover, 2010; Sakoglu et al., 2010), a consequent body of rs-fMRI research has rapidly blossomed to investigate the variation of rs-fMRI measures over time and capitalize on the wealth of information contained within the time-varying features of intrinsic brain activity (Calhoun et al., 2014; Hutchison et al., 2013; Preti et al., 2017). Benefiting from the advantages of dynamic analysis, schizophrenia has been the most widely studied condition at the current stage, offering us sufficient material to improve understanding of this disorder. Multiple dynamic approaches involving both local and relational measures have been used to help interpreting distinct aspects of schizophrenia (Damaraju et al., 2014; Du et al., 2016, 2017; Fu et al., 2018; Rashid et al., 2016), going beyond the stationary characterization.

Recently, Yan et al. provided a comprehensive examination of the spatial (volume-wise concordance) and temporal (voxel-wise concordance) coupling relationships among these aforementioned rs-fMRI measures (Yan et al., 2017). They found that these measures show a high degree of covariation and the concordance shows stable inter-individual difference and correlates with age, suggestive of a functional significance. Since schizophrenia patients exhibit abnormalities in static and dynamic brain activity characterized by alterations in multiple rs-fMRI measures, we hypothesized that concordance among these measures would be disrupted in schizophrenia.

## 2. Materials and methods

### 2.1. Participants

Data used in preparation of this article were obtained from the SchizConnect database (http://schizconnect.org). As such, the investigators within SchizConnect contributed to the design and implementation of SchizConnect and/or provided data but did not participate in analysis or writing of this report. Within the SchizConnect database, we used a search query to identify datasets that included: (1) schizophrenia patients diagnosed using the structured clinical interview for DSM-IV (SCID) and healthy controls screened according to the DSM-IV criteria, the age range of whom went from 20 to 60; (2) resting-state fMRI and high-resolution T1-weighted images collected on 3.0-T MR systems; (3) demographic and clinical information. This resulted in two available datasets, one from the Center of Biomedical Research Excellence (COBRE) data repository and the other from the Neuromorphometry by Computer Algorithm Chicago (NMorphCH) data repository. The sample included ninety-six schizophrenia patients and 120 healthy controls. Severity of psychotic symptoms was assessed in patients using Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) in the COBRE dataset, and using the Scale for Assessment for Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for Assessment for Negative Symptoms (SANS) (Andreasen, 1989) in the NMorphCH dataset. Onset age, duration of illness and antipsychotic medication usage operationalized as the chlorpromazine (CPZ) equivalents (Leucht et al., 2014; Woods, 2003) were available for patients in the COBRE dataset. Written informed consent was obtained from all participants, and the studies were approved by the regional ethics committees.

### 2.2. MRI data acquisition

The COBRE data were collected using a 3.0-T MR scanner (Trio Tim; Siemens) and specific information regarding the acquisition parameters was available in a previous study (Cetin et al., 2014). High resolution T1-weighted structural images were acquired using a five-echo MPRAGE sequence with the following parameters: repetition time (TR) = 2530 ms; echo time (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms; inversion time (TI) = 1200 ms; flip angle (FA) = 7°; field of view (FOV) = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; 192 sagittal slices. Resting-state fMRI images were acquired using a gradient-echo echo planar imaging (GRE-EPI) sequence with TR/TE = 2000/29 ms; FA = 75°; FOV = 240 mm × 240 mm; matrix = 64 × 64; slice thickness = 3.5 mm; gap = 1.05 mm; 33 interleaved transverse slices; 150 volumes.

The NMorphCH data were also collected using a 3.0-T Siemens Trio Tim scanner. T1-weighted images were acquired using a MPRAGE sequence with the following parameters: TR/TE/TI = 2400/3.16/1000 ms; FA = 8°; FOV = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; 176 sagittal slices. Resting-state fMRI had two scanning protocols, which were both acquired using a GRE-EPI sequence. Protocol 1 was available for 28 patients and 26 controls with TR/TE = 2200/27 ms; FA = 90°; FOV = 256 mm × 256 mm; matrix = 64 × 64; slice thickness = 4 mm; no gap; 36 interleaved transverse slices; 164 volumes. Protocol 2 was available for 15 patients and 16 controls with TR/TE = 2500/20 ms; FA = 80°; FOV = 220 mm × 206 mm; matrix = 128 × 120; slice thickness = 3 mm; no gap; 40 interleaved transverse slices; 164 volumes.

### 2.3. fMRI data preprocessing

Resting-state BOLD data were preprocessed using Statistical Parametric Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing & Analysis for Brain Imaging (DPABI, http://rfmri.org/dpabi) (Yan et al., 2016). The first 5 volumes for each participant were discarded to allow the signal to reach equilibrium and the