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# A deviant EEG brain microstate in acute, neuroleptic-naive schizophrenics at rest

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**Abstract** Momentary brain electric field configurations are manifestations of momentary global functional states of the brain. Field configurations tend to persist over some time in the sub-second range ("microstates") and concentrate within few classes of configurations. Accordingly, brain field data can be reduced efficiently into sequences of re-occurring classes of brain microstates, not overlapping in time. Different configurations must have been caused by different active neural ensembles, and thus different microstates assumedly implement different functions. The question arises whether the aberrant schizophrenic mentation is associated with specific changes in the repertory of microstates. Continuous sequences of brain electric field maps (multichannel EEG resting data) from 9 neuroleptic-naive, first-episode, acute schizophrenics and from 18 matched controls were analyzed. The map series were assigned to four individual microstate classes; these were tested for differences between groups.

One microstate class displayed significantly different field configurations and shorter durations in patients than controls; degree of shortening correlated with severity of paranoid symptomatology. The three other microstate classes showed no group differences related to psychopathology. Schizophrenic thinking apparently is not a continuous bias in brain functions, but consists of intermittent occurrences of inappropriate brain microstates that open access to inadequate processing strategies and context information

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## Introduction

Research into the pathophysiology of schizophrenic states and traits includes many fields such as psychosocial and psychodynamic approaches (e.g., Docherty 1996; Strauss 1989), functional and structural brain studies (e.g., Koukkou et al. 1993; Chua and McKenna 1995; Andreasen 1997), neuropathology (e.g., Weinberger 1996), neurochemistry (e.g., Lieberman and Koreen 1993), and genetics (e.g., Crow 1995). All approaches reported differences between schizophrenics and controls which are not pathognomonic for schizophrenia and show overlap with normals. No full explanation of the pathophysiological mechanisms leading to predisposition for symtpoms (trait research) and/or to manifestation of symptoms (state research) is currently available.

Since Eugen Bleuler (1950/1911), main aspects of the clinical diagnosis of schizophrenia included the occurrence of dysfunctional thoughts and emotions which, however, are not present continuously and exhibit unpredictable fluctuations. Thus, it appears important to establish bottom-up descriptions of brain functional states during schizophrenic mentation. Many studies showed that untreated schizophrenics show aberrations in various EEG measurements such as different power spectra (Miyauchi et al. 1990; Galderisi et al. 1992; Gattaz et al. 1992; John et al. 1994; Omori et al. 1995) and increased dimensional complexities (Koukkou et al. 1993; Saito et al. 1998), indicating that schizophrenics have an a priori different disposition to respond to new information (Koukkou et al. 1991). This hypothesis is supported by EEG components of the orienting response where deviant responses to verbal stimuli have been observed in schizophrenics (e.g., Koukkou 1982).

The measures of power spectra, coherence, and complexity employed in these studies account for states in the range of seconds. To investigate brain processes that change in the sub-second range such as everyday thinking, the functional brain state must be described with the appropriate time resolution. A satisfying time resolution in milliseconds is available in EEG and MEG measurements where momentary brain state is reflected directly by the momentary spatial configuration of the brain electric field. Changes of brain electric field configuration can only be caused by changes of the active neural elements, and such change most probably implies changes of brain function. Without further assumptions about the putative generators of the observed configurations, sequences of momentary functional brain states can be established by assessing the changes of the brain electric field configuration as function of time (Lehmann 1987; Wackermann et al. 1993; Strik and Lehmann 1993).

Changes of the brain electric field configuration are discontinuous; a given field configuration tends to remain quasi-stable for a sub-second time epoch before it quickly changes into a different configuration. These periods of quasi-stable field configuration were called microstates and were suggested to reflect basic steps in brain information processing in spontaneous and event-related studies (Lehmann et al. 1987, 1998; Brandeis and Lehmann 1989; Lehmann 1990; Koenig et al. 1998). In addition, the observed microstate configurations concentrated in a few classes of field configurations which can be identified by spatial clustering (Wackermann et al. 1993; Pascual-Marqui et al. 1995). In order to obtain a quantification of brain electric field data in the time domain, it is thus reasonable and effective to consider the measured EEG as a non-linear sequence of re-occurring classes of brain electric microstates that do not overlap in time. Describing the EEG in terms of microstate classes is an efficient data reduction and yields a repertory of brain microstate classes and their spatial configurations, quantifying the number of times each microstate class was visited, and the mean duration of these visits.

Considering the general state-dependency of information processing in the brain, we hypothesized that the schizophrenics' deviant thoughts and behavior originate from deviant functional microstates that provide an aberrant platform for information processing strategies and context.

The present study established individual repertories of functional brain microstates in neuroleptic-naive, first-episode, productive schizophrenic patients and in matched healthy controls, recorded during a no-taks resting condition with closed eyes. We examined the repertories of the patients' microstates for general or specific abnormalities, and for possible correlations with the severity of schizophrenic symptomatology.

## Methods and material

During six years, all patients newly admitted to the acute psychosis ward of the University Hospital of Psychiatriy, Berne, were candidates for this study. If a patient was admitted because of the severity of productive, positive schizophrenic symptomatology, if this was a first episode, and if there was no report of prior medication, routine EEG recording was attempted before initiation of medication. At discharge, careful review of the successfully recorded patients excluded cases with psychoactive medication before admission, brain pathology, drug use, alcoholism, birth complications, and pathological clinical EEG findings. Eventually, nine patients (6 female, 3 male; mean age 24.82 ± 6.67 years) qualified; five were diagnosed as schizophrenia of the paranoid type (DSM-IV, 295.30) and 4 as schizophreniform disorder (DSM-IV 295.40).

On the recording day, the psychopathological state was assessed using the AMP (Arbeitsgemeinschaft für Methodik in der Psychiatrie) system (Scharfetter 1971; Guy and Ban 1982 for an English introduction to the revised version AMDP). The 123 AMP symptom scores were pooled into syndrome scores (Baumann and Stieglitz 1983). The three syndromes closely related to schizophrenic symptomatology (the hallucinatory-desintegrative, paranoid and catatonic syndrome) were used for further analysis.

Eighteen controls participated, two controls matched for each patient in age (mean 25.05 ± 6.32 years), gender, and basic education. They were recruited among employees and acquaintances and met the exclusion criteria above. The study met all requirements of the hospital's Ethics Committee.

Subjects were seated in a sound-shielded Faraday chamber with a window for visual contact, and were informed about the procedure. 19-electrode EEG (10/20 positions) against linked earlobes was recorded under closed eyes resting condition (amplified bandpass 1–30 Hz, continuous digitization at 128 Hz).

From the first 4 minutes of EEG, the first 20 artifact-free 2-second epochs were selected off-line, digitally bandpassed (2–20 Hz), and recomputed against average reference (removal of spatial DC) into sequences of momentary maps of the brain electric field's topographic configurations (landscapes). As in previous studies (Lehmann et al. 1987; Strik and Lehmann 1993; Wackermann et al. 1993), for optimal signal-to-noise ratio, only those maps that occurred at momentary maxima of the Global Field Power curve (GFP) were used for microstate analysis. There was no difference (unpaired t-test $t = 0.12$; $df = 25$; n.s.) between number of GFP maxima/second of controls and patients, which indicates that there is no evidence for a group difference in unspecific arousal.

Microstate analysis is based on the rationale that different map configurations (landscapes, but disregarding polarity) of the brain field reflect different functional states. Assigning the maps to different microstates can be done by sequential (e.g., Lehmann et al. 1987; Strik and Lehmann 1993) or global approaches (Pascual-Marqui et al. 1995). A global approach was used, a modification (Pascual-Marqui et al. 1995) of the classical k-means clustering. (The employed programs are available at the web location www.keyinst.unizh.ch.) Global approaches allow direct assignment of all maps to few classes (clusters). Contrary to sequential approaches, global approaches define microstates post hoc, and tend to lower microstate duration estimates.

The principle of clustering is reviewed in Fig. 1, illustrating the clustering of a map sequence into 2 classes, with a mean map for each class. The procedure can be repeated aiming at more classes. The optimal number of classes is determined by the minimum of the cross-validation index which considers both the number of used classes and the percent variance explained by the class mean maps (Pascual-Marqui et al. 1995).

We computed class mean maps separately for each subject, testing the entire range of 1 to 10 classes. The optimal number of classes was either 3 (1 patient, 8 controls), 4 (7 patients, 10 controls), or 5 (1 patient). Patients tended to a higher optimal number of classes ($x^2 = 4.80$; $df = 2$; $p = 0.091$). However, the median was 4 in both groups, and there was no significant difference between controls and patients in the variance explained by 4 class mean maps (patients: 83.4%, controls: 85.0%; unpaired t-test, $t = 0.95$; $df = 25$; $p = 0.35$). Thus, in order to provide for comparability between subjects and to allow direct statistics over subjects, 4 classes were used for each subject, yielding 4 individual class mean maps.

From maps to microstates: Each map of a given subject was assigned to the best-fitting individual class mean map. A microstate

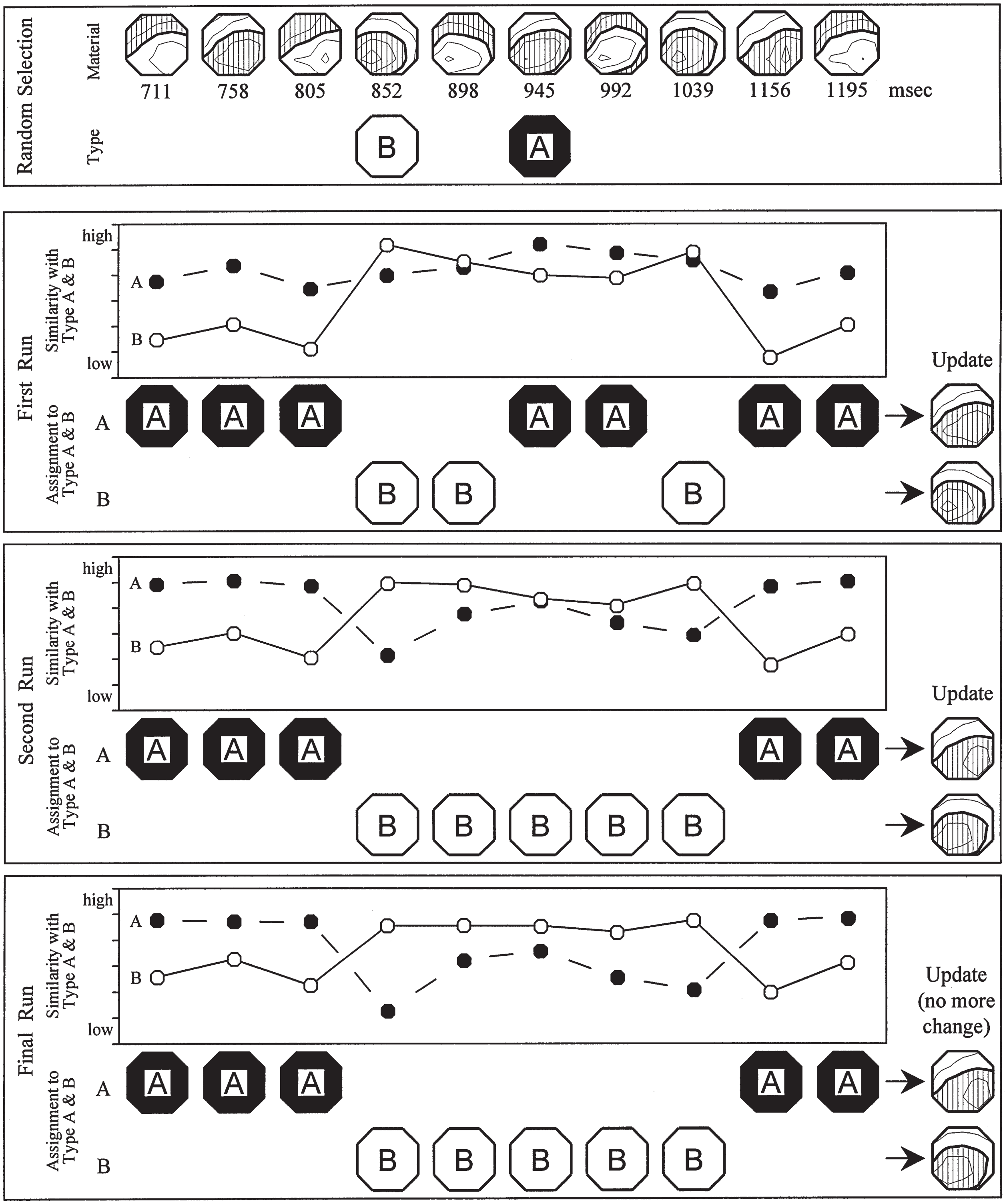


**Fig. 1** Example of clustering of maps into map classes. Clustering a sequence of 10 momentary maps into 2 class mean maps. First box: the maps (normalized potential maps with equidistant contour lines; nose up, left ear left, hatched areas = negative against average reference). Two randomly selected, starting prototype maps are labeled A (white) and B (black). Second box: first run; similarity of spatial configuration of each prototype map with each of the 10 maps is computed using the squared correlation coefficient to omit the maps' polarities; the highest value determines the assignment, shown by black (similarity to A) or white (similarity to B) symbols. Separately for each class, the prototype maps are updated combining all assigned maps, by computing the first spatial principal component of the maps and thereby maximizing the common variance while disregarding map polarity (right: updated maps). Third Box: this is repeated in the second and later runs until no further changes in assignment occur, and thus 2 prototypes are established as 2 class mean maps (final run, last box). Eventually, the percentage of the variance of the data explained by the 2 class mean maps is determined. Explained variance might change depending on selected starting prototype maps. To find the solution with maximal explained variance, the entire procedure was repeated 20 times with newly randomly selected starting prototype maps

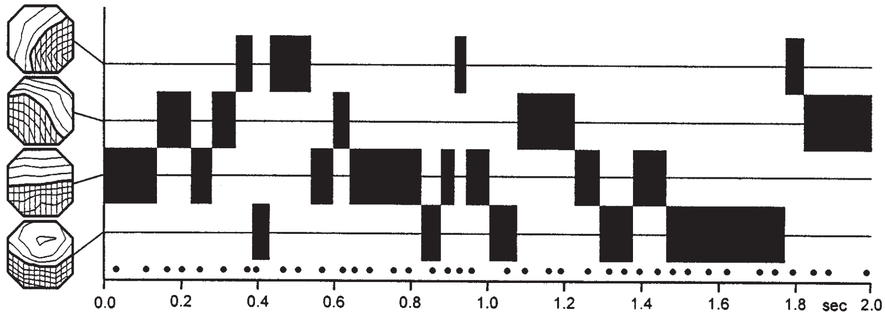


**Fig. 2** Assignment of maps to microstate classes. Assignment of a 2-second sequence of momentary maps (dots along the bottom line) to 4 microstate classes (normalized potential microstate maps, equidistant contour lines, with arbitrary polarity labeling, on the left, with attached assignment lines). Assignment of the momentary maps to a given microstate class are shown by blocks on the corresponding assignment lines, resulting in microstate durations (horizontal)

was defined as a continuous epoch during which the maps belonged to the same class mean map; microstate start and end points were centered between the occurrence times of the neighboring maps. Each microstate thus was identified as belonging to one of the four individual class mean maps; therefore, the latter are now called individual microstate maps that describe four individual microstate classes. Figure 2 shows a 2-second epoch of maps assigned to 4 microstate classes.

For each subject and each microstate class, mean microstate duration, mean number of microstate occurrences per second, and mean percentage of covered total analysis time was computed. As control, we computed mean microstate durations for all material after randomization of the map sequences. In all 27 subjects, mean microstate duration was longer in the original than in the randomized map sequences.

The procedure to establish correspondence of the individual microstate classes across subjects and to compute mean maps over subjects for the 4 microstate classes treated separately the sets of individual microstate maps of the patients ($4 \times 9 = 36$ maps) and controls ($4 \times 18 = 72$ maps). Mean maps of the 4 microstate classes across subjects were computed by (A) arbitrarily selecting 4 maps from the set as initial prototypes, (B) testing, in each subject, all possible permutations of the 4 individual microstate maps for best fit with the 4 prototype maps (disregarding polarity, see Fig. 1) and updating the prototypes by averaging the best-fit permutated individual microstate maps. (B) was repeated until the assignments changed no more. The procedure was restarted 20 times at (A), arbitrarily selecting 4 new initial prototypes. The result with smallest inter-subject variance was accepted and yielded a mean map for each microstate class of either set. For each subject, each of the 4 individual microstate classes thus was assigned to a mean map of a different microstate class.

The resulting mean maps of the $2 \times 4$ microstate classes (4 each for controls and patients) were paired so that the 4 pairs had minimal average map dissimilarity (Lehmann et al. 1987; Wackermann et al. 1993). These pairs were arbitrarily labeled as microstate classes A–D.

Statistics: Separately for each of the 4 microstate classes, the configuration of their mean maps over subjects was compared between controls and patients using a randomization test (Manly 1991): Map dissimilarity between the mean maps of the two groups was computed. Then, the individual microstate maps of controls and patients were randomly assigned to two groups, the maps were averaged within these groups, and a new dissimilarity value between these arbitrary mean maps was computed. 5000 such randomized re-assignments yielded the distribution of map dissimilarity values under the null hypothesis. Chance probability of obtaining map differences larger or equal to the observed difference between controls and patients was established.

For each microstate measure (microstate occurrences, microstate duration and percent total time covered), a separate two way ANOVA was performed (subject group $\times$ microstate class). Significant results including group were post hoc tested using unpaired t-tests. In case of significant differences, the correlations of the measure with the three schizophrenia-relevant AMP syndrome scores of symptomatology were established by Pearson product-moment correlations.

Reported p-values are double-ended. Where indicated, Bonferroni correction was used.

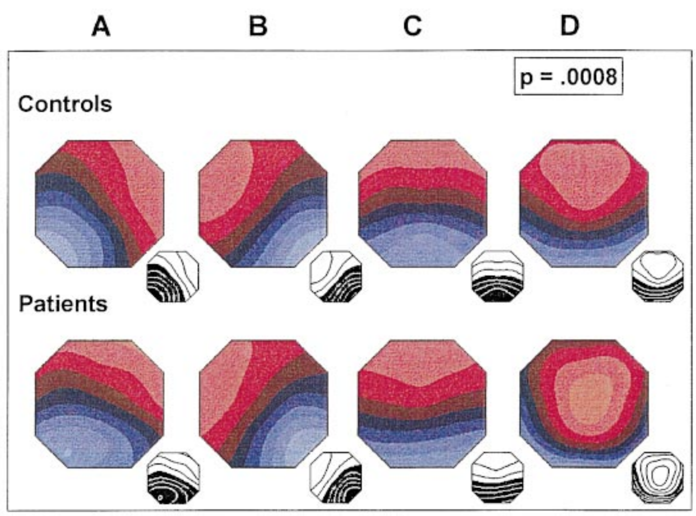


**Fig. 3** Microstate classes of patients and controls. Mean normalized equipotential maps of the four microstate classes (A–D) of the patients and controls; the spatial configurations of the class D maps differed signficantly (Bonferroni-corrected p value). Using a linear color scale, the map areas of opposite polarity are arbitrarily coded in blue and red; the small inset maps display the identical information in black and white

## Results

The mean maps of the 8 microstate classes (4 each for patients and controls) are shown in Fig. 3. 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. The microstates of class D showed a highly significant difference of spatial configuration between patients and controls ($p = 0.0002$, Bonferroni corrected $p = 0.0008$) while the classes A, B and C showed no significant differences.

The three parameters duration, occurrence, and total time for the 4 microstate classes are illustrated in Fig. 4. Microstate mean duration varied between 65 and 86 ms in patients and controls for the different microstate classes. Two-way ANOVA (subject group × microstate class) showed no main effect of group, but a significant interaction between group and microstate class ($F = 5.50$; $df = 3,75$; $p = 0.0054$ after Bonferroni correction). This interaction was due to significantly shorter microstates of class D of the patients (65.5 ms; $SE = 2.84$) than of the controls (84.5 ms; $SE = 3.54$) shown in post hoc t-tests ($t = 3.50$; $df = 25$; $p = 0.0018$). The other 3 microstate classes yielded no significant differences.

Correlation analysis revealed that the severity of the paranoid syndrome increased with decreasing duration of the microstates of class D ($r = -0.84$; $n = 9$; $p = 0.0046$, after Bonferroni correction $p = 0.014$). Thus, the shortening of microstates of class D in patients was more pronounced in patients with more severe paranoid symptomatology.

Microstate occurrence ranged between 2.7 and 4.0 microstates/second. ANOVA yielded no main effect of group, but again, a significant interaction between group and microstate class ($F = 3.63$; $df = 3,75$; $p = 0.049$ after Bonferroni correction). This interaction was due to significantly more frequent microstates of class A in patients (3.38/s; SE = 0.18) than controls (2.66/s; $SE = 0.17$)) as shown by the post hoc t-test ($t = 2.61$; $df = 25$; $p = 0.015$). There were no significant correlations of occurrence of microstate of class A with psychopathology. The other 3 microstate classes had no significant differences between patients and controls.

Percent of total time covered by the different microstate classes ranged between 19.0% and 33.7%. ANOVA showed a significant interaction of group with microstate class ($F = 4.74$; $df = 3,75$; $p = 0.013$ after Bonferroni correction). The post hoc t-tests showed that the patients compared with the controls tended to spend more percent of total time in microstates of class A (24.7% versus 19.0%; $SE = 2.11$ and 1.76, respectively: $t = 1.96$; $df = 25$; $p = 0.061$), and significantly less percent total time in class D (20.3% versus 29.0%; $SE = 2.08$ and 1.23, respectively: $t = 3.82$; $df = 25$; $p = 0.00079$). Since total time is always 100%, a group main effect is not applicable here. There were no significant correlations with psychopathology.

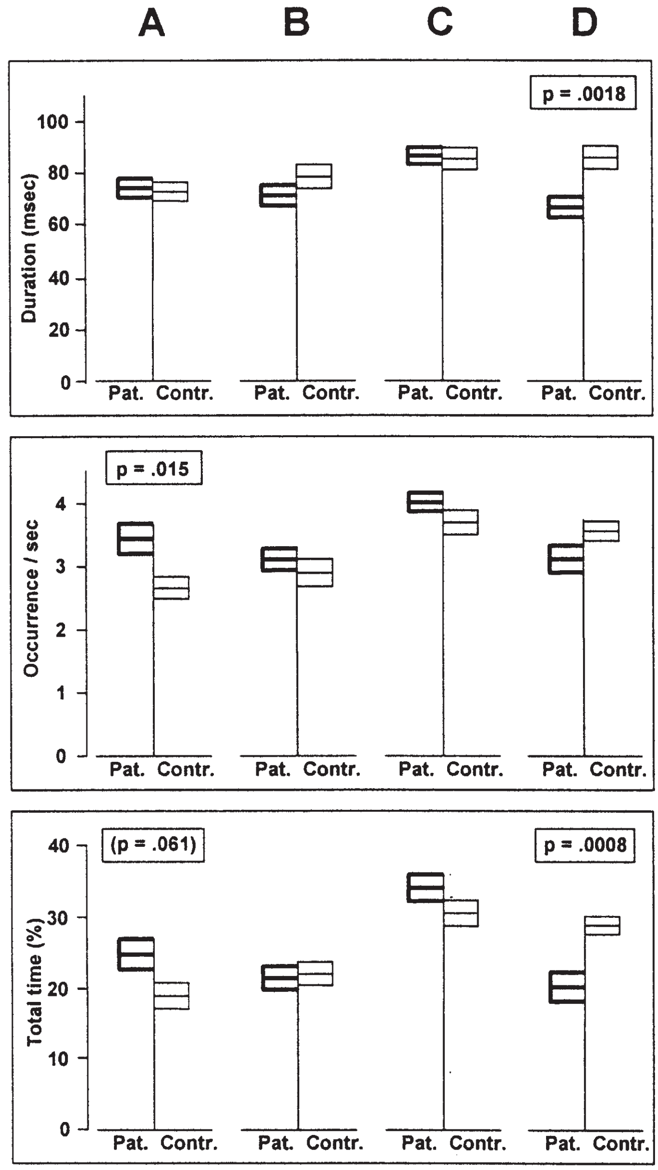


**Fig. 4** Microstate statistics. Duration, occurrence/second, and percent total time covered, of the 4 microstate classes (A–D) of patients and controls. In the graphs, the three lines in the "flags" indicate mean and ± standard errors of the patients (heavy lines) and controls (thin lines). Significant differences between controls and schizophrenics are indicated by their p-values

## Discussion

Different topographic configurations of the brain's electric field must reflect activity of different neural networks and, thus, suggest different functions. Because field configurations are discrete and change quasi stepwise, parsing the sequences of momentary fields into microstates can isolate the building blocks of cognition and emotion, putative "atoms of thought" (Lehmann et al. 1990). This sequential quality of the analysis is not in contradiction with parallel processing, as each step can be conceived as the activity of large multifocal neural networks with distributed parallel processing (Mesulam 1990).

Four microstate classes were used to classify the data. Three of them were similar in spatial configuration for patients and controls; only one, class D, was significantly different, in the patients showing a central and not an anterior location of maximal potential. The patients' deviant class D microstates covered about 20% of total time, occurred about three times/second, and lasted on the average about 65 ms – the shortest of all 8 classes. The durations of the deviant microstates of class D in our patients were systematically shorter with increasing severity of the paranoid syndrome. This correlation between class D microstate duration and schizophrenic symptomatology was further and independently supported by the observation that the corresponding, but non-identical class D microstates in controls had a significantly longer mean duration and covered a higher percentage of time. The time deficit in the patients was compensated by increased occurrence of class A microstates.

Our results strongly imply that the schizophrenic condition does not result from continuously biased brain functions, but from recurring, deviant microstates interspersed in a sequence of apparently normal microstates. The rapid intermittence of the phenomenon as well as the similar total number of Global Field Power maxima/second in patients and controls makes the hypothesis of differences in longer lasting, unspecific processes such as arousal unlikely.

It is well known that information processing strategies and accessible memory contents depend on the brain's functional state (Eich 1980; Koukkou and Lehmann 1983) such as physiological varieties (excitation, relaxation, sleep stages; e.g., Cavallero et al. 1992), developmental stages (e.g., Gathercole 1998) or induced conditions (alcohol, drugs; e.g., Spitzer et al. 1996); state-dependency has also been shown on the EEG microstate level (Kondakor et al. 1993). Hence, our finding of a deviant class of brain microstates in schizophrenics suggests that schizophrenics recurringly use processing strategies and access memory contents which differ from those normally available. These deviant microstates could thus give rise to the irregulatities of thought, emotion, and behavior that result in the diagnosis of schizophrenia. In never-treated schizophrenics, EEG power spectral analyses that concern extended time epochs in the second range previously also had pointed to deviant brain states as cause of deviant information processing (Miyauchi et al. 1990; Gattaz et al. 1992; John et al. 1994; Omori et al. 1995). Schizophrenics generally showed increased slow (delta-slow theta) activity, normally a sign of lowered vigilance, and increased fast (beta) activity, normally a sign of increased vigilance. This dissociation of vigilance markers (Koukkou et al. 1993) was interpreted as co-occurrence of basically divergent brain functional states, as a dissociated state that permits access to inadequate processing strategies and memory contents. The conclusion of an inadequate integration and utilization of brain functions and memory contents in schizophrenics were complemented by EEG analyses of neuroleptic-naive schizophrenics that assessed local or regional features of brain electric acitivty and found increased dimensional complexity (Koukkou et al. 1993; Saito et al. 1998), interpreted as increase of independent, simultaneously active brain processes and loosened or degraded functional connectivity (see also Friston 1996).

Knowledge of the functional significance of different microstate topographies still is very limited and therefore, the following are only speculative comments: the class A microstates; which occurred in patients more frequent than normal, had an electric field axis that was right anterior-left posterior (class B's axis was left anterior-right posterior). In normal, microstates of class A's characteristics were associated with spontaneous, non-imagery, abstract thoughts, and of class B's characteristics with spontaneous visual imagery (Lehmann et al. 1998); hence, the increase of class A might relate to thought disturbances and to the predominantly non-visual character of mentation (hallucinations) in acute psychoses. The class D microstates with their more posterior extreme in our patients were reminiscent of event-related brain fields related to absence of focused attention, while the more anterior localization in our controls resembled fields during focused attention (Brandeis and Lehmann 1989). Since more time spent in microstates D correlated with lighter paranoid symptomatology, this suggests that although the deviant microstates implement degraded attentional mechanisms, their more frequent occurrence improved their functional efficacy.

Since Bleuler (1924), who described schizophrenics as "incapable of holding the train of throught in the proper channels", disturbances of various attentional functions and specifically, selective attention, have been a major theme in schizophrenia research (e.g., Zubin 1975; Nuechterlein and Dawson 1984). They were considered as important factors in a wide range of experiments revealing information processing deficits in schizophrenics under high processing load, multiple task and distracting conditions that require rapidity and efficiency (see Braff 1993). On one side, the successful execution of these attention-involving tasks depends on frontal lobe functions (Fuster 1989), in particular working memory (Goldman-Rakic 1994). Indeed, frontal lobe abnormalities were demonstrated in schizophrenic subjects (e.g., Weinberger et al. 1994). On the other side, these tasks require extensive interaction and functional integration of the prefrontal cortex with other cortical and subcortical brain structures (Fuster 1989). The functional connectivity between these brain regions also seems to be disturbed in schizophrenic patients (Friston and Frith 1995; Andreasen 1997), leading to an "imbalance of neural activity at diverse sites rather than abnormal function at a single location" (Liddle, 1996).

The present study thus extended findings of altered brain functions in schizophrenia by supplying the high time resolution necessary to study human information processing. The results are well embedded into previously proposed frameworks of working memory dysfunctions during schizophrenia (Koukkou et al. 1991; Golman-Rakic

1994) and allow a further investigation of the functional significance of the schizophrenia-related brain states, namely whether they have a normal function in other conditions or at an earlier developmental stage.

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