Comprehensive Psychiatry 89 (2019) 16–21

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Resting-state brain entropy in schizophrenia

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ARTICLE INFO

ABSTRACT

Background: The human brain presents ongoing temporal fluctuations whose dynamic range indicates the capacity of information processing and can be approximately quantified with entropy. Using functional magnetic resonance imaging (fMRI), recent studies have shown a stable distribution pattern of temporal brain entropy (tBEN) in healthy subjects, which may be affected by neuropsychiatric diseases such as schizophrenia. Assessing tBEN may reciprocally provide a new tool to characterize those disorders.

Methods: The current study aimed to identify tBEN changes in schizophrenia patients using publicly available data from the Centers of Biomedical Research Excellence (COBRE) project. Forty-three schizophrenia patients and 59 sex- and age-matched healthy control subjects were included, and tBEN was calculated from their resting-state fMRI scans.

Results: Compared with healthy controls, patients showed decreased tBEN in the right middle prefrontal cortex, bilateral thalamus, right hippocampus and bilateral caudate and increased tBEN in the left lingual gyrus, left precuneus, right fusiform face area and right superior occipital gyrus. In schizophrenia patients, tBEN in the left cuneus and middle occipital gyrus was negatively correlated with the positive and negative syndrome scores (PANSS). Age of onset was inversely correlated with tBEN in the right fusiform gyrus and left insula.

Conclusion: Our findings demonstrate a detrimental tBEN reduction in schizophrenia that is related to clinical characteristics. The tBEN increase in a few regions might be a result of tBEN redistribution across the whole brain in schizophrenia.

1. Introduction

Schizophrenia is a chronic mental disorder characterized by general cognitive dysfunction that ranges from basic sensory to higher-order deficits. The clinical characteristics of schizophrenia are divided into a range of positive symptoms, including delusions, hallucinations and paranoia, and negative symptoms, such as stereotyped thinking, blunted affect and emotional withdrawal [1,2]. However, the neural mechanisms underlying these widespread dysfunctions are still not clear. Functional magnetic resonance imaging (fMRI) provides a non-invasive means to map regional brain activity and has been increasingly adopted in schizophrenia studies [3]. These studies have mainly focused on specific brain dysfunctions or disconnections between particular regions [4,5]. One important characteristic of brain activity that has not been given much attention is temporal brain activity dynamics.

The human brain is a dynamic functional system presenting ongoing fluctuating activity. Such dynamic activity represents a way to process the endless internal and external information. The range of dynamics then relates to the capacity of information processing, which can be approximately quantified with entropy, with high entropy indicating large irregularity. Entropy calculation is often based on electrophysiological data because of the large data samples easily acquired within a short time. Using electroencephalography (EEG) or magnetoencephalography (MEG), both increased and decreased tBEN have been reported in schizophrenia [6–8]. However, electrophysiological methods often lack the spatial resolution to map regional tBEN. Using fMRI, we and others have assessed whole brain tBEN mapping [9,10], revealing reliable tBEN distribution patterns in normal brain [9], as well as their alterations in ageing [11,12], relapsing-remitting multiple sclerosis [13], attention-deficit/hyperactivity disorder [14], chronic smoking [15] (the increased tBEN can be reduced after effective treatment [16]), and cocaine addiction [17]. We recently demonstrated that resting-state tBEN can be modulated by neuromodulations [18,19]. Using a relatively large sample [16], we further demonstrated that tBEN was independent of cerebral blood flow and the amplitude of low-frequency fluctuations in most of the brain, indicating that tBEN provided a unique view of brain activity. These studies clearly showed tBEN as a novel brain activity measure carrying high potential for studying complex brain disorders, including schizophrenia.

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https://doi.org/10.1016/j.comppsych.2018.11.015

Two recent studies have examined tBEN in schizophrenia. Based on fMRI data acquired from 13 patients and 16 controls during a Cyberball social exclusion task, Sokunbi et al. [20] reported increased entropy in the left inferior frontal gyrus and left Brodmann area 47. No statistically significant correlation ($p > 0.05$) was found between brain entropy and any of the Positive and Negative Syndrome Scale (PANSS) scores (positive, negative, general and total score), which might be mainly due to the small sample size. By examining tBEN at different time scales, Yang et al. [10] reported that patients with schizophrenia had a trend of higher tBEN, which was flipped to the opposite direction (lower tBEN) when tBEN was calculated from downsampled fMRI time series. By assessing tBEN at differently downsampled fMRI time series, they also found a reduction of entropy change rate (with respect to the data downsampling factor) in schizophrenia patients compared to controls. The PANSS positive score was negatively correlated with entropy in the fusiform face area and temporal pole, whereas the PANSS negative scores was negatively correlated with entropy in the left posterior lobe of the cerebellum. One issue was that downsampling resting-state fMRI (rsfMRI) data shortened the length of the data available, making the tBEN calculation less stable. Moreover, the frequency band of the signal was pushed closer to the range of the low-frequency drift, which was often considered noise.

This study represented a full expansion of our preliminary study [21] and served to provide new evidence to schizophrenia-related entropy alterations and their clinical implications. We hypothesized that schizophrenia patients had regional tBEN alterations compared to healthy controls and tBEN was related to clinical measurement of schizophrenia patients.

2. Materials and methods

2.1. Participants

Forty-three patients with schizophrenia (SCZ; mean age: 39 ± 14 yrs.; range: 19–65; 10 females) and 59 age-similar healthy controls (HC; mean age: 35 ± 11 yrs.; range: 18–65; 19 females) were included in the present study. The characteristics of the participants are specified in Table 1. These participants were part of the Centers of Biomedical Research Excellence (COBRE) open-source dataset deposited at the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) platform (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html). The initial release of the COBRE dataset included 148 participants. 36 subjects were excluded based on the following criteria: 1) left (N = 11) or mixed-handedness (N = 4); 2) poor quality fMRI images (signal loss) or insufficient phenotypic data (N = 6); 3) comorbid depression (N = 1); and 4) large head motions (see the following section for the details) during the rsfMRI scan (N = 24).

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) was used for diagnosing schizophrenia. Both patients and controls had no history of neurological disorder, mental retardation, severe head trauma, or a current diagnosis of substance abuse or dependence. The research protocols were carried out in accordance with the Declaration of Helsinki and were approved by the local Institutional Review Board (IRB). Informed consent was obtained before participation.

Table 1
Demographics and clinical information of the study sample.

	SCZ	HC	df	t/x^2 value	*p*-Value
No. of subjects	43	59			
Age (years)	39.2 (13.7)	35 (11)	100	1.7	0.097
Age range	19–65	18–65			
Sex (M/F)	33/10	40/19	1	0.98	0.32
Age of illness onset (years)	21.2 (8.4)				
Illness duration (years)	18 (12.7)				
PANSS positive	14 (4.4)				
PANSS negative	14.5 (4.9)				
PANSS general	28.3 (7.9)				
PANSS total	56.9 (12.8)				

Note: SCZ = schizophrenia, HC = controls. PANSS, Positive and Negative Syndrome Scale.

2.2. Image acquisition and preprocessing

Image data were acquired with a single 3-T Siemens Trio scanner (Siemens AG, Medical Solutions, Erlangen, Germany). Participants were instructed to relax and remain still with their eyes open during the scan for 5 min. A T2-weighted gradient-echo EPI pulse sequence was acquired in an interleaved order to measure brain oxygenation level-dependent (BOLD) signal (TR/TE = 2000/29 ms, flip angle = 75°, slice thickness = 3.5 mm, slice gap = 1.05 mm, matrix = 64 × 64, voxel size = 3.75 mm × 3.75 mm × 4.55 mm, 150 vol). A high-resolution T1-weighted anatomical image in the sagittal orientation was acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE = 2530/1.64 ms, flip angle = 7°, matrix = 256 × 256, 1 mm^3 isotropic spatial resolution) for visualization and localization of the functional data. Image acquisition parameters are found at the COBRE website (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html).

Functional image preprocessing was performed using the Data Processing Assistant for Resting-State fMRI [22] and Statistical Parametric Mapping (SPM8, Wellcome Department, London, UK, http://www.fil.ion.ucl.ac.uk/spm). For each dataset, the first 5 functional volumes were discarded to allow for magnetization equilibration effects and the adaptation of the participants to the circumstances. The remaining images for further preprocessing were first corrected for time delay between slices, and then were realigned to the first volume for head-motion correction. The realigning step provided a record of head motions by estimating the translations in each direction and the rotations in angular motion about each axis for each of the consecutive volumes. All participants included in this study exhibited a maximum displacement of <2 mm at each axis and an angular motion of <2 for each axis. After the head motion correction, the images were normalized into a standard stereotactic space as defined by the Montreal Neurological Institute (MNI) (resampling voxel size = 3 × 3 × 3 mm^3), and smoothing with a 4-mm full width at half maximum Gaussian kernel.

2.3. Entropy calculation

Whole brain entropy maps of all participants were calculated using the Brain Entropy mapping toolbox (https://cfn.upenn.edu/~zewang/BENtbx.php). Sample entropy [23] was used as the approximate format of the entropy measure to quantify the temporal irregularity (incoherence) of a time series by calculating the negative natural logarithm of an estimate of the conditional probability that subseries (epochs) of "m" consecutive data points match within a tolerance "r" also match when the examination window, m increases to be m + 1. m was set to be 3 and r was 0.6 based on previous work [9,13,15]. tBEN was calculated for all intracranial voxels, and was standardized by subtracting the mean and dividing by the standard deviation to control global variations across different participants [24].

2.4. Statistical analysis

To examine tBEN difference between schizophrenia patients and healthy controls, a two-sample *t*-test was performed on the individual subjects' tBEN maps. Multiple comparison correction was performed using Gaussian Random Field theory (GRF) using a threshold of voxelwise $p < 0.005$ ($Z > 2.87$) and a clusterwise threshold of $p < 0.05$ [25]. To compare the differences of demographic data between the two groups, a two-sample t-test was used for continuous variables and Chi-square test for categorical variables. The height threshold of statistical significance was set to $p < 0.05$.

2.5. Correlations between tBEN and the clinical evaluation of schizophrenia

Pearson's correlation analysis was performed between the tBEN map and clinical variables (the PANSS positive and negative scores, age of onset, and age of duration) in the schizophrenia group. The statistical threshold was set at $p < 0.05$ after correction of multiple comparisons using GRF with $Z > 2.87$ and voxel $p < 0.005$ [25].

3. Results

The tBEN comparison results are shown in Fig. 1 and Table 2. Compared to healthy controls, schizophrenia patients showed significantly decreased tBEN in the right middle prefrontal cortex, bilateral thalamus, right hippocampus, and bilateral caudate ($p < 0.05$, GRF corrected, Fig. 1). Increased tBEN was found in the left lingual gyrus, left precuneus, right fusiform face area and right superior occipital gyrus.

Fig. 2 and Table 3 summarize the correlations between the tBEN and clinical variables. The PANSS positive score was negatively correlated with the tBEN in the left cuneus (correlation coefficient r at peak voxel = −0.51), and the PANSS negative score was negatively correlated with the tBEN in the left middle occipital gyrus (MOG, r = −0.55). Age of onset was negatively correlated with the tBEN in the right fusiform face area (FFA, r = −0.56) and left insula (r = −0.58).

Table 2
Altered tBEN in schizophrenia patients.

Anatomical region	Cluster size (Voxels)	Peak t-Value	Peak MNI (X Y Z) Coordinates (mm)
Decreased in schizophrenia			
Thalamus L	30	−5.01	−12,−15,18
Thalamus R	32	−4.87	18,−18,18
Hippocampus R	10	−4.18	21,−36,3
Caudate R	44	−4.68	15,12,15
Middle frontal gyrus R	8	−3.75	27,42,39
Increased in schizophrenia			
Fusiform gyrus R	28	4.28	30,−78,−9
Lingual L	25	4.61	−15,−87,−12
Superior occipital gyrus R	9	5.22	24,−81,27
Precuneus L	8	3.59	−6,−42,63

Abbreviation: tBEN, temporal brain entropy; R, right side; L, left side; MNI, Montreal Neurological Institute coordinates. Significance level was defined at voxel $p < 0.005$, cluster $p < 0.05$, GRF corrected.

4. Discussion

Entropy indicates the system irregularity and then the capacity of information processing. In this study, we aimed to characterize temporal brain entropy (tBEN) in schizophrenia using resting-state fMRI based on two rationales: first, tBEN mapping is relatively new to schizophrenia; second, tBEN is different from other more widely used brain activity measures [16] and may reveal new brain signatures related to disease which cannot be revealed by other methods. Compared to controls, schizophrenia patients showed reduced tBEN in prefrontal cortex and subcortical nuclei but increased tBEN in the left lingual gyrus, left precuneus, right fusiform face area and right superior occipital gyrus. In schizophrenia patients, tBEN was negatively correlated with the PANSS positive and negative scores in the left cuneus and middle occipital gyrus.

Thalamus is a hub area sending and receiving information for both cortical and subcortical regions. Reduced tBEN in the thalamus suggests a reduced thalamus activity irregularity and information processing capacity, which should be added to the disease-related alterations of the thalamus in previous work [26–29]. This finding was consistent with previous studies about thalamus functional connectivity and regional homogeneity of brain activity [30,31]. Prior studies have found altered resting-state functional connectivity between the thalamus and cortex in schizophrenia [32,33]. The alterations were characterized by decreased thalamic connectivity with the prefrontal cortex, dorsal striatum, and cerebellum and increased thalamic connectivity with motor and somatomotor cortex areas in schizophrenia patients compared to healthy controls. These over−/under-connectivity disruptions in thalamic provide the evidence that thalamic connectivity may not differentiate between the prefrontal and motor cortex, possibly reflective of somatomotor gating and top-down control disturbances. Another study showed that first-episode schizophrenia patients showed a significant decrease in regional homogeneity (ReHo) values in the left thalamus compared with that in the healthy control group [31]. Meanwhile, it is worth to note that functional connectivity refers to the data coherence between two regions, but tBEN is a local brain measure, which explains the discrepancy to the bidirectional thalamic functional connectivity changes reported in [32,33]. The hippocampus has been shown to be pivotal to resting-state brain activity in a recent optogenetic study [34], where the authors found that low-frequency hippocampal excitatory neural activity could propagate to the whole-brain and modulate brain-wide functional connectivity. It has also been highly implicated in schizophrenia with reported hippocampal tissue volume reduction [35], shape changes [36], hyperperfusion [37], and hypermetabolism [38,39]. Reduced hippocampal tBEN in schizophrenia reveals a new format of hippocampal impairment in schizophrenia, reduced hippocampal information processing, which might be either the result of the aforementioned structural and metabolic hippocampal changes [36–39]. Reduced tBEN in the caudate might be related to the abnormal dopamine neuron activity in schizophrenia [40] particularly due to the key role of dopamine in cellular information processing. Decreased tBEN in middle prefrontal cortex is partly consistent with the tBEN reduction in the inferior frontal cortex reported in previous study [10] based on a small sample size (13 patients and 16 controls' fMRI data). The tBEN reductions in the middle prefrontal cortex are consistent with the impairments to the various high-order brain functions in schizophrenia [41,42].

While the above tBEN reduction findings indicate hypo-information processing-related functional deficits in schizophrenia, the increased tBEN may correspond to the well-known hyper-status in the disease such as hallucinations and delusions. Increased tBEN in the right fusiform face area and left lingual gyrus in schizophrenia patients is in line with the escalated visual and imaginary problems of patients with schizophrenia due to the disruptions to normal information (such as au-

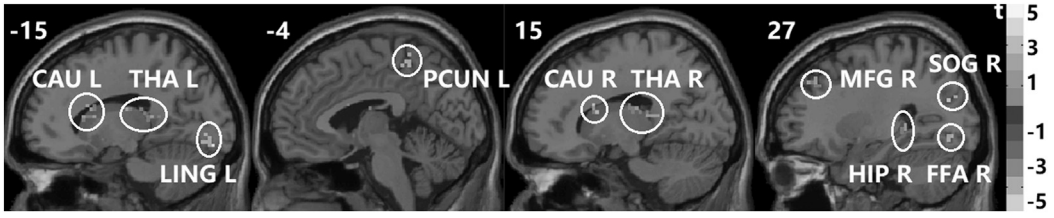

Fig. 1. Altered tBEN in schizophrenia patients. Red and blue indicate higher and lower tBEN in schizophrenia patients, respectively. The number above each image represents the slice number (mm) in Montreal Neurological Institute (MNI) space. The color bar represents the display window for t-values. L, left side; R, right side; MFG, middle prefrontal cortex; THA, thalamus; HIP, hippocampus; CAU, caudate; PCUN; FFA, fusiform face area; SOG, superior occipital gyrus.

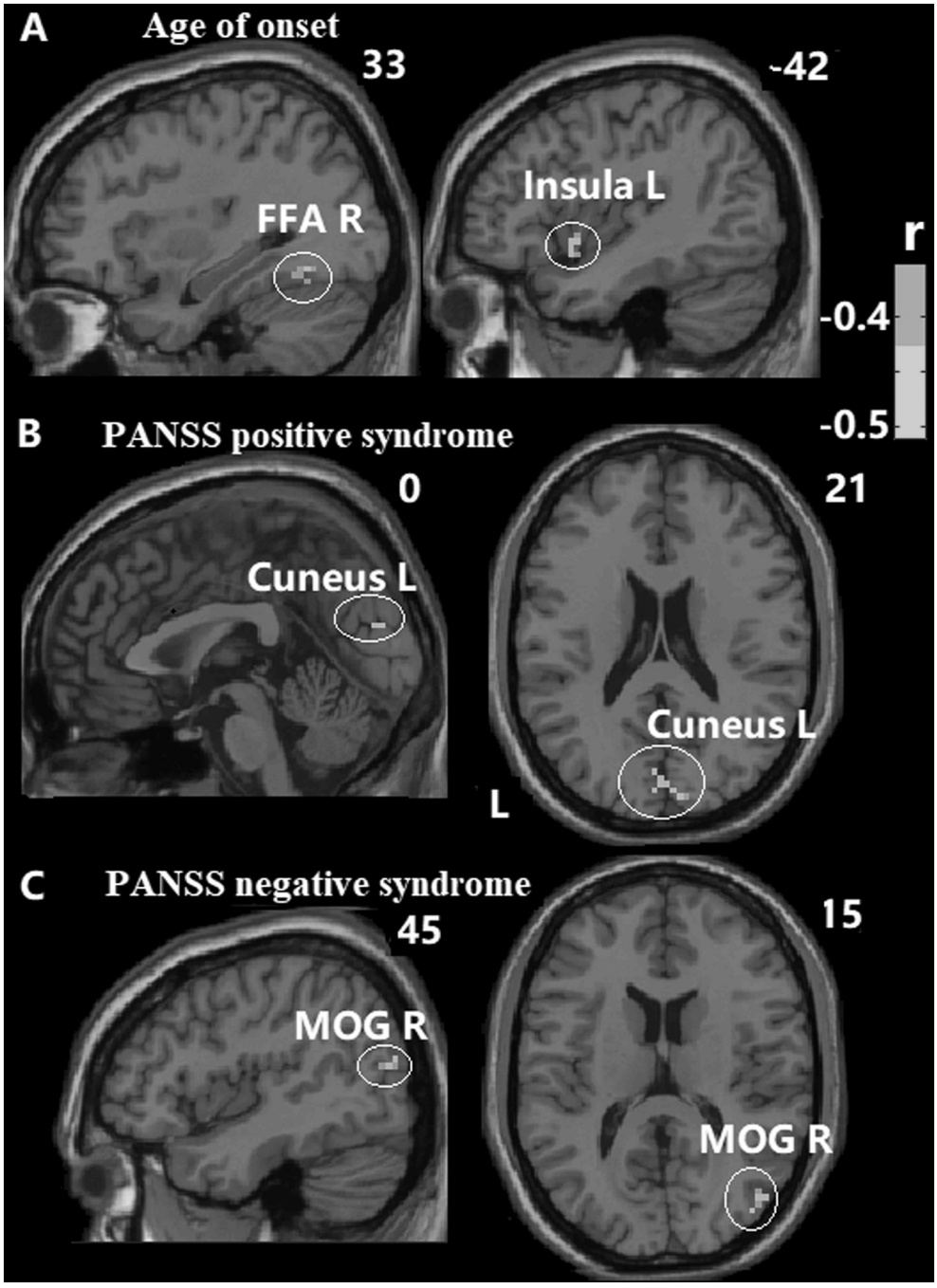

Fig. 2. Correlations between clinical variables and tBEN values in schizophrenia patients. Higher tBEN was related to earlier disease onset (A); lower tBEN was correlated with higher PANSS positive scale (B); lower tBEN was correlated with higher PANSS negative scale (C). Significance level was defined at voxel level $p < 0.005$, cluster $p < 0.05$, GRF corrected. The left side of the image at the coronal plane corresponds to the right side of the brain. The color bar represents the display window for the r values (correlation coefficients). FFA, fusiform face area; MOG, middle occipital gyrus.

ditory, visual, and smell) processing [43]. This postulation was further supported by our clinical association analysis results. The fusiform face area is a part of the human visual system that might be specialized for face recognition [44]. The lingual gyrus is linked to vision processing. Increased tBEN in those areas including the superior occipital cortex may reflect the hyper-processing of facial and vision signals, in consistent with the characteristic delusion and hallucination symptoms in schizophrenia [45]. The precuneus is a hub area in the default mode network [46] and its resting-state brain activity is often believed to facilitate brain function when task is involved. Increased tBEN in the precuneus may represent a means to compensate the aforementioned tBEN reductions and the dysfunctions.

The tBEN was related to the PANSS positive and negative symptom scores for schizophrenia. The associations highlighted the visual area and the cuneus. The PANSS positive score was negatively correlated with tBEN of the cuneus, and the PANSS negative score was negatively correlated with tBEN of the middle occipital gyrus. These negative associations are consistent with the results reported in previous study [10]. We also found a negative correlation between age of illness onset and tBEN in the fusiform face area and insula. Insula is associated with emotion or regulation of somatosensory control function; fusiform face area is associated with vision and somatosensory information processing. As schizophrenia patients often have hyper-activity regarding those functions, our findings of lower tBEN in fusiform and insula corresponding

Table 3
Regions showing a significant correlation between clinical variables and the tBEN in schizophrenia patients.

Anatomical region	Cluster size (voxels)	Peak r-Value	Peak MNI (X Y Z) coordinates (mm)
Age of onset			
Fusiform face area R	11	−0.56	33,−60,−12
Insula L	7	−0.58	−42,9,−6
Age of duration			
No			
PANSS positive syndrome			
Cuneus L	10	−0.51	0,−84,21
PANSS negative syndrome			
Middle occipital gyrus R	15	−0.55	45,−75,15

All brain clusters had p value < 0.05 corrected for multiple comparisons using GRF.
L, left; R, right; r, correlation coefficient.

to later disease onset may suggest a disease protecting effect in the brain.

While part of our tBEN findings are consistent with previous studies using other resting-state brain activity metrics (e.g., amplitude of low frequency fluctuations [ALFF] and functional connectivity), tBEN differs from them by considering the temporal dynamics of brain activity for the entire acquired signal spectrum rather than focusing on the low frequency part only as ALFF does. It is a regional measure rather than an inter-regional one like functional connectivity does. A recent across-modality analysis has demonstrated that tBEN is independent of ALFF and cerebral blood flow in most of brain cortex [16]. The moderate sample size used in this study represents a limitation, which may limit the power for revealing some subtle effects. A larger cohort will be necessary to demonstrate the generalizability of the findings in this preliminary study.

5. Conclusions

Overall, we demonstrated a detrimental tBEN reduction in schizophrenia which was related to clinical measures. The tBEN reduction was accompanied by tBEN increase in different brain areas, of which some might be related to schizophrenic abnormalities and the other might be a result of tBEN redistribution across the whole brain. These findings are in complementary to current schizophrenia neuroimaging research literature with evidence of altered brain activity irregularity and information processing capacity. The tBEN alteration and BEN vs symptom correlation patterns might provide potential markers for schizophrenia.

Acknowledgements

This study was supported by the Natural Science Foundation of Zhejiang Province Grant LZ15H180001, LY17H180007, the Youth 1000 Talent Program of China, the National Natural Science Foundation of China (No. 61671198), and the cultivation project of the province-leveled preponderant characteristic discipline in the College of Education of Hangzhou Normal University (No. 18JYXK036).

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