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Event-related potential P300 microstate topography during visual one- and two-dimensional tasks in chronic schizophrenics

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Abstract Reports on left-lateralized abnormalities of component P300 of event-related brain potentials (ERP) in schizophrenics typically did not vary task difficulties. We collected 16-channel ERP in 13 chronic, medicated schizophrenics (25 ± 4.9 years) and 13 matched controls in a visual P300 paradigm with targets defined by one or two stimulus dimensions (C1: color; C2: color and tilt); subjects key-pressed to targets. The mean target-ERP map landscapes were assessed numerically by the locations of the positive and negative map-area centroids. The centroids' time-space trajectories were searched for the P300 microstate landscape defined by the positive centroid posterior of the negative centroid. At P300 microstate centre latencies in C1, patients' maps tended to a right shift of the positive centroid ($p < 0.10$); in C2 the anterior centroid was more posterior ($p < 0.07$) and the posterior (positive) centroid more anterior ($p < 0.03$), but without left-right difference. Duration of P300 microstate in C2 was shorter in patients (232 vs 347 ms; $p < 0.03$) and the latency of maximal strength of P300 microstate increased significantly in patients (C1: 459 vs 376 ms; C2: 585 vs 525 ms). In summary only the one-dimensional task C1 supported left-sided abnormalities; the two-dimensional task C2 produced abnormal P300 microstate map landscapes in schizophrenics, but no abnormal lateralization. Thus, information processing involved clearly aberrant neural populations in schizophrenics, different when processing one and two stimulus dimensions. The lack of lateralization in the two-dimensional task supported the view that left-temporal abnormality in schizophrenics is only one of several task-dependent aberrations.

Key words P300 microstate topography · Chronic schizophrenics · Lateralization · Task difficulty · ERP microstates

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Introduction

The component "P300" of event-related potential (ERP) waveshapes is an interesting psychophysiological operationalization of cognitive processes (see Pritchard 1981), hypothesized to reflect controlled processing (Rösler 1983). P300 is observed in the so-called oddball paradigm (Donchin 1981), which consists of a sequence of tones of which 10–20% are replaced randomly by distinctly higher- or lower-pitched tones ("odd" or "rare" events); the subject has to count or respond to the rare tones (the "targets"). Typically, ERP waveshapes show a prominent positivity (the P300 component) over the central-parietal areas approximately 300 ms after the target tones; this is not observed after the non-target tones.

An important part of the symptomatology of schizophrenia concerns disturbances in cognitive-emotional information processing. Accordingly, P300 was expected to be aberrant, and indeed, reduced amplitude and, less consistently, increased latency of P300, was repeatedly reported (Baribeau-Braun et al. 1983; Roth et al. 1980; Pritchard 1986; Kemali et al. 1991). However, Strik et al. (1994a) could not confirm the amplitude reduction when using reference-independent assessments of the global electric field strength of P300 in residual schizophrenics, Michie et al. (1990) found reduction only in parietal areas, and Ford et al. (1994) reported normal P300 amplitudes in a visual P300 task.

P300 studies also repeatedly reported a topographic abnormality in schizophrenics, a decreased P300 amplitude on the left side and thus a shift of the P300 field peak to the right side (Kemali et al. 1991; McCarley et al. 1991; Morstyn et al. 1983; Faux et al. 1990; Strik et al. 1994a, b), and left-handed schizophrenics showed inverted lateralization of this asymmetry (Holinger et al. 1992). The asymmetry was interpreted as decreased activity of the left temporal area during cognitive processing in the right-handed schizophrenics because this area contributes crucially to the P300 (Halgren et al. 1980). In line with this interpretation is the report by McCarley et al. (1993) on correlations between left posterior superior temporal gyrus volume and left hemispheric P300 amplitude reductions in schizophrenics, and of Heidrich and Strik (in press) on right-lateralized P300 peaks associated with impaired performance in the Verbal Pairs Associates Test indicative of left temporal function. However, the asymmetry was not confirmed by Michie et al. (1990) and Pfefferbaum et al. (1989, 1991). The reports on left-sided ERP abnormality aroused interest because of results obtained with other techniques which suggested left-hemispheric functional or structural aberrations in schizophrenia (e.g. post-mortem anatomy: Bogerts et al. 1985; overview: Crow 1990; PET: Friston et al. 1992; MRI: McCarley et al. 1993).

On the other hand, there are numerous reports about other putative locations of functional or structural abnormalities in schizophrenics. Although major factors, such as method of examination, symptomatology, disease duration, medication and possibly task type, should be partialled out and might explain some of the discrepancies, an overview shows that no unique localization has been agreed upon. Besides the left-temporal areas, reports have implicated, for example, frontal areas (Ingvar and Franzen 1974; Williamson 1987; Gattaz et al. 1992; Klausner et al. 1992), prefrontal areas (Weinberger et al. 1986), the right hemisphere (Largen et al. 1984; Venables 1984) and bilateral areas (the third ventricle, Iacono et al. 1988); for a review of some lateralization studies see Flor-Henry and Gruzelier (1983).

In typical P300 studies in schizophrenics, the information processing task of the oddball paradigm has required a discrimination between non-target and target events along one perceptual dimension (e.g. pitch). More demanding two-dimensional visual discrimination tasks involving different brain mechanisms have been used in several studies with normal subjects (e.g. Previc and Harter 1982; Hillyard and Münte 1984; Wijers et al. 1989; Kenemans et al. 1995). Experimental evidence generally suggests that schizophrenics may have a deficit in the control functions which govern the mobilization, allocation and control of attention or information-processing resources (Gjerde 1983; Grillon et al. 1990; Kochi 1992; Kochi et al. 1992). Consequently, schizophrenics are expected to show increasing aberrations from normal results with increasing difficulty of a task. The question arises whether higher and different demands on information processing would confirm and enhance the reported aberrations in P300 topography in schizophrenics. Because different types of tasks draw upon different brain mechanisms, one might alternatively expect that different brain areas might be identified as deficient depending on the task employed (e.g. O'Donnell et al. 1993).

The ERP analysis began as analysis of waveshapes from one or very few "active" scalp electrodes (see Donchin 1981), and waveshape-oriented analysis typically is still being used for multi-channel field data. This implies non-unique and therefore non-comprehensive analysis, because waveshapes depend on the arbitrarily pre-selected reference. The issue is illustrated in the study by Strik et al. (1994a) where the amplitudes at pre-selected electrode sites did not reflect reliably the overall strength of the widely distributed P300 potential field. An alternative, non-biased space-time approach considers the spatial configuration of the momentary brain potential field as basic analysis entity. The rationale is that different configurations of the potential field (different "landscapes") must have been generated by the activity of different neuronal assemblies. We note that momentary potential landscapes are independent of the chosen reference (Lehmann 1987; Pascual-Marqui and Lehmann 1993a, b). It is parsimonious to assume that the activities of different neuronal assemblies subserve different functions. Hence, a key for comprehensive brain field analysis in the study of brain functions is the identification of different field map landscapes. Using segmentation algorithms, this approach parses the series of the ERP field maps into brain electric "functional microstates", brief epochs in the sub-second range which are characterized by quasi-stable landscapes of the maps (Lehmann 1987; Lehmann and Skrandies 1980). Differences in microstates between groups identified qualitative changes in the ERP generating processes in normal subjects in different perceptual and cognitive conditions (Brandeis and Lehmann 1989; Lehmann 1990; Koenig and Lehmann 1996).

When viewing multi-channel ERP recordings as a series of map landscapes, the conventional P300 waveshape component can be re-defined as a microstate. The P300 microstate landscape in normals is characterized by an anterior negativity and a posterior positivity around 300–450 ms post stimulus (see e.g. Donchin et al. 1978). Its latency can be defined as the time of maximal electric strength of the field (Global Field Power; Lehmann and Skrandies 1980) within the P300 microstate. Unbiased comparisons between map landscapes might be done using global measures (Global Map Dissimilarity; Lehmann and Skrandies 1980) or by assessing numerically the maps with various topographic features which imply data reduction, such as the locations of the maximal and minimal potentials (Lehmann 1987) or the locations of the centroid of the positive and negative map areas (Appendix B in Wackermann et al. 1993).

Based on the hypothesis that increased task load exposes more clearly aberrations of the cognitive brain mechanisms in the patients, we used a modified, visual P300 design with three types of non-target events and with a one- and two-dimensional task condition, i.e. the tasks were more difficult in the sense that they required

discriminations along one or two perceptual dimensions within the same modality. The two rare non-targets had been added to the one-dimensional condition so as to make it comparable with the two-dimensional condition. In order to obtain unbiased information on timing and spatial configuration of the brain field generated by the active neural elements, space-oriented field analysis techniques were applied, including the identification of the P300 component as a functional microstate defined by the spatial distribution of its electric field.

Subjects and methods

The patients were 13 male schizophrenics (mean age 26.7 years, range 17–30 years), recruited from the referrals to the Outpatient Department of the Kitasato University East Hospital. They were diagnosed according to DSM-III-R. The mean duration of illness was 4.2 (SD 4.0) years; the mean BPRS score was 41.9 (SD 11.3) points and the mean SANS score was 58.3 (SD 19.9). All patients received continued antipsychotic medication at optimal individual dosages; the mean equivalent chlorpromazine dosage was 942 (SD 818) mg/day. The controls were 13 male, healthy adults (mean age 25.3 years, range 21–42 years), matched in education. They were recruited via advertisements within the university, and accepted in the order of application, and a small financial remuneration was paid. History of head trauma, drug addiction and neurological brain disease were exclusion criteria for both subject groups. All patients and controls were right-handed and had intact colour vision, and were not selected as to EEG criteria. All subjects had signed forms of informed consent.

Stimuli and experimental conditions

The visual stimuli consisted of two simultaneously displayed elements (see Fig. 1) with their centres separated by 6.1 cm, and a fixation point between the elements. There was a colour dimension (red or blue); a form dimension (disk of 4.3 cm diameter or square of 4.3 * 4.3 cm) and a tilt dimension (lines through the targets, at 45° ascending to the right or at 45° ascending to the left). The viewing distance was 180 cm; accordingly, the outer borders of the two elements were viewed at 3.3° visual angle. The stimuli were displayed side by side for 100 ms on a CRT screen at random intervals of 1500–2500 ms, controlled by a microcomputer.

Two stimuli conditions were employed (Fig. 1), each using one type of rare target stimuli (15% probability), two types of rare non-target stimuli (each 15%) and one type of frequent non-target stimuli (55%). The types were randomly sequenced in one of two arrangements: (a) the elements arranged as in Fig. 1, or (b) the elements with reversed arrangement, i.e. the left element on the right and the right one left (not illustrated).

In condition 1 targets differed from non-targets on only one perceptual dimension, colour. The target was always a blue disk; blue did not occur in non-targets, and hence, only colour had to be discriminated. In condition 2 targets differed from non-targets on two perceptual dimensions, colour and tilt. The target was always a blue disk with a right tilt; because non-targets included blue disks with a left tilt and red disks with a right tilt, colour as well as tilt had to be discriminated.

Procedure

After electrode attachment, the subjects were comfortably seated in a soundshielded Faraday room. They were asked to press a microswitch with their right thumb as quickly and accurately as possible whenever a target stimulus occurred.

The experimental conditions 1 and 2 were presented in random order across subjects. Each condition lasted approximately 10 min;

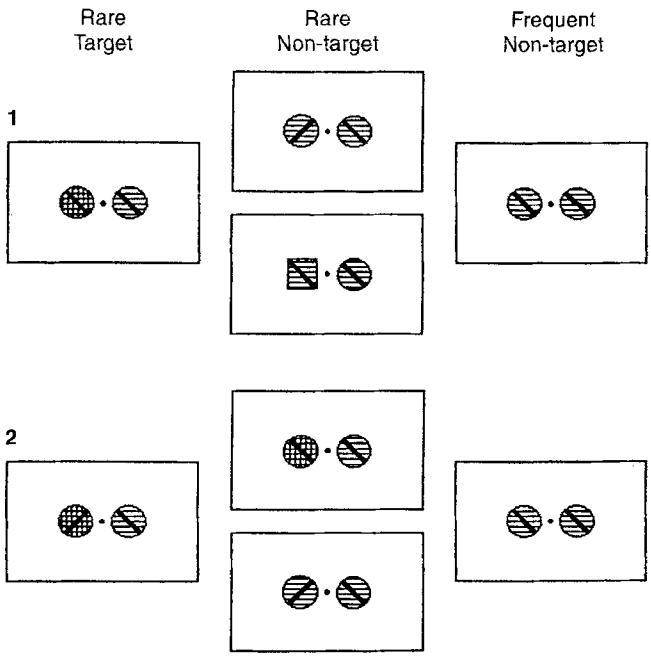


Fig. 1 The visual stimuli (the left-right reversed second set is not shown). *Left:* rare target stimuli; *centre:* rare non-target stimuli; *right:* frequent stimuli, used in experimental condition 1 *(top)* and 2 *(bottom)*. The actual monitor display used a black background; the visual elements were blue *(cross hatched)* or red *(horizontal stripes)*; all *slanted lines* in the visual elements were white. The *fixation marks* between the elements were red

there was an intermission of 5 min between conditions. Approximately 340 stimuli were presented during each condition.

The EEG was recorded with Ag-AgCl electrodes from 16 scalp sites of the 10–20 System (F3/4, F7/8, C3/4, P3/4, O1/2, T3/4, T5/6, Cz and Pz) referred to linked ear lobes, amplified with a bandpass of 1–70 Hz and stored on FM analog tape. The ERP's were averaged off-line using 250 samples/s for ADC over a period of 1024 ms after each target stimulus, using a Brain Atlas system (BioLogic, Mundelein, IL., USA) with its automatic artefact rejection set to ± 98 microV. The average ERP consisted of 40 sweeps.

ERP map sequences and data conditioning

The averaged ERP data were transformed into sequences of momentary potential distribution maps. Spatial DC offset was removed (recomputation to the so-called average reference), and a temporal bandpass restriction of 1–30 Hz was applied (FIR filter).

Comparing map landscapes

Global, numerical, pairwise comparisons of the spatial configuration of maps were done using the correlation coefficient (r) which is directly related to the measure of Global Map Dissimilarity (Lehmann and Skrandies 1980; Appendix in Wackermann et al. 1993) because the square root of (2*(1-r)) is equal to Global Map Dissimilarity (Brandeis et al. 1993). Comparing each map of one ERP map sequence with all maps of another ERP map sequence, "map landscape correlation matrices" were established. Thus, for two map series consisting of, for example, 100 maps each, 10000 correlations were computed.

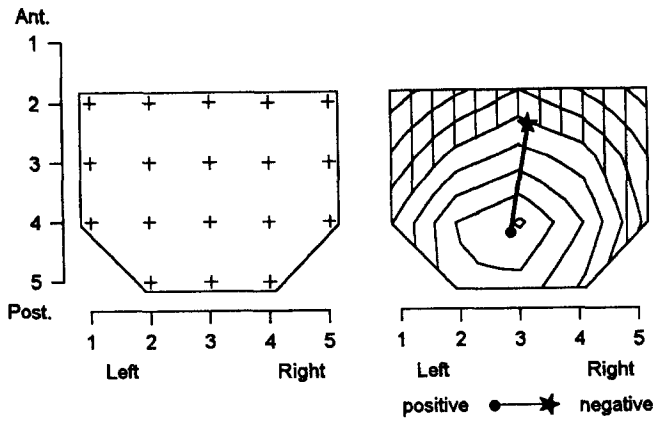


Fig. 2 *Left:* Array of the 16 recording electrodes *(crosses)* within the 10/20 system. Electrode positions are defined by row number (anterior-posterior, vertical) and column number (left-right, horizontal) of the two-dimensional electrode matrix. Cz (vertex) is at 3,3. Note that the most posterior electrode pair O1/O2 in reality has about the same lateral separation as the more anterior pairs. *Right:* momentary potential distribution map displayed as equipotential line map (equipotential lines in steps of 0.43 microV); positive areas white, negative areas striped. Three-neighbour interpolations for Fz and Oz. The locations of the centroids of the positive area *(star)* and negative area *(dot)* are connected by a *line*. Head seen from above, left ear left

Fig. 3 Grand mean trajectories along the anterior-posterior scalp axis (vertical) of the locations of the centroids of the positive *(heavy lines)* and negative *(light lines)* map areas as functions of time (horizontal), for controls and schizophrenics, in conditions 1 and 2. The time segments showing the P300 topography with posterior positivity are indicated by *dashed* lines. The centre latencies within these P300 segments (microstates) are marked by *arrowheads*. Trajectories are displayed only for the FIR-filtered portion of the data, i.e. from 100–924 ms latency

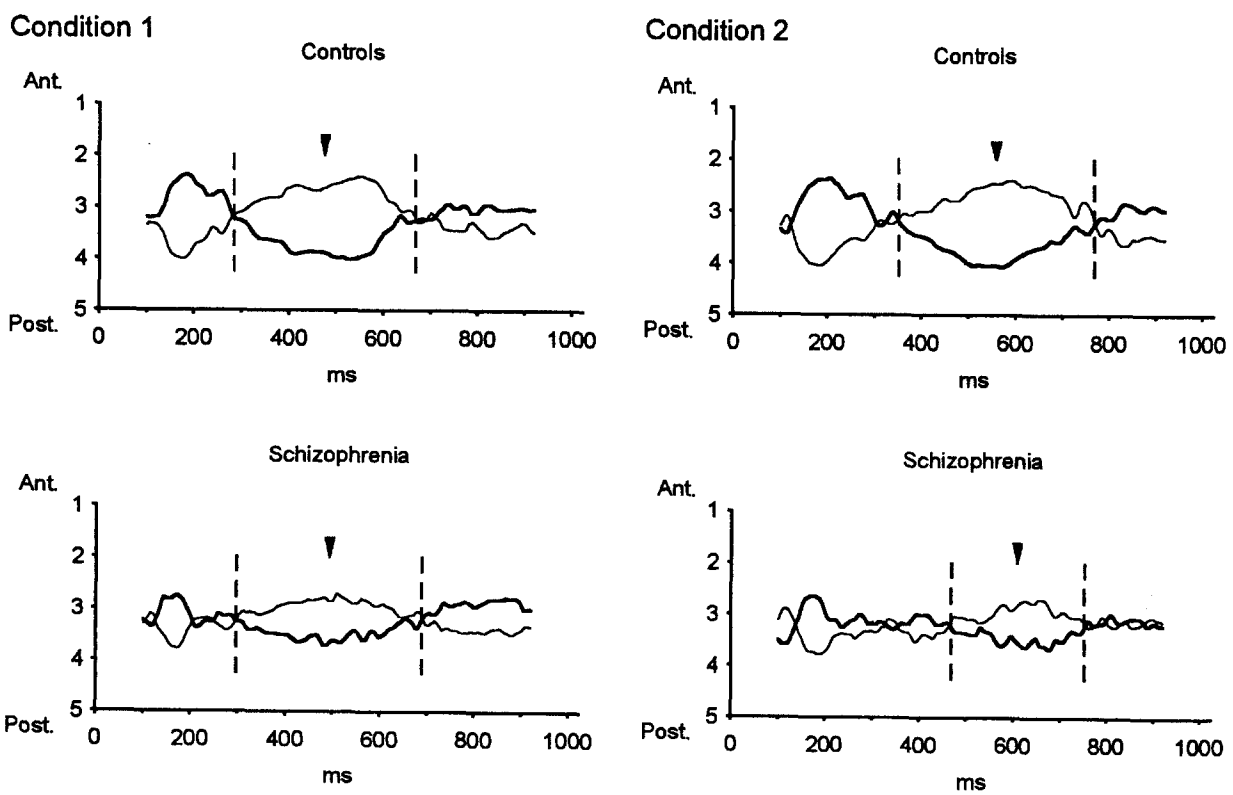
Numerical assessment of map landscape

The landscape of each map, i.e. the spatial configuration of its potential distribution, was assessed numerically by the locations of the centroids of the positive and negative map areas (Wackermann et al. 1993; Appendix B). In this way four parameters were obtained for each map: the location of the centroid of the positive map area on the left-right axis and on the anterior-posterior axis; and the location of the negative map area centroid on the left-right axis and on the anterior-posterior axis. The locations were expressed as values within the electrode array using electrode distances as measuring unit. An example is shown in Fig. 2. Trajectories of the centroid locations along the anterior-posterior and left-right head axes as a function of time were constructed. The individual trajectories were averaged across subjects for both experimental conditions and subject groups. These four mean trajectories are plotted in Fig. 3.

Identification of the P300 microstate

The P300 component was identified as that time segment or "microstate" in the ERP map sequence which showed the typical P300 landscape, consisting of an anterior negative and posterior positive potential distribution (Donchin et al. 1978; Koga and Suzuki 1987).

This P300 landscape where the positive centroid was posterior of the negative one was identified in the mean centroid trajectories (Fig. 3). The beginning and the end of the P300 microstate segment was determined as the crossing points of the trajectories of the positive and negative mean centroids along the anterior-posterior spatial axis. In Fig. 3 the dashed lines indicate these crossing points which demarcated the P300 microstates. The midpoints were used as group centre latencies (arrowheads in Fig. 3). This evaluation was done for both experimental conditions and both groups. The P300 microstate for controls (patients) in C1 covered 284–668 (296–688) ms; in C2, 352–768 (468–752) ms. The centre latencies thus were 476 (492) ms in C1, and 560 (608) ms in C2.



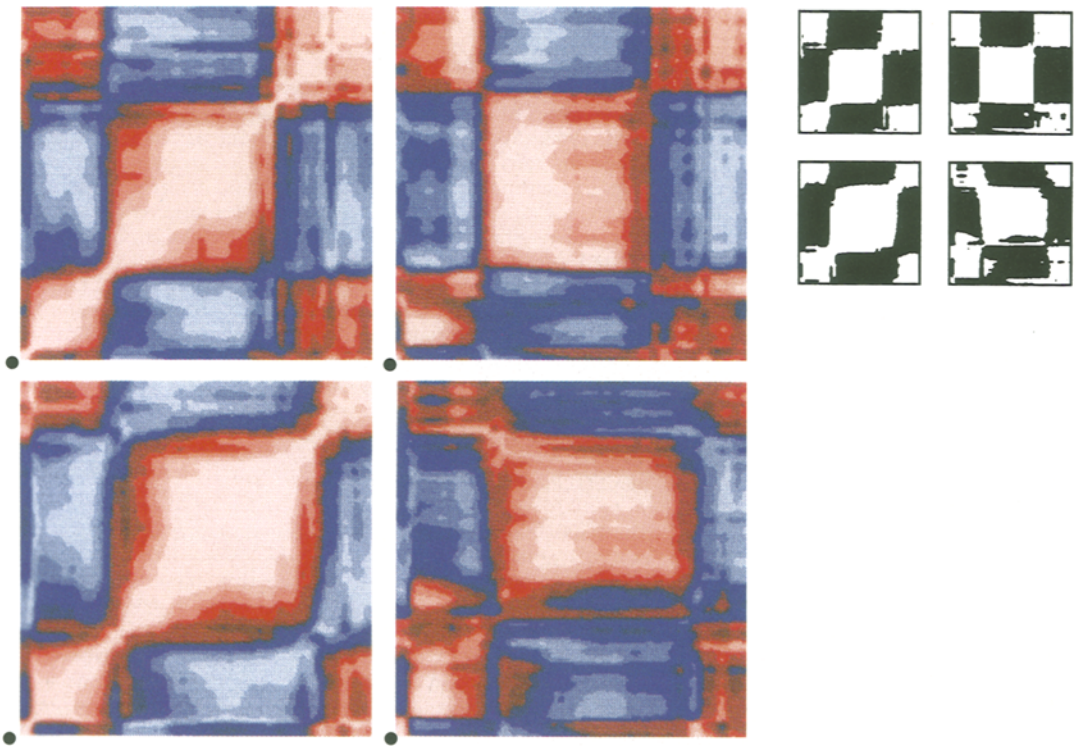


Fig. 4 Matrices of correlations between map landscapes. Each graph displays the similarity between two series of mean event related potential (ERP) maps where all maps of one series are correlated with all maps of the other series. Origin is the left lower corner *(dot)*; time runs up and to the right; thus, maps of equal latency are compared along the diagonal from the lower left corner to the upper right corner. In all graphs only the FIR-filtered maps between 100 and 924 ms are displayed (as in Fig. 3); centre graph, hence, is at 512 ms latency. For other explanations see Fig. 5. *Upper two graphs:* condition 1; *lower two graphs:* condition 2. *Two left graphs:* mean ERP maps of the normals vs themselves (therefore completely symmetrical around the diagonal); *two right graphs:* mean ERP maps of the normals (horizontal) vs those of the schizophrenics (vertical). The colour scale ranges from light red (high positive correlation) to dark red (low positive correlation) to dark blue (low negative correlation) to light blue (high negative correlation). The inset on the right shows the same data as a black and white schematic: positive correlations are white, negative correlations are black. Note the strong asymmetry of the correlations of normal vs schizophrenic data in condition 2, where the normals' (horizontal) P300 microstate starts much earlier than that of the patients (vertical)

Analysis of P300 microstate maps

We used the P300 ERP maps at their group centre latencies. For each subject and condition, the map's landscape at group centre latency was assessed by its two centroid locations (see above), and the map's electric strength was assessed by its Global Field Power (GFP; Lehmann and Skrandies 1980).

Time measurements of the P300 microstate

The latency of the maximal value of GFP (maximal electric field strength) within the appropriate P300 microstate was determined for each subject in both conditions and subject groups. Furthermore, the duration and latencies of the beginning and end of the P300 microstate was determined from the individual centroid trajectories of each subject in both conditions and subject groups.

Statistics

Exploratory data analysis was performed; unpaired t-tests ($df = 24$) were used; double-ended p-values are reported except for the confirmatory testing of the hypotheses of a right-shifted positive centroid and an increased P300 latency which were based on the literature.

Results

Overview of differences between ERP map sequences

The ERP map sequences were averaged over subjects for both conditions and groups. For each condition Global Map Dissimilarity was computed between all maps of the mean map sequence of the patients and of the controls (Fig. 4, right), and between all maps of the mean map sequence of the controls with themselves (Fig. 4, left), resulting in what is called now "landscape correlation matrices".

The autocorrelation matrices between map series vs themselves (left graphs) showed the expected pictures, symmetrical around the diagonal time axis from the lower left to the upper right corner as shown in Fig. 5. Along this time axis the sequential microstates are clearly visible in Fig. 4 (left) as a sequence of almost quadratic areas of high correlation, with the P300 microstate located at the centre. The correlations between the mean maps of controls and patients (Fig. 4, right) are at first glance reasonably symmetrical for C1. However, closer inspection re-

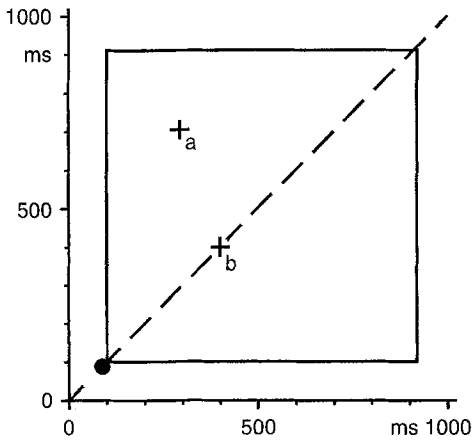


Fig. 5 a, b The map landscape correlation matrices of Fig. 4. The two compared ERP map sequences form the horizontal and vertical axes. Only the FIR-filtered maps between 100 and 924 ms are used; their various landscape correlations cover the illustrated square area, corresponding to the squares of Fig. 4. Two examples of map comparisons are illustrated by *crosses:* **a** is the correlation entry for the comparison between the map at 292 ms latency of the map sequence on the horizontal axis and the map at 708 ms latency of the map sequence on the vertical axis; **b** compares the maps at 400 ms latency on both axes. Along the diagonal from the lower left to the upper right corner *(dashed line)* are the comparisons between maps of identical latency on both axes

veals that the centre area of high correlation does not show the maximal correlation along the diagonal symmetry axis, but that during the entire P300 microstate, the patients' maps correlated higher with the early than with the late P300 maps of the normals. For C2 the correlation matrix is clearly asymmetrical: The centre area of high correlation (P300) starts earlier and lasts much longer in controls than in patients. Again, maximal correlation did not follow the diagonal symmetry axis: During much of the P300 period, the patients' maps correlated higher with about centre-latency normal maps than with their time-corresponding normal maps.

P300 map landscapes

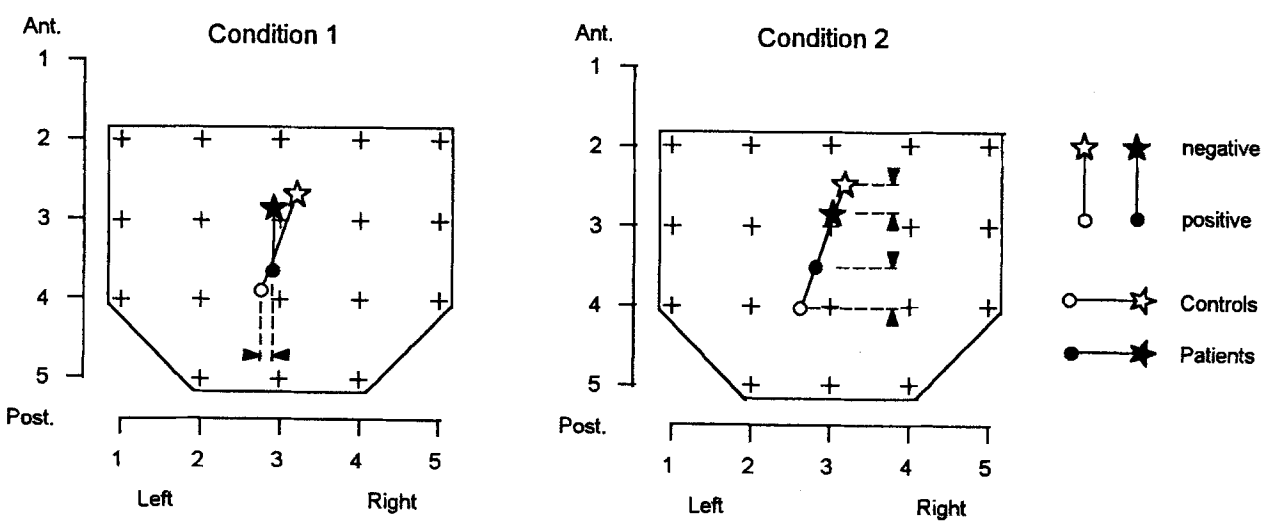
Figure 6 shows the mean locations of the landscape centroids of the P300 maps at group centre latency for conditions 1 and 2 in controls and schizophrenics. None of the landscape differences as represented by the centroids reached significant double-ended p-values in condition 1. However, accepting the reported reduction of P300 amplitude over the left hemisphere and thus a field shift towards the right as hypothesis for single-ended confirmatory testing, there was a statistical trend in our data with a single-ended $p < 0.10$.

In condition 2 there were statistical differences of interest along the anterior-posterior axis: The positive (posterior) centroid was more anterior ($p < 0.03$) and the negative (anterior) centroid was more posterior ($p < 0.07$) in patients than in controls. Thus, the anterior-posterior distance between centroids was smaller in patients than in controls. Tested directly, this difference was significant at $p < 0.04$. There were no statistically relevant differences along the left-right axis.

P300 landscape strength (Global Field Power, GFP)

At group centre latency, GFP was significantly smaller in schizophrenics than in controls in condition 2: 1.21 microV/electrode (SD 0.50) for schizophrenics vs 1.76 (SD 0.83) for controls, with $p = 0.05$. There was no significant difference in condition 1 (mean 1.74, SD 0.61 for patients; mean 1.69, SD 0.80 for controls).

Fig. 6 The locations of the mean (across subjects) map centroids at P300 centre latencies for conditions 1 and 2. Patients: *solid symbols*; controls: *open symbols;* Negative centroids: *stars;* positive centroids: *circles*. Statistically interesting differences indicated by *arrowheads:* In condition 1 the positive centroid was more to the right in the patients; in condition 2 the negative centroid was more posterior and the positive centroid more anterior in the patients than in the controls



Time measurements of P300 microstate characteristics

The latencies of maximal GFP within the P300 microstate in confirmatory testing were significantly longer as reported in the literature for waveshape-type analyses. In condition 1 for the patients compared with the controls: 459 ms vs 377 ms, respectively, single-ended $p = 0.005$; in condition 2: 585 ms vs 525 ms, respectively, single-ended $p = 0.05$.

In C1 the mean duration of the P300 microstate tended to be shorter for patients (277 vs 368 ms in controls, double-ended $p < 0.07$); mean latency for the beginning in patients was 371 and for controls 315 ms; for the end 648 and 683 ms, respectively (no significant differences). In C2 the mean duration was significantly shorter in patients, 232 vs 347 ms in controls, at double-ended $p < 0.03$. In fact, the difference was caused by the increased beginning latency of 474 vs 373 ms, at double-ended $p < 0.03$. The end latencies (means 706 vs 719 ms) did not differ significantly.

Discussion

For the comparisons of the present results with those of other studies we note that our one-dimensional task differed somewhat from the standard paradigm, and that our ERP field analysis approach was not restricted to test maximized, pre-selected waveshape features, but comprehensively considered the complete map data with particular interest in the spatial configuration of the ERP fields.

The resulting overview of the landscape correlation matrices demonstrated the occurrence of distinct ERP microstates in the normals and the patients. The matrices indicated some abnormalities in condition 1, but much stronger deviations from the norm in the more demanding condition 2.

In both conditions the schizophrenics showed an increase in latency time of maximal strength of P300 microstate. Latency delays of the P300 component have been reported in several studies (Baribeau-Braun et al. 1983; Kemali et al. 1991; Kutcher et al. 1987; Kathmann et al. 1995), even in unmedicated schizophrenics (Blackwood et al. 1987). The issue remains controversial, however, because other authors have not been able to replicate the finding (e.g. Roth et al. 1980; Pritchard 1986; McCarley et al. 1991; Strik et al. 1994a, b; Ford et al. 1994). We note that our different, non-biased analysis and the altered oddball paradigm support the presence of latency delays in this visual P300 task in medicated patients.

The often-reported shift of the P300 to the right in schizophrenics (see Introduction) showed up in our data only as a statistical trend in confirmatory testing in condition 1, and was not found in condition 2. Our non-selective analysis approach is not likely to be responsible for this result because Strik et al. (1994b) showed that this reference-independent, comprehensive method of field analysis is superior in detecting P300 map differences than other, more statistical approaches. It is conceivable that the right shift emerges only in special conditions and within certain latencies. This is suggested by the failure of Pfefferbaum et al. (1989) to confirm the right-shift even with conventional waveshape analysis. On the other hand, Faux et al. (1993) observed the shift in unmedicated patients, thereby excluding possible drug effects. One possible explanation is the stimulus modality, because the results of Alexander et al. (1995) suggest that in normals the topographic features of visual P300 are different from those of auditory P300, and our modified paradigm might have contributed to the less distinct lateralization.

There was no overall ERP strength decrease in condition 1, to some extent contradicting the literature which, however, used single-channel or pre-selected-channel waveshape-type analyses. Our results are thus in agreement with Strik et al. (1994a, b) who used the conventional oddball design but the same analysis method as the present study. These authors had argued convincingly that an analysis which is restricted to the midline-recorded channel will detect decreased ERP amplitude (ERP strength) if the field peak shifts away from the midline, although there might have been no overall difference in strength.

Condition 2 with its two-dimensional task with higher demands on the within-modality organization of perceptual processes resulted in reduced P300 Global Field Power values in the patients, unlike the one-dimensional task. The result suggests that fewer neural elements participated in the response to the target stimuli in schizophrenics than in controls. The observation of clearly delayed onset and shortened duration of P300 microstate in condition 2 might be seen as additional reflections of the reduced power of the response. The reduction of neuronal engagement is in line with the proposal of Place and Gilmore (1980) that schizophrenic patients are deficient in the perceptual organization of visual stimuli (see also e.g. Grillon et al. 1990; Kochi 1992).

In the P300 microstate maps of the schizophrenics, condition 2 caused a posterior shift of the negative centroid and an anterior shift of the positive centroid, resulting in a significantly shorter distance between the centroid locations; this proves that the landscape of the P300 field was different in the patients. Because different landscapes of potential distributions are indicative of different active neural generators (Lehmann 1987, 1990), we conclude that an at least partially different neural population processed the two within-modality perceptual dimensions in the schizophrenics as compared with controls during the P300 microstate. However, this difference did not involve the right-left axis, and thus does not support theories about a general left-sided deficit in schizophrenia. Obviously, the lateralization finding in condition 1 reflected the properties of the task.

It is noteworthy that O'Donnell et al. (1993) had observed bilateral abnormalities of an earlier ERP component (the "N2" component) in chronic schizophrenics, indicative of the possibility that malfunctioning of different brain areas is reflected by different ERP components, and thus, that the exclusive consideration of the P300 compo-

nent in the classical P300 condition cannot provide an exhaustive account of all disturbances. As reviewed in the Introduction, the literature on EEG, ERP, PET and MRI is not at all unanimous about the brain localization of structural or functional deficits in schizophrenia, not even about their lateralization, although there is a preponderance of reports implicating left areas.

P300 is hypothesized to reflect the controlled, serial processing mode (e.g. Rösler 1981), and Egeth (1966) concluded that the disturbance of within-modality multidimensional stimulus processing implies a disturbance of serial processing. However, our effects on two-dimensional P300 cannot settle the question of whether automatic or controlled processing functions are disturbed in schizophrenia, because Frith (1981) as well as Venables (1984) argued that failure of the automatic mode indirectly leads to dysfunction of the controlled mode because of the resulting overload condition in the controlled mode.

In summary, the present data suggest that the known left-temporal abnormality in P300 ERP's of schizophrenics might occur predominantly in the classical P300 paradigm; the modified, more demanding two-dimensional paradigm resulted in other spatial abnormalities, not just "more of the same". This appears reasonable, because different processing demands are expected to challenge different processing mechanisms, and in case of insufficiency make their malfunctioning evident; unchallenged, an insufficient mechanism naturally remains mute. A well-known example for such detection strategy is Weinberger et al's. (1986) identification of pre-frontal abnormalities in schizophrenics in a specific task situtation, the Wisconsin Card Sorting Test. Hence, generalizations about putative locations of functional disturbances should not be based on an isolated, specific experimental paradigm. It is suggested that the left-temporal deficit is only one of several possible aberrations which might vary depending on the task.

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References

Alexander JE, Porjesz B, Bauer LO, Kuperman S, Morzorati S, O'Conner SJ, Rohrbaugh J, Begleiter H, Polich J (1995) P300 hemispheric amplitude asymmetries from a visual oddball task. Psychophysiology 32:467–475

Baribeau-Braun J, Picton TW, Gosselin JY (1983) Schizophrenia: a neurophysiological evaluation of abnormal information processing. Science 219:874–876

Blackwood DHR, Whalley LJ, Christie JE, Blackburn JM, St. Clair DM, McInnes A (1987) Changes in auditory P3 event-related potential in schizophrenia and depression. Br J Psychiatry 150:154–160

Bogerts B, Meertz E, Schonfeldt-Bausch R (1985) Basal ganglia and limbic system pathology in schizophrenia: a morphometric study of brain volume and shrinkage. Arch Gen Psychiatry 42: 784–790

Brandeis D, Lehmann D (1989) Segments of event-related potential map series reveal landscape changes with visual attention and subjective contours. Electroenceph Clin Neurophysiol 73: 507–519

Brandeis D, Naylor H, Halliday R, Callaway E, Yano L (1993) Scopolamine effects on visual information processing, attention, and event-related potential map latencies. Psychophysiology 29:315–336

Crow T (1990) Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophr Bull 16:433–443

Donchin E (1981) Surprise!... Surprise? Psychophysiology 18: 493–515

Donchin E, Ritter W, McCallum WC (1978) Cognitive psychophysiology; the endogenous components of the ERP. In: Callaway E, Tueting P, Koslow SH (eds) Event-related brain potentials in man. Academic Press, New York, pp 349–411

Egeth HE (1966) Parallel vs serial processes in multidimensional stimulus discrimination. Percept Psychophys 1:245–252

Faux SF, Shenton ME, McCarley RW, Nestor PG, Marcy B, Ludwig A (1990) Presentation of P300 event-related potential topographic asymmetries in schizophrenia with use of either linked-ear or nose reference sites. Electroenceph Clin Neurophysiol 75:378–391

Faux SF, McCarley RW, Nestor PG, Shenton ME, Pollak SD, Penhune V, Mondrow E, Marcy B, Peterson A, Horvath T, Davis KL (1993) P300 topography asymmetries are present in unmedicated schizophrenics. Electroenceph Clin Neurophysiol 88:32–41

Flor-Henry P, Gruzelier J (1983) Laterality and psychopathology. Developments in psychiatry, vol 6. Elsevier, Amsterdam

Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A (1994) ERPs in schizophrenia: effects of antipsychotic medication. Biol Psychiatry 36:153–170

Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RSJ (1992) The left medial temporal region and schizophrenia. Brain 115:367–382

Frith CD (1981) Schizophrenia: an abnormality of consciousness? In: Underwood G, Stevens R (eds) Aspects of consciousness, vol 2. Academic Press, London, pp 149–168

Gattaz WF, Mayer S, Ziegler P, Platz M, Gasser T (1992) Hypofrontality on topographic EEG in Schizophrenia. Eur Arch Psychiatry Clin Neurosci 241:328–332

Gjerde PF (1983) Attentional capacity dysfunction and arousal in schizophrenia. Psychol Bull 93:57–72

Grillon C, Courchesne E, Ameli R, Geyer MA, Braff DL (1990) Increased distractibility in schizophrenic patients. Arch Gen Psychiatry 47:171–179

Halgren E, Squires N, Wilson GL, Rohrbaugh JW, Babb TL, Crandall PH (1980) Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. Science 210:803–805

Heidrich A, Strik WK (in press) Auditory P300 topography and neuropsychological test performance: evidence for left hemispheric dysfunction in schizophrenia. Biol Psychiatry (in press)

Hillyard SA, Münte TF (1984) Selective attention to color and location: an analysis with event-related brain potentials. Percept Psychophys 36:185–198

Holinger DP, Faux SF, Shenton ME, Sokol NS, Seidman LJ, Green AI, McCarley RW (1992) Reversed temporal region asymmetries of P300 topography in left- and right-handed schizophrenic subjects. Electroenceph Clin Neurophysiol 84:532–537

Iacono WG, Moreau M, Beiser M, Fleming JAE, Lin TY, Flak B (1988) Ventricular size and sulcal size at the onset of psychosis. Am J Psychiatry 145:820–824

Ingvar DH, Franzen D (1974) Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 50:425–462

Kathmann N, Wagner M, Rendtorf N, Schochlin C, Engel RR (1995) Information processing during eye tracking as revealed by event-related potentials in schizophrenics, alcoholics and healthy controls. Schizophr Res 16:145–156

Kemali D, Galderisi S, Maj M, Mucci A, DiGregorio M (1991) Lateralization patterns of event-related potential and performance indices in schizophrenia: relationship to clinical state and neuroleptic treatment. Int J Psychophysiol 10:225–230

Kenemans JL, Smulders FTY, Kok A (1995) Selective processing of two-dimensional visual stimuli in young and old subjects: electrophysiological analysis. Psychophysiology 32:108–120

Klausner JD, Sweeney JA, Deck MD, Haas GL, Kelly AB (1992) Clinical correlates of cerebral ventricular enlargement in schizophrenia. Further evidence for frontal lobe disease. J Nerv Ment Dis 180:407–412

Kochi K (1992) Psychophysiological study on the disturbance of pattern cognition in schizophrenia. Jpn J Electroenceph Electromyogr (Nouha to Kindenzu) 20:277–288 (in Japanese)

Kochi K, Koga Y, Murasaki M (1992) Disturbance of allocation of processing resource in schizophrenia; a study of dual task processing using ERP. Seishinigaku 34:1097–1102 (in Japanese)

Koenig T, Lehmann D (1996) Microstates in language-related brain potential maps show noun-verb differences. Brain Language 53:169–182

Koga Y, Suzuki I (1987) Three-dimensional EEG display. Adv Biol Psychiatry 16:117–131

Kutcher SP, Blackwood DHR, St. Clair D, Gaskell DF, Muir WJ (1987) Auditory P300 in borderline personality disorder and schizophrenia. Arch Gen Psychiatry 44:645–650

Largen HW, Smith RC, Calderon M, Baumberger R, Lu RB, Schoolar JC, Ravichandran GK (1984) Abnormalities of brain structure and density in schizophrenia. Biol Psychiatry 19:991–1013

Lehmann D (1987) Principles of spatial analysis. In: Gevins A, Remond A (eds) Handbook of electroencephalography and clinical neurophysiology, vol 1. Methods of analysis of brain electrical and magnetic signals. Elsevier, Amsterdam, pp 309–354

Lehmann D (1990) Brain electric microstate and cognition: the atoms of thought. In: John ER (ed) Machinery of the mind. Birkhauser, Boston, pp 209–244

Lehmann D, Skrandies W (1980) Reference-free identification of components of checkerboard evoked multichannel potential fields. Electroenceph Clin Neurophysiol 48:609–621

McCarley RW, Shenton ME, Nestor PG, Holinger DP (1991) Is there P300 asymmetry in schizophrenia? (Letter to the Editor) Arch Gen Psychiatry 48:380–381

McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kinikis R, Nestor PG, Jolesz FA (1993) Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch Gen Psychiatry 50:190–197

Michie PT, Fox AM, Ward PB, Catts SV, McConaghy N (1990) Event-related potential indicates of selective attention and cortical lateralization in schizophrenia. Psychophysiol 27:209–227

Morstyn R, Duffy FH, McCarley RW (1983) Altered P300 topography in schizophrenia. Arch Gen Psychiatry 40:729–734

O'Donnell BF, Shenton ME, McCarley RW, Faux SF, Smith RS, Salisbury DE, Nestor PG, Pollak SD, Kikinis R, Jolesz FA (1993) The auditory N2 component in schizophrenia: relationship to MRI temporal lobe grey matter and to other ERP abnormalities. Biol Psychiatry 34:26–40

Pascual-Marqui RD, Lehmann D (1993a) Comparison of topographic maps and the reference electrode: comments on two papers by Desmedt and collaborators. Electroenceph Clin Neurophysiol 88:530–531

Pascual-Marqui RD, Lehmann D (1993b) Topographic maps, source localization inference, and the reference electrode: comments on a paper by Desmedt et al. Electroenceph Clin Neurophysiol 88:532–533

Place EJS, Gilmore GC (1980) Perceptual organization in schizophrenia. J Abnorm Psychol 89:409–418

Pfefferbaum A, Ford JM, White PM, Roth WT (1989) P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. Arch Gen Psychiatry 46:1035–1044

Pfefferbaum A, Ford JM, White PM, Roth WT, Mathalon DH (1991) Letter to the Editor. Arch Gen Psychiatry 48:381–383

Previc FH, Harter MR (1982) Electrophysiological and behavioral incidents of selective attention to multifeature gratings. Percept Psychophys 32:465–472

Pritchard WS (1981) Psychophysiology of P300. Psychol Bull 89:506–540

Pritchard WS (1986) Cognitive event-related potential correlates of schizophrenia. Psychol Bull 100:43–66

Rösler F (1983) Endogenous ERPs and cognition: probes, prospects and pitfalls in matching pieces of the mind-body puzzle. In: Gaillard AWK, Ritter W (eds) Tutorials in event-related potential research: endogenous components. North-Holland, Amsterdam, pp 9–35. References within pp 407–447

Roth WT, Pfefferbaum A, Horvath TB, Berger PA, Kopell BS (1980) P3 reduction in auditory evoked potentials of schizophrenics. Electroenceph Clin Neurophysiol 49:497–505

Strik WK, Dierks T, Franzek E, Stöber G, Maurer K (1994a) P300 in schizophrenia: interactions between amplitudes and topography. Biol Psychiatry 35:850–856

Strik WK, Dierks T, Franzek E, Stöber G, Maurer K (1994b) P300 asymmetries in schizophrenia revisited with reference-independent methods. Psychiatry Res 55:153–166

Venables PH (1984) Cerebral mechanisms, autonomic responsiveness and attention in schizophrenia. In: Spaulding WD, Cole JK (eds) Theories in schizophrenia and psychosis. Nebraska symposium on motivation 1983, vol 31. University of Nebraska Press, Lincoln, Nebraska, pp 47–91

Wackermann J, Lehmann D, Michel CM, Strik WK (1993) Adaptive segmentation of spontaneous EEG map series into spatially defined microstates. Int J Psychophysiol 14:269–283

Weinberger DR, Berman KF, Zec RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional blood flow evidence. Arch Gen Psychiatry 43:114–124

Wijers AA, Mulder G, Okita T, Mulder LJM (1989) An ERP study on memory search and selective attention to letter size and conjunctions of letter size and color. Psychophysiol 26:529–547

Williamson P (1987) Hypofrontality in schizophrenia: a review of the evidence. Can J Psychiatry 32:399–404