Pathology and compensation during visual signal processing in schizophrenia - spatial analysis of event-related potentials

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Abstract. Correlations between measures of attention and topographical abnormalities of evoked cortical potentials elicited during the Continuous Attention Test (CAT) were assessed in 50 schizophrenic patients, compared to 50 healthy subjects. For each group and for each CAT condition evoked responses consisted of six successive epochs (segments) of stable spatially configured potentials. Quantitative descriptors of those configurations (Lehmann 1987) were referred to the CAT data. In patients: (1) segments III-V were delayed, (2) in the non-target condition, diminished global field power (GFP) emerged, coexisting either with lower amplitude of posterior potentials in segment I and II or with lower amplitude of a central positive potential in segment V, (3) an altered topographic pattern of responses to the target stimulus occurred. In healthy subjects detection of the target (as compared to the non-target condition) was associated with a shift of the location of the positive potential in segments IV and V from a central towards the prefrontal area. In patients, in segment V a similar shift reached frontal, but not prefrontal areas, and additionally, the central areas remained active. Delayed latency and low GFP in segment V in the non-target condition in patients correlated with poor CAT performance. A more posterior location of the positive centroid in segment V during detection of the target correlated with better CAT results, and the associated GFP increase with less prolonged reaction time. The data revealed a possible compensatory role of central and frontal areas in the face of weakened prefrontal functions in schizophrenia.

Key words: schizophrenia, attention, event-related potentials, microstates

INTRODUCTION

Despite numerous studies on event-related potentials (ERP), little is known about the link between electrophysiological processes and cognitive functions in man. Research on schizophrenia is not the exception, although distorted cognitive functions are the core of schizophrenic symptomatology.

There are several reasons for this. First, the stimuli used to obtain the evoked potentials are often simple and only weakly engage cognitive procedures. Second, even in complex paradigms, in which the stimuli make up neuropsychological tests, the behavioural results are often considered with respect to their co-existence rather than correlation with ERP findings. Finally, the ability to define such links is restricted, because the majority of electrophysiological studies on schizophrenia has been performed (and the majority of EP abnormalities has been found) using auditory stimuli, while neuropsychological tests, known as the best technique to reveal disturbances typical for schizophrenia, are visual tests (for review see Cornblatt and Keilp 1994).

A unique series of studies by R. Strandburg (Strandburg et al. 1990, 1991, 1994a,b) on visual potentials evoked during work on the Span of Apprehension Task (SPAN) or Continuous Performance Test (CPT) in schizophrenic children and adults revealed numerous ERP abnormalities. However, no specific correlations with the behavioural data were found. More successful was a study on visual potentials elicited by the items of the Continuous Attention Test (CAT) in medicated adult schizophrenic patients (Basińska 1998). Numerous correlations between test results and ERP findings confirmed pathologies in both automatic and conscious stage of processing. Furthermore, some correlations suggested the coexistence of compensatory features, related to the early frontal P3 component.

However, „the brain produces an ever-changing electromagnetic field – not packs of line tracings" (Lehmann 1990). The traditional approach, i.e. analysis of the time-course of potentials at selected electrode sites (chosen as the most relevant), may produce misleading results. An atypical amplitude of a component at a given lead may result not from altered excitability of respective generators, but from their atypical location. Ectopic cortical activity in schizophrenia has been widely hypothesised. Until now, consideration has been given mostly to the laterality phenomena, i.e., the unexpected activity of non-dominant areas, homological with respect to the fields responsible for a given function (Green 1978), hypothetically caused by insufficient or mixed hemispheric dominance and disturbed hemispheric balance (Doty 1989, Gruzelier 1991). This theory, as explanatory for either hallucinatory or splitting phenomena in schizophrenia, has been supported by the evidence pointing to a dysfunction of the left (dominant) hemisphere (Faux et al. 1990, 1993, Strik et al. 1994), hyperactivity of the right one (Günther et al. 1986) or disturbed lateralisation (Piran et al. 1982, Green et al. 1989, Lauerma et al. 1994, Tyler et al. 1995).

However, these lateralised ectopic phenomena do not explain abnormal features occurring at midline locations, such as an increase in the amplitude of the early frontal P3 component, which was found to accompany the detection of CAT targets only in patients (Basińska 1998). This was the rationale for the present complementary study concerning spatial analysis of ERPs elicited during performance of the CAT.

The CAT (Tiplady 1992) is a modified variant of the CPT-IP (Continuous Performance Test - Identical Pairs version), which has been described as the most specific (differentiating) tool in studies on attentional deficits in schizophrenia (Cornblatt and Erlenmeier-Kimling 1985, Winters et al. 1991). For example, the CAT appeared to differentiate between schizophrenic patients and both depressive and healthy subjects (Kasperska et al. 1997).

For the purposes of spatial analysis, an approach introduced by Lehmann (1987) was adopted. The crucial finding underlying the method is the observation that, regardless of the continuous evolution of potential in the local leads, the global spatial configuration (a map) of an ERP registered on the scalp and referred to the average electrode remains relatively constant during certain epochs of time elapsing after an exposure to a stimulus. Such a sequence of a few stable states of the brain may reflect successive stages of stimulus processing (microstates). Spatial analysis of an ERP (described in detail in the methods) resolves itself into the two stages. The first stage is to divide the time course of an ERP into epochs (segments) characterised by a stable distribution of potential on the scalp. In the next stage the consecutive stable configurations of potential are analysed. Each of them is depicted by one momentary map of potential, chosen from the whole respective segment as the most representative sample. Due to introduction of a few scalar parameters related to spatial distribution of potential, each configuration may be quantified and submitted for further analyses.

In order to indicate a link between electrophysiological and behavioural findings, the descriptors of the maps related to successive segments were referred to the results of the CAT.

METHODS

Subjects

Fifty adult right-handed males (mean age 34.9 ± 9.5 years) with a diagnosis of schizophrenia according to DSM-IV (paranoid or undifferentiated type) and free of any other diagnoses were examined. The patients were in a stable phase of illness (partial remission) and were taking supportive doses of neuroleptic drugs. Mean intensity of symptoms according to the PANSS scale (Kay et al. 1992) was 34 ± 18. Mean daily dose of neuroleptic drugs, converted to chlorpromazine equivalents, was 250 ± 165 mg. None of the patients received anticholinergic medication. Prior to the study informed consent was obtained from each subject.

Their results were compared to the data from 50 adult right-handed healthy male volunteers (mean age 33.0 ± 9.6 years) with neither personal nor family history of neurological or mental disturbances.

Procedure

THE CONTINUOUS ATTENTION TASK

The test was performed in a darkened, partially sound-proof room. Visual CAT stimuli were presented on a 14" monochromatic display with luminance of 10 cd/m^2, at a distance of 1 m from the eyes of the subject. Stimulus exposure lasted 50 ms, and the interval between two successive stimuli varied randomly within the range of 1 to 2.5 s. The battery of randomly presented stimuli consisted of 40 target, 160 non-target and 40 atypical stimuli. Reactions for atypical stimuli (digits), introduced in our laboratory as a modification of the original CAT, are not analysed in this paper. Each of the 200 typical CAT stimuli was a geometrical pattern - 3 x 3 matrix (10 x 10 cm) formed by the quasi-random combination of 5 bright and 4 dark squares. A target stimulus was defined as a direct repetition of any pattern and occurred with the probability of 0.16. Subjects indicated target detection by the immediate pressing of the button held in the dominant hand. The duration of a CAT session was approximately 8 min. In order to yield a larger number of hits, necessary for averaging the potentials evoked by detected target stimuli, total results from 3 consecutive sessions of the CAT were assessed.

ELECTROPHYSIOLOGICAL DATA RECORDING

EEG signal was recorded from 21 locations, according to the 10-20 system with additional Fpz and Oz electrodes. The movements of the left eye were recorded in a separate channel to allow subsequent artifact removal. Impedance of all electrodes was maintained below 5 k . The EEG signal, referenced to linked mastoids, was amplified, filtered in the bandpass 0.15-30 Hz and digitised at a 500 Hz sampling frequency and 12 bit resolution (Brainscope, M&I). The computer with the EEG recording software (EASYS2, Neuroscience) had an input from the stimulus-generating computer, which provided on-line registration of markers of either CAT stimuli or reactions of subjects. Evoked potentials were differentiated into classes dependent either on the kind of stimulus (target or non-target) or reaction (i.e. button press or lack of reaction). Averaging into these classes was performed off-line, after manual rejection of artifacts, and was related to pre-stimulus average EEG baseline. Averaging was not performed if the individual number of trials within a class after artifact removal was less than 30.

Data analysis

PSYCHOMETRIC RESULTS

In the CAT we assessed the number of omissions (unidentified target stimuli) and commissions (button presses in response to non-target signals). These data were converted into standardised indices (Pigache 1976): the omission index, $I_O = O/T$, the commission index, $I_C = C/N$, and the detection index, $I_D = 1 - I_O - C/N$ (with C/N as a correction for accidental hits), where O - number of omissions, C - number of commissions, T - total number of target stimuli, N - total number of non-target stimuli.

Those indices were combined in order to get a final total index of errors:

$I_E = (1 - I_D) + I_C = O/T + 2C/N$.

Mean reaction time was also measured.

Correlations of all the psychometric data with age, duration of illness, PANSS score and dose of drugs were examined.

SPATIAL ANALYSIS OF ERPs

In each individual, two classes of potentials were assessed: for ignored non-target and for detected target stimuli. The evoked responses were analysed in the 1,000 ms post-stimulus time-window (500 samples). Individual averaged potentials at the 21 leads were converted to the average reference. For each sample, the measurements at the 21 points on the scalp, after interpolation, resulted in a momentary map of potential. A series of 500 successive momentary maps of the ERP was the substrate for the spatial analysis.

According to the Lehmann's (1987) approach, the first step into the spatial analysis of an ERP is to divide a series of the successive maps into epochs (segments), characterised by a relatively constant spatial configuration of the potential. In order to simplify that procedure, a description of each map may be reduced to the values of a few descriptors, as presented below.

Thus, due to the application of the average reference, each momentary map has contributions from both positive and negative potential components. Its description may be then replaced by co-ordinates of two "points of gravity" of positive and negative potential - centroids C+ and C-. Positions of these points along either sagittal or transverse axis are defined in a range from 1 to 5 in the anterior-posterior or left-right dimension, respectively. While the locations of the two centroids represent distribution of potential on the scalp, the global field power (GFP) describes a "hilliness" of a map, as a standard deviation of potential at all electrodes related to the average reference (Lehmann and Skrandies 1980). Dissimilarity (DISS, in a range 0 to 1) compares two successive maps, normalised with respect to the GFP. It peaks during maximal instantaneous changes in spatial configuration (which may mark borders of segments), while its minima correspond to the moments of the greatest stability of potential (usually coexisting with the highest strength of a field, as a peak of the GFP – Fig.1).

An adaptive segmentation performed on the grand-mean ERP and based on a time-function of the DISS was adopted (Brandeis et al. 1995, van Leeuven et al. 1998). In this study, it was performed separately on each of the four grand-mean ERPs: for each of the two classes of potentials in each diagnostic group. Such a separation allowed to avoid any artifacts resulting from possible shifts in segment borders between the groups or conditions. The SPACE 4B computer program, starting from curves of a grand-mean evoked potential at all leads, re-vealed time-courses of the GFP, DISS and locations of both centroids along the sagittal (AP) and transverse (LR) axes. The borders of successive segments of an ERP for each group-by-condition combination were then indicated by peaks of the respective grand-mean DISS curve.

As the second step, within each segment of a grand-mean response, one representative map of the potential was chosen, corresponding to the moment of maximal stability (minimal DISS) of the spatial configuration. Usually it co-incided with the maximal value of the global field power. Grand-mean maps for respective segments were then compared between groups or conditions.

The four sets of grand-mean segment borders were then also used as a basis for a measurement of respective individual values of the spatial descriptors, necessary either for the statistical comparison between groups and conditions, or to determine correlations between them and the behavioural data. In each subject, on each of the two average potentials (i.e. for each condition) the SPACE 4B revealed individual time-courses of GFP, DISS and locations of the centroids. Within the time-boundaries defined for respective grand-mean segment, a map for a moment of the individual minimal DISS value was found. Its latency, measured from an onset of a stimulus exposure, as well as instantaneous values of the GFP and co-ordinates of the centroids, were measured as individual descriptors representative for a given segment (as related to a hypothetical microstate).

Statistics

Due to the non-normal distribution of results of the CAT in the control group, for between-group comparison of the psychometric results non-parametric Mann-Whitney U-test was applied.

Data from all subjects were included in the results derived from the grand-average potentials (i.e. segmentation, grand-mean maps). The grand-mean maps of potential, representative for particular segments were compared between groups or conditions by *t*-tests, performed for each electrode site. The results of these tests were presented as maps of *t* (*t*-maps).

Individual electrophysiological parameters, i.e. latencies and spatial descriptors of the successive configurations of potential were compared between groups and/or conditions by MANOVA (SPSS 4.0 software package, Norusis 1990). For each parameter, its values for the
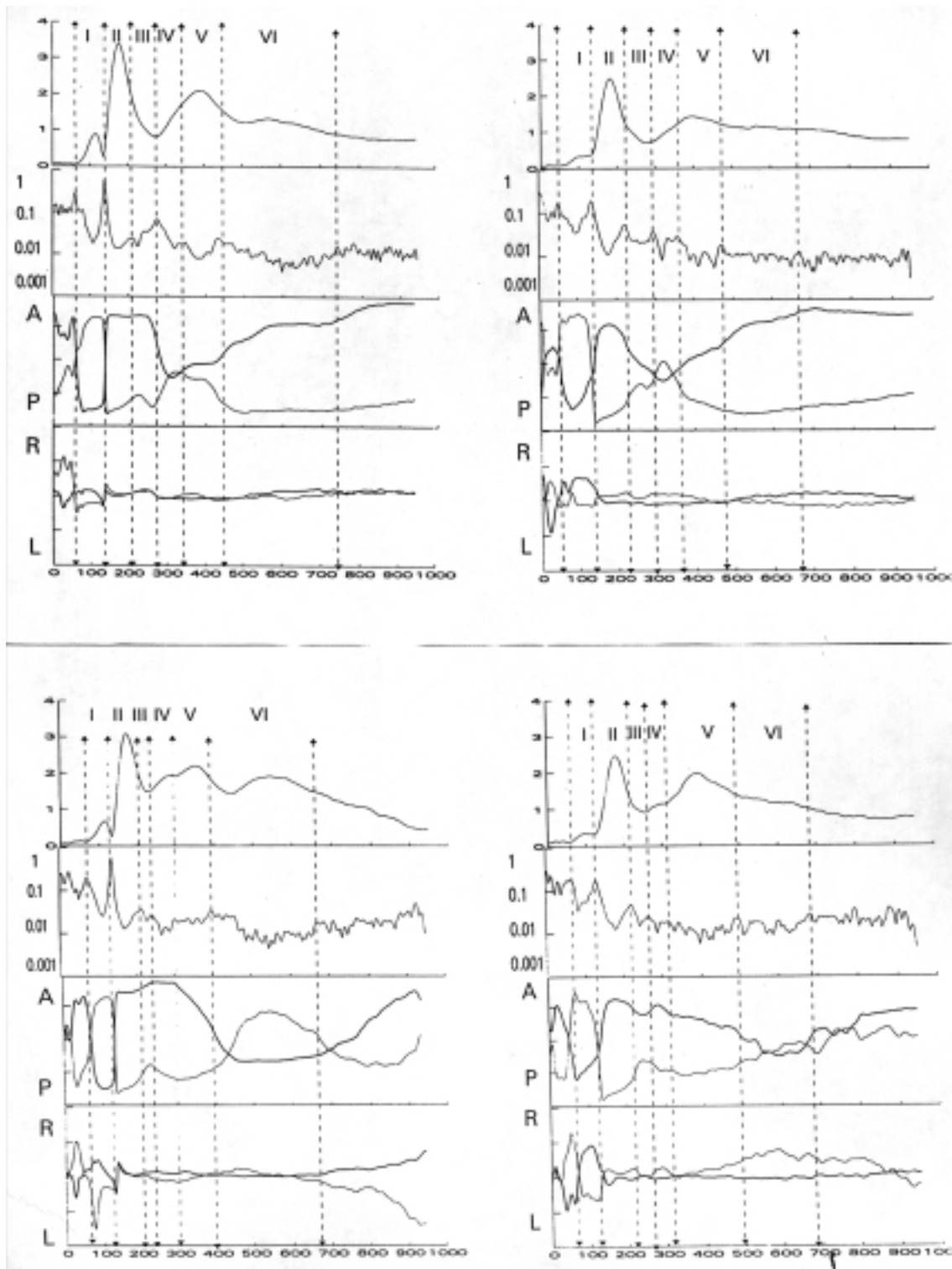
Fig. 1. Segmentation of grand-average potentials following non-target (upper row) and target (lower row) stimuli in healthy subjects (left column, *n* = 50) and schizophrenic patients (right column, *n* = 50). Each block includes four diagrams, i.e. time-courses of: global field power GFP; dissimilarity DISS (in logarithmic scale); location of centroids: C+ (thick line) and C- (thin line) along the sagittal axis, when A (anterior) corresponds to the value 1 and P (posterior) – to the value 5; location of the same centroids along the transverse axis, when L (left) corresponds to the value 1 and R (right) – to the value 5.

maps representing the consecutive segments were submitted, as one set of data, for two-way MANOVA by group and condition. Segments, as a result *per se*, were not taken into account as a third independent dimension for MANOVA. The significant results were supported by univariate analysis (ANOVA) indicating relevant variables. In order to provide full interpretation, lower-order (one-way) analyses of significant results were performed. Cases with a lack of a stable configuration (no definite minimum of DISS or maximum of GFP) in at least one of the grand-average segments in any condition, dropped out from two-way MANOVA as cases with missing data. However, those subjects could be included into some lower-order (one-way) analyses.

Psychometric and electrophysiological data were correlated using the Spearman rank correlation test, which was also used for correlations of the both sorts of data with age, duration of illness, PANSS score and dose of drugs.

As a criterion of significance the $P = 0.05$ in two-tailed tests was adopted.

RESULTS

Psychometric data

In the group of patients the detection index was lower than in the control group ($I_D = 0.56 \pm 0.21$ vs. 0.93 ± 0.06, $U = 90.0$, $P<0.00005$), while the error index was much higher ($I_E = 0.47 \pm 0.21$ vs. 0.08 ± 0.07, $U = 89.0$, $P<0.00005$) largely due to omissions ($I_O = 0.41 \pm 0.21$ vs. 0.06 ± 0.06, $U = 86.0$, $P<0.00005$). The commission indices in both groups were similar ($I_C = 0.03 \pm 0.05$ vs. 0.02 ± 0.03, *NS*).

Reaction time was significantly longer in the group of patients (582 ms ± 70 vs. 518 ms ± 73, $U = 646.5$, $P = 0.0001$). In both groups there were no relationships between reaction time and test indices. There were also no significant correlations between CAT results and age, duration of illness, PANNS score or doses of drugs.

Electrophysiological data

The segmentation in each diagnostic group revealed six segments in grand-mean ERPs following either non-target or target stimuli (Fig. 1). In other words, regardless of the group or the condition, the responses related to the CAT stimuli consisted of six consecutive spatial configurations of potential.

Comparison of the grand-mean maps related to the segments

As shown in Fig. 2A, t-maps of differences: (potential in the patients) – (potential in the control group) revealed in the non-target condition significantly lower amplitudes of left-side posterior positive potential in segment I, bilateral posterior negative potential in segment II and central positive potential in segment V in patients. In the target condition (Fig. 2B) those differences for segments I and II lost their significance, while in segment V the difference changed a sign.

If we assess change in the spatial configuration, accompanying the detection of the target, we are concerned with the difference: (potential in target condition) - (potential in the non-target one). In healthy subjects we can observe (Fig. 3A) an anterior shift of a positive potential in segments IV and V, either as a significant increase predominantly at prefrontal leads or as a decrease at central and parietal locations. Similar comparison in patients (Fig. 3B) also revealed in segments IV and V an increase of a positive potential at anterior leads. However, it was less significant than in healthy subjects and in segment V occurred in frontal, but not prefrontal area. Furthermore, contrary to the results in the control group, there was no decrease in the positive potential at central or parietal leads.

In both groups, detection of the target was accompanied by a significant increase in the parietal positive potential in segment VI.

Latencies

The time-boundaries of respective grand-average segments differed between groups and conditions (Fig.1). The two-way MANOVA for latencies of the six moments (one in a segment) of the most stable configuration of potential revealed both group ($F_{6,109} = 9.63$, $P<0.0005$) and condition ($F_{6,109} = 2.19$, $P=0.049$) main effects and no group by condition interaction.

As indicated by two-way ANOVAs, the group effect was due to the differences in the latencies related to segments III, IV and V ($F_{1,114} = 21.61$, $P<0.0005$; $F_{1,114} = 28.63$, $P<0.0005$ and $F_{1,114} = 35.18$, $P<0.0005$, respectively). Following lower-order analyses, the latencies of the moments of the stabilised configuration of potential in segments from III up appeared to be delayed in patients, as compared to those in the healthy subjects, either following non-target or target stimuli (Table I.).
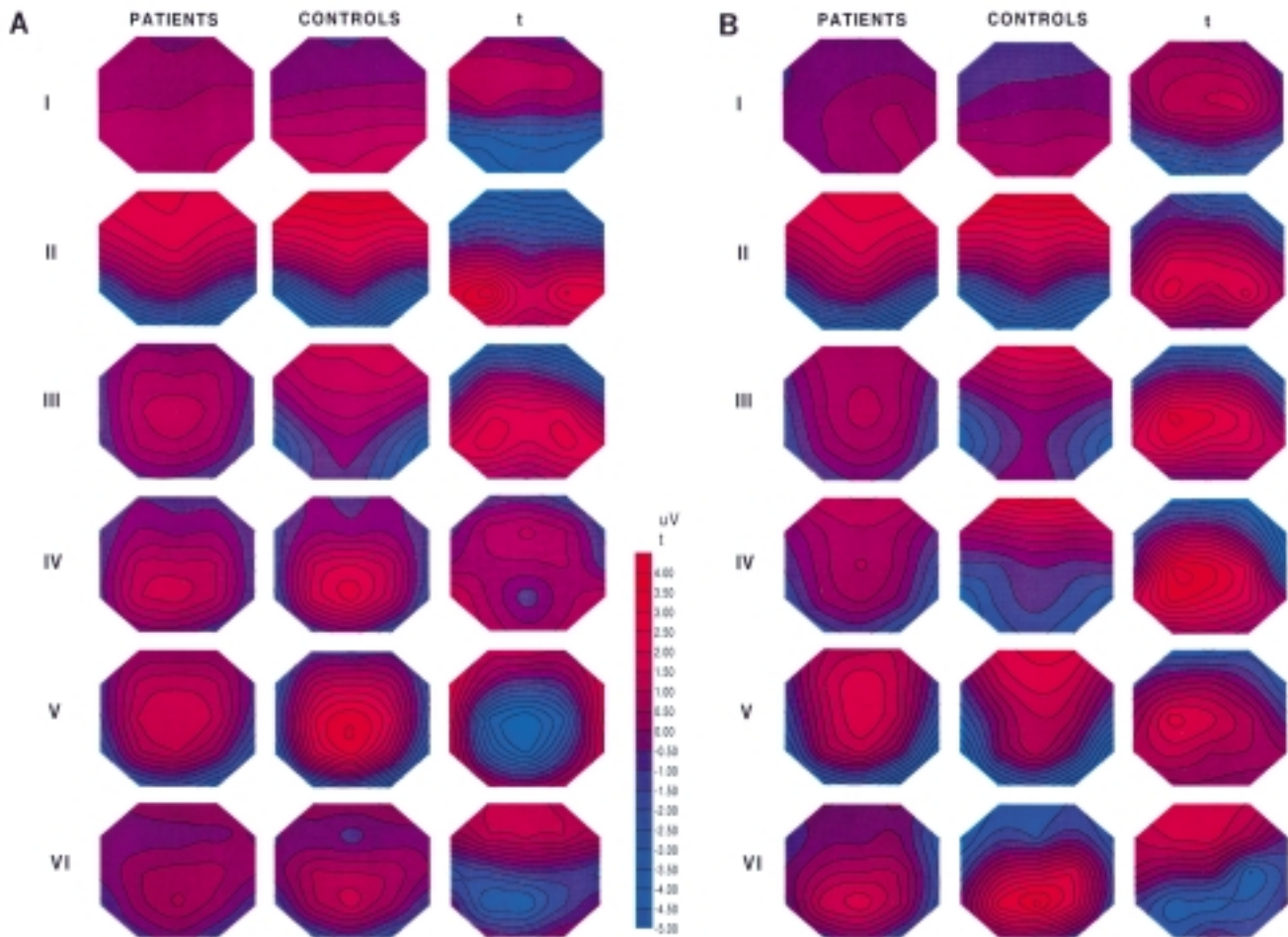
Fig. 2. Differences between the groups, related to the ERP following non-target (A) and target (B) stimuli. In each block: left column, the grand-average maps for subsequent segments of the ERP in patients ($n = 50$); central column, the maps for respective segments in the healthy subjects ($n = 50$); right column – t-maps of the „patients - healthy subjects" differences.

The condition main effect was due (as shown by ANOVAs) to latencies in segments V and VI ($F_{1,114} = 4.39$, $P=0.038$ and $F_{1,114} = 4.38$, $P=0.038$, respectively). Lower-order analysis revealed a shortening of the latency of the moment of the greatest stability of configuration in segment V after target stimuli as compared to non-target ones, but only in the control group (Table II).

GFP

A two-way MANOVA on the six peak GFP (related to the representative maps for the six segments) revealed both group ($F_{6,109} = 4.11$, $P = 0.001$) and condition main effect ($F_{6,109} = 7.43$, $P<0.0005$) and no group by condition interaction.

The group effect was due to the differences in GFP in all segments except II and VI, i.e.: I ($F_{1,114} = 12.24$, $P=0.001$), III ($F_{1,114} = 14.79$, $P<0.0005$), IV ($F_{1,114} = 5.30$, $P=0.023$) and V ($F_{1,114} = 9.01$, $P=0.003$). Lower- -order analysis indicated that in patients (as compared to the control group) a significantly lower peak GFP occurred in segments I-V after non-target stimuli (Table I). However, after target stimuli those differences faded to trends only ($P<0.1$), and disappeared for the GFP in segment II.

The explanation was provided by analysis of the condition effect, which was due to the differences in the peak GFP in segments: II ($F_{1,114} = 4.30$, $P=0.040$), V ($F_{1,114} = 8.78$, $P=0.004$) and VI ($F_{1,114} = 39.45$, $P<0.0005$). One-way analyses for each group revealed significant condition effects either in healthy subjects ($F_{6,73} = 3.82$, $P=0.003$) or in the group of patients ($F_{6,75} =$
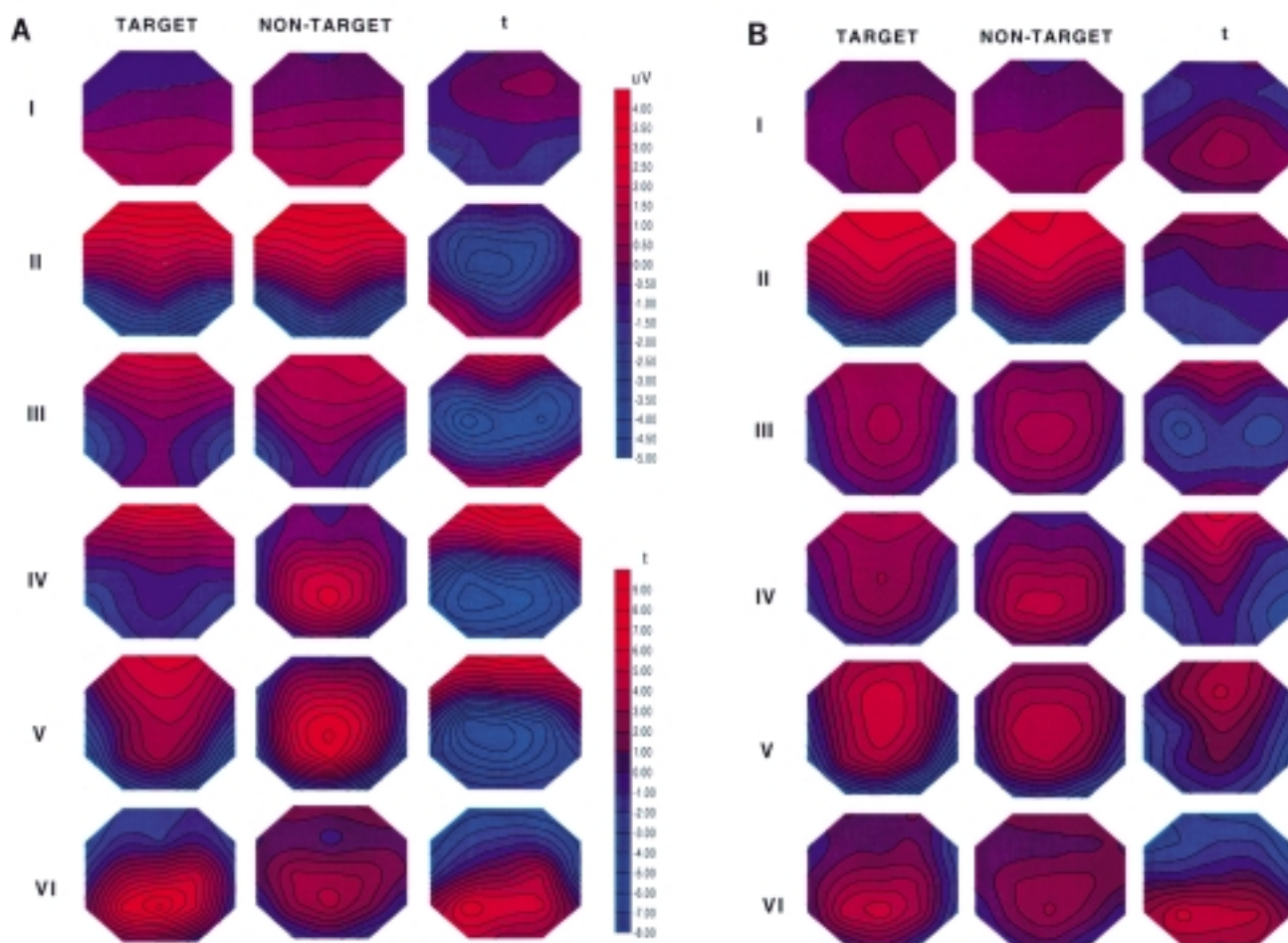
Fig. 3. Pattern of detection of the target. Grand average maps of potential for subsequent segments in the group of the healthy subjects (block A) and schizophrenic patients (block B). In each block: left column, maps of segments following target stimulus; central column, maps of segments following non-target stimulus; right column, *t*-maps of the „target - non-target" differences.

4.67, P=0.001). In the control group, the condition effect consisted of an increase in the GFP peak in segment VI in the target condition, as compared to that in the non-target one (Table II). In patients, an increase in a peak GFP during the detection of the target occurred, apart from segment VI, also in segments II, IV and V.

Location of the centroids along the sagittal (AP) axis

The two-way MANOVAs regarding the locations of the positive (C+) or the negative centroid (C-) in configurations representing the six segments revealed both group (for the C+: $F_{6,109} = 3.55$, P=0.003, for the C-: $F_{6,109} = 2.67$, P=0.019) and condition main effects (for

the C+: $F_{6,109} = 5.40$, P<0.0005, for the C-: $F_{6,109} = 6.40$, P<0.0005) and no group by condition interaction.

The group main effects were due to the differences in locations of the C+ in segment I ($F_{1,114} = 4.12$, P=0.045), the C- in segment II ($F_{1,114} = 5.61$, P=0.020) and the C+ in segments IV and V ($F_{1,114} = 9.07$, P=0.003 and $F_{1,114} = 8.52$, P=0.005, respectively). Lower-order analyses revealed in the non-target condition a more anterior location of the C+ in segment I and more posterior location of the C- in segment II in patients as compared to the control group (Table I). In the target condition those differences decreased to the level of a trend, while location of the C+ in segments IV and V appeared to be significantly more posterior as compared to that in healthy subjects.

TABLE I

Lower-order analysis following the two-way MANOVA: the group effect. Significant between-group differences for each condition analysed separately. SCH , schizophrenic patients; CTR, the control group

Parameter	Condition	Segment	Mean values ± standard deviation SCH vs. CTR	Test, significance
Latency	Non-target	III	246 ms ± 18 vs. 237 ms ± 16	$F_{1,81} = 8.54$, $P=0.005$
		IV	318 ms ± 22 vs. 300 ms ± 24	$F_{1,81} = 8.54$, $P=0.005$
		V	413 ms ± 43 vs. 388 ms ± 28	$F_{1,81} = 11.35$, $P=0.001$
	Target	III	247 ms ± 22 vs. 228 ms ± 16	$F_{1,72} = 15.40$, $P<0.0005$
		IV	317 ms ± 27 vs. 290 ms ± 25	$F_{1,72} = 22.73$, $P<0.0005$
		V	414 ms ± 32 vs. 354 ms ± 33	$F_{1,72} = 49.00$, $P<0.0005$
		VI	576 ms ± 50 vs. 546 ms ± 65	$F_{1,72} = 4.47$, $P=0.038$
GFP	Non-target	I	1.25 ± 0.64 vs. 1.93 ± 1.39	$F_{1,81} = 7.94$, $P=0.006$
		II	3.21 ± 1.32 vs. 4.23 ± 1.82	$F_{1,81} = 26.86$, $P<0.0005$
		III	1.72 ± 0.69 vs. 2.76 ± 1.23	$F_{1,81} = 9.19$, $P=0.003$
		IV	1.80 ± 0.79 vs. 2.64 ± 1.12	$F_{1,81} = 15.85$, $P<0.0005$
		V	2.44 ± 1.26 vs. 3.24 ± 1.33	$F_{1,81} = 16.23$, $P<0.0005$
	Target			
Co-ordinates of the centroids in sagittal (AP) dimension	Non-target	I	3.76 ± 0.71 vs. 4.06 ± 0.67	$F_{1,42} = 9.72$, $P=0.003$
		II	4.45 ± 0.17 vs. 4.37 ± 0.19	$F_{1,42} = 5.20$, $P=0.032$
		IV	2.68 ± 0.28 vs. 2.19 ± 0.47	$F_{1,72} = 16.20$, $P<0.0005$
	Target	V	2.98 ± 0.44 vs. 2.55 ± 0.38	$F_{1,72} = 14.45$, $P<0.0005$

In the condition effects were included the differences in locations of both centroids in segments IV (for C+ $F_{1,114} = 23.88$, $P<0.0005$, for C- $F_{1,114} = 19.52$, $P<0.0005$) and V (for C+ $F_{1,114} = 16.37$, $P<0.0005$, for C- $F_{1,114} = 5.25$, $P=0.025$). In a one-way comparison with the non-target condition (Fig. 4)the response to the target stimuli in each group was characterized by an anterior shift of the C+ in segment IV and V. This was less significant in patients (Table II).

Location of the centroids along the transverse (LR) axis

The two-way group by condition MANOVA revealed neither main effects nor interactions regarding the locations of either the positive or negative centroids.

The only correlation of the ERP results with medical data was a link between an increase of GFP in segment V during detection of the target and a dosage of neuroleptic medication (=+0.34, $P=0.02$). There were no correlations of the data with age, duration of illness nor PANSS score.

Correlations between the behavioural data and the ERP parameters

Spearman rank order correlations revealed numerous links between the spatial descriptors of ERPs and indices of CAT performance in both groups. Those found in the healthy subjects are not directly linked with the current topic of schizophrenia and will be not discussed here. I will focus attention on the correlations related to alterations in ERPs observed the in schizophrenic patients.

Longer latency of the moment of the stabilised configuration for segment V in patients correlated with higher index of errors IE in both non-target and target conditions (=+0.39, $P=0.006$ and =+0.38, $P=0.08$). Low GFP in the non-target condition revealed significant correlations also only for segment V: it correlated with a higher index of errors (=-0.046, $P=0.002$), but following target stimuli – with longer reaction time (=-0.37, $P=0.010$). An increase of the GFP following detection of the target in segment V correlated with shorter time of reaction (=-0.40, $P=0.005$). More posterior location of

TABLE II

Lower-order analysis following the two-way MANOVA: the condition effect. Significant between-condition differences in each group analysed separately. SCH, schizophrenic patients; CTR, the control group

Parameter	Group	Segment	Mean values ± standard deviation Target vs. non-target	Test, significance
Latency	CTR	V	354 ms ± 33 vs. 388 ms ± 28	$F_{1,78} = 17.66, P<0.0005$
	SCH	II	3.53 ± 1.10 vs. 3.21 ± 1.32	$F_{1,80} = 6.49, P=0.013$
		IV	2.01 ± 0.54 vs. 1.80 ± 0.79	$F_{1,80} = 7.70, P=0.007$
		V	3.78 ± 0.85 vs. 2.44 ± 1.26	$F_{1,80} = 7.22, P=0.009$
		VI	2.44 ± 0.73 vs. 1.44 ± 0.52	$F_{1,80} = 14.51, P=0.001$
	CTR	VI	3.17 ± 0.85 vs. 1.35 ± 0.99	$F_{1,78} = 18.78, P<0.0005$
Co-ordinates of the centroids in sagittal (AP) dimension	SCH	IV	2.68 ± 0.28 vs. 3.12 ± 0.46	$F_{1,80} = 10.59, P=0.002$
		V	2.98 ± 0.44 vs. 3.35 ± 0.58	$F_{1,80} = 4.61, P=0.036$
	CTR	IV	2.19 ± 0.47 vs. 3.41 ± 0.85	$F_{1,78} = 9.06, P=0.004$
		V	2.55 ± 0.38 vs. 3.50 ± 0.75	$F_{1,78} = 14.07, P<0.0005$

the C+ in segment V following the target in patients correlated with lower index of errors (= -0.33, $P=0.025$) and with shorter time of reaction (= -0.50, $P=0.005$).

DISCUSSION

A high number of CAT errors, mainly contributed by omissions, is a typical result in schizophrenic patients performing the test from the CPT-IP series (Cornblatt et al. 1989; Nuechterlein 1991). Longer reaction time in patients has also been reported before (i.e. Strandburg 1994b). The low index of commissions, similar to that found in the control group, argues against the possibility of bad comprehension of the instruction in patients. In previous studies, CPT-IP distinguished schizophrenic patients from other types of patients. It is thus less probable that the inferior CAT results are a non-specific effect, accompanying psychiatric illnesses in general (Cornblatt and Erlenmeyer-Kimling 1985, Winters et al. 1991, Kasperska et al. 1997). Likewise in Nuechterlein (1991) and Bergman et al. (1992), there were no correlations between the test results and duration of the illness.

Independence of CAT results of PANSS score in clinically stable, remitted patients, confirms the high sensitivity of the CAT for disturbances of attention in schizophrenia even with subclinical expression of the disorder.

On the other hand, it may be argued that the more omissions and longer reaction times may be due to concurrent neuroleptic medication. The final answer to that question will be found only by the study on unmedicated patients, which is now in progress. However, according to the existing evidence, it is less likely that an influence of medication could play a crucial role in present results. First, studies with the CPT revealed a negligible detriment, or even an improving effect, of phenothiazines on the test performance (Spohn et al. 1977, Harvey et al. 1990). Second, in the previous studies with the CAT (Kasperska et al. 1997) there were no direct correlations between psychometric data and doses of drugs, while there were definite differences in CAT performance depending on diagnosis. And finally, in the present study, the only electrophysiological finding in patients, which correlated with doses of medication, correlated also with better, not worse, performance on the CAT.

Spatial analysis revealed that time-boundaries of segments may vary depending on group or condition. In patients, delayed latencies of stable configurations for segments III-V (and VI following the target) were observed. Those differences are more pronounced in response to the target stimulus: in healthy subjects a shortening of the latency of the moment of stabilised configuration for segment V occurs, while in patients it does not.

In healthy subjects, some of the configurations, thanks to their stable latencies or unequivocal topography, may be related to the phases of processing known from the traditional approach. The segment I, with a positive potential in occipital areas, corresponds to the

phase of the visual P1 component. The definite negativity in occipital and postero-temporal areas in segment II corresponds to the component N1. The parietal positivity dominating in segment VI and increasing during detection of the target, is the P3 (P3b) component. Segments III-V are more difficult for interpretation and will be discussed below. The response to the target, as compared to that following the non-target stimuli, in healthy subjects consists of: (1) shortening of latency of the moment of the maximally stabilised configuration in segment V, (2) change in location of a positive potential in segments IV and V from the central towards the prefrontal location, and (3) an increase of the GFP in segment VI, which accompanies an increase of a parietal positive potential (P3b).

If we now project into that schedule the results obtained in the group of patients, we will find differences both in the non-target and target conditions.

The response to non-target stimuli in patients reveals lower (than in healthy subjects) values of GFP in segments I-V, accompanied by topographic abnormalities in segments I, II and V (Fig. 2A). In segment I, a more anterior location of the positive centroid, as related to lower amplitude of the positive potential at occipital and postero-temporal areas, more significant at the left side, correspond to a decreased P1 component. Diminished amplitude of the P1 in schizophrenia has been observed before, most often as a bilateral feature (Romani et al. 1996, Matsuoka et al. 1996). In segment II, a more poste-

rior location of the negative centroid, resulting from lower amplitudes of a posterior negative potential, corresponded to a lower N1 component. The difference appears to be the most significant at lateral parietal leads P3 and P4. A lower N1 component in schizophrenia has been reported (Roth et al. 1980, Ford et al. 1994, Frangou et al. 1997), however, there were few reports using the visual modality (John et al. 1994). A lack of relevant correlations disables an unequivocal clinical interpretation of the anomalies in microstates I and II. However, those are only spatial analogues to the results concerning the components P1 and N1, revealed in the former study and discussed in detail in the corresponding paper (Basińska 1998).

The most significant difference in the non-target condition is related to lower amplitude of the central positive potential in segment V. Both its latency and topography fit the early P3 component, which has been shown to be delayed and low in the non-target condition in schizophrenic patients (Basińska 1998). Likewise the low amplitude and delayed latency of the early P3, low values of the GFP peak and its delayed latency in segment V correlate with an index of CAT errors. These findings suggest an identity of the early P3 component and the central positive potential in segment (and assumed microstate) V.

During detection of the target in patients, due to increased amplitudes of potential (expressed in increased GFP) the topographic differences observed in segments I and II loose their significance, and in V even change
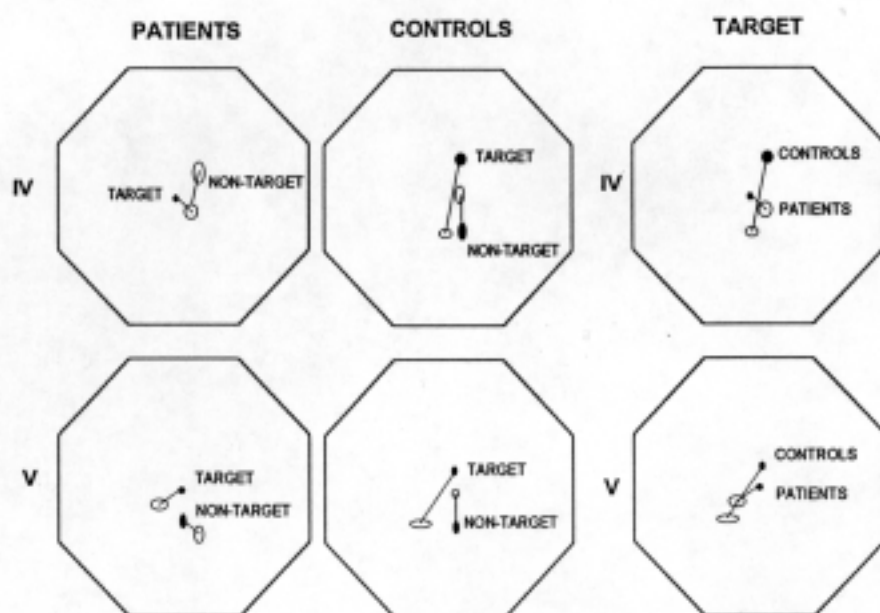

Fig. 4. A target effect in segments IV and V. On the left: positions of the centroids in non-target and target conditions in patients and in the control group. On the right: positions of centroids in the target condition compared between the two groups. Black ellipse, the positive centroid; white ellipse, the negative one. Axes of the ellipses represent standard errors of co-ordinates measured in sagittal and transverse dimension.

their sign (Fig. 2B). The latter change is accompanied by an anteriorly directed shift of positive centroid in segment V (as well as in the preceding IV), resembling the reaction to the target in healthy subjects, but more restricted in its extent. The more posterior location of the C+ in microstate V in patients (Fig. 4) results from the two reasons. First, during detection of the target (Fig. 3B), as compared to that in the control group (Fig. 3A), there was weak activation over the prefrontal area in microstate V, and an increase of positive potential occurred mainly in frontal, but not prefrontal, locations. Second, in patients the decrease of positive potential at central region occurs neither in microstate IV or V, contrary to that in the control group. Hence, the positive potential in microstate V following target stimulus in patients dominates in frontal and central regions, while in healthy subjects it dominates in the prefrontal region.

The related correlations help to clarify the phenomena in microstate V in patients. An increase in GFP, like an increase in amplitude of the early P3 at frontal and central locations in the former study (prefrontal leads were not analysed), is an atypical element of reaction to the target, and likewise correlates with shorter reaction time. The more posterior location of the positive centroid in segment V in the target condition in patients correlates with both shorter reaction time and better CAT performance. However, it is nearly impossible that such benefit would be due to weak activation in prefrontal area. Hypofrontality in schizophrenia is well known (Weinberger 1986, Buchsbaum et al. 1990, Szelenberger et al. 1991) and unequivocally assessed as pathology. Accordingly, some other reasons of a more posterior location of the positive centroid in microstate V must be responsible for the relative improvement of the test performance in patients. These could be sustained activity in central regions and/or involvement of frontal areas.

Such a conclusion confirms the suggestion regarding compensatory processes in patients, revealed before (1998) as an increase of frontal and central amplitude of the early P3 during detection of the target, and now explained as an engagement of alternative cognitive resources in the face of dysfunction of the prefrontal processes. Topographies of microstate V in both groups point to the central areas as active during analysis of non-target stimuli, which are physically similar to targets and likewise must be consciously evaluated. Correlation between index of errors and low GFP in segment V in the non-target condition (dependent on amplitude of the early P3) implies that the more function of centrally

located resources is affected, the less efficient is their improving role in the detection of the target. Apparent target effects on topography of microstate V in healthy subjects imply that different cognitive strategies are engaged during coping with non-target and target stimuli, which are physically similar but differ in their task-relevance. It may be proposed then that microstate V in the target condition is not the same as microstate V in the non-target condition. Moreover, in the target condition, microstate V in patients seems to not be the same phase of processing that it is in the healthy subjects.

It may be wondered whether the postulated compensatory activity in microstate V following target stimuli in patients is overestimated. On the t-maps of between--group differences in target condition (Fig. 2B) it seems to be, at least in part, the result of a left-side excess of potential originating from segments III and IV. The related maps reveal in healthy subjects an asymmetry in central locations (with slightly more negative values at the left side), which does not occur in patients. That difference in symmetry between the groups is still present in microstate V but only overlaps, and does not affect the features occurring along sagittal axis. The central left--side excess of potential in patients in segments III-V, observed only following target stimuli, may be related to motor reactions, as a lower amplitude of the negative readiness potential (Deecke and Kornhuber 1977). In the discussion of the former study (1998) it was specified in detail, that possible events related to pre-motor potentials could not be responsible for specific alterations in the early P3 range, following response to the CAT target in patients. However, a lower readiness potential may occur in patients independently. In such a case, if it markedly influenced topographic changes in microstate V, it should not be associated with better CAT performance.

Contrary to the results of microstate V, there were no correlations between CAT performance and the descriptors of microstate VI in patients, despite a lower amplitude of parietal positivity (P3b) in the target condith {many psychiatric and neurological disorders (Pfefferbaum et al. 1984, Diner et al. 1985, Frank et al. 1994, Schröder et al. 1994, Karayanidis et al. 1995, Kemner et al. 1995), will be not analysed here. However, it is a well-known marker of worsened cognitive functioning and its lack of correlation with the CAT results is surprising. It is worth noting that in the existing literature, a component designated as „P3", if revealed during a classical odd-ball paradigm, is a reaction to both task-relevant and rare deviant stimuli. Hence, P3 may

actually be made of two components: P3b and „novelty" P3a (Squires 1975, Courchesne 1975). Moreover, in many studies the P3 is still defined as „the higher positive amplitude" in a broad late latency range. In the study of Basińska (1998), the amplitude of the early P3 appeared to be higher than that of P3b even in the target condition. All these facts suggest that many of features traditionally attributed to the P3b may be in fact due to properties of earlier P3 components. It should be stressed that the early P3, assigned by the author as „P3a" in the former paper, is not the same as the „novelty" P3a. In the CAT paradigm the early P3 occurs following both non-target and target stimuli, which are physically the same, hence neither rare nor deviant. However, both early P3 and P3a components dominate in frontal or central areas and their interrelation demands further studies. Early frontal P3 has been well demonstrated following visual (Strandburg et al. 1994a) as well as auditory stimuli (Anderer et al. 1998, Turetsky et al. 1998). Comerchero and Polich (1999) suggested that its generation is determined by the difficulty of target/non-target discrimination. However, in their investigations that component was assessed only in non-target condition. In the study of Basińska (1998) early P3 was higher in healthy subjects, who discriminated more easily.

Considering altered ERP in patients, it is important to remember the possible influence of neuroleptic medication. In microstates I and II such an influence, although less probable in exogenous components, cannot be definitely excluded. In particular, it could be responsible for the lower amplitudes of the posterior components P1 and N1 in the non-target condition. However, an increase of the GFP in segment II following exposure of the target, occurring only in the group of patients, as a sign of abnormal hyperarousability after repeated stimulus (Basińska 1998) seems to deny drug-induced suppression of the N1 component. Furthermore, there were the reports of no change in amplitude of potentials (Ford et al. 1994) or even their partial normalisation (Mintz et al. 1995) after neuroleptic treatment. Following the conclusions of Spohn et al. (1977) and Harvey et al. (1990), concerning an influence of the medication on CPT results, it may be postulated that supportive doses in clinically stable patients (contrary to those administered acutely) are not responsible for the ERP findings related to poorer detection.

Finally, the only ERP finding in patients which correlated with doses of drugs in the present study correlated also with shorter (less prolonged) time of reaction. That finding of an increase of GFP in segment V during detection of the target might be a result of treatment. It is related to increased activity in central and frontal regions, which was postulated above to be compensatory to inhibited prefrontal functions. However, two findings are relevant: first, in the former study (Basińska 1998) shortened reaction time correlated significantly with an increase in the amplitude of the early P3 only in frontal, not central, locations. In a study using an auditory oddball paradigm, an increase in P3 in the course of post-treatment normalisation was maximal also in frontal areas (Coburn et al. 1998). Second, in the present study, the more posterior location of the positive centroid in patients, to a greater extent influenced by the activity in the central rather than that in the frontal sites, does not correlate with medication at all. However, it correlates not only with shorter reaction time but also with better CAT performance. Although it is too early for definite conclusions, it may be hypothesised that compensatory changes in the topography of microstate V in remitted patients result either from medication (activating frontal regions) or independent processes (involving centrally located structures), arising from individual reserves of motivational and intellectual resources.

ACKNOWLEDGEMENTS

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