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Native EEG and treatment effects in neuroleptic-naïve schizophrenic patients: Time and frequency domain approaches

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Abstract

Time domain analysis of electroencephalography (EEG) can identify subsecond periods of quasi-stable brain states. These so-called microstates assumingly correspond to basic units of cognition and emotion. On the other hand, Global Field Synchronization (GFS) is a frequency domain measure to estimate functional synchronization of brain processes on a global level for each EEG frequency band [Koenig, T., Lehmann, D., Saito, N., Kuginuki, T., Kinoshita, T., Koukkou, M., 2001. Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naive patients with schizophrenia: preliminary results. Schizophr Res. 50, 55-60.]. Using these time and frequency domain analyzes, several previous studies reported shortened microstate duration in specific microstate classes and decreased GFS in theta band in drug naïve schizophrenia compared to controls. The purpose of this study was to investigate changes of these EEG parameters after drug treatment in drug naïve schizophrenia. EEG analysis was performed in 21 drug-naive patients and 21 healthy controls. 14 patients were reevaluated 2–8 weeks (mean 4.3) after the initiation of drug administration. The results extended findings of treatment effect on brain functions in schizophrenia, and imply that shortened duration of specific microstate classes seems a state marker especially in patients with later neuroleptic responsive, while lower theta GFS seems a state-related phenomenon and that higher gamma GFS is a trait like phenomenon.

Keywords: EEG microstate; Non-responder; Responder; Schizophrenia; Synchronization; Treatment

1. Introduction

Schizophrenia exhibits a syndrome characterized by widespread impairment of cognitive functions, but the replicated locations of structural and functional abnormalities demonstrated by brain imaging methods are only subtle. To explain the underlying pathophysiology, a functional disconnection of various large-scale neural networks (Weinberger et al., 1992; Liddle, 1996; Friston, 1999; Andreasen, 2000) or disturbed neuronal cooperation (Meyer-Lindenberg et al., 2001) in functional loops (Bressler, 2003; Strik and Dierks, 2004) seems more appropriate than the presence of delimited lesions.

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The activity of sufficiently large cortical networks produces electric fields on the scalp which can be measured with EEG. Due to intrinsic properties of the EEG, these scalp fields provide limited information about the location of these networks, but the information on the timing of activity is detailed. EEG may thus be better suited than other methods to investigate the temporal dynamics of neural interactions within cortical networks while it will be less informative about the spatial structure of the networks' elements.

When investigating the temporal dynamics of normal resting EEG in the time- or frequency domain, one observes oscillations that tend to be synchronized across electrodes (Lehmann et al., 1987; Koenig et al., 2005a, b): Time-domain analysis of EEG shows subsecond time periods that have a quasi-stable scalp electric fields. This indicates that the signals temporal dynamics were similar across electrodes, and therefore also across the brain regions that have contributed to the observed field. These transiently stable EEG periods, the so-called microstates, indicate the presence of short-lasting synchronized states (Koenig et al., 2005a,b) and have been hypothesized to represent basic building blocks of human information processing (Lehmann et al., 1987). They have been shown to depend on cognitive state and follow narrowly defined developmental norms (Koenig et al., 2002). In resting state EEG of unmedicated patients with schizophrenia, specific microstates with defined scalp fields (i.e. representing specific networks) have been shown to be significantly shortened (Koenig et al., 1999; Lehmann et al., 2005; Strelets et al., 2003). This shortening has been hypothesized to indicate premature termination of specific classes of mental operations and could partially be related to the presence of paranoid symptoms.

In frequency transformed EEG data, evidence for synchronization of cortical networks comes from the observation that for a given frequency, the electrodes phases tend to concentrate around a single angle across electrodes (Lehmann and Michel, 1989; Koenig et al., 2005a,b). The presence of a single phase angle across electrodes indicates total synchronization of all processes at that frequency. Different brain processes operating at the same frequency thus tend to prefer a common pace. We have developed a method called Global Field Synchronization (GFS) that quantifies the amount of common phase across electrodes for different frequency bands (Koenig et al., 2001). When comparing resting state GFS of unmedicated patients with schizophrenia to healthy controls, we found significantly reduced amount of common phase across electrodes in the patients in the theta band. Since theta activity in an awake resting state has been associated with working memory functions, we had suggested that this effect might be related to a temporal misalignment of working memory functions in schizophrenia.

The present study investigated another dataset of resting state EEG of schizophrenic patients. Their EEG was recorded twice, once before onset of any medication, and once when patients were under neuroleptic treatment and symptoms had partly remitted. We wanted to know whether we could replicate the above mentioned abnormalities in microstate duration and theta band synchronization, and whether these abnormalities would change under treatment, i.e. whether they represent state or trait markers. Finally, we wanted to know whether these abnormalities would be different in the EEG of patients that would later respond or not respond to neuroleptic treatment.

2. Methods

2.1. Subject

All data were collected from patients presenting at the Department of Psychiatry and Neurobiology, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan. The subjects included in the study were 15 patients with schizophrenia and 6 with schizophreniform disorder (11 men and 10 women) diagnosed according to the DSM-IV criteria (American Psychiatric Association, 1994) at the time of the first EEG recording. Eventually, all of the schizophreniform disorder patients were later diagnosed as having schizophrenia. 19 patients fulfilled the DSM-IV criteria for paranoid type and 2 for disorganized type. None of the patients had ever been treated with neuroleptics before the first EEG recording. Treatment was initiated after the first EEG. The choice of drugs and dosage were decided by the psychiatrists in charge.

Seven of 21 patients did not receive the second EEG recording. All of them were out-patients. 4 of these patients refused the second EEG recording and 3 patients were hospitalized elsewhere. These 7 patients (mean BPRS score = 45.3) tended to have less psychotic symptoms before drug administration as compared with the other 14 patients (mean BPRS score = 56.2, $t = 1.84$, effect size = 0.491, $df = 13$, $p = 0.080$) who agreed to participate in a second EEG recording after drug administration. The second EEG took place 2–8 weeks (mean 4.3) after the initiation of drug administration. At that time, 13 of these 14 patients received conventional dopamine-blocking neuroleptics, one patient received a serotonin–dopamine antagonist. 12 patients received

additional drugs (anticholinergic or antihistaminergic drugs, benzodiazepine derivatives).The study contained no limitations for the available therapies and the therapeutic choices were completely based on each patient's condition. At the time of the second EEG, mean risperidone equivalent dose (Toru, 1983; Inagaki et al., 2001) was 3.2 mg/day (0.5–6.5 mg). On the day of the EEG recordings, each patient was assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). For further analysis, patients were considered responders if their BPRS score decreased more than 20% ($n=7$) and non-responders if it did not ($n=7$) (Stip and Mancini-Marie, 2004). Responders were not significantly different from non-responders in age, gender, baseline BPRS score, risperidone equivalent dose on the day of the 2nd EEG, treatment periods, and duration of the disease.

21 healthy volunteers were recruited as controls among staff members of Kanazawa University Hospital and their family members. Controls had no personal or family history of psychiatric or neurological disease and were functioning normally and independently in their daily lives. Controls were not significantly different from the patients in age or gender. All participants were right-handed. The demographics of all groups are shown in Table 1. The study followed the rules and regulations of hospital regarding patients' studies and personal information, and follows the Declaration of Helsinki. Informed consent was obtained from all participants.

2.2. EEG recording

The subjects were recorded while lying in a soundproof, light-controlled recording room. Electrodes were attached to the scalp with paste at the following positions of the International 10-20 System: Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, P3, P4, Pz, T5, T6, O1, and O2, reference was linked earlobes. Eye-movements were monitored with an additional EOG channel. Electrode-impedances were kept below 5 kΩ. The EEG was filtered (1.5 to 60 Hz bandpass), amplified, digitized (sampling rate 200 Hz) and stored using an 18-channel electroencephalograph (EEG-44189, Nihon Kohden, Tokyo, Japan). All subjects were instructed to relax and keep their eyes closed throughout the recording period.

From the recorded data, epochs of 2.56 s (512 data points) duration recorded in the eyes-closed but awake state were selected. Epochs with eye movements, blinks, muscle activities or other artifacts were removed based on visual inspection. The number of available epochs per subject ranged from 16 to 55. All epochs were recomputed against common average reference.

2.3. EEG microstate analysis

The microstate analysis followed the standard procedure used in earlier work (Koenig et al., 2002). The selected EEG epochs were digitally band pass filtered from 2–20 Hz. Global Field Power (GFP), which quantifies the overall potential variance across the set of electrodes, was computed at each sample in time. Since topography remains stable around peaks of GFP and changes during the troughs, only topographies at momentary maxima of the GFP were further analyzed. A modified version of the K-mean clustering algorithm (Pascual-Marqui et al., 1995) was instructed to seek four classes of microstate topography and to assign each EEG topography to one of these classes. This number of classes has previously been found to be optimal, using a cross validation criterion, and was maintained for compatibility with previous studies. Microstate class topographies were computed individually and averaged across subjects using a permutation algorithm that maximized the common variance over subjects (Koenig et al., 1999). The obtained microstate classes were

Table 1
Demographic characteristics of all subjects

Group	Healthy control	Drug naïve schizophrenia	Patient with follow up data		
			All	Responder	Non-responder
Total number	21	21	14	7	7
Male/female	11/10	11/10	5/9	2/5	3/4
Age (range) years	28.4 (20–53)	28.1 (18–48)	29.5 (18–52)	33.6 (18–52)	25.4 (21–38)
BPRS score before treatment (range)	–	52.6 (28–76)	56.2 (37–76)	58.9 (41–76)	53.6 (37–75)
BPRS score after treatment (range)	–	–	43.6 (24–73)	33.9 (24–47)	53.3 (37–73)
Risperidone equivalent dose on the day of the 2nd EEG (range) mg	–	–	3.2 (0.5–6.5)	2.6 (0.5–4.7)	3.8 (0.8–6.5)
Treatment period (range) weeks	–	–	4.3 (2–8)	4.3 (2–8)	4.3 (4–6)
Duration of the disease (range) months	–	24.2 (1–140)	23.6 (1–140)	38.0 (1–140)	9.3 (1–24)

BPRS, Brief Psychiatric Rating Scale.

labeled A–D according to their similarities to the previously reported microstate class topographies. In the presented study, the four microstate classes accounted for a mean of 79.1% (S.D.: 6.4%) of the data variance across healthy controls, and of 75.2% (S.D.: 5.6%) across patients with schizophrenia.

Within each subject, microstates were identified as continuous epochs within which all topographies were assigned to the same class. For each subject, per-class microstate parameters were computed, consisting of mean microstate duration ("duration"), mean number of microstates per second ("occurrence") and percentage of total analysis time occupied in that state ("percent total time").

2.4. Global Field Synchronization

The computation of Global Field Synchronization (GFS) has been described elsewhere (Koenig et al., 2001, 2005a,b) and is briefly reviewed here: The frequency transformation of a single EEG channel yields, for each frequency, a complex number that can be displayed as a two-dimensional vector. The length of this vector is the power and the direction is the phase. The more all electrodes tend to have a common phase orientation, the more there is evidence for synchronous activity of the brain processes determining the EEG at the investigated frequency. The amount of common phase orientation (GFS) is assessed using the eigenvalues of the vectors (Koenig et al., 2001). GFS is defined as the fraction of total power across electrodes that can be explained by a single phase. GFS thus ranges from 0 to 1, high GFS values indicate the presence of a single, predominant phase over all electrodes; low GFS indicates the absence of such a common phase. In the current study, GFS values were computed for each epoch and each frequency point in steps of 0.39 Hz. Within each subject, the GFS values were averaged over epochs and collapsed into the frequency bands proposed by Kubicki et al. (1979): delta (1.6–5.9 Hz), theta (6.3–7.8 Hz), alpha-1 (8.2–10.2 Hz), alpha-2 (10.5–12.1 Hz), beta-1 (12.5–18.0 Hz), beta-2 (18.4–21.1 Hz), beta-3 (21.5–30.1 Hz). In addition, we added gamma (30.5–40.2 Hz) band.

2.5. Statistics

Since the patient sample differed from that of previous studies (Koenig et al., 1999, 2001; Strelets et al., 2003; Lehmann et al., 2005) in duration of illness and medication status, we did not establish a-priori hypotheses for the difference between patients and controls, but used double-ended *t*-tests to explore the differences in each microstate class and GFS. Where a significant difference was found, we hypothesized that drug administration induced the opposite effect, because some previous studies suggested that the dysfunction of neural connectivity normalized after treatment in schizophrenia (Stephan et al., 2001; Mendrek et al., 2004). Treatment effects were thus tested using single-ended *t*-tests. For completeness, the other effects of treatment were explored using double-ended *t*-tests. Relationships among changes of BPRS scores, changes of EEG parameters and risperidone equivalent dose were analyzed using Pearson's correlation coefficients. In addition, comparison of EEG parameters between responder and non-responder were also done using double-ended *t*-tests. Statistical significance was set at $p<0.05$.

3. Results

3.1. Comparison between patient and control group

The averaged 4 microstate classes for patients and controls are shown in Fig. 1. Both groups had two microstate classes (A and B) with diagonal axis orientations of the mapped field, one class (C) with a clear anterior–posterior orientation, and one (D) with a fronto-central extreme location. Our four class model maps were very similar to the four class model maps obtained in a large, normative study on nearly 500 subjects (Koenig et al., 2002). The three parameters duration, occurrence, and total time for the 4 microstate classes are shown in Table 2 (see also Fig. 2). Microstate mean duration varied between 53.9 and 82.7 ms in patients and controls for the different microstate classes. *t*-tests demonstrated significantly shorter durations of

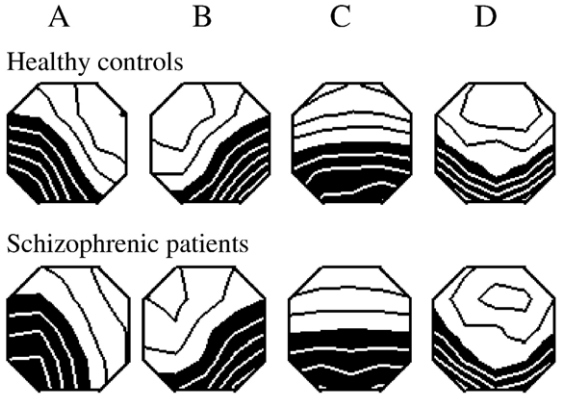

Fig. 1. Microstate classes of schizophrenic patients and healthy controls. Mean normalized equipotential maps of the four microstate classes (A–D) of the patients and controls. Using a linear scale, the map areas of opposite polarity are arbitrarily coded in black and white.

class D (t=3.10, effect size=0.478, df=40, p=0.002) and shorter overall microstate duration (t=2.23, effect size=0.344, df=40, p=0.032) in the patients compared to controls. Microstate occurrence ranged between 3.01 and 4.64 microstates/s/class. Patients had significantly more microstates of class B (t=2.14, effect size=0.330, df=40, p=0.039) and C (t=2.99, effect size=0.461, df=40, p=0.005). There was also a tendency for increased overall microstate occurrence in patients (t=1.95, effect size=0.300, df=40, p=0.059). Percent of total time covered by the different microstate classes ranged between 18.2% and 33.6%. t-tests indicated significantly less percent total time in microstates of class D (t=2.83, effect size=0.437, df=40, p=0.007) in patients compared to controls.

The results of the group comparisons of GFS are shown in Table 3. Patients had smaller mean GFS than controls in the theta band (t=2.03, effect size=0.313, df=40, double-ended p=0.049) and had larger mean GFS in the gamma band (t=4.67, effect size=0.721, df=40, double-ended p<0.001). In the other frequency bands, no significant differences were found.

3.2. Comparison between pre- and post-treatment in patient group

According to the significant differences between patients and controls, we hypothesized that drug administration induced an increase in duration of class D, an increase of overall microstate duration, decreases in occurrence of class B and C, and an increase in total time (%) of class D. However, none of these hypotheses was supported by the single-ended t-tests. Further explorative statistics failed to demonstrate any significant change in microstate parameters after treatment.

There were however a significant negative correlations between changes of BPRS score and duration of class D (r=−0.709, p=0.003) and overall microstate duration (r=−0.689, p=0.005), and there were positive correlations between changes of BPRS score and occurrence of class A (r=0.618, p=0.016), class C (r=0.670, p=0.007) and overall microstate occurrence (r=0.721, p=0.003) (Fig. 3). Furthermore, there was a significant negative correlation (r=−0.578, p=0.029) between change of total time of class B and risperidone

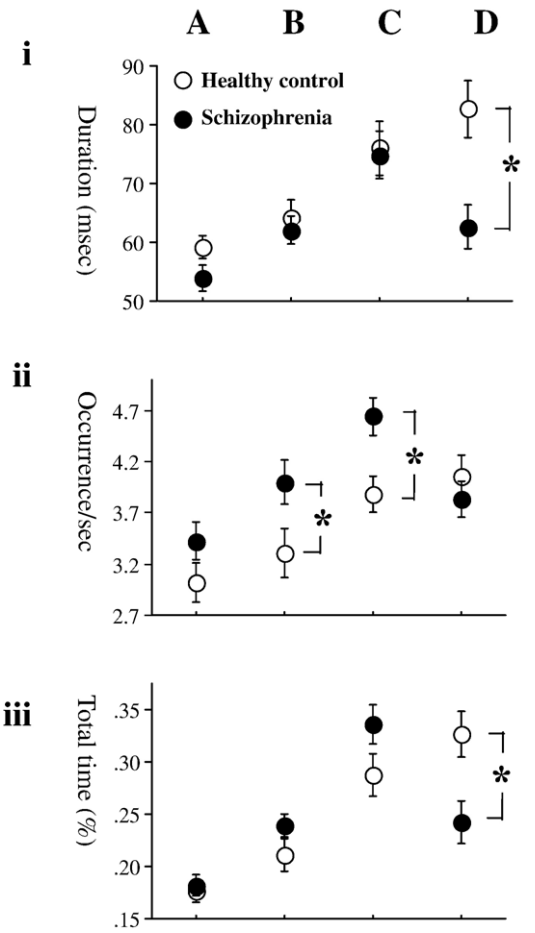

Fig. 2. Microstate statistics. Duration (i), occurrence/s (ii), and percent total time covered (iii), of the 4 microstate classes (A–D) of controls (n=21; open circle), drug naïve patients with schizophrenia (n=21; closed circle). Whiskers indicate±S.E. An asterisk indicates differences at p<.05 in the double-ended t-test.

Table 2
Mean microstate parameters (SD) in patients with schizophrenia (n=21) and healthy control (n=21)

	Schizophrenia	Control	t value	p value (2-tailed t-test)
Mean duration (ms)				
Class A	53.9 (10.4)	59.1 (9.1)	−1.74	n.s.
Class B	62.0 (10.6)	64.3 (14.0)	−.58	n.s.
Class C	74.8 (18.5)	76.0 (21.3)	−.19	n.s.
Class D	62.6 (17.5)	82.7(21.9)	−3.10	.002
Total	63.3 (10.0)	70.5 (10.9)	−2.23	.032
Mean occurrence (/s)				
Class A	3.43 (.72)	3.01 (.78)	1.54	n.s.
Class B	4.00 (.98)	3.31 (1.18)	2.14	.039
Class C	4.64 (.84)	3.88 (.18)	2.99	.005
Class D	3.83 (.80)	4.06 (.91)	−.87	n.s.
Total	15.90 (2.67)	14.27 (2.76)	1.95	n.s.
Mean total time (%)				
Class A	18.2 (4.6)	17.6 (4.8)	.39	n.s.
Class B	24.0 (5.0)	21.0 (7.2)	1.52	n.s.
Class C	33.6 (8.5)	28.8 (9.4)	1.77	n.s.
Class D	24.2 (9.1)	32.6 (10.1)	−2.83	.007

Significance was determined by unpaired t-test.

Table 3
Mean (SD) GFS in patients with schizophrenia (n=21) and healthy control subjects (n=21)

GFS	Schizophrenia	Healthy control	t value	p value (2-tailed t-test)
Delta band	.55 (.02)	.56 (.03)	−0.51	n.s.
Theta band	.55 (.02)	.57 (.03)	−2.03	.049
Alpha-1 band	.63 (.06)	.64 (.07)	−0.71	n.s.
Alpha-2 band	.62 (.05)	.63 (.06)	−0.78	n.s.
Beta-1 band	.53 (.03)	.55 (.03)	−1.22	n.s.
Beta-2 band	.53 (.04)	.53 (.03)	−0.67	n.s.
Beta-3 band	.48 (.04)	.48 (.02)	0.70	n.s.
Gamma band	.50 (.05)	.44 (.03)	4.67	<.001

GFS, Global field synchronization.

equivalent dose at the time of the second EEG recording.

According to the significant differences between patients and controls, we hypothesized that drug administration induced an increase in GFS for theta band and decrease for gamma band. As hypothesized, mean theta GFS increased significantly after drug administration (t=2.02, effect size=0.540, df=13, single-ended p=0.032). In addition, in the alpha-2 band, GFS decreased significantly (t=2.19, effect size=0.585, df=13, double-ended p=0.048). However, there were no significant changes in the other frequency bands (Table 4). None of the computed correlations was significant; there was thus no evidence that changes in GFS with treatment were related to changes of BPRS score or risperidone equivalent dose.

3.3. Comparison between responders and non-responders

The absence of significant treatment effects in patients was in contrast to the significant correlations between changes of BPRS score and microstate parameters. Thus, patients were divided into responders and non-responders (response was defined as more than 20% improvement in BPRS total score) and one-way ANOVAs were computed including the data of controls, responders and non-responders.

When comparing microstate parameters before treatment, microstate duration differed significantly between groups in class A (F=5.08; df=2,30; p=0.012), class D (F=6.48; df=2,30; p=0.004), and in overall microstate duration (F=5.21; df=2,30; p=0.011). Post-hoc t-tests demonstrated that responder had significantly shorter durations than non-responder or healthy control in these classes. The occurrence of microstates was different in class B (F=4.41; df=2,30; p=0.020), class C (F=9.08; df=2,30; p=0.001), and of overall microstate occurrence (F=4.80; df=2,30; p=0.015). Post-hoc t-tests demonstrated that responders had significant more microstates than non-responder or healthy control in these classes. In microstate total time, groups differed in class D (F=3.94; df=2,30; p=0.030), which resulted from responders having significantly lower total time compared to healthy controls. The results of pre-treatment group comparisons are resumed in Table 5.

When comparing the percent change in microstate parameters induced by treatment (Table 6), responders

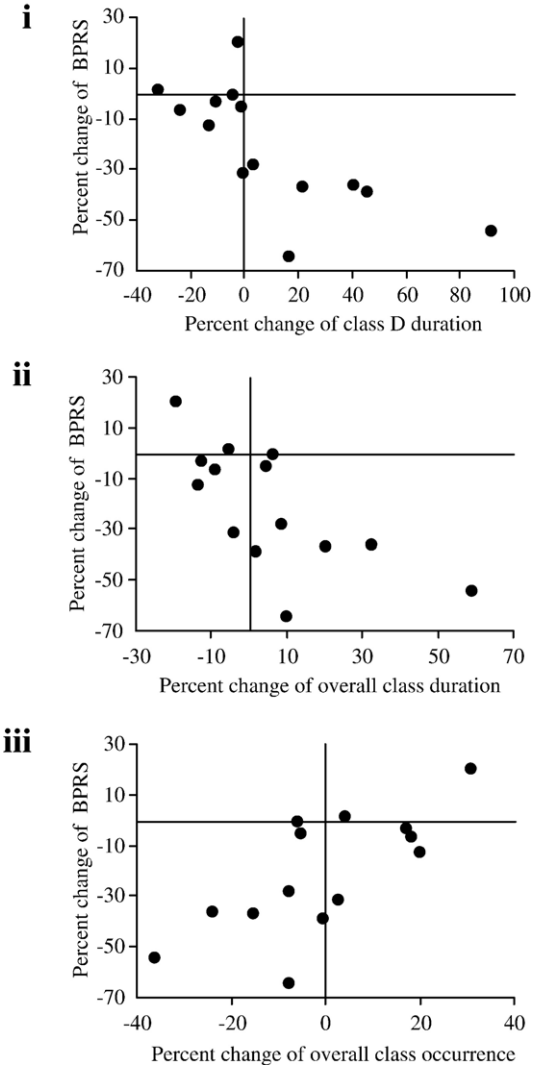

Fig. 3. (i) Correlation between percent changes of BPRS score and that of class D duration (r=−.709, p=.003). (ii) Correlation between percent changes of BPRS score and overall microstate duration (r=−.689, p=.005). (iii) Correlation between percent changes of BPRS score and that of overall microstate occurrence (r=.721, p=.003).

Table 4
Mean (SD) GFS before and after treatment in patients with schizophrenia ($n=14$)

GPS	Pre-treatment	Post-treatment	t value	p value (2-tailed t-test)	p value (1-tailed t-test)
Delta band	.55 (.02)	.55 (.02)	−0.18	n.s.	–
Theta band	.55 (.02)	.56 (.03)	−2.02	n.s.	.032
Alpha-1 band	.63 (.07)	.62 (.05)	0.24	n.s.	–
Alpha-2 band	.61 (.04)	.59 (.04)	2.19	.048	–
Beta-1 band	.53 (.03)	.53 (.03)	0.72	n.s.	–
Beta-2 band	.52 (.04)	.51 (.03)	0.79	n.s.	–
Beta-3 band	.49 (.04)	.48 (.02)	0.66	n.s.	–
Gamma band	.51 (.05)	.48 (.05)	−1.38	n.s.	n.s.

GFS, Global field synchronization.

increased duration of microstates of class A ($t=2.20$, effect size=0.588, $df=13$, $p=0.048$), class D ($t=3.43$, effect size=0.917, $df=13$, $p=0.005$) and of overall microstate duration ($t=2.85$, effect size=0.762, $df=13$, $p=0.015$) compared to non-responders. Responders also decreased occurrence of microstates of class C ($t=3.61$, effect size=0.965, $df=13$, $p=0.004$) and of overall microstate occurrence ($t=3.24$, effect size=0.866, $df=13$, $p=0.007$) compared to non-responders. There was no differential treatment effects in percent total time covered.

The analysis of GFS yielded no difference in drug response between responders and non-responders.

4. Discussion

The present results replicated previous reports on reduced synchronization of brain functions in specific brain states in neuroleptic naïve patients with schizophrenia (Koenig et al., 2001). As in a previous report, theta-band GFS was lower in unmedicated patients compared to controls. Also, microstates were shortened in these patients, which is consistent with several earlier reports (Koenig et al., 1999; Strelets et al., 2003; Lehmann et al., 2005). The observation that this shortening affected mainly one microstate class (class D) is also in agreement with these previous reports.

Although the distribution of the active networks that account for the observed microstate classes is unknown, different microstate classes must imply different networks. Different microstate classes thus assumingly represent different mental functions. The observation that a specific class of microstates is shortened in patients with schizophrenia thus suggests that selective types of synchronized neural networks, and thus different types of mental operations terminate prematurely, which might

Table 5
Mean microstate parameters (SD) in responder ($n=7$) and non-responder ($n=7$), and healthy control ($n=21$)

	Responder	Non-responder	Control	F value	p value	Post-hoc (2-tailed t-test)
Mean duration (ms)						
Class A	46.2 (6.7)	60.1 (13.7)	59.1 (9.1)	5.08	0.012	Res<Non, Ctr
Class B	57.9 (9.4)	65.7 (9.8)	64.3 (14.0)	0.84	n.s.	
Class C	71.2 (15.3)	83.8 (25.2)	76.0 (21.3)	0.65	n.s.	
Class D	51.6 (10.8)	75.6 (19.4)	82.7(21.9)	6.48	0.004	Res<Non, Ctr
Total	56.7 (7.9)	71.3 (10.2)	70.5 (10.9)	5.21	0.011	Res<Non, Ctr
Mean occurrence (/s)						
Class A	3.79 (.62)	2.90 (.85)	3.01 (.78)	2.63	n.s.	
Class B	4.64 (1.06)	3.33 (.95)	3.31 (1.18)	4.41	0.020	Res>Non, Ctr
Class C	5.25 (.60)	3.98 (.67)	3.88 (.18)	9.08	0.001	Res>Non, Ctr
Class D	3.97 (.70)	3.72 (1.11)	4.06 (.91)	0.37	n.s.	
Total	17.65 (2.26)	13.92 (2.69)	14.27 (2.76)	4.80	0.015	Res>Non, Ctr
Mean total time (%)						
Class A	17.2 (2.4)	17.4 (6.2)	17.6 (4.8)	0.02	n.s.	
Class B	26.1 (4.7)	21.2 (5.5)	21.0 (7.2)	1.65	n.s.	
Class C	36.0 (6.5)	32.9 (11.6)	28.8 (9.4)	1.73	n.s.	
Class D	20.7 (7.1)	28.5 (10.9)	32.6 (10.1)	3.94	0.030	Res<Ctr

Significance was determined by one way ANOVA.
Res, Responder group; Non, non-responder group; Ctr, healthy control group.

Table 6
Mean percent change in microstate parameters (SD) in responder ($n=7$) and non-responder ($n=7$)

	Responder	Non-responder	t value	p value (2-tailed t-test)
Mean duration (%)				
Class A	24.3 (27.6)	−2.4 (16.3)	2.20	.048
Class B	23.4 (27.1)	1.7 (17.7)	1.77	n.s.
Class C	1.4 (30.1)	−4.7 (34.6)	0.35	n.s.
Class D	30.9 (31.7)	−12.9 (11.7)	3.43	.005
Total	18.0 (21.5)	−7.4 (9.5)	2.85	.015
Mean occurrence (%)				
Class A	−10.3 (25.2)	18.8 (29.3)	−2.00	n.s.
Class B	−7.2 (24.7)	26.7 (40.1)	−1.91	n.s.
Class C	−23.4 (12.2)	8.9 (20.4)	3.61	.004
Class D	−3.8 (23.4)	5.4 (28.2)	−0.66	n.s.
Total	−12.9 (13.7)	11.1 (14.0)	3.24	.007
Mean total time (%)				
Class A	9.3 (31.7)	14.8 (33.3)	−0.319	n.s.
Class B	14.1 (42.1)	33.8 (60.6)	−0.706	n.s.
Class C	−21.2 (25.7)	6.9 (52.0)	−1.284	n.s.
Class D	22.0 (35.5)	−7.6 (31.7)	1.646	n.s.

Significance was determined by unpaired t-test.

permit for the abnormal thoughts and experiences reported by the patients. It is noteworthy that in a large normative study across a large age span (Koenig et al., 2001), we found that duration of microstates of class D was shortest around the age of 20, which is the typical age of onset of schizophrenia.

In first-episode, medication-naïve schizophrenia, increased occurrence and total time in class A were also reported (Koenig et al., 1999; Lehmann et al., 2005). Although we found similar tendencies, these results were not significant and, instead, increased occurrence in class B and C were found. These discrepancies may come from the different clinical profile of the subjects. Our subjects in this study were medication-naïve schizophrenics, however, some of them were not first-episode and had long durations of illness (Table 1).

Reduced synchronization of large scale brain processes may contribute to lower GFS in the theta frequency band in schizophrenia, which is consistent with recent concepts that a functional disconnection of various large-scale neural networks (Weinberger et al., 1992; Liddle, 1996; Friston, 1999; Andreasen, 2000) or disturbed neuronal cooperation (Meyer-Lindenberg et al., 2001) explains the underlying psychopathology in schizophrenia. In addition, Gevins et al. (1997) reported that intensity of theta band activity was positively correlated to working memory functions. Although we cannot draw any definitive conclusion about any cognitive dysfunction because of lack of cognitive evaluation, the changes in GFS might be related to brain functions such as working memory that are poorly assessed by the BPRS.

The present study demonstrated higher gamma synchronization during resting state in schizophrenia. Most previous studies investigating gamma activity in schizophrenia have focused on event related phase locked oscillations and have reported that reduced gamma oscillations were associated with psychomotor poverty (Lee et al., 2003). Although gamma activity during resting condition in schizophrenia is still controversial, our finding was supported by previous studies reporting that hallucinations were associated with increased gamma activity (Baldeweg et al., 1998) and that schizophrenia patients with auditory hallucination showed increased EEG amplitudes in high EEG frequencies (Lee et al., 2006). These findings suggest that even in a resting condition, the brains of schizophrenics with positive symptoms act as if they were experiencing actual stimulations.

Treatment resulted, as hypothesized, in an increase of theta band GFS and thus a change of this measure towards values observed in normal controls. However, over all patients, we failed to find a similar change of deviant microstate features with treatment. These changes became only apparent when a subgroup of patients that actually responded to the treatment was considered. Interestingly, this same subgroup of responders accounted for all of the significant microstate differences observed between patients and controls before treatment. Controls and non-responders were not statistically distinguishable before treatment. Our data therefore suggests that EEG microstates may identify a subgroup of patients that show abnormalities in specific biological state markers; and that these state markers change with treatment, as does the clinical picture. If the same state markers are apparently normal before treatment, treatment will induce less change, and a clinical response to treatment is less likely to occur.

The limitations of this treatment response study are given by the use of various kinds of psychoactive drugs, and the relative small number of subjects when dividing patients into responders and non-responders. In addition, the design of the study did not allow to strictly distinguish changes in brain function attributable to primary pharmacological effects from changes attributable to alteration in clinical state. However, the present study extended findings of treatment effect on brain functions in schizophrenia by supplying the high time resolution necessary to study human information processing, or by supplying the high frequency resolution necessary to study synchronization of cortical networks, and suggested that shortened duration of specific microstate classes is a state marker especially in neuroleptic

responsive patients with schizophrenia, and that lower theta GFS is a state-related phenomenon which is independent of neuroleptic responsiveness assessed by BPRS scores.

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Contributors

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Conflict of interest

The authors declare that they have no conflicts of interest.

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References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Washington, D.C. (DSM-IV).

Andreasen, N.C., 2000. Schizophrenia: the fundamental questions. Brain Res. Brain Res. Rev. 31, 106–112.

Baldeweg, T., Spence, S., Hirsch, S.R., Gruzelier, J., 1998. Gamma-band electroencephalographic oscillations in a patient with somatic hallucinations. Lancet 22, 601–620.

Bressler, S.L., 2003. Cortical coordination dynamics and the disorganization syndrome in schizophrenia. Neuropsychopharmacology 28 (Suppl 1), S35–S39.

Friston, K.J., 1999. Schizophrenia and the disconnection hypothesis. Acta Psychiatr. Scand., Suppl. 395, 68–79.

Gevins, A., Smith, M.E., McEvoy, L., Yu, D., 1997. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cereb. Cortex 7, 374–385.

Inagaki, A., Inada, T., Fujii, Y., 2001. Dose equivalence of psychotropic drugs. Part XV; Dose equivalence of novel neuroleptics. Perospirone. Jpn. J. Clin. psychopharmacol. 6, 869–870.

Koenig, T., Lehmann, D., Merlo, M.C., Kochi, K., Hell, D., Koukkou, M., 1999. A deviant EEG brain microstate in acute, neuroleptic-naive schizophrenics at rest. Eur. Arch. Psychiatry Clin. Neurosci. 249, 205–211.

Koenig, T., Lehmann, D., Saito, N., Kuginuki, T., Kinoshita, T., Koukkou, M., 2001. Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naive patients with schizophrenia: preliminary results. Schizophr. Res. 50, 55–60.

Koenig, T., Prichep, L., Lehmann, D., Sosa, P.V., Braeker, E., Kleinlogel, H., Isenhart, R., John, E.R., 2002. Millisecond by millisecond, year by year: normative EEG microstates and developmental stages. NeuroImage 16, 41–48.

Koenig, T., Studer, D., Hubl, D., Melie, L., Strik, W.K., 2005a. Brain connectivity at different time-scales measured with EEG. Philos. Trans. R. Soc. Lond., B Biol. Sci. 29, 1015–1023.

Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L.O., John, E.R., Jelic, V., 2005b. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol. Aging 26, 165–171.

Kubicki, S., Herrmann, W.M., Fichte, K., Freund, G., 1979. Reflections on the topics: EEG frequency bands and regulation of vigilance. Pharmakopsychiatr. Neuro-Psychopharmakol. 12, 237–245.

Lee, K.H., Williams, L.M., Breakspear, M., Gordon, E., 2003. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. Brain Res. Brain Res. Rev. 41, 57–78.

Lee, S.H., Wynn, J.K., Green, M.F., Kim, H., Lee, K.J., Nam, M., Park, J.K., Chung, Y.C., 2006. Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations. Schizophr. Res. 83, 111–119.

Lehmann, D., Michel, C.M., 1989. Intracerebral dipole sources of EEG FFT power maps. Brain Topogr. 2, 155–164.

Lehmann, D., Ozaki, H., Pal, I., 1987. EEG alpha map series: brain micro-states by space-oriented adaptive segmentation. Electroencephalogr. Clin. Neurophysiol. 67, 271–288.

Lehmann, D., Faber, P.L., Galderisi, S., Herrmann, W.M., Kinoshita, T., Koukkou, M., Mucci, A., Pascual-Marqui, R.D., Saito, N., Wackermann, J., Winterer, G., Koenig, T., 2005. EEG microstate duration and syntax in acute, medication-naïve, first episode schizophrenia: a multi-center study. Psychiatry Res. 28, 141–156.

Liddle, P.F., 1996. Functional imaging—schizophrenia. Br. Med. Bull. 52, 486–494.

Mendrek, A., Laurens, K.R., Kiehl, K.A., Ngan, E.T., Stip, E., Liddle, P.F., 2004. Changes in distributed neural circuitry function in patients with first-episode schizophrenia. Br. J. Psychiatry 185, 205–214.

Meyer-Lindenberg, A., Poline, J.B., Kohn, P.D., Holt, J.L., Egan, M.F., Weinberger, D.R., Berman, K.F., 2001. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am. J. Psychiatry 158, 1809–1817.

Overall, J.E., Gorham, D.R., 1962. The Brief Rating Psychiatric Scale. Psychol. Rep. 10, 799–812.

Pascual-Marqui, R.D., Michel, C.M., Lehmann, D., 1995. Segmentation of brain electrical activity into microstates: model estimation and validation. IEEE Trans. Biomed. Eng. 42, 658–665.

Stephan, K.E., Magnotta, V.A., White, T., Arndt, S., Flaum, M., O'Leary, D.S., Andreasen, N.C., 2001. Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. Psychol. Med. 31, 1065–1078.

Stip, E., Mancini-Marie, A., 2004. Cognitive function and depression in symptom resolution in schizophrenia patients treated with an atypical antipsychotic. Brain Cogn. 55, 463–465.

Strelets, V., Faber, P.L., Golikova, J., Novototsky-Vlasov, V., Koenig, T., Gianotti, L.R., Gruzelier, J.H., Lehmann, D., 2003. Chronic schizophrenics with positive symptomatology have shortened EEG microstate durations. Clin. Neurophysiol. 114, 2043–2051.

Strik, W.K., Dierks, T., 2004. How modern neurophysiology can help to understand schizophrenia. Schweiz. Arch. Neurol. Psychiatr. 8, 368–374.

Toru, M., 1983. Pharmacology of Schizophrenics. Chugai Medical Press, Tokyo.

Weinberger, D.R., Berman, K.F., Suddath, R., Torrey, E.F., 1992. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am. J. Psychiatry 149, 890–897.