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Antipsychotics reverse abnormal EEG complexity in drug-naïve schizophrenia: A multiscale entropy analysis

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Abstract

Multiscale entropy (MSE) analysis is a novel entropy-based approach for measuring dynamical complexity in physiological systems over a range of temporal scales. To evaluate this analytic approach as an aid to elucidating the pathophysiologic mechanisms in schizophrenia, we examined MSE in EEG activity in drug-naïve schizophrenia subjects pre- and post-treatment with antipsychotics in comparison with traditional EEG analysis. We recorded eyes-closed resting state EEG from frontal, temporal, parietal and occipital regions in drug-naïve 22 schizophrenia and 24 age-matched healthy control subjects. Fifteen patients were re-evaluated within 2–8 weeks after the initiation of antipsychotic treatment. For each participant, MSE was calculated on one continuous 60 second epoch for each experimental session. Schizophrenia subjects showed significantly higher complexity at higher time scales (lower frequencies), than that of healthy controls in fronto-centro-temporal, but not in parieto-occipital regions. Post-treatment, this higher complexity decreased to healthy control subject levels selectively in fronto-central regions, while the increased complexity in temporal sites remained higher. Comparative power analysis identified spectral slowing in frontal regions in pre-treatment schizophrenia subjects, consistent with previous findings, whereas no antipsychotic treatment effect was observed. In summary, multiscale entropy measures identified abnormal dynamical EEG signal complexity in anterior brain areas in schizophrenia that normalized selectively in fronto-central areas with antipsychotic treatment. These findings show that entropy-based analytic methods may serve as a novel approach for characterizing and understanding abnormal cortical dynamics in schizophrenia, and elucidating the therapeutic mechanisms of antipsychotics.

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Keywords

Drug-naïve schizophrenia; Electroencephalography (EEG); Complexity; Multiscale entropy (MSE); Antipsychotics

Introduction

Since the “disconnection hypothesis” was proposed as a pathophysiologic mechanism in schizophrenia (Friston, 1998), there has been accumulating evidence of abnormal functional connectivity in schizophrenia. The disconnection hypothesis proposes that there exist failures in spatio-temporal interactions in the brains of schizophrenia patients. There are a number of reports of *spatial disorganization* in schizophrenia in both morphological (Mandl et al., 2008; Rosenberger et al., 2008; Spoletini et al., 2009) and physiological studies (Kasai et al., 2002; Pae et al., 2003; Winterer et al., 2003) including functional magnetic resonance imaging (fMRI) (Garritty et al., 2007; Prata et al., 2009). In addition to referring to *spatial disorganization* across cortical regions, the term “disconnection hypothesis” may also be extended to denote *temporal disorganization* of sequentially expressed dynamical states within cortical regions (Breakspear, 2006). Because current neural activity can be influenced by past neural processes that have been stored dynamically through feedback loops at multiple, hierarchic levels of cortical processing (Fell et al., 2000), neurophysiologic signals may reflect history effects in underlying dynamics. If temporal disorganization of neural dynamics could play an important role in the pathophysiology of schizophrenia, effective ways of evaluating the temporal integration in neurophysiologic signals will be essential for investigating temporal disconnection in schizophrenia.

Electrophysiological methods provide the temporal resolution (milliseconds) to examine normal and pathologic temporal dynamics that may be obscured by some neuroimaging modalities (e.g., fMRI, positron emission tomography) that temporally smooth the neural signal. Many of the studies of temporal dynamics in schizophrenia have focused on the ability of neurons to engage in synchronous activity, examining spatially local (Cho et al., 2006; Spencer et al., 2004) or long-range indices (Uhlhaas et al., 2006) of such coordinated activations. However, these approaches have examined synchronous electroencephalographic (EEG) activity, i.e., activity that is phase-locked across trials with respect to particular task events or neuronal oscillations that are phase locked to each other, either within or across brain areas. Alternate methods may be necessary, then, to examine processes that involve the integration of activations across varying time scales in the service of information processing.

Nonlinear dynamical approaches to characterizing complex temporal dynamics have revealed novel insights into a wide range of physiological systems from autonomic (Yeragani et al., 2005), respiratory (Caldirola et al., 2004), to neural activity (Stam, 2005) in psychiatric disorders (Pincus, 2006). The activity of neural networks can be described as nonlinear dynamic processes regulated by multiple couplings and feedback loops within and across multiple neuronal populations. As such, analytic tools developed to characterize nonlinear dynamical processes may be fruitfully applied to brain signals and may be useful for understanding mechanisms of disease in psychiatric disorders (Stam, 2005). There is a growing literature reporting nonlinear EEG analyses in psychiatric disorders, and initial applications to disorders such as schizophrenia provide evidence for the possible utility of nonlinear methods to understanding pathophysiologic processes in this illness (Irisawa et al., 2006; Jalili et al., 2007; Jeong et al., 1998; Keshavan et al., 2004; Kikuchi et al., 2007; Kim et al., 2000; Koenig et al., 2001; Koukkou et al., 1993; Lee et al., 2001; Li et al., 2008; Micheloyannis et al., 2006; Raghavendra et al., 2009; Rubinov et al., 2009; Sabeti et al., 2009).

One approach to the nonlinear estimation of dynamical EEG activity is complexity analysis. Among complexity analysis approaches, entropy-based algorithms have been useful and robust estimators for evaluating EEG regularity or predictability. Approximate entropy (ApEn) (Pincus, 1995; Pincus, 1991) and its refined version, sample entropy (SampEn; Richman and Moorman, 2000) were developed as practically tractable physiological measures in view of their robustness to noise and finitude of data sets, and can be applied to stochastic, nonlinear-deterministic and composite processes (Pincus and Goldberger, 1994; Richman and Moorman, 2000). These two entropy indices have been successfully applied to EEG analysis in Alzheimer's disease (Abasolo et al., 2005), seizures (Yum et al., 2008), anesthesiology (Jordan et al., 2008), hypoxia (Papadelis et al., 2007) and sleep (Burioka et al., 2005). Recently, Costa and colleagues (2002, 2005) introduced multiscale entropy (MSE), a useful extension of such methods to multiple time scales, in recognition of the likelihood that dynamical complexity of biological signals may operate across a range of temporal scales. Since interactions due to both local dense interconnectivity and sparse long-range excitatory projections give rise to the outputs of neuronal networks (Friston et al., 1995; Tononi et al., 1994), the resulting dynamics could be expected to operate at multiple scales. Further, evidence from previous EEG studies indicate that pathophysiological processes may be measurable at specific frequency bands (i.e., time scales) in schizophrenia (Boutros et al., 2008; Kargieman et al., 2007; Koenig et al., 2001; Kikuchi et al., 2007), suggesting that pathologic processes in the temporal integration of information may similarly manifest at particular time scales. MSE approaches, being well suited to assessing complexity across multiple time scales, have been fruitfully applied to EEG data, providing novel insight into physiological mechanisms in neuronal spiking patterns in human (Bhattacharya et al., 2005), studies of aging (McIntosh et al., 2008; Takahashi et al., 2009) and dementia (Escudero et al., 2006). Many nonlinear EEG approaches have demonstrated alterations in interactions across cortical regions (Breakspear et al., 2003; Irisawa et al., 2006; Jalili et al., 2007; Kikuchi et al., 2007; Koenig et al., 2001; Micheloyannis et al., 2006; Rubinov et al., 2009) or in temporal complexity (Jeong et al., 1998; Keshavan et al., 2004; Kim et al., 2000; Koukkou et al., 1993; Lee et al., 2001; Li et al., 2008; Raghavendra et al., 2009; Sabeti et al., 2009). However, there have been no studies that investigate temporal complexity across multiple time scales in schizophrenia.

In the present study, our aim was to examine possible disturbances in the complexity of EEG signals across multiple time scales in schizophrenia and the possible effects of antipsychotic treatment. To this end, we investigated resting state EEG activity using MSE in drug-naïve schizophrenia subjects pre- and post-treatment with antipsychotics. To aid in the interpretation of results, we also complemented these analyses with more traditional power analysis as well as simulations of signals at different frequencies.

Methods and Materials

Subjects

Twenty two patients (14 male, 8 female) with mean age of 25.6 years (18–38, SD: 4.8) who met DSM-IV criteria for schizophrenia or schizophreniform disorder were recruited from the Department of Psychiatry and Neurobiology, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan. The patients diagnosed with schizophreniform disorder at the time of our study were later diagnosed as having schizophrenia. None of the patients had ever been treated with neuroleptics before the first EEG recording. Treatment was initiated after the first EEG recording. There were no limitations on the type or dosage of medications, which was left to the discretion of the patient's treating psychiatrist. Fifteen patients (8 male, 7 female) with mean age of 25.7 years (18–38, SD: 5.1) received the second EEG recording. The second EEG took place after 2–8 weeks of antipsychotic treatment. Most patients were treated with conventional dopamine-blocking neuroleptics, with a few patients receiving serotonin-

dopamine antagonists. Some patients additionally received anticholinergic agents, antihistaminergic agents or benzodiazepine derivatives. At the time of the second EEG, mean risperidone equivalent dose (Inagaki et al., 2001; Toru, 1983) was 3.1 mg/day (range: 0.5 – 6.5 mg). The patients' symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) on the day of the EEG recordings. From among the staff of Kanazawa University Hospital and their family members, twenty four healthy controls (14 male, 10 female) with mean age of 24.0 years (20–35, SD: 4.8) were recruited. They were group-matched to the patients for age, gender, but the control group had more years of education than the schizophrenia group (Table 1). Controls had no personal or family history of psychiatric or neurological disease. All subjects were right-handed. Subjects with major medical or neurological conditions including epilepsy, significant head trauma or electroconvulsive shock treatment in the past, or a lifetime history of alcohol or drug dependence were excluded. Demographics are summarized in Table 1. The protocol of the study was approved by the Ethics Committee of the Kanazawa University. The study followed the rules and regulations of the University hospital regarding patient studies and personal information, and following Declaration of Helsinki guidelines. Informed consent was obtained from all participants.

EEG recording

The subjects were studied while lying in an electrically shielded, soundproof, light-controlled recording room. Standard scalp electrodes were placed in accordance with the International 10–20 System: Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, P3, P4, Pz, T5, T6, O1, and O2, referenced to linked ear lobe electrodes. Eye movements were monitored using additional electro-oculographic channels. The EEG was recorded at 200 Hz sample frequency with a 1.5 to 60 Hz bandpass filter, and using an 18-channel system (EEG-44189, Nihon Kohden, Tokyo, Japan). Impedances were kept less than 5 kΩ. Other pre-processing steps were not conducted (i.e., filtering, artifacts removal or data reconstruction), because of the likelihood that such processing could introduce distortions in the data that could affect the MSE assessments.

For each participant, MSE was calculated on one continuous 60 second (12000 data points) artifact-free epoch. Artifacts such as eye movements, blinks, muscle activities or other artifacts were visually identified and excluded. Finally, eye movement artifacts were seen in some subjects in Fp1 and Fp2; therefore we excluded these two sites from the analysis.

Multiscale entropy (MSE)

The MSE method quantifies the degree of complexity in a time series at multiple temporal scales using a coarse-graining procedure (Costa et al., 2002, 2005). Irregularity at each scale is measured by SampEn, a correlation entropy version of Kolmogorov-Sinai entropy (Kolmogorov, 1958), which is well suited for analyzing short and noisy experimental data (Richman et al., 2004; Richman and Moorman, 2000).

SampEn is the negative of the logarithmic conditional probability that two sequences of m consecutive data points which are similar to each other (within given tolerance r) will remain similar at the next point ($m + 1$) in the data set (N), where N is the length of the time series. Considering the EEG time series $\{x_1, x_2, \dots, x_N\}$ as observations of a stochastic variable x , dynamic SampEn is defined as: $h_{\text{samp}}(r, m, N) = \log_e [C_{m+1}(r)/C_m(r)]$, where $C_m(r) = \{\text{number of pairs } (i, j) \text{ with } |x_i^m - x_j^m| < r, i \neq j\} / \{\text{number of all probable pairs, i.e. } (N - m + 1)(N - m)\}$. Therein, x^m is a vector of m sample time series of $(N - m)$ length, and $|x_i^m - x_j^m|$ denotes the distance between points x_i^m and x_j^m in the space of dimension m , and r is the effective filter for measuring consistency of time series.

In the analysis, we first embedded the time series into a m dimensional space in the form of a vector $x^m_i = \{x_i, x_{i+1}, \dots, x_{i+m-1}\}$ and counted the points which stay around x^m_i within distance r . Then, we summed up all counts to produce the numerator of $C_m(r)$, a measure of correlation by its definition. $-\log_e [C_m(r)]$ is the information content, and the difference in information content for vectors of length m and $m+1$, $h_{\text{samp}}(r, m, N) = (-\log_e [C_m(r)]) - (-\log_e [C_{m+1}(r)])$, defines the rate of information content loss, or alternatively, a measure of entropy production rate. (For details of the SampEn algorithm see Richman et al., 2004; Richman and Moorman, 2000).

For the extension to multiple time scales, the original EEG time series $\{x_1, x_2, \dots, x_N\}$ was coarse-grained by the scale factor (SF) τ , with non-overlapping windows as follows:

$$y_j^{(\tau)} = (1/\tau) \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leq j \leq N/\tau$$

Then, the SampEn was calculated for each series $\{y^{(\tau)}\}$. For the coarse-grained time series at SF $\tau = 1$, the time series $\{y^{(1)}\}$ was simply identical to the original time series; SampEn values for low SFs captured short-range temporal irregularity, while high SFs captured long-range temporal irregularity. Various theoretical and clinical applications have shown that $m = 1$ or 2 , and $r = 0.1 - 0.25$ of the standard deviation of the data points provides good statistical validity for SampEn (Lake et al., 2002; Richman et al., 2004). For the present analyses, we used a time series of length $N = 12000$ (i.e., $60\text{-s} \times 200\text{ Hz}$) with $m = 2$ and $r = 0.2$, which are values that have been successfully applied in our previous study (Takahashi et al., 2009). The calculation of MSE was carried out using developed in-house with Mathematica 5.2 (Wolfram Research, Inc.).

Power analysis

We performed power analysis as a comparative, more conventional EEG analysis. A Hanning window was applied to each artifact-free 2.56-s epoch (sampling rate 200 Hz) and the spectral density was calculated using a fast Fourier transform (FFT) using a computer program specifically designed for EEG, 'BIMUTAS II' (Kissei-Comtec). From each 60-s epoch used for MSE analyses, 23 artifact-free consecutive epochs were selected to calculate absolute EEG power. The following standard band frequencies were studied: delta (2–6 Hz), theta (6–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–40 Hz). For statistical analyses, the relative band power at each band was calculated as power in each frequency divided by total power across all frequency band.

Simulations

To investigate how specific spectral components are expressed in the MSE measure, we produced three simulated time series, adding $1/f$ noise to three different, pure sinusoidal rhythms (2.5, 5 Hz and 10 Hz). Simulated signals were based on a sample frequency of 200 Hz with sample length of $N = 16384$ (2^{13}), approximating the length of experimental data $N = 12000$ (i.e., $60\text{-sec} \times 200\text{ Hz}$). We then performed MSE analysis for these three types of simulated signals ten times and averaged across runs. Fig. 1 demonstrates the averaged MSE curves for each of the simulated signals. The signal simulations were carried out using self-produced software developed with Mathematica 5.2 (Wolfram Research, Inc.).

The 10 Hz time series generated increases in SampEn value across smaller SFs (peak at SF 6) while the 5 and 2.5 Hz rhythms generated increased SampEn value at larger SFs (peaks at SFs

12 and 24, respectively) (Fig. 1). These results indicate that SampEn values at smaller SFs reflect temporal dynamical complexity of higher frequency signals, while larger SFs reflect those at lower frequencies.

Statistical analysis

Statistical analyses were carried out using SPSS (SPSS Windows ver. 17; SPSS Japan Inc., Tokyo, Japan). SampEn values at each SF were found to have a skewed distribution and were therefore log-transformed to approximate a normal distribution. The alpha significance level was set at 0.01 to balance the potential for type I and type II error. The Greenhouse-Geisser adjustment was applied to the degrees of freedom for all analyses.

For MSE analyses, repeated measures analysis of variance (ANOVA), with group (schizophrenia: pre- or post-treatment vs. healthy control) as between-subject factors, and hemisphere (left vs. right) and SF (t: 40 scales) as within-subject factors, was performed to test for group differences at each of the paired electrode sites (i.e., F3/4, F7/8, C3/4, P3/4, T5/6 and O1/2). Additionally, repeated measures ANOVA, with treatment (pre-treatment vs. post-treatment), hemisphere (left vs. right) and SF (t: 40 scales) as within-subject factors were used to assess the effect of antipsychotic treatment. For intermediate electrode sites (Fz and Pz), repeated measures ANOVA were performed analogously to that of the paired sites but without hemisphere as a within-subject factor. For significant group-by-SF or treatment-by-SF interactions, independent or paired *t*-tests were used to compare group or treatment differences separately for each SF.

For relative power analyses, we similarly performed repeated measures ANOVA and post-hoc *t*-tests, with band (five frequency bands) as a within-subject factor instead of SF.

For the group of schizophrenia patients, Spearman's rank-order correlations were used to evaluate potential associations between MSE values and clinical data. We selected the electrode sites which showed significant increase compared to healthy controls. As a data reduction measure, we binned MSE values into the following three groups: SF 1–5, SF 6–20 and SF 21–40 (Table 3). We first examined correlations between individuals' clinical data (e.g., age, duration of the illness, BPRS scores before treatment) and averaged MSE values at pre-treatment. Then, in order to clarify the possible associations between changes in MSE values and clinical improvement or medication effects, correlations between percent change of MSE and BPRS scores during treatment (with pre-treatment as the baseline) and risperidone equivalent dose were calculated. Here, MSE values across SF 31–40 in Fz as a representative site and Pz as a comparative site were selected, because the former showed significant change with antipsychotic treatment while the latter did not (Fig. 2d).

Results

Healthy control vs. schizophrenia (pre- and post-treatment)

Table 2 summarizes the ANOVA on MSE results for healthy control and schizophrenia patient (i.e., pre- and post-treatment) subjects. The testing for group differences between healthy controls and pre-treatment schizophrenia patients revealed no group-by-hemisphere-by-SF interaction in any of the paired electrode sites. However, a significant main effect for group in F3/4, F7/8 and T5/6, and a significant group-by-SF interaction was identified in F3/4, F7/8, C3/4 and T5/6 (Fig. 2a). For intermediate electrodes, a significant main effect for group and a group-by-SF interaction was identified in Fz, but not in Pz (Fig. 2a).

For the post-treatment data, the main effects and group-by-SF interactions previously observed for fronto-central brain areas disappeared (F3/4, F7/8, C3/4 and Fz) (Fig. 2b). T5/6 revealed a trend towards a main effect for group and group-by-SF interaction (Fig. 2b).

Post-hoc unpaired *t*-tests were conducted to assess the significant main effect for group and group-by-SF interaction between healthy control and schizophrenia patients (i.e., pre- and post-treatment). Significant increases in higher SFs were identified in fronto-centro-temporal regions in patients pre-treatment. Post-treatment, these increases were decreased to healthy control levels in fronto-central, but not in temporal regions (Fig. 2a,b and d).

Pre- vs. post-treatment in schizophrenia group

Table 2 summarizes the MSE ANOVA results for pre- and post-treatment schizophrenia patient subjects. The ANOVA revealed no treatment-by-hemisphere-by-SF interaction in any of the paired electrode sites. However, a significant treatment-by-SF interaction was identified in F3/4, F7/8 and a trend for C3/4 but not in T5/6, P3/4 and O1/2 (Fig. 2c). A trend level main effect for treatment was found in F3/4. In intermediate electrodes, a significant treatment-by-SF interaction and a trend level main effect for treatment was identified for Fz, but not for Pz (Fig. 2c).

Post-hoc paired *t*-tests were conducted to assess the significant treatment-by-SF interaction between pre- and post-treatment in schizophrenia subjects. Treatment with antipsychotics significantly decreased the MSE value at higher SFs in fronto-central regions (Fig. 2c and d).

In order to understand the potential effect of clinical symptom change and medications, we additionally performed analysis of covariance (ANCOVA), with clinical symptom change (post- minus pre-treatment divided by pre-treatment BPRS scores) and medication dose (risperidone equivalent dose) as covariates. However, clinical symptom change and medication dose did not qualitatively alter the results of ANOVA (data not presented).

Power analysis

Results of ANOVA testing for group differences between healthy control and pre-treatment schizophrenia patients revealed no group-by-hemisphere-by-band interaction and no main effect for group in any of the paired electrode sites. However, a significant group-by-band interaction was identified in F7/8 [$F(4,176) = 6.5, P = 0.005$] and a similar trend in F3/4 [$F(4,176) = 4.0, P = 0.03$] (Fig. 3). For intermediate electrodes, no significant main effect for group, but a trend-level group-by-band interaction was identified in Fz [$F(4,176) = 3.6, P = 0.04$] (Fig. 3). Results of ANOVA testing for group difference between healthy control and post-treatment schizophrenia patient revealed no group-by-hemisphere-by-band interaction and no main effect for group in any of the paired electrode sites. However, a significant group-by-band interaction was identified in F7/8 [$F(4,148) = 6.5, P = 0.004$] and a trend in F3/4 [$F(4,148) = 5.2, P = 0.012$] and O1/2 [$F(4,148) = 5.7, P = 0.012$] (Fig. 3). For intermediate electrodes, no significant main effect for group was identified. However, a significant group-by-band interaction was identified in Fz [$F(4,148) = 5.9, P = 0.017$], but not in Pz (Fig. 3).

Results of ANOVA testing for treatment effect in schizophrenia patients revealed no interaction or treatment effect in any of the electrode sites (Fig. 3).

Post-hoc unpaired *t*-tests between healthy controls and pre-treatment schizophrenia subjects identified an increase of delta power in F3/4, C4 and F7/8 and decrease of alpha power in F8 (Fig. 3). Post-hoc unpaired *t*-tests between healthy controls and post-treatment schizophrenia subjects identified an increase of delta power in O1/2, theta power in F8 and decrease of alpha power in F8, Fz and O1/2 (Fig. 3).

Correlations of MSE values with clinical variables in schizophrenia patient

Pre-treatment, there were no significant correlations between clinical variables (age, duration of the illness and BPRS score before treatment) and averaged MSE values in any of the

electrode sites (Table 3). As for the possible associations between changes in MSE values and clinical improvement or medication effect, there were no significant correlations in either Fz or Pz (Table 4).

Discussion

Here, we report the first investigation of dynamical temporal complexity in EEG using *MSE* in drug-naïve schizophrenia patients both pre- and post-antipsychotic treatment. SampEn is ideal for analyzing finite and noisy experimental datasets (Pincus, 2006) and, applied at multiple time scales, can characterize multi-temporal range correlations in time series as an index of complexity inherent in the signal's dynamics (Costa et al., 2002, 2005). The main finding of this study is that schizophrenia patients showed significantly higher EEG complexity over higher SFs than that of control subjects in fronto-centro-temporal brain regions. Interestingly, this high EEG complexity in schizophrenia patients was attenuated with antipsychotic treatment to the control subjects' level in fronto-central regions, whereas temporal regions tended to remain higher. Abnormally increased EEG complexity over higher SFs in schizophrenia may represent disturbed long-range temporal correlations, an indication of breakdown in the temporal integration necessary for the flow or representation of sequence information in cognition (Breakspear, 2006).

Regarding the spatial distribution of our findings, our results agree well with previous reports of functional abnormality in fronto-temporal regions in schizophrenia using EEG (Bob et al., 2008; Kasai et al., 2002; Pae et al., 2003; Winterer et al., 2003) or fMRI (Garritty et al., 2007; Prata et al., 2009). Similarly, anterior brain regions including temporal regions have been well described to be altered in schizophrenia using traditional EEG nonlinear methods such as Lyapunov exponent or correlation dimension (Jeong et al., 1998; Kim et al., 2000; Na et al., 2002; Raghavendra et al., 2009; Saito et al., 1998) though varying in their reports of increased vs. decreased complexity. Increases in EEG signal complexity could be interpreted as evidence for the “disconnection hypothesis” in schizophrenia (Friston, 1998). Friston (1996) assessed the relationship between the degree of neural connectivity and complexity using synthetic neuronal models, finding that aberrant or reduced connectivity increased EEG signal complexity. Our findings of increases in EEG complexity in fronto-centro-temporal regions may thus reflect abnormal network connectivity and interpreted in terms of the “disconnection hypothesis”. Further, as an extension of Friston's hypothesis, it could be speculated that this higher complexity was ameliorated by antipsychotics through dopaminergic modulation, especially in frontal regions (Friston, 1996).

It is worth noting that we did not find any group differences at SF = 1, i.e., in the noncoarse-grained data. Similarly, SampEn values at other small SFs did not show abnormalities, whereas group differences were revealed at higher SFs. These results, together with the simulation results that showed low frequency modulations being indexed by high SF changes, are consistent with previous findings of spectral “slowing” in schizophrenia patients, particularly in frontal regions (Boutros et al., 2008).

In attempting to understanding the basis for abnormally high EEG complexity, some insights may be gained from several animal studies which have demonstrated disorganized neuronal firing patterns in pharmacological models of schizophrenia using *N*-methyl-D-aspartate receptor (NMDA-R) antagonists (Jackson et al., 2004; Kargieman et al., 2007; Suzuki et al., 2002) or DOI (1-[2,5-dimethoxy-4-iodophenyl-2-aminopropane]) (Celada et al., 2008). Interestingly, all these studies consistently demonstrated increases in abnormal neural firing patterns after NMDA-R antagonist administration. Jackson et al. (2004) found disorganized spike activity in prefrontal cortex associated with behavioral impairment in freely moving rats after NMDA-R antagonist administration. Kargieman et al. (2007) found cortical

desynchronization and temporal disorganization of pyramidal neurons discharges in the low frequency range (0.3 – 4 Hz) in prefrontal cortex after NMDA-R antagonist administration. Similarly, Celada et al. (2008) demonstrated the disruption of cortical activity in lower frequency synchrony after DOI injection. Interestingly, these altered neuronal activities were reversed with both typical (haloperidol) and atypical (clozapine) antipsychotics (Celada et al., 2008; Kargieman et al., 2007). Consistent with the findings of the current study, these studies suggest that a critical characteristic of frontal cortical neurophysiology in schizophrenia may be increases in disorganized spiking activity in lower frequencies and that one of the crucial roles of treatment may be in ameliorating the neurophysiological abnormalities through dopamine receptor blockade.

It is also important to note that although spectral slowing was identified in frontal regions, we did not find any spectral changes with antipsychotic treatment. This suggests that MSE may offer additional complementary neurophysiological information that is more sensitive than power analysis in terms of treatment effects. However, it is unclear why there appeared to be differential sensitivity to treatment effects across the frontal vs. temporal cortices. One possibility may be that while both the temporal and frontal cortices have consistent findings of structural anomalies (Honea et al., 2005; Shenton et al., 2001), the pathophysiologic changes in the frontal cortex may be more sensitive to treatment effects compared with the temporal cortex. Consistent with this idea is that animal studies have shown that disturbed prefrontal cortical function can be reversed by antipsychotics (Celada et al., 2008; Kargieman et al., 2007) although similar studies need to be performed in the temporal cortex to confirm differential sensitivity to treatment effects. However, these speculations regarding our EEG findings are at best tentative due to the difficulty of inferring activations from specific cortical areas from EEG scalp topography distributions. Electrical activity in each scalp electrode might not have its origin in the brain area directly underneath the recording site, and may indeed be due to multiple proximal or distal sites. Putative complexity in EEG signals may therefore arise from a mixture of sources or reflect true complexity from a single source which may, in turn, arise as an emergent property from mutual interactions across multiple cortical regions.

To explore any potential direct effects of medications on complexity (e.g., effects that might be observed when antipsychotics are administered to healthy controls), no significant correlations were identified between medication dose and MSE change. Although we are not able to make any definitive conclusions regarding the exact mechanism by which abnormal EEG complexity normalized, this lack of correlation is consistent with the medications not having any direct effects on the observed complexity changes.

Some other potential limitations to our study need to be considered. Most of our patients were taking typical antipsychotics, whereas most reports examining treatment effects on clinical status and cognitive function were based on atypical antipsychotics. Differences in typical vs. atypical antipsychotics are highlighted by studies such as Honey et al. (1999) who demonstrated functional activation in frontal regions after substitution of risperidone for typical antipsychotics. However, while the variability in the type, dose and duration of antipsychotic treatment is a limitation of the study, it may also support the generalizability of the results to heterogeneous clinical treatment situations.

Finally, there are some technical limitations that could apply to any study employing MSE. Thuraingham and Gottwald (2006) highlighted the importance of considering sampling time and the relationship between various time scales (e.g., correlation time, period of possible nonlinear oscillations) when using MSE in order to avoid spurious interpretations. For instance, using the Lorenz system, they demonstrated that if the sampling time was much greater than correlation time, then the chaotic behavior with finite correlation length is not revealed, with the MSE profile appearing similar to that for white noise. However, since a full description of

physiologically relevant nonlinear dynamics in EEG signals is still incomplete (Stam, 2005), it is difficult to know a priori the experimental parameters (e.g., sampling time and frequency) that will adequately capture all relevant brain dynamics and pathophysiologic processes at the critical time scales. Additionally, studies employing MSE analyses are open to the problem of multiple comparisons due to the many SFs that are examined, thereby potentially inflating the possibility of type I error. However, since the repeated measures across adjacent SFs were highly correlated, a strict Bonferroni correction was not applied in our analysis as it would have been overly conservative and likely produce type II error. Rather, an alpha of 0.01 was selected as a ‘statistical filter’ to balance between the potential for type I and type II error.

In conclusion, our findings highlight the potential usefulness of MSE in EEG studies of abnormal temporal dynamics in schizophrenia. The findings of this study are consistent with the idea that the therapeutic effects of antipsychotics via dopamine receptor blockade may be the ameliorating of abnormal increases in the complexity of prefrontal cortical activity. Additional longitudinal studies, examining treatment response and including individuals on different types of medications, are necessary to extend the current findings. The findings suggest that MSE approaches can contribute insights regarding pathophysiologic and therapeutic mechanisms in schizophrenia through the detection of EEG signal complexity at multiple time scales.

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Fig. 1. Results of the MSE analysis for simulated pure sinusoidal rhythms (i.e., 2.5 (red line), 5 (green line) and 10 Hz (blue line)) with 1/f noise. Sample entropy values were calculated up to 100 scale factors.

Fig. 2. Multiscale entropy (MSE) analysis of 22 pre-treatment schizophrenia (red line), 15 post-treatment schizophrenia (green line) and 24 healthy control subjects (blue line). Each panel presents the average of the intermediate, left and right hemisphere MSE values. (a)

Comparisons between healthy control and pre-treatment schizophrenia subjects. (b)
Comparisons between healthy control and post-treatment schizophrenia subjects. (c)
Comparisons between pre-treatment schizophrenia and post-treatment schizophrenia subjects.
(d) Summary of MSE profiles for healthy controls and pre- and post-treatment schizophrenia.
Post-hoc comparisons between groups: $P < 0.01$ (light blue shaded areas) and $P < 0.001$ (dark blue shaded areas).

Fig. 3.

Relative power analysis of 22 pre-treatment schizophrenia (red line), 15 post-treatment schizophrenia (green line) and 24 healthy control subjects (blue line). Each panel presents the average of the intermediate, left and right hemisphere relative power values. *Post-hoc* comparisons between groups: * $P < 0.01$ (healthy control vs. pre-treatment schizophrenia subjects) and † $P < 0.001$ (healthy control vs. post-treatment schizophrenia subjects).

Demographic and clinical characteristics in normal control subjects and schizophrenia patients

Table 1

	Healthy controls (n = 24)	Pre-treatment drug naïve schizophrenia (n = 22)	Post-treatment drug naïve schizophrenia (n = 15)
Female/male	10/14	8/14	7/8
Age, years	24.0 (4.8)	25.6 (4.8)	25.7 (5.1)
Education, years	15.9 (2.0)	14.5 (2.2)	14.3 (2.1)
Duration of the illness, months	NA	21.1 (27.8)	19.0 (30.7)
BPRS score before treatment	NA	49.3 (13.2)	51.2 (14.2)
BPRS score after treatment	NA	NA	43.2 (14.6)
Risperidone equivalent dose on the day of the 2 nd EEG, mg/day	NA	NA	3.2 (1.9)

Values represent mean (SD).

Abbreviation: BPRS, Brief Psychiatric Rating Scale

Table 2

ANOVA results for multiscale entropy (MSE) analysis between (healthy vs. schizophrenia) and within (schizophrenia) groups at each paired and single electrode sites

Healthy controls vs. Pre-treatment schizophrenia			Healthy controls vs. Post-treatment schizophrenia		Pre-treatment schizophrenia vs. Post-treatment schizophrenia	
	Group effect	Group × Scale factor	Group effect	Group × Scale factor	Treatment effect	Treatment × Scale factor
F3/4	$F = 9.7, P = 0.003$	$F = 5.9, P = 0.0006$	$F = 1.6, P = 0.22$	$F = 1.1, P = 0.36$	$F = 7.0, P = 0.02$	$F = 6.6, P = 0.002$
F7/8	$F = 13.6, P = 0.0006$	$F = 8.0, P = 0.00005$	$F = 6.3, P = 0.017$	$F = 1.5, P = 0.21$	$F = 1.2, P = 0.28$	$F = 6.1, P = 0.003$
C3/4	$F = 5.8, P = 0.02$	$F = 5.2, P = 0.002$	$F = 2.9, P = 0.10$	$F = 2.2, P = 0.083$	$F = 1.1, P = 0.31$	$F = 3.9, P = 0.013$
P3/4	$F = .53, P = 0.47$	$F = 1.0, P = 0.40$	$F = 0.92, P = 0.34$	$F = 10.8, P = 0.15$	$F = 0.1, P = 0.76$	$F = 10.6, P = 0.22$
T5/6	$F = 7.3, P = 0.01$	$F = 4.1, P = 0.010$	$F = 5.1, P = 0.03$	$F = 3.8, P = 0.016$	$F = 0.005, P = 0.94$	$F = 1.0, P = 0.37$
O1/2	$F = 67, P = 0.42$	$F = 2.1, P = 0.11$	$F = 5.9, P = 0.02$	$F = 1.9, P = 0.14$	$F = 2.6, P = 0.13$	$F = 1.1, P = 0.36$
Fz	$F = 7.3, P = 0.010$	$F = 5.3, P = 0.002$	$F = 1.7, P = 0.20$	$F = 1.0, P = 0.39$	$F = 4.8, P = 0.047$	$F = 4.9, P = 0.005$
Pz	$F = 0.94, P = 0.34$	$F = 1.8, P = 0.15$	$F = 1.7, P = 0.20$	$F = 2.1, P = 0.10$	$F = .35, P = 0.56$	$F = 1.7, P = 0.19$

Scale factor: 1 – 40. For clarity, $P < 0.01$ are shown in bold.

Table 3

Correlations between individuals' characteristic data and averaged MSE vales at pre-treatment

	Age	Duration of the illness	BPRS score before treatment
F3			
SF 1-5	-0.12	0.30	-0.08
SF 6-20	-0.23	0.13	-0.36
SF 21-40	-0.25	0.25	-0.19
F4			
SF 1-5	-0.16	0.23	-0.08
SF 6-20	-0.33	0.14	-0.39
SF 21-40	-0.34	0.22	-0.17
Fz			
SF 1-5	-0.17	0.26	-0.17
SF 6-20	-0.40	0.12	-0.28
SF 21-40	-0.40	0.10	0.10
F7			
SF 1-5	-0.25	0.12	-0.10
SF 6-20	-0.17	0.14	-0.16
SF 21-40	-0.03	0.35	-0.12
F8			
SF 1-5	-0.17	0.18	-0.03
SF 6-20	-0.27	0.06	-0.20
SF 21-40	-0.02	0.31	-0.18
C3			
SF 1-5	-0.12	0.30	-0.05
SF 6-20	-0.30	0.04	-0.15
SF 21-40	-0.29	0.11	0.10
C4			
SF 1-5	-0.14	0.35	-0.12
SF 6-20	-0.32	0.18	-0.19
SF 21-40	-0.31	0.17	-0.02
T5			
SF 1-5	-0.06	0.35	-0.09
SF 6-20	-0.35	0.03	-0.29
SF 21-40	0.12	0.07	-0.16
T6			
SF 1-5	0.12	0.16	-0.31
SF 6-20	-0.24	0.02	-0.42
SF 21-40	-0.05	-0.05	-0.34

Abbreviations: BPRS, Brief Psychiatric Rating Scale; MSE, multiscale entropy; SF, scale factor. No significant correlations (at $\alpha = 0.05$) were identified between individuals' characteristic data and averaged MSE vales at pre-treatment.

Table 4

Correlations between percent change of MSE and BPRS scores during treatment/risperidone equivalent dose

	Risperidone equivalent dose	Percent change in BPRS score
Fz (SF 31–40)	0.49	0.39
Pz (SF 31–40)	0.44	0.43

Abbreviation: MSE, multiscale entropy; BPRS, Brief Psychiatric Rating Scale Percent change of MSE and BPRS score were calculated using the pre-treatment condition as a baseline. No significant correlations (at $\alpha=0.05$) were identified between percent change of MSE and BPRS scores during treatment/risperidone equivalent dose.