Decreased Resting-State Brain Activity Complexity in Schizophrenia Characterized by Both Increased Regularity and Randomness

Albert C. Yang,[1,2,3,4]* Chen-Jee Hong,[1,2] Yin-Jay Liou,[1,2] Kai-Lin Huang,[1,2]
Chu-Chung Huang,[5] Mu-En Liu,[1,2] Men-Tzung Lo,[3] Norden E. Huang,[3]
Chung-Kang Peng,[4] Ching-Po Lin,[5] and Shih-Jen Tsai[1,2]

[1]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[2]Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[3]Center for Dynamical Biomarkers and Translational Medicine, National Central University,
Chungli, Taiwan
[4]Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical
Center/Harvard Medical School, Boston, Massachusetts
[5]Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

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Abstract: Schizophrenia is characterized by heterogeneous pathophysiology. Using multiscale entropy (MSE) analysis, which enables capturing complex dynamics of time series, we characterized MSE patterns of blood-oxygen-level-dependent (BOLD) signals across different time scales and determined whether BOLD activity in patients with schizophrenia exhibits increased complexity (increased entropy in all time scales), decreased complexity toward regularity (decreased entropy in all time scales), or decreased complexity toward uncorrelated randomness (high entropy in short time scales followed by decayed entropy as the time scale increases). We recruited 105 patients with schizophrenia with an age of onset between 18 and 35 years and 210 age- and sex-matched healthy volunteers. Results showed that MSE of BOLD signals in patients with schizophrenia exhibited two routes of decreased BOLD complexity toward either regular or random patterns. Reduced BOLD complexity toward regular patterns was observed in the cerebellum and temporal, middle, and superior frontal regions, and reduced BOLD complexity toward randomness was observed extensively in the inferior frontal, occipital, and postcentral cortices as well as in the insula and middle cingulum. Furthermore, we determined that the two types of complexity change were associated differently with psychopathology; specifically, the regular type of BOLD complexity change was associated with positive symptoms of schizophrenia, whereas the randomness type of BOLD complexity was associated with negative symptoms of the illness. These results collectively suggested that resting-state dynamics in schizophrenia exhibit two

routes of pathologic change toward regular or random patterns, which contribute to the differences in syndrome domains of psychosis in patients with schizophrenia. *Hum Brain Mapp 36:2174–2186, 2015.*   © 2015 Wiley Periodicals, Inc.

Key words: schizophrenia; complexity; multiscale entropy; randomness; regularity

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INTRODUCTION

The unpredictable nature of behavioral patterns in schizophrenia and other mental illnesses has implicated the use of chaos and complexity theories to understand the complex behaviors of patients with psychiatric disorders [Breakspear, 2006; Ehlers, 1995; Paulus and Braff, 2003; Tschacher et al., 1997]. From a systemic perspective, complexity reflects the ability of the brain to adapt to a constantly changing environment. Such adaptation is often impaired in schizophrenia and other mental illnesses, leading to abnormal behavioral patterns and impaired cognitive and psychosocial functions [Bassett and Gazzaniga, 2011]. Therefore, studies of complexity in brain activities may provide insights into how behavioral patterns of schizophrenia are linked to the pathophysiology of brain functions. Because of advances in brain activity monitoring and quantitative measures of system dynamics, schizophrenia research has increasingly focused on the complexity analysis of neurophysiologic signals acquired from schizophrenic patients [Bassett and Gazzaniga, 2011; Bullmore and Sporns, 2009; Keshavan et al., 2004; Kotini and Anninos, 2002; Lee et al., 2001; Meunier et al., 2009; Takahashi et al., 2010] (for reviews see [Fernandez et al., 2013; Takahashi, 2013]). In this context, complexity theory may provide a useful clinical tool for the psychiatric evaluation of symptom severity and predicting treatment outcomes.

The altered brain complexity in schizophrenia has been studied using electroencephalography [Keshavan et al., 2004; Koukkou et al., 1993; Li et al., 2008; Raghavendra et al., 2009; Takahashi et al., 2010], magnetoencephalography [Fernandez et al., 2011], and structural imaging of gyri folding [Narr et al., 2004]. The analysis of the complexity of blood-oxygen-level-dependent (BOLD) signals obtained from resting-state functional magnetic resonance imaging (fMRI) has attracted considerable interest. Previous studies have indicated that the nonlinear properties of resting-state brain function can serve as a marker for aging and mental illness [Meunier et al., 2009], as implicated in Alzheimer's disease [Liu et al., 2013; Maxim et al., 2005], attention-deficit hyperactivity disorder [Anderson et al., 2006; Sokunbi et al., 2013], autism [Lai et al., 2011], and aging [McIntosh et al., in press; Smith et al., 2014; Yang et al., 2014a, 2013a]. Although BOLD signals were considered hemodynamic responses rather than direct measures of neuronal activity in a previous study [Fox and Raichle, 2007], these data provide evidence that altered nonlinear, time-varying properties of BOLD signals are influenced by the disease state and may provide a novel neuroimaging approach for investigating brain dysfunction associated with aging and mental illness. Several studies have investigated the complexity of brain activity in schizophrenia using resting-state fMRI [Bassett et al., 2012; Sokunbi et al., 2014]. The wavelet entropy used by Bassett et al. [2012] was insufficient for assessing the difference in the complexity of regional BOLD activity between patients with schizophrenia and healthy subjects. Sokunbi et al. [2014] showed that schizophrenia had increased randomness of BOLD activity by analyzing single-scale sample entropy and the Hurst exponent, leading to the questionable conclusion that brain complexity was increased in patients with schizophrenia.

We and others had recently applied the multiscale entropy (MSE) method [Costa et al., 2002] to assess the complexity of BOLD signals in healthy aging cohorts [Yang et al., 2014a, 2013b] and in different brain areas of white matter and ventricular space [McDonough and Nashiro, 2014; Smith et al., 2014]. The MSE method provides a profile of entropy across multiple time scales and, thus, enables extracting a signature of complexity from physiologic signals not included in traditional methods based on the mean or variance and conventional entropy methods used to measure entropy in a single time scale [Chialvo, 2002; Costa et al., 2005]. With MSE analysis, a healthy physiologic process is typically represented by a complex fluctuation with consistent entropy values over different time scales, and reduced complexity in pathologic processes can exhibit either increased regularity (i.e., decreased entropy in all time scales) or increased randomness (i.e., high entropy in short time scales followed by rapid decay in entropy as the length of time scales increases). In contrast to the single-scale entropy method, which is simply a measure of regularity [Lake et al., 2002; Pincus and Goldberger, 1994; Richman and Moorman, 2000], a MSE profile enables differentiating true complexity from uncorrelated randomness, which does not contain meaningful information and cannot be regarded as a complex state [Goldberger et al., 2002a,b]. Therefore, increased regularity and randomness at the extreme of the dynamic process represent the reduced complexity that can be observed in various medical conditions, such as heart rate variability in congestive heart failure and atrial fibrillation [Goldberger et al., 2002b].

According to our previous review [Yang and Tsai, 2013], this generic loss of complexity scheme has not been tested in a large cohort of patients with mental illness using

functional brain imaging. Such an investigation may reveal crucial information regarding whether brain processes in patients with mental illness exhibit increased complexity or reduced complexity toward regularity or uncorrelated randomness compared with those in healthy people. We hypothesized that schizophrenia is associated with the loss of multiple-time-scale complexity (either toward regularity or uncorrelated randomness), and investigated the entropy profiles of resting-state fMRI signals across time scales in patients with schizophrenia, and determined the relationship between the complexity of resting-state brain activity and relevant psychopathologic assessments.

MATERIALS AND METHODS

Study Participants

The study cohort consisted of 315 Han Chinese participants who were recruited from the Department of Psychiatry at Taipei Veterans General Hospital, Taiwan. The patient group consisted of 105 patients with schizophrenia (45 men, 60 women; mean age: 42.8 ± 9.4 years), among which 91 (86.6%) patients were referred from outpatient clinics and 14 (13.3%) patients were from the inpatient unit. To increase the homogeneity of the schizophrenic group, we enrolled patients with an age of onset between 18 and 35 years and an age at fMRI scanning between 20 and 60 years. All schizophrenic patients were evaluated by a board-certificated psychiatrist and diagnosed according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Diagnoses of schizophrenia were validated using the Mini-International Neuropsychiatric Interview [Sheehan et al., 1998]. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate psychotic symptoms [Kay et al., 1987]. Chlorpromazine (CPZ) equivalent dosages were computed according to American Psychiatric Association guidelines.

The comparison group consisted of 210 healthy volunteers (89 men, 121 women; mean age: 42.9 ± 11.3 years) who were recruited from a healthy aging cohort and matched according to age and sex at a 2:1 control-to-patient ratio [Yang et al., 2014a, 2013b]. Healthy subjects were evaluated by a trained research assistant using the Mini-International Neuropsychiatric Interview to exclude the presence of psychiatric disorders [Sheehan et al., 1998]. The comparison participants had no personal or family history (first-degree relatives) of psychiatric disorders. Exclusion criteria for the participants were severe medical illness, cognitive impairment (a Mini Mental State Examination Score lower than 24), borderline personality disorder, a history of head trauma or neurological disease, and a lifetime history of substance abuse disorder. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital. Demographic and clinical data on the participants are presented in Table I.

TABLE I. Demographics and clinical characteristics

Variables	Schizophrenia ($n = 105$)		Healthy Control ($n = 210$)		t or χ^2	P
	Mean	SD	Mean	SD		
Age at scan (years)	42.8	9.4	42.9	11.3	.08	.94
Gender, female	60	57.1%	121	57.6%	.01	.92
Handedness, right	101	96.2%	204	97.1%	.01	.92
Age of illness onset (years)	25.4	5.0				
Illness duration (years)	17.4	9.4				
PANSS total	38.3	9.2				
PANSS positive	9.6	3.2				
PANSS negative	9.4	5.2				
PANSS general	20.3	3.9				
CPZ equivalents	491.3	390.1				

Categorical data are given as number (%)
PANSS, Positive and Negative Syndrome Scale; CPZ, Chlorpromazine equivalent dosage

fMRI Scanning and Image Processing

fMRI scanning was performed at National Yang-Ming University using a 3.0T Siemens MRI scanner (Siemens, Erlangen, Germany) equipped with a 12-channel head coil. All fMRI experiments were performed in the morning. The scanning protocol was consistent with that described in our prior reports [Yang et al., 2014a, 2013b]. T2*-weighted images with BOLD contrast were measured using a 43-slice gradient echo-planar imaging (EPI) sequence with a repetition time (TR) of 2,500 ms, an echo time (TE) of 27 ms, a field of view (FoV) of 200 mm, a flip angle of 77°, a matrix size of 64 × 64, and a voxel size of 3.44 × 3.44 × 3.40 mm. In each run, 200 EPI volume images were acquired along the AC–PC plane. High-resolution structural 192-slice T1 images were acquired using a 3D magnetization-prepared rapid gradient echo sequence with a TR of 2,530 ms, a TE of 3.5 ms, a TI of 1,100 ms, a FOV of 256 mm, and a flip angle of 7°. The duration of the fMRI scanning procedure was approximately 15 min for each participant.

The resting-state fMRI images were preprocessed using Data Processing Assistant for Resting-State fMRI toolbox [Chao-Gan and Yu-Feng, 2010] implemented in Matlab (MathWorks, Natick, MA). The preprocessing included slice-timing corrected, realigned, and normalized to the standard stereotaxic space of the Montreal Neurological Institute (MNI) EPI template and resampled to a 3-mm^3 voxel. The covariates of the BOLD time series were regressed out before complexity analysis was performed, including the time courses of six head motions and their derivatives and cerebrospinal fluids. No global signal regression was performed to avoid introducing distortion into the time series data [Anderson et al., 2011; Murphy
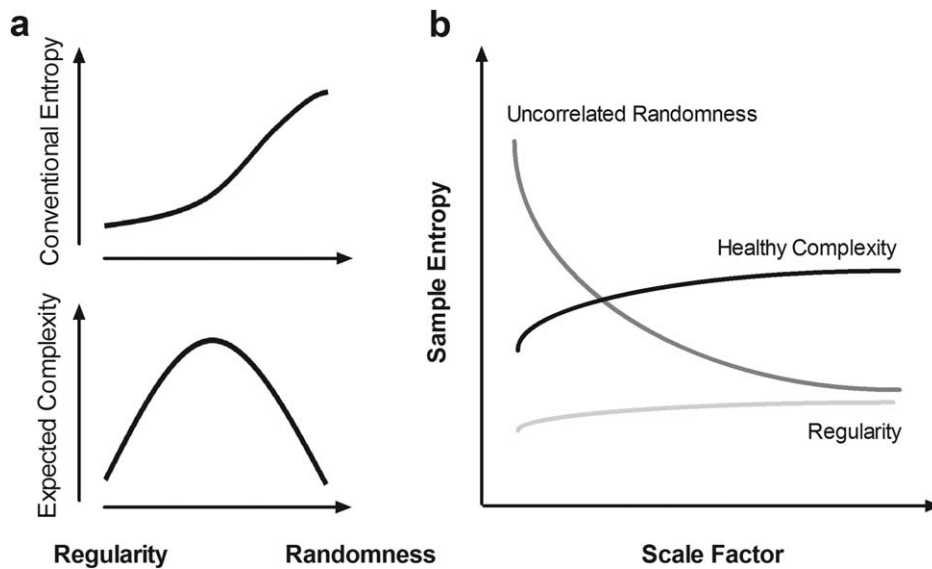
Figure 1.

Conceptual difference between randomness and complexity. (**a**) Conventional entropy is a measure of irregularity based on the single shortest time scale and involves assigning a higher entropy value to uncorrelated randomness, which is often observed in pathologic disease and presumed to convey less information than $1/f$ noise [Goldberger et al., 2002a,b]. The relationship between the expected complexity measure and randomness is inverse U-shaped; regularity and uncorrelated randomness are associated with reduced complexity, whereas meaningful complexity is in between [Buzsaki and Draguhn, 2004; Goldberger et al., 2002b]. (**b**) Multiscale entropy [Costa et al., 2002] cap- tures the concept that complex dynamics typically arise from multiple time scales; a generic approach to measuring global complexity involves considering multiple time scales in a given physical system [Fogedby, 1992; Zang, 1991]. In this context, uncorrelated randomness (dark gray line) has high entropy in the shortest time scale, but its entropy decays as the scale factor on a coarse time scale increases. By contrast, healthy complexity (black line) maintains entropy across all time scales, and regularity (light gray line) represents low entropy in all scale factors.

et al., 2009]. Physiological noise was minimized using band-pass temporal filtering (0.01–0.08 Hz). The voxels representing white matter and cerebrospinal fluids were excluded from the analysis using a gray matter mask, which was defined using a cohort-specific gray matter mask ($N = 315$) thresholding for partial volume estimates at 0.25. All participants exhibited a maximum displace- ment of less than 1.5 mm at each axis and an angular motion of less than 1.5° for each plane. The first five data points (12.5 s) in each BOLD time series were discarded because of the instability of initial MRI scanning; thus, 195 data points on each time series were used in analyses.

Analysis of the MSE of BOLD Signals

A conceptual illustration of MSE is provided in Figure 1. A conventional entropy method involves measuring irregularity and assigning a higher value when the irregu- larity of a given signal is increased. However, because con- ventional entropy is measured in the shortest time scale, the measured irregularity can represent either true com- plexity or merely uncorrelated randomness. Therefore, increased irregularity does not imply increased complexity [Goldberger, 1996; Goldberger et al., 2002b]. An ideal com- plexity measure assigns a high value to signals with a long-range correlation and other nonlinear properties (e.g., $1/f$ noise) and assigns a low value to signals with either regularity or uncorrelated randomness.

According to the theory that complex dynamics arise from multiple time scales and that a generic approach for measuring global complexity must consider multiple time scales in a given physical system [Fogedby, 1992; Zang, 1991], MSE analysis [Costa et al., 2002, 2005] was devel- oped to estimate sample entropy in multiple time scales using a coarse-graining procedure. Sample entropy is used in MSE analysis because it provides greater consistency and is less dependent on a given signal length compared with other entropy methods [Richman and Moorman, 2000]. MSE calculation can be summarized in the follow- ing three steps: (a) constructing coarse-grained time series according to different scale factors; (b) quantifying the sample entropy of each coarse-grained time series; and (c) examining the sample entropy profile over a range of scales. According to this method, the length of each coarse-grained time series is equal to the length of the

original time series divided by the scale factor. For Scale 1, the time series is merely the original time series.

Sample entropy is defined by the negative natural logarithm of the conditional probability that a dataset of length N, having repeated itself within a tolerance of r (similarity factor) for m points (pattern length), will also repeat itself for $m + 1$ points without allowing self-matches [Richman and Moorman, 2000]. We have previously used the parameters for MSE calculation from relatively short BOLD signals using the parameters $m = 1$ and $r = 0.35$ and scale factors up to 5 [Yang et al., 2014a, 2013a].

For a complexity analysis at the voxelwise level, the MSE of the BOLD signal was computed for all gray matter voxels to create a whole-brain MSE parametric map for subsequent group analysis. In addition, each BOLD time series was normalized for the zero mean and unit standard deviation before MSE analysis. Instead of averaging entropy across all scale factors as a proxy of the complexity index [Lu et al., 2012; Norris et al., 2009; Yang et al., 2014a, 2013b], we followed the patterns of three types of complexity change proposed by Costa et al. [2002 and 2005] to classify the MSE profiles of BOLD signals in each gray matter voxel.

Using the MSE of BOLD signals from healthy subjects as the reference, we investigated whether the MSE of BOLD signals from patients with schizophrenia showed increased complexity (i.e., increased entropy in all scales), reduced complexity toward regularity (i.e., decreased entropy in all scales), or reduced complexity toward randomness (i.e., increased entropy in short scales followed by rapid decay in entropy as the scale factors increase). The random type of MSE profile represented a unique property of uncorrelated randomness that cannot be captured by simply averaging the entropy of all scale factors; therefore, the slope of entropy decay was used as an indicator of complexity change in the random type of complexity changes.

Statistical Analysis

Statistical analysis of the MSE parametric imaging data was conducted using the MATLAB . Regional between-group differences in the whole-brain MSE mapping of each time scale were examined using the general linear model (GLM). Because age, sex, and handedness were well matched in the patient and control groups, we assessed the main effect of schizophrenia on MSE complexity without introducing covariates to the GLM. To assess the association between the type of MSE complexity change and the psychopatholgy, we regressed the clinical variables (age of onset, duration of illness, CPZ dosage, and PANSS scores) with the mean MSE value of all scale factors at the voxelwise level for increased MSE complexity or the regularity type of MSE complexity changes. For the randomness type of MSE complexity change, we regressed the clinical variables with the slope of entropy decay across all scale factors. For all voxelwise analyses, significant brain clusters with peak coordinates in the MNI

space were reported only if the P value corrected for multiple comparisons using the familywise error (FWE) rate was lower than 0.05 at the cluster level.

RESULTS

Between-Group Comparison of MSE Profiles in Different Time Scales

Figure 2 shows the regional between-group differences in the MSE of BOLD signals among all scale factors at the voxelwise level. Observing MSE profiles (i.e., patterns of between-group entropy differences in a scale of 1–5) showed that, in schizophrenic patients, BOLD signals in the occipital, inferior frontal, and postcentral cortices exhibited a pattern of increased entropy in Scales 1 and 2, followed by decreased entropy in Scales 3–5, compared with the BOLD entropy of healthy subjects. However, entropy in the temporal cortex was reduced in all scale factors in schizophrenic patients. These observations suggested that schizophrenia exhibits two patterns of scale-related entropy change in different brain regions.

Quantification of Different Types of Complexity Change According to MSE Profile

Figure 3 shows MSE profiles extracted from the inferior temporal cortex and inferior frontal cortex. The MSE profile in the inferior temporal cortex (Fig. 3a) showed that patients with schizophrenia exhibited a reduction in entropy in all scale factors compared with healthy controls, suggesting that a regular type of complexity changes occurred in this brain region. However, the MSE profile in the inferior frontal cortex (Fig. 3b) showed that, relative to the controls, the patients with schizophrenia exhibited increased entropy in short scales, followed by decreased complexity as the scale factor increased, suggesting a pattern of complexity changes toward randomness. This randomness pattern is distinguishable from the increased physiologic complexity that is expected to occur when entropy increases in all scale factors. The regular type of complexity change was quantified according to the average sample entropy across all scale factors, whereas the random type of complexity change was assessed using the slope of entropy decay. The effect size for the difference in complexity metrics between schizophrenia and healthy subjects was 0.47 for inferior temporal cortex and 0.45 for inferior frontal cortex.

Figure 4 shows that most brain regions exhibited a random pattern of BOLD complexity changes, whereas few brain regions showed decreased complexity toward regular patterns. Table II details the significant brain regions for each type of complexity change. No brain region in patients with schizophrenia exhibited significantly increased complexity compared with the brain regions of healthy subjects. Schizophrenic patients showed decreased complexity
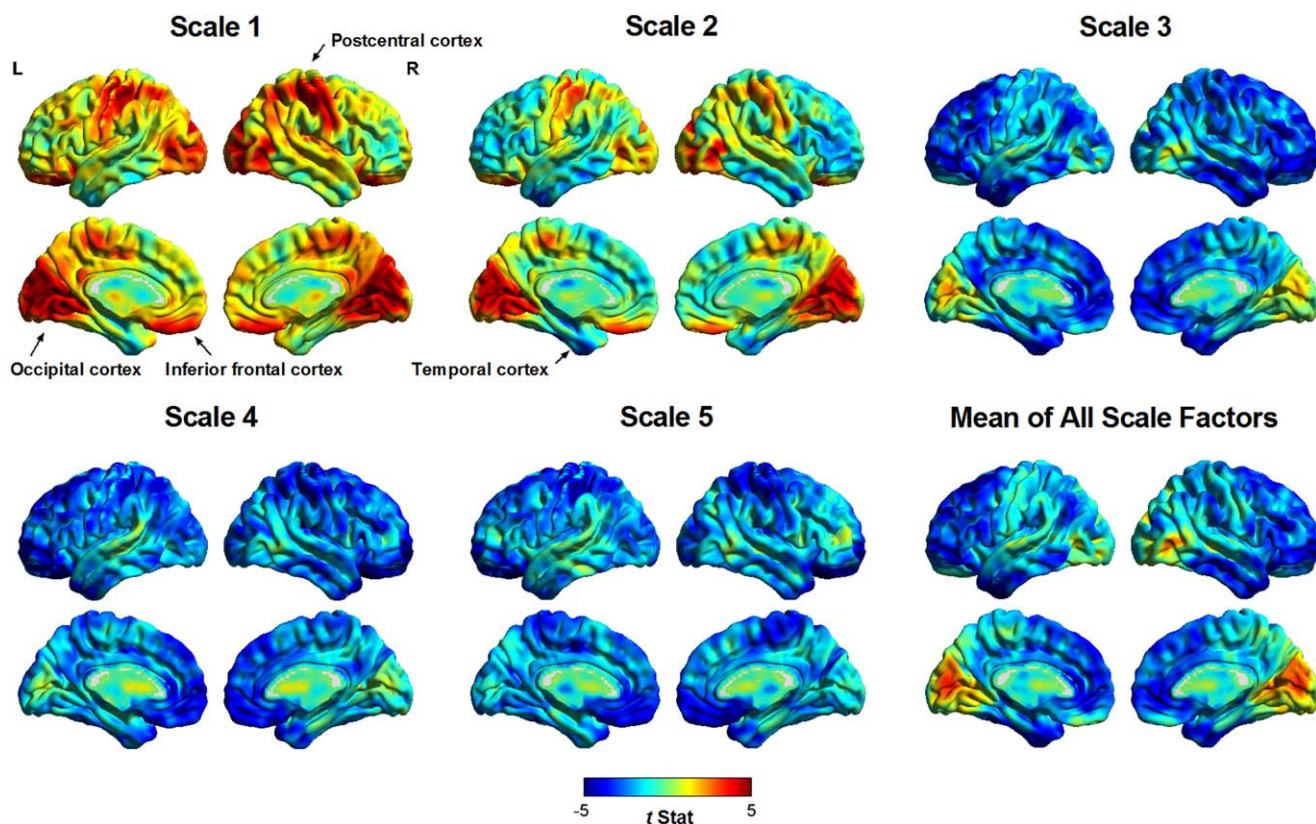
Figure 2.

Regional differences in the MSE complexity of resting-state BOLD activity in all scale factors between patients with schizophrenia and healthy subjects. A positive *t* value (warm color spectrum) represents a higher MSE value in patients with schizophrenia than in healthy subjects, and vice versa for results shown with negative *t* values (cool color spectrum). Visual inspection suggested two patterns of pathologic change in patients with schizophrenia. The occipital, postcentral, and infe- rior frontal cortices of patients with schizophrenia exhibited increased entropy (randomness) in short time scales (Scales 1 and 2) and reduced entropy (regularity) in coarse time scales (Scales 3–5) compared with those of healthy volunteers. By con- trast, the inferior temporal cortex exhibited reduced entropy (regularity) across all scale factors. These two patterns of entropy change were consistent with a shift in BOLD dynamics toward randomness and regularity, respectively.

toward regular patterns in the left inferior temporal (peak $t = -5.62$), right inferior temporal ($t = -5.52$), right middle frontal ($t = -5.73$), left middle frontal ($t = -4.74$), left supe- rior frontal ($t = -4.47$), and left supplementary motor corti- ces ($t = -3.39$) as well as the anterior lobe ($t = -3.99$) and posterior lobe of the cerebellum ($t = -6.10$). Conversely, decreased complexity toward randomness was observed in patients with schizophrenia in clusters of the inferior frontal ($t = -6.35$), postcentral ($t = -5.23$), and occipital cortices ($t = -6.57$) as well as the right insula ($t = -4.18$) and left middle cingulum ($t = -4.48$).

Correlation of the Type of Complexity Change with Psychopathology

Table III summarizes the correlation between the regular type of complexity change and psychopathology. The

results showed that the PANSS positive syndrome score was negatively correlated with MSE complexity in the right fusiform gyrus (correlation coefficient *r* at peak voxel $= -0.40$) and the left fusiform and temporal pole of the middle temporal region ($r = -0.35$), whereas the PANSS negative syndrome score was negatively correlated with MSE complexity in the left posterior lobe of the cere- bellum ($r = -0.53$).

Table IV summarizes the correlation between the random- ness type of complexity change and psychopathology. Age of onset was correlated positively with the slope of MSE change in the left medial orbitofrontal gyrus ($r = 0.61$). The duration of illness was correlated negatively with the slope of MSE change in the right lingual gyrus ($r = -0.50$) and right postcentral gyrus ($r = -0.44$). The PANSS negative syndrome score was correlated negatively with the slope of MSE change in the left orbitofrontal gyrus ($r = -0.43$), left
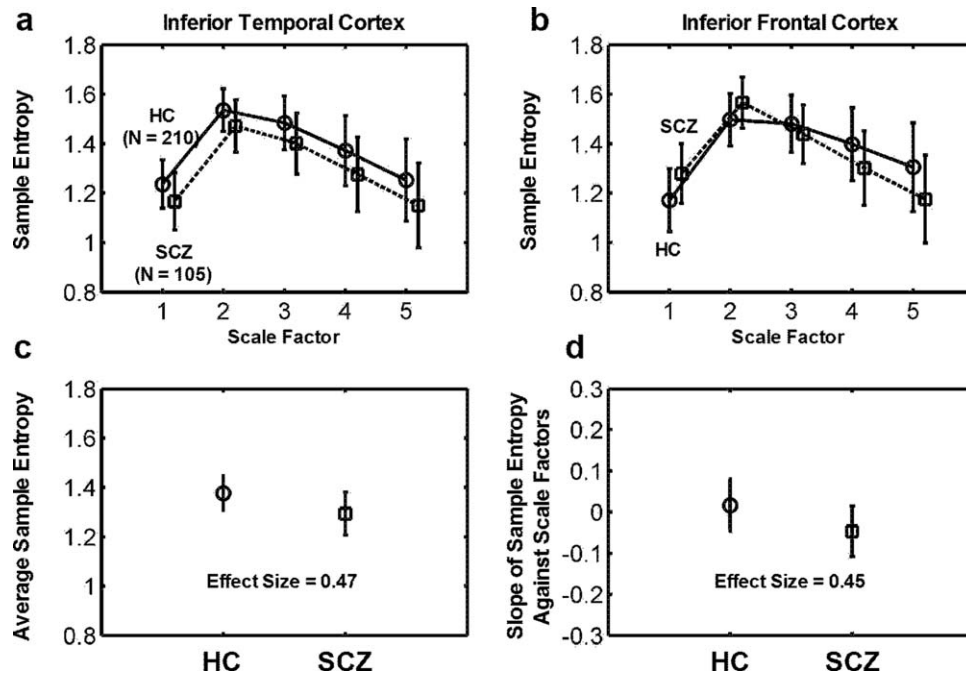
Figure 3.

Two types of complexity change according to the MSE complexity profile of BOLD signals (scale factor vs. mean ± SD of sample entropy) extracted from (**a**) the inferior temporal cortex and (**b**) the inferior frontal cortex. The MSE complexity profile of (a) the inferior temporal cortex showed lower BOLD sample entropy in patients with schizophrenia (SCZ) than in healthy comparison (HC) subjects in all scale factors ($P_{FWE} < 0.05$). By contrast, the MSE complexity profile of (b) the inferior frontal cortex showed higher BOLD entropy in SCZ than in HC in Scale 1, and the entropy values in SCZ exhibited a crossover with the MSE profile of HC. SCZ exhibited a lower BOLD entropy than HC in Scales 4 and 5 (P_{FWE} were < 0.05 in Scales 1, 4, and 5). We defined two quantitative measures for assessing these two types of complexity change toward (a) regularity and (b) randomness. (**c**) For the regularity type of complexity change, we used the average sample entropy as an index to assess the extent of increased regularity of BOLD signals in SCZ. (**d**) For the randomness type of complexity change, we used the slope of the sample entropy against scale factors 1–5 to assess the extent of increased randomness of BOLD signals in SCZ.

middle occipital gyrus ($r = -0.44$), right cuneus and part of the superior occipital gyrus ($r = -0.52$), left cuneus and part of the superior occipital gyrus ($r = -0.46$), left postcentral gyrus and superior parietal gyrus ($r = -0.46$), and right postcentral gyrus ($r = 0.46$). The CPZ dosage, PANSS score in general psychopathology, and total PANSS score were not associated with any type of complexity change. All brain clusters reported in the results had FWE-corrected P values lower than 0.05.

DISCUSSION

The current analyses show that patients with schizophrenia exhibit a reduced resting-state fMRI complexity compared with healthy subjects. Furthermore, in contrast to conventional entropy analysis, in which single-time-scale regularity is measured, the MSE profiles in different time scales reveal two routes of decreased BOLD complexity toward either a regular or random pattern. Reduced

BOLD complexity toward the regular pattern is observed in the cerebellum and temporal, middle, and superior frontal regions, and reduced BOLD complexity toward the random process is observed extensively in the inferior frontal, occipital, and postcentral cortices as well as in the insula and middle cingulum. We determine that these two types of complexity change are associated with psychopathology and clinical variables differently. Collectively, these results suggest that resting-state dynamics in patients with schizophrenia exhibit two patterns of pathologic change toward regular or random patterns, and these patterns may contribute to the differences in the syndrome domains of psychosis in schizophrenia.

Implication of Different Types of Complexity Change in the Pathophysiology of Schizophrenia

MSE profile analysis introduces the notion that the neither the extremes of complete regularity nor complete
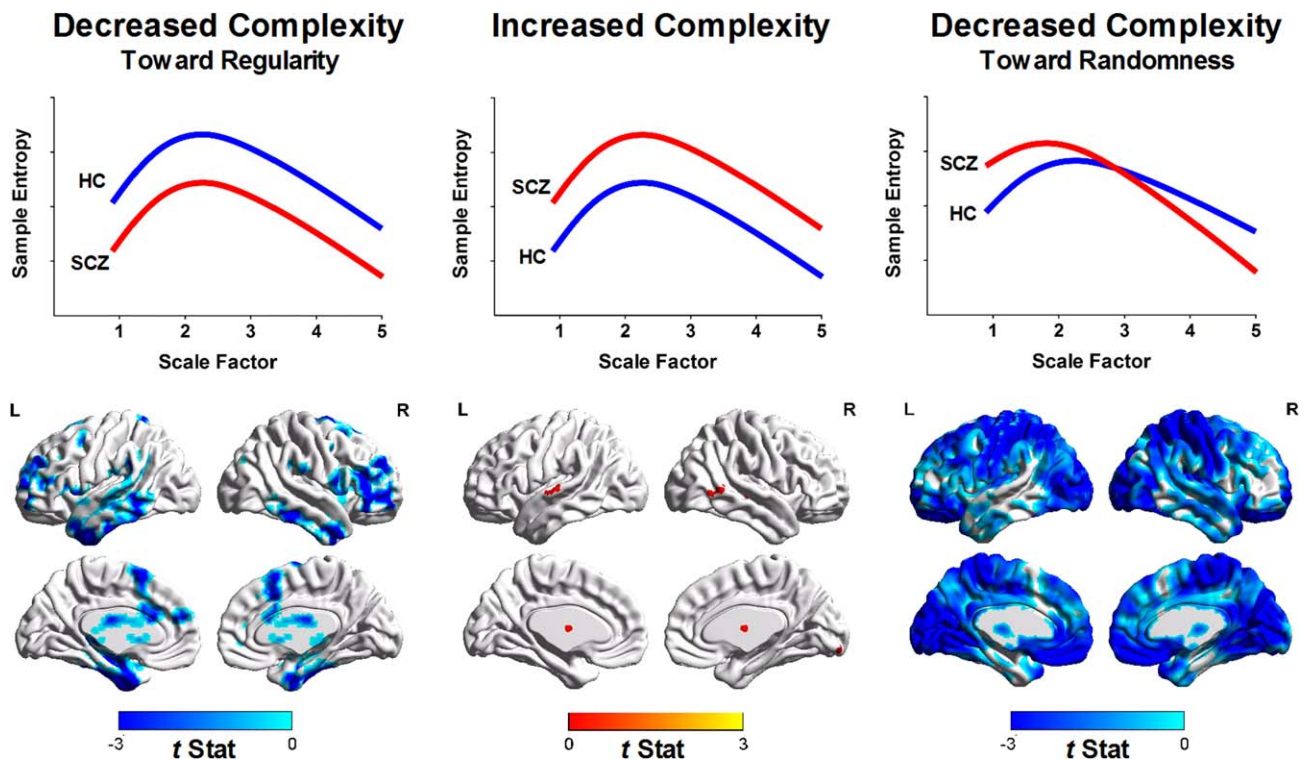
Figure 4.

Quantification of complexity changes in patients with schizophrenia (SCZ) relative to healthy controls (HC) according to MSE profiles. (Left) Brain regions with the regularity type of complexity changes of BOLD signals (i.e., decreased sample entropy over all scale factors in SCZ relative to HC). (Middle) Brain regions with increased complexity of BOLD signals (i.e., increased sample entropy over all scale factors in SCZ relative to HC). Color shown in brain mapping represents raw *t*-statistics of difference of MSE profile between SCZ and HC. No significant brain cluster was observed in this type of complexity change after correction for multiple comparisons. (Right) Brain regions with the randomness type of complexity change (i.e., increased sample entropy in short time scales followed by decay of sample entropy as the scale factor increases).

randomness are complex [Costa et al., 2005]. However, the alteration of system complexity toward regularity or randomness represents two distinct physical or biological processes. For example, heart rate fluctuation under different pathologic conditions may exhibit a loss of variability toward regularity (e.g., congestive heart failure) or the emergence of uncorrelated randomness (e.g., atrial fibrillation) [Goldberger et al., 2002a]. Likewise, our findings regarding the MSE profiles of BOLD signals toward regular or random patterns suggest that schizophrenia is characterized by two pathologic processes. This observation warrants future studies to investigate the specificity of these pathologic changes of MSE profile associated with schizophrenia and assess the difference in brain complexity with other mental illness or different brain states (e.g., sleep or psychedelic state).

Although the exact biological mechanisms contributing to these two types of complexity change were not delineated in this study, the differential associations of BOLD MSE profiles with psychopathology may provide clues. The PANSS positive syndrome score is associated with the fusiform gyrus and middle temporal gyrus, which exhibit a regular pattern of reduction in complexity; previous studies have shown that these brain regions are associated with auditory or imaginary hallucinations [Lawrie et al., 2002; Santhouse et al., 2000; Shergill et al., 2000]. One explanation, although speculative, is that the core of positive symptoms in schizophrenia is characterized by repetitive and involuntary hallucinatory experiences and fixed delusional thoughts, which manifest the lack of variability and may be linked to the loss of brain complexity toward regular patterns in the temporal and dorsal prefrontal regions (Table II).

Conversely, the PANSS negative syndrome score is associated with a random type of reduction in complexity among brain regions, involving the orbitofrontal, occipital, and postcentral cortices (Table IV). These brain regions are related to affect and sensory processing. The duration of illness was negatively correlated with reduced complexity in the postcentral cortex. These results collectively suggest

TABLE II. Regions showing significant changes in the MSE complexity profiles of BOLD signals from patients with schizophrenia

Brain region[a]	BA	MNI coordinates (mm)			Volume (mm³)[b]	Peak t
		x	y	z		
Increased complexity						
None						
Decreased complexity toward regularity						
L inferior temporal gyrus	20/21	−39	0	−42	19,710	−5.62
R inferior temporal gyrus	20/21	36	6	−39	13,743	−5.52
R middle frontal gyrus	10	30	63	−3	10,206	−5.73
L middle frontal gyrus	10	−33	63	3	2,268	−4.74
L superior forntal gyrus	10/9	−27	54	33	864	−4.47
R superior frotnal gyrus	10/9	18	54	33	1,539	−4.84
L supplementary motor area		3	12	57	1,026	−3.99
R/L cerebellum posterior lobe		−33	−75	45	39,744	−6.10
L cerebellum anterior lobe		−27	−57	−30	1,674	−3.99
Decreased complexity toward randomness						
L/R inferior frontal gyrus	11/47	−18	30	−27	48,600	−6.35
L/R occipital lobe	18/19	18	−84	30	98,955	−5.23
R insula		39	−27	18	2,727	−4.18
L/R postcentral gyrus	6/3	−48	−21	60	95,175	−6.57
L middle cingulum	24	−12	−9	42	1,755	−4.48

All brain clusters had P value < 0.05 corrected for multiple comparisons using familywise error methods.
[a]L, left; R, right; BA, Brodmann area
[b]Volume was computed from cluster size ($3 \times 3 \times 3$ mm voxel).

that a random type of reduction in BOLD complexity is linked to chronicity and negative symptoms of schizophrenia. Furthermore, erratic brain activity in these brain regions is consistent with the impaired sensory gating and sensory overload commonly observed in patients with schizophrenia [Bak et al., 2014; Brockhaus-Dumke et al., 2008; Judd et al., 1992].

Other associations of psychopathology with decreased BOLD complexity are consistent with clinical presentations of schizophrenia. The negative correlation between the PANSS negative syndrome score and the regular type of reduced complexity in the cerebellum is consistent with recent findings of reduced complexity of postural sway in

schizophrenia [Kent et al., 2012]. The positive correlation between age of onset and MSE complexity in the orbitofrontal region indicated that an earlier onset of illness is associated with a stronger degree of reduction in brain complexity toward randomness.

Remarks on Complexity Measures

The term complexity has been broadly used in neuroscience research. Various nonlinear methods have been applied to quantify the complexity of a neurophysiological time series in the temporal dimension, including the power–law spectra [Tagliazucchi et al., 2014; Zarahn et al.,

TABLE III. Regions showing a significant correlation between clinical variables and the regular type of complexity change in patients with schizophrenia

Brain region[a]	BA	MNI coordinates (mm)			Volume (mm³)[b]	Peak t
		x	y	z		
PANSS positive syndrome						
R fusiform gyrus	20	24	−12	−42	1,647	−4.43
L fusiform gyrus and temporal pole of middle temporal gyrus	38	−15	−3	−42	1,458	−3.85
PANSS negative syndrome						
L cerebelum posterior lobe		−42	−69	−30	1,782	−6.42

All brain clusters had P value < 0.05 corrected for multiple comparisons using familywise error methods.
[a]L, left; R, right; BA, Brodmann area
[b]Volume was computed from cluster size ($3 \times 3 \times 3$ mm voxel).

TABLE IV. Regions showing a significant correlation between clinical variables and the randomness type of complexity change in schizophrenia

Brain region[a]	BA	MNI coordinates (mm)			Volume (mm³)[b]	Peak t
		x	y	z		
Age of onset						
L medial orbitofrontal gyrus	11	3	39	−12	2,025	7.84
Duration of illness						
R lingual gyrus	18	9	−67	0	918	−5.79
R postcentral gyrus	40	48	−36	56	999	−4.97
PANSS negative syndrome						
L orbitalfrontal gyrus	11	6	54	−24	3,753	−4.85
L middle occipital gyrus	18	−27	−96	6	864	−4.99
R cuneus and superior occipital gyrus	19	15	−93	33	1,242	−6.23
L cuneus and superior occipital gyrus	19	−15	−93	33	1,026	−5.25
L postcentral gyrus and superior parietal gyrus	2	−36	−51	63	1,134	−5.24
R postcentral gyrus	3	42	−36	66	1,188	−5.27

All brain clusters had P value < 0.05 corrected for multiple comparisons using familywise error methods.
[a]L, left; R, right; BA, Brodmann area
[b]Volume was computed from cluster size ($3 \times 3 \times 3$ mm voxel).

1997], Hurst exponent [Bullmore et al., 2001; Lai et al., 2011], fractal dimension [Rubinov et al., 2009], Lyapunov exponent [Xie et al., 2008], and Lempel–Ziv complexity [Fernandez et al., 2011], as reviewed by Fernandez et al. [2013] and Takahashi [2013]. However, both increases and decreases in the complexity of brain signals have been reported in schizophrenic patients. The inconsistencies among the results of these studies may have been caused by differences in the study population, definition of the various types of complexity methods, or (most plausibly) by the simple up-and-down approach used to detect complexity changes in a single time scale along the continuum of regularity toward randomness, leading to the confusing conclusion that randomness is complex in certain cases. Therefore, MSE profile analysis across time scales provides crucial information on the complex dynamics of underlying processes and enables differentiating meaningful complexity from uncorrelated randomness [Chialvo, 2002; Costa et al., 2002; Takahashi et al., 2010; Yang et al., 2013c]. Such notion complements the monotonic view of entropy changes in different brain states [Carhart-Harris et al., 2014; Tagliazucchi et al., 2014].

Furthermore, the relationship between the variability of local activity and connectivity strength in a given brain region remains underexplored. Bassett et al. [2012] showed that the complexity of a time series from an individual brain region is strongly predictive of the overall functional connectivity of the brain, and the strength of this relationship is altered in patients with schizophrenia. Recently, we reported that reduced BOLD complexity in elderly apolipoprotein E carriers exhibited a compensatory increase in functional connectivity between the posterior cingulum and frontal regions [Yang et al., 2014a]. The relationship between BOLD temporal complexity and spatial connectiv-

ity is likely nonlinear. A recent study based on Human Connectome Project data showed that BOLD complexity was negatively correlated with functional connectivity in short scales, but was positively correlated with functional connectivity in long scales [McDonough and Nashiro, 2014]. Incorporating both temporal and spatial complexity methods in future studies may facilitate elucidating the pathophysiology of schizophrenia in the context of the complex brain network.

Although the generic feature of dynamical complexity detected by the MSE method is independent of signal characteristics [Costa et al., 2005], the equivalence of MSE complexity metrics between resting-state fMRI signals and electrophysiological time series is yet to be determined. The resting-state fMRI signal and electrophysiological time series (such as electroencephalographic signals) certainly carry different aspects of neuronal information via distinct mechanisms. The former is based on neurovascular coupling which its hemodynamic response is in low frequency range (<0.1 Hz), whereas the latter is typically a measure of electrical activity over the scalp and is within a much higher frequency range (∼1–50 Hz). From the signal analysis point of view, the MSE calculation for these two types of signals captures dynamical information in very different time scales. Hence, we anticipate that MSE profile of BOLD signals may be equivalent of long time scale part of MSE profile of EEG signals (i.e., applying a large scale factor to EEG signals in coarse-graining procedure).

Limitations

There are several limitations to our findings. First, although our results did not show that reduced resting-state complexity was correlated with antipsychotic

dosages, little is known about the effects of antipsychotic drugs on BOLD signals. A meta-analysis revealed no common effect of antipsychotics on BOLD signals; however, antipsychotics with various affinities for the dopamine D2-receptor may influence BOLD activity [Rder et al., 2013]. A future study categorizing patients with schizophrenia according to various outcomes or classes of antipsychotics may clarify this effect. Second, the extent of the scale factor used in MSE analysis was limited to the length of BOLD time series (195 data points); therefore, the MSE complexity profiles based on scales of 1–5 may have captured only a portion of the underlying dynamics, unlike long resting-state fMRI signals such as those used in the Human Connectome Project [McDonough and Nashiro, 2014; Van Essen et al., 2013]. However, we suggest that this limitation had little effect on our data because previous MSE analyses of other physiologic signals [Costa et al., 2002, 2005] and BOLD signals in various brain regions [McDonough and Nashiro, 2014; Smith et al., 2014] suggested that randomness and meaningful complexity could be differentiated in the shortest scale factors. Third, we did not perform global signal regression to prevent distortion in BOLD signals; however, another study identified a difference in global signals between patients with schizophrenia and healthy subjects [Yang et al., 2014b]; this difference warrants further study of the effects of global signals on MSE estimates in healthy and disease populations. Finally, the relationship between the complexity of BOLD signals and their frequency components has not been established. Such study will facilitate delineating the functional relevance of BOLD complexity.

CONCLUSION

Using MSE profile analysis, we evaluate the complexity of resting-state brain activity in patients with schizophrenia and its relationship with the psychopathology of illness. Our findings represent a novel perspective on the temporal dynamics of functional brain activity and enhance the understanding of the various pathophysiologic processes in schizophrenia. On a broader scale, analyzing the complexity of the human brain at the temporal dimension may facilitate developing clinically useful imaging biomarkers.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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