APPLICATION OF REGION EFFICIENCY INDEX IN FUNCTIONAL CONNECTIVITY ANALYSIS OF SCHIZOPHRENIA

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SUMMARY

Background: *Functional connections (FCs) methodology based on functional MRI data is an effective lever to investigate macroscopic neural activity patterns underlying critical aspects of cognition and behavior in schizophrenia (SZs). Dysconnectivity hypothesis are important features of SZs. However, region properties of brain network have been less investigated by special markers of graph indexes in general mental disorders.*

Subjects and methods: *Region efficiency index are introduced to explore the information integration capacity among different regions and subsystems. The important process is to uncover noticeable edge weight and region efficiency of FCs in 67 healthy controls and 53 chronic schizophrenia (SZs) patients.*

Results: *Forty-five abnormal edges with significant P-values of FCs weight scores are discovered. There is abnormal thalamic-cortical FCs in SZs. Importantly, hippocampus L, hippocampus R, and parahippocampal gyrus L are endowed with significantly different node efficiency scores in SZs patients. The scores of hippocampus L is consistent with motor retardation, lack of judgment and insight, and poor impulse control.*

Conclusions: *Though strict contrastive study, it can be infer that the brain information integration is dysfunction in schizophrenia. Meanwhile, it is worth stressing that efficiency is a meaningful biological marker to excavating schizophrenic psychopathology.*

Key words: *resting-state functional MRI - functional connectivity - efficiency - chronic schizophrenia*

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INTRODUCTION

Schizophrenia (SZs) is a severe and chronically psychiatric disorder of high heritability (Murray et al. 2015). The endophenotype and mechanisms of SZs are unclear. The SZs patients are diagnosed by psychotic features of positive, negative and cognitive deficits symptoms (Schultz & Andreasen 1999, Freedman 2003). The main psychosis treatment for SZs patients is prone to antipsychotic medication, which apace mitigate positive symptoms, fail to significantly improve negative symptoms and cognitive dysfunction behaviors however (Vieweg et al. 1995, Buchanan 2007). Due to the inherently unsatisfactory efficacy, designing new objectively diagnostic methods and searching the disease regions in neuropathology are burning questions about SZs (Neméth et al. 2017).

As a complex system, the brain can be modeled as a connectome of nodes and edges graphically (Sporns et al. 2004). Functional MRI, a non-invasive technique, detects brain activity by measuring the associated changes in blood flow to study brain anatomy. Functional connections (FCs) provide a framework in which to explore the multivariate matrix of functional interactions between brain regional signals, where subject can be defined as a network whose nodes are brain regions. The edges are FCs, represented coordinated spontaneous oscillations in the rate of neuronal activity of local regions (Bassett et al. 2012).

The researches of neuropathology and pathophysiology of schizophrenia generally, and functional neuro-imaging particularly, have highlighted a number of anatomical structures and widespread dysfunctional results in SZs patients (Boyer et al. 2007, Byne et al. 2009). The patient has an enlarged ventricle. In generally, there are reduced gray matter volumes, aberrant activity and dysconnectivity characteristics along with dispersed cortical regions. As a physical brain dysfunction, schizophrenia do not solely arise from isolated damage of one or a few local brain cortices; rather, it is likely the predominant product of pathological alterations distributed throughout interconnected neural systems (He et al. 2007). A long-term goal is devote to find the disease roots on dysfunctional circuit wirings at mesoscopic nerve tract links, or dysfunctional connections at macroscopical brain regions, for developing new drugs or other therapeutic scheme on these meso or macro-connections.

Advances in network science and graph theory have improved our ability to study the spatial and topological organizational layout of neural connectivity maps in detail (Bassett & Sprons 2017). The graph theory method address aberrant topological properties of brain network (Bassett et al. 2012, Sporns et al. 2005). In order to searching disease roots by fMRI data, the aim of this work is to introduce the graph index - efficiency, and propose one feasible method to locating the diseased cortex ground on FCs in SZs. In particular, regional efficiency of quantifies a concrete measure of the importance of each node with all other connected nodes in brain network. Therefore, regional efficiency for testing the destroyed information integration and separation characteristic in FCs of SZs

Constructed the correlation matrix and quantified efficiency index (i.e., RE-scores), the research scheme is divided into edge FCs weight and region efficiency analyses. Investigated predominantly the abnormalities of overall whole brain edge attributes, corresponding 45 abnormal edges with distinct P-values of FCs weight scores are found. There are cortico-thalamic and hippocampus-thalamic dysconnections in SZs patients. Importantly, node efficiency analysis based on FCs suggests that the HIP and PHG has significant abnormal scores. It implicates THA, HIP, and PHG deficits come with diseases can contribute to connection problems in the cortex, and cognitive deficits to the psychosis diagnosed in SZs.

SUBJECTS AND METHODS

Demographic features and clinical symptoms

The dataset (including 72 chronic SZs and 67 healthy controls (HCs)) is collected from the center for Biomedical Research Excellence-COBRE, chronic (Mayer et al. 2013). Functional scans under resting-state conditions from 53 chronic SZs and 67 HCs are included in this study. All patients are identified according to the DSM-IV diagnostic criteria (First et al. 2015) by qualified psychiatrists utilizing all available clinical symptoms including a diagnostic interview, clinical case notes, treating clinician's observations and informant reports. Symptom severity is measured using the positive and negative syndrome scale (PANSS) assessment (Kay et al. 1987), which is given to all patients either one week before the MRI scan or one week after it. Exclusion criteria included the presence of other DSM-IV disorders, the history of substance abuse; and the clinically significant head trauma. All HCs are assessed in accordance with DSM-IV criteria as being free of SZs and other Axis I disorders and none has any neurological diseases, suffer from clinically significant head trauma or has a history of substance dependence. Written informed consent was obtained from all individual participants, and research procedures and ethical guidelines are followed in accordance with the Institutional Review Boards (IRB) of the USA. All participants provide written informed consent prior to entering the study. Details of the acquisition of the dataset is provided below (Table 1).

Imaging acquisition and data preprocessing

All the imaging data were acquired using a 3-T Siemens Trio Tim MRI scanner with a twelve channel phased array head coil. Rest-state data are collected with single-shot full k-space echo-planar imaging with ramp sampling correction using the inter commissural line as a reference (TR: 2 s, TE: 29 ms, matrix size: 64×64, 32 slices, voxel size: 3×3×4 mm^3). A multi-echo MPRAGE sequence is used with the following parameters: TR/TE/TI=2530/(1.64, 3.5, 5.36, 7.22, 9.08)/900 ms, FOV=256×256 mm^2, flip angle =7°, slab thickness = 176 mm, matrix =256×256×176, voxel size= 1×1×1 mm^3, pixel bandwidth =650 Hz, number of echos is 5, total scan time = 6 min. With five echoes, the TR, TI and time to encode partitions for the MEM-PR are similar to that of a conventional MPRAGE, resulting in similar GM/WM/CSF contrast.

For all fMRI data, first 10 volumes are discarded to allow for scanner stabilization and subjects' adaptation to the environment. The fMRI data preprocessing is hence conducted by software Matlab 2016b, SPM8 and DPARSF. The remaining functional scans are first corrected for within-scan acquisition time differences between slices, followed by realignment to the middle volume to correct for inter-scan head motion. Subsequently, functional scans are spatially normalized to a standard template and resampled to 3×3×3 mm^3. After normalization, the BOLD signal of every voxel is first detrended to abandon linear trend and then pass through a band-pass filter (0.01-0.08 Hz) to reduce low-frequency drift and high-frequency physiological noise. Finally, nuisance covariates, including head motion parameters, global mean signals, white matter signals and cerebrospinal signals, are regressed out from the BOLD signals. After data preprocessing, a time series is extracted for each ROI region by averaging the signals of all voxels within that region.

Table 1. Data are delineated as the range of minimum-maximum (mean SD)

Variable	SZs (Mean±SD(range))	HCs (Mean±SD(range))	P-value
Sample size	53	67	
Gender(male/female)	42/11	46/21	0.1927[a]
Current age	36.75±13.6775(18-64)	34.8209±11.2841(18-65)	0.3978[b]
Handedness(Both/Right/Left)	1/42/10	1/65/1	0.0045[a]
Education (years)	13.2041±1.8255(10-20)	14.0200±1.8680(10-18)	0.0242[b]
Duration of current episode(years)	14.9434±11.9959(0-47)		
PANSS (Positive)	14.9434±4.6052(7-25)		
PANSS (Negative)	14.4340±5.2606(8-29)		
PANSS (General)	30.0755±8.2808(16-56)		

[a] the P-value is obtained by a two-tail Pearson Chi-square test; [b] the P-value is obtained using a two-sample two-tail T-test

Table 2. The special edges of different C-scores sequence are strictly selected when they satisfy the FDR correction P<0.05 in the dataset

- INS.L *versus* IFGoperc.R (P=0.0005, 0.2569/0.3855)
- CUN.L *versus* PCG.L (P=0.0004, 0.2701/0.1531)
- LING.L *versus* CUN.L (P=3.1469e-07, 0.4363/0.6156)
- LING.L *versus* CUN.R (P=7.5814e-05, 0.4565/0.6024)
- LING.R *versus* CUN.L (P=2.837e-05, 0.4405/0.5932)
- LING.R *versus* CUN.R (P=0.0001, 0.4864/0.62519)
- MOG.L *versus* PCG.R (P=0.0002, 0.1363/0.04369)
- FFG.R *versus* CUN.L (P=0.0003, 0.1264/0.2574)
- FFG.R *versus* CUN.R (P=0.0002, 0.1651/0.3051)
- PCUN.R *versus* SOG.R (P=0.0001, 0.2920/0.1657)
- CAU.L *versus* PHG.R (P=0.0001, 0.1135/0.0330)
- CAU.R *versus* PHG.L (P=0.0001, 0.1381/0.0460)
- PUT.L *versus* SMG.R (P=0.0001, 0.0938/0.2023)
- PUT.R *versus* SMG.R (P=2.0413e-05, 0.1507/0.2844)
- PAL.L *versus* PHG.L (P=0.0002, 0.2154/0.09520)
- PAL.L *versus* SMG.R (P=0.0002, 0.0607/0.1534)
- PAL.R *versus* PHG.L (P==0.0001, 0.1969/0.0744)
- PAL.R *versus* SMG.R (P=0.0003, 0.0944/0.1925)
- THA.L *versus* MFG.R (P=9.9037e-06, 0.0232/0.1195)
- THA.L *versus* HIP.R (P=0.0003, 0.2754/0.1493)
- THA.L *versus* PHG.L (P=3.8445e-05, 0.1964/0.0693)
- THA.L *versus* PHG.R (P=9.7401e-06, 0.1599/0.0443)
- THA.R *versus* MFG.R (P=1.8489e-06, 0.0392/0.1613)
- THA.R *versus* HIP.R (P=0.0004, 0.3236/0.1950)
- THA.R *versus* PoCG.L (P=0.0004, 0.1094/0.0326)
- HES.L *versus* THA.R (P=0.0004, 0.2227/0.1034)
- HES.R *versus* THA.R (P=0.0003, 0.2555/0.1245)
- STG.R *versus* PreCG.R (P=0.0005, 0.3123/0.4473)
- STG.R *versus* THA.L (P=0.0004, 0.1787/0.0692)
- STG.R *versus* THA.R (P=9.8737e-06, 0.2235/0.0808)
- TPOsup.L *versus* CAU.R (P=0.0004, 0.1656/0.07082)
- TPOsup.R *versus* IPL.R (P=0.0004, 0.0190/0.0905)
- TPOsup.R *versus* CAU.L (P=8.1961e-05, 0.1603/0.0602)
- TPOsup.R *versus* CAU.R (P=0.0005, 0.1610/0.0667)
- MTG.L *versus* PAL.L (P=0.0002, 0.1793/0.0753)
- MTG.L *versus* PAL.R (P=0.0003, 0.1478/0.0533)
- MTG.L *versus* THA.L (P=0.0004, 0.1525/0.0612)
- MTG.L *versus* THA.R (P=0.0003, 0.0990/0.0274)
- MTG.R *versus* PoCG.L (P=2.2004e-05, 0.0435/0.1597)
- MTG.R *versus* PAL.R (P=6.6873e-05, 0.1544/0.0573)
- TPOmid.R *versus* SFGdor.R (P=0.0002, 0.1742/0.07683)
- TPOmid.R *versus* CAU.L (P=3.924e-05, 0.1481/0.0568)
- ITG.L *versus* PHG.R (P=0.0003, 0.3801/0.2476)
- ITG.L *versus* AMYG.L (P=0.0002, 0.3272/0.1784)
- ITG.L *versus* AMYG.R (P=7.8754e-06, 0.3018/0.1509)

Quantitative assessment reveals that there are 42 edges out of 4005 ones meeting the criteria. These abnormal edges are showed in the Figure1. The abnormal edges are presented in the form - "*region 1 versus region 2 (P-value, mean (C_{Pat})/mean(C_{Nor}))*", where mean(C_{Pat}) is $\sum_s C_{i,j,s}$, which stands for the mean scores of all subjects in the special edge. The same is for mean (C_{Nor}).

Characteristics identification of FCs and regional efficiency

R-fMRI signal X_i at time point t of s-th subject. For every pair of time series $x_{i,t,s}$ and $x_{j,t,s}$ from two regions, Pearson correlation coefficient is

$$F_{i,j,s} = \text{corr}(x_{i,t,s}, x_{j,t,s}),$$

where $i,j \in N$ and N is the node set. Note that the correlation matrix F may have both positive and negative values as a result of pairwise correlations of time series. As the biological connotation of negative correlation between two regions is ambiguous, we define all the negative coefficient values as 0, if $F_{i,j,s}<0$.

For the s-th subject, "Global efficiency" of the network is

$$\overline{E}_s = \frac{1}{n}\sum_{i \in N}\frac{\sum_{j \in N, j \neq i} d_{i,j,s}^{-1}}{n-1},$$

where $d_{i,j,s}$ is the shortest weight path length between nodes i and j.

$$d_{i,j,s} = \sum_{F_{u,v,s} \in g_{i \rightarrow j}} H(F_{u,v,s}),$$

where H is an inverse from weight to length, $g_{i \rightarrow j}$ is the shortest weighted path between i and j. The $F_{u,v,s}$ is connection weights between u and v. "Weight local efficiency of node i" is

$$E_{l,s} = \frac{1}{n}\sum_{i \in N}\frac{\sum_{j,h \in N, j \neq i}(F_{i,j,s}F_{i,h,s}[d_{j,h,s}(N_i)]^{-1})^{1/3}}{k_{i,s}(k_{i,s}-1)},$$

where $k_{i,s}=\sum_{j \in N}F_{i,j,s}$. The $d_{j,h,s}(N_j)$ is the length of shortest path between j and h, which contains only neighbors of i. The values of region efficiency are labeled as RE-scores.

Statistical Analyses

The clusters with significant differences were evaluated using regions of interest (ROI) analysis. Each ROI was a 9-mm isotropic cube including 27 voxels, centered by AAL 90 Sat the Montreal Neurological Institute coordinates of the local maxima. Between the two groups were performed by using a two-sample two-tailed t-test for each FCs (pass the FDR correction P<0.05). Then, this work also computed the RE-scores of each ROIs regions and used a two-sample two-tailed t-test to determine if the RE-scores of FCs was significantly different between the two groups (passing the FDR correction P<0.05). Meanwhile, spearman correlation analysis was then performed between these RE-scores and symptom severity of disease.

The abbreviation of AAL-based regions

The abbreviation - PreCG: Precenral gyrus; SFGdor: Superior frontal dorsal gyrus; ORBsup: Orbitofrontal superior cortex; MFG: Middle frontal gryus; ORBmid: Orbitofrontal middle cortex; IFGoperc: Inferior frontal opercula gyrus; IFGtriang: Inferior frontal triangular

gyrus; ORBinf: Orbitofrontal inferior cortex; ROL: Rolandic operculum; SMA: Supplementary motor area; OLF: Olfactory; SFGmed: Superior frontal medial gyrus; ORBsupmed: Orbitofrontal superior medial cortex; REC: Pectus gyrus; INS: Insula; ACG: Anterior cingulate gyrus; DCG: Median cingulate and paracingulate gyri; PCG: Posterior cingulate gyrus; HIP: Hippocampus; PHG: Parahippocampal gyrus; AMYG: Amygdala; CAL: Calcarine fissure.

RESULTS

Abnormal edges with different FCs between SZs and HCs

In this subsection, an important focus is on exploring the concrete edges of different FCs weight in SZs and HCs by whole brain connectivity analysis. The different edges are strictly selected when they satisfy that P-value pass the FDR correction P<0.05 in the dataset. Quantitative assessment reveals there are 45 edges out of 4005 ones meeting the criteria, which are presented in the table 2 for the succinctly expresses. Meanwhile, a schematic diagram of abnormal edges in brain are shown in the Figure 1. Importantly, the abnormal edges - THA.L *versus* MFG.R, THA.L *versus* HIP.R, THA.L *versus* PHG.L, THA.L *versus* PHG.R, THA.R *versus* MFG.R, THA.R *versus* HIP.R, THA.R *versus* PoCG.L, HES.L *versus* THA.R, HES.R *versus* THA.R, STG.R *versus* THA.L, STG.R *versus* THA.R, MTG.L *versus* THA.L, MTG.L *versus* THA.R - show preliminary evidences for cortico-thalamic and hippocampus-thalamic dysconnections in SZs.

Abnormal regions with different scores of efficiency index in SZs

Firstly, the global effciency between SZs and HCs have no significant difference (P=0.4049). Importantly, T-test of efficiency index experiments are executed to seek out the regions of significant RE-scores in the dataset. We perform T-test between SZs and matched HCs for all 90 brain regions, and obtained results (passing the FDR correction P<0.05) as follows: HIP.L (P=7.3028e-04), HIP.R (P=2.1872e-04), and PHG.L (P=0.0014). The sorts of all 90 regions with RE-scores are provided in Figure 2. The abnormal regions are shown in Figure 3.
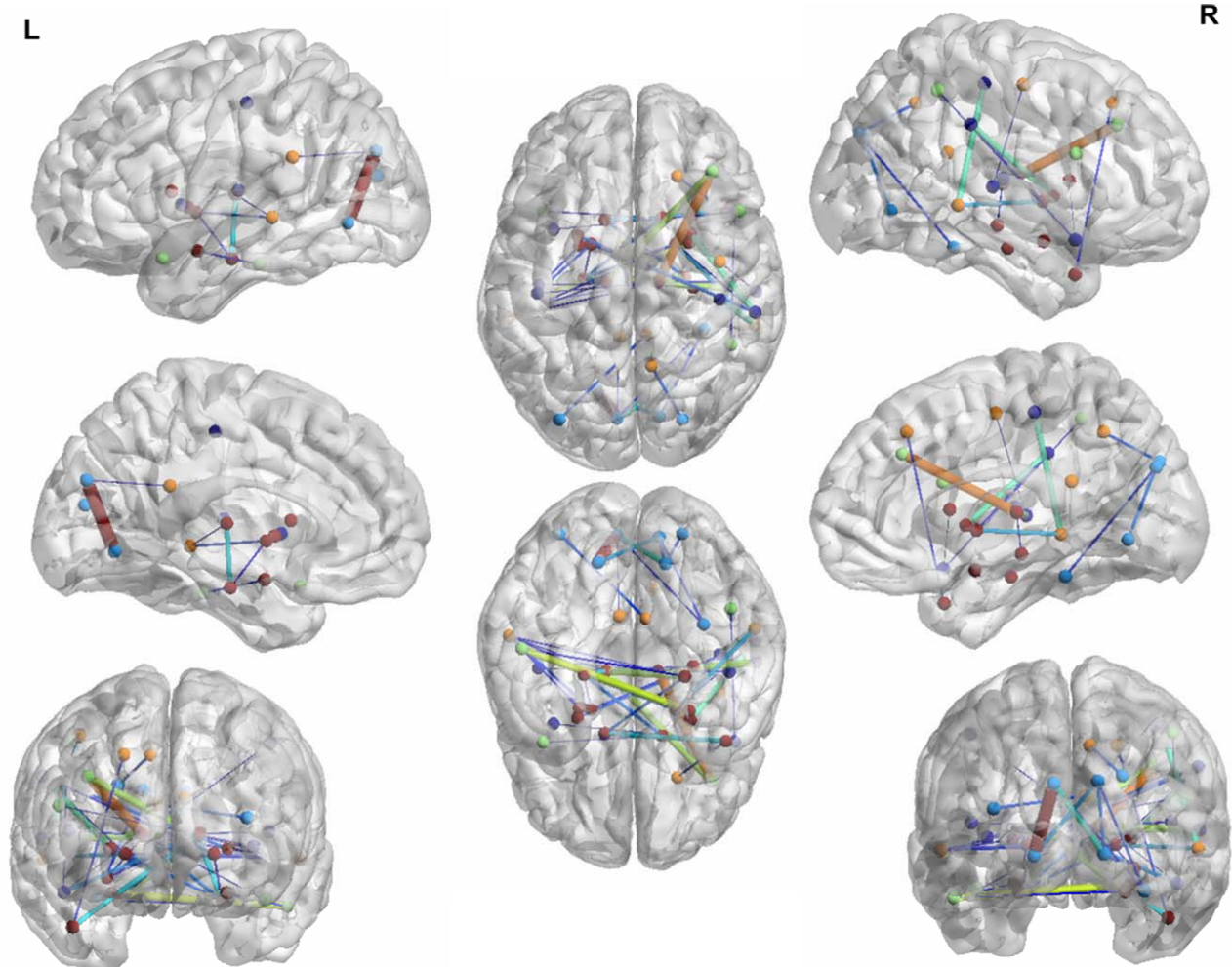

Figure 1. A schematic diagram shows the forty-five edges with significant P-values of AAL-based FCs weight (passing the FDR correction P<0.05). The different colors stand for cortical modules. The thickness of edges only refers to significant level of P-values
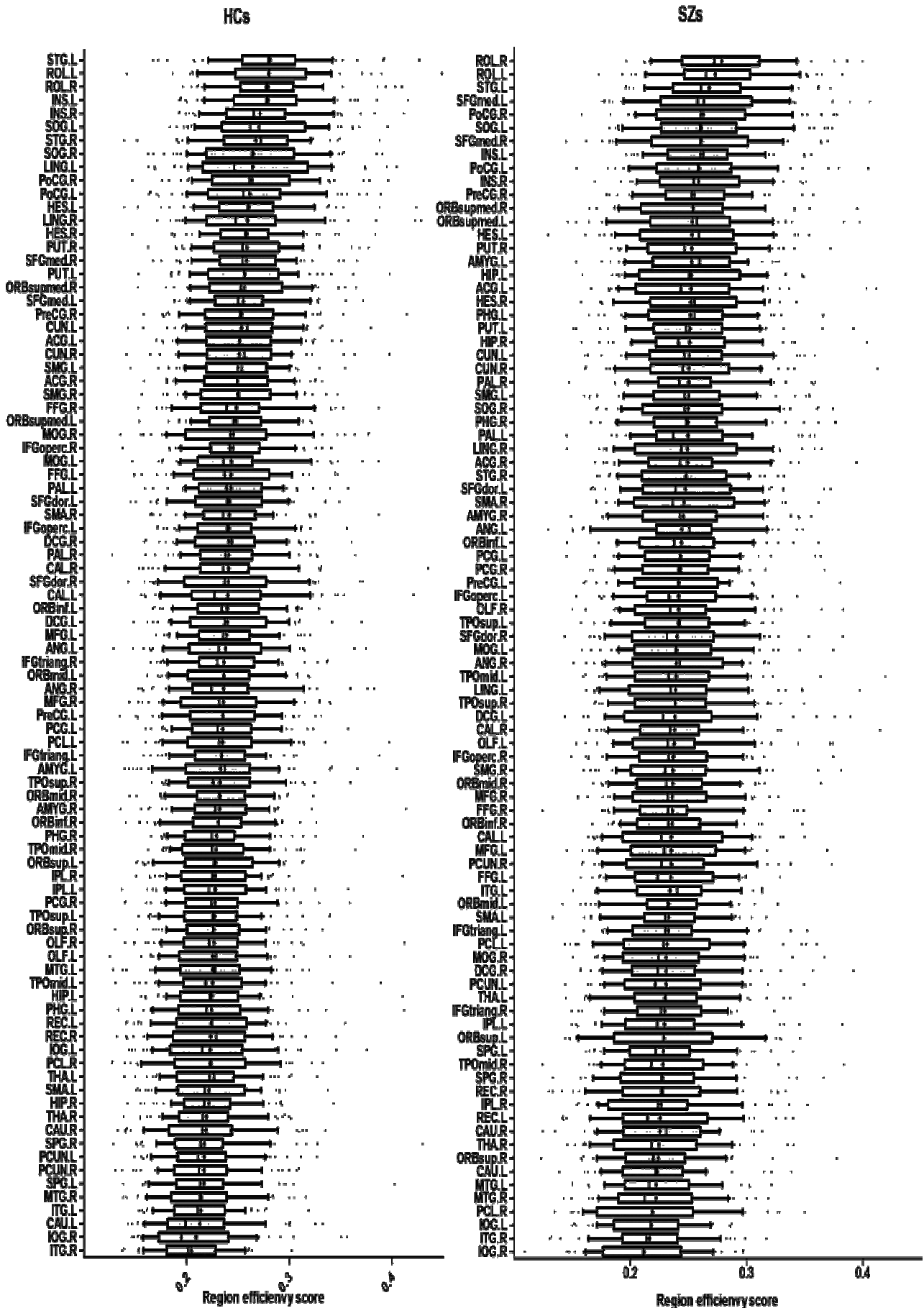
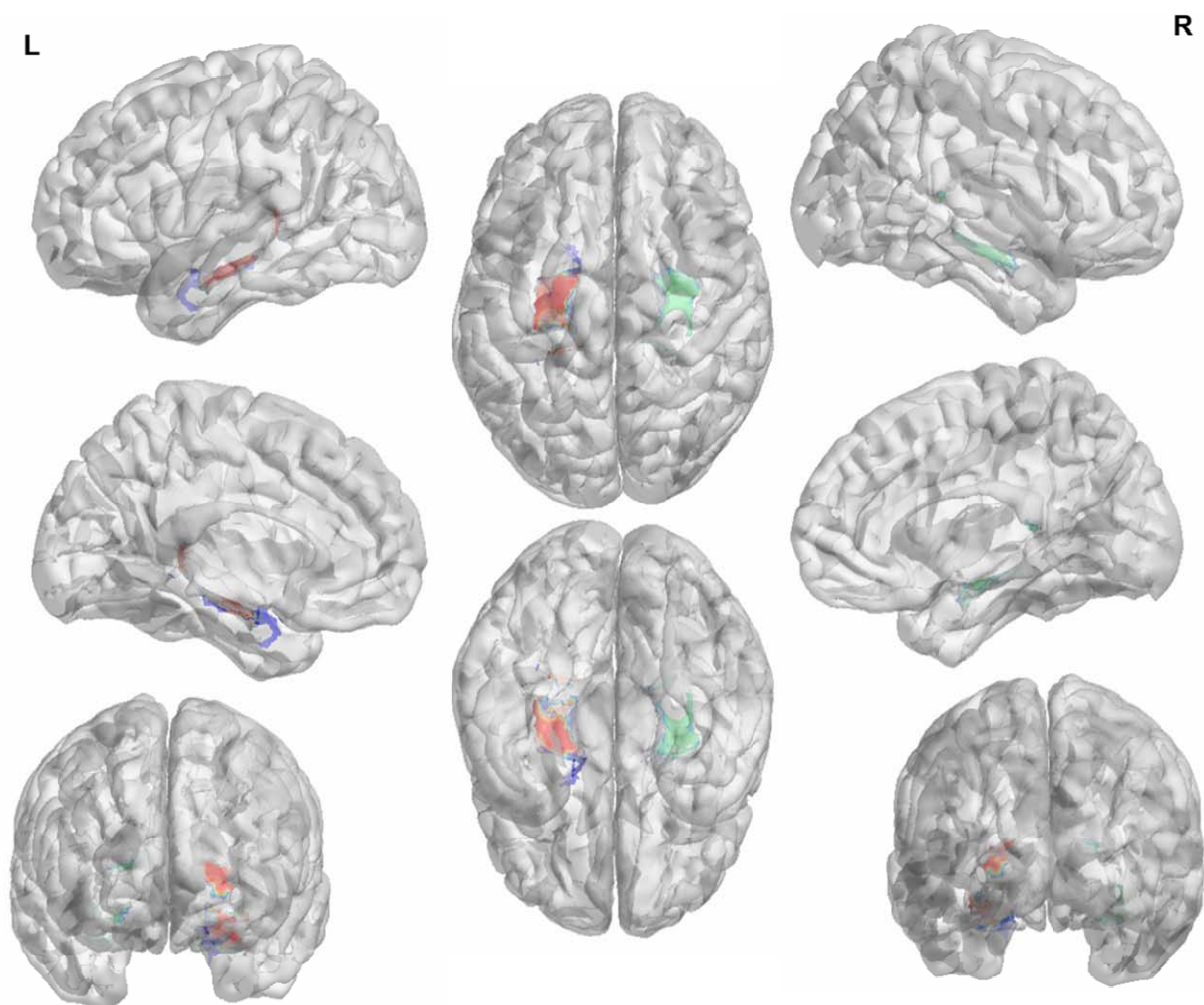**Figure 2.** The ALL 90 brain regions ordered from low to high by their RE-scores

Figure 3. The brain regions show significant P-values (passing the FDR correction P<0.05) of RE-scores between HCs and SZs patients. Colors only stand for the regions - HIP.L (P=7.3028e-04), HIP.R (P=2.1872e-04), and PHG.L (P=0.0014)

Correlations between RE-scores and symptom severity

Spearman correlation between scores of above three regions and PANSS scores are surveyed. Results are presented in the form - *"Region with Symptom (correlation strength, P-value)"*. The HIP.L with motor retardation (r=0.3043, P=0.0267), HIP.L with lack of judgment and insight (r=-0.2831, P= 0.0400), and HIP.L with poor impulse control (r=-0.2739, P= 0.0472).

DISCUSSION

The SZs is a serious mental disorder characterized by symptoms such as hallucinations or disorganized thinking, loss of goal-directed behaviors, social withdrawal and cognitive impairments (Schultz & Andreasen 1999). Psychosis maybe arises from anatomical disruption of association fiber tracts, and reformulated later in terms of psychopathology, which is shown abnormal distributed brain activity and functional connectivity in SZs. Resting state FCs analysis has revealed changes of the brain intrinsic topographical organization in psychiatric disorders (Bassett et al. 2012). Application of FCs in clinical population studies are challenging traditional disease classifications and helping to clarify biological relationships among clinical syndromes (Matthews & Hampshire 2006).

Region efficiency investigates the brain information process of FCs

Cognitive functions are integrated and coordinated different features of neurocognition information by the binding processes. The optimal brain requires a suitable balance between local specialization and global integration of brain functional activity, enabling the rapid extraction of information and the generation of coherent brain states (Tononi et al. 1998, Bassett & Sprons 2017). It implies that one region abnormalities are more likely to occur in the presence of other structural or functional changes within an abnormal neural network and not in isolation.

It has been generally accepted that diseased roots of schizophrenia led to a disturbance of the normal optimal balance in parallel information processing of the brain

subsystems, which would tend to make information propagation under the abnormal states. Combining FCs weight and efficiency scores provide more comprehensive descriptions of altered brain connectivity which are introduced to test the priori hypotheses - the brain's information integration are destroyed underlying SZs (Sporns et al. 2004, He et al. 2007). In particular, edges ground on FCs assure effective interactions or rapid transfer of information between regions, which are essential for functional integration. Regions and subsystems assure the modularized information processing segregated functions from one to another. Therefore, regions with abnormal RE-scores of FCs in SZs mirror the disordered information integration and specialization.

Abnormal THA explored by FCs in SZs patients

The finding is essentially a data-driven verification of thalamic-cortical dysconnectivity in SZs. The THA, generally believed to act as a relay station, has the function of relaying information between different subcortical areas and the cerebral cortex. Many different functions are linked to various regions of the THA. A series of researches or reviews of morphometric neuroimaging studies employing deformation, voxel-based and region of interest methodologies suggest that thalamic shrinkage volume appear to be important contributors to ventricular enlargement in SZs (Konick et al. 2001, Gaser et al. 2004, Sim et al. 2006). Neuronal loss of thalamic is associated with various cellular and neuropil abnormalities, for the perturbation of cortico-thalamic networks (Byne et al. 2009). There is an increase in thalamic volume and an association with late onset SZs, neuroleptic treatment and improvement of psychopathology scores during treatment.

Rest-state function MRI studies have revealed reduced activity (diminished metabolicrate) in the THA (Buchsbaum et al. 1996), and aberrant FCs between the THA and prefrontal cortex has been found in SZs (Heckers et al. 2000). Specifically, the mediodorsal THA may adjust the connectivity (signaling strength) of the circuits in the cortex appropriate for the current context, and make better complex decisions by wiring the many associations on which decisions depend into concrete connected cortical circuits. The STG.R *versus* THA.L, STG.R *versus* THA.R are support for the hypothesis that thalamic regions connection to particular parts of the mesio-temporal lobe provide differentiation of the functioning of recollective and familiarity memory. Importantly, the abnormal edges - THA.L *versus* MFG.R, THA.R *versus* MFG.R, STG.R *versus* THA.R - show preliminary evidences for cortico-thalamic dysconnection in SZs. Rest-state function MRI studies have revealed reduced activity (diminished metabolicrate) in the thalamus. And aberrant FCs between the thalamus and prefrontal cortex in schizophrenics have also been discovered (Welsh et al. 2010). Specifically, the mediodorsal thalamus may adjust the connectivity (signaling amplitude) of the circuits in the cortex appropriate for the current context, and make better complex decisions by wiring the many associations on which decisions depend into concrete connected cortical circuits. The STG.R *versus* THA.R is support for the hypothesis that thalamic regions connection to particular parts of the mesio-temporal lobe provide differentiation of the functioning of recollective and familiarity memory.

Abnormal HIP and PHG identified by RE-scores in SZs

The HIP function have three main ideas - response inhibition, episodic memory, and spatial cognition, which are seen as working together and not mutually exclusive, however, the precise nature of the roles remain widely debated. Many morphometric neuroimaging reports have found reductions of HIP size, related to affected glutamatergic pathways and abnormal dopamine releases, which may be due to genetics, faulty neurodevelopment or abnormal neural plasticity in SZs. The HIP may be central to the pathology of SZs, both in the neural and physiological effects. Several lines of evidence implicate changes in the synaptic organization and connectivity, in and from the HIP (Harrison 2004). Many studies have found dysfunction in the synaptic circuitry within the HIP and its activity on the prefrontal cortex. HIP dysfunctions might produce an alteration of dopamine release in the basal ganglia, thereby indirectly affecting the integration of information in the prefrontal cortex (Gorwood et al. 2008). It is also frequently observed that HIP dysfunctions might account for the disturbances in long-term memory (Boyer et al. 2007).

The PHG plays an important role in the encoding and recognition of environmental scenes. For social context, the right PHG in particular has functions beyond the contextualizing of visual background. The lobe may play a crucial role in identifying social context as well, including paralinguistic elements of verbal communication. The PHG has been hypothesized to have important function in memory recollection, sending information from the hippocampus to the association areas. Abnormalities in HIP-PHG function are the prominent features in SZs. Dysfunction of this region could trigger inadequate activation of right language areas during auditory hallucinations (Diederen et al. 2010). The PHG was reduced significantly on the left side in patients with chronic SZs compared with HCs (Razi et al. 1999). The pathophysiological mechanism underlying the inability of SZs to properly engage the HIP-PHG function during episodic memory is related to genetic risk for the disorder (Di et al. 2013). The HIP and PHG alterations play any role in causing the psychotic symptoms, which are the most important features of schizophrenia.

Several experimental and statistical limitations

Region efficiency index provides information on identifying possible profound traits of encephalopathy dysfunction pathology. The limitations need to be continuous improvement of methodology to assemble our next work has following components. Firstly, although characterized the extent of dysfunction, correlation coefficient between S-scores and PANSS sub-scores need to be analyzed adequately. It will be necessary to divide PANSS scores into parts according to the disease severity, and execute relevant assay. Secondly, an interesting question is studying changeability evolvement rule in longitudinal fMRI data. It will continue to find the first-episode SZs and first degree relative groups data. In addition, the neurobiological and structural bases of detailed interrogation are poorly studied. Brain networks may be viewed as "intermediate phenotypes" which are situated between the domains of genetics and molecular systems, and the expression of individual and collective behavior in the environment. The work will focus on clarifying the physiology mechanisms which results in systematic deficits of network interactions in SZs.

CONCLUSION

According to the destroyed functional separation and integration hypothesis in the context of network neuroscience, region efficiency index is introduced to search the abnormal regions ground on the whole brain FCs level. Importantly, HIP and PHG in SZs are endowed with disordered RE-scores. Caudate R are related to the symptoms of SZs about motor retardation, lack of judgment and insight and poor impulse control. Region efficiency index provides information on identifying possible profound traits of encephalopathy dysfunction pathology. Although current approach has only been applied to one of the major brain atypical disorders - not least SZs, it is easily extended to other forms of neuro-degenerative, developmental or psychiatric disorders.

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