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ORIGINAL PAPER

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Markers from event-related potential subcomponents and reaction time for information processing dysfunction in schizophrenia

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Abstract Event-related potentials (ERPs) can serve as markers for cognitive processing stages. Identification of those ERPs altered in schizophrenia offer information about cognitive dysfunction. Auditory evoked potentials (AEPs) were elicited within an oddball paradigm in 35 schizophrenic patients and compared with 35 healthy controls. N100 and P200, as well as N200, frontal P300 and parietal P300 subcomponents, were separated using dipole source analysis. The amplitudes of the N100 and the parietal P300 measured in schizophrenics were diminished. The input-related processing stages (N100 and P200) were not altered, whereas later, the deviant and task-related processes (N200, frontal P300, parietal P300 and reaction time) were significantly prolonged in schizophrenia.

Key words Schizophrenia · Cognitive · Auditory evoked potentials · Reaction time

Introduction

Research on cognitive processes can be improved by the differentiation of event-related potentials (ERPs). Event-related potentials can indicate cognitive processing stages. Accordingly, it is of interest that only some of the ERP components, N100, P200, N200 and P300, are affected in schizophrenia, whereas others are not attenuated. These specific alterations of some ERP components can offer knowledge about cognitive dysfunction.

The ERPs N100 and P200 occur at approximately 80–150 and 150–250 ms after stimuli such as acoustic tones, as a negative–positive deflection obligatory. They reflect input-related processes (Knott and Lappiere 1987). On the other hand, N200 and P300 are non-obligatory potentials that occur at approximately 180–250 ms after deviant stimuli and 250–500 ms after task-relevant stimuli. N200 is typically evoked by the active discrimination of target stimuli from various other stimuli and might reflect stimulus categorisation. It seems to be closely coupled to stimulus evaluation processes (Hillyard and Kutas 1983). P300 is elicited after completion of a task which is related to deviant stimuli and is thought to reflect the automatic reorientation of attention (Hillyard and Kutas 1983; Donchin 1981; Verleger 1988). The delineation between input-related registration processes (N100, P200) and deviant (N200) or task-related (P300) processes is possible by the differentiation of ERPs. Interestingly, an early attempt to delineate the type of information processing carried out in schizophrenics was made by Kraepelin (1913), who distinguished between an intact registration of attention and an impaired active or directed attention.

The ERP components N100 (e.g. Cohen et al. 1973), N200 (e.g. Ogura et al. 1991; O'Donnell et al. 1993) and P300 (e.g. Roth et al. 1981) have been found to be reduced in schizophrenic patients in comparison with healthy controls. Furthermore, P300 has been considered to be a trait marker for schizophrenic vulnerability (Pritchard 1986; Duncan 1988). Whereas the changes in amplitude decrements are solid results, those in the latency measurements of the ERP components N100, P200, N200 as well as P300 revealed inconsistent findings (Roth et al. 1980; Rist and Cohen 1987).

The clinical relevance and the research implications of ERP findings in schizophrenia have been limited by methodological problems. The ERPs are composed of subcomponents which overlap when recorded at the scalp and which differ in function and generators (Ruchkin et al. 1987; Halgren et al. 1995; Knight et al. 1997). These ERP subcomponents often have not been considered. Furthermore, the reliability of ERP measurements have only been moderate (Roth et al. 1975; Fabiani et al. 1987).

A methodological advance is the dipole source analysis BESA with the N100–P200 dipole model (Scherg and

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von Cramon 1985) and the recently developed dipole model of the auditory P300 (Hegerl and Frodl-Bauch 1997). Overlapping ERP subcomponents can be separated and reliability and validity of ERP measurements can be enhanced using this method (Hegerl and Frodl-Bauch 1997; Frodl-Bauch et al., in press).

To date, no studies using subcomponent analysis (dipole source analysis) of ERPs have been done to discriminate different cognitive processing stages altered in schizophrenics. The subcomponents tangential N100/P200, radial N100/P200, N200, parietal P300 and frontal P300, as well as reaction time, could serve as markers for various information processing dysfunctions in schizophrenia. The present study applied subcomponent analysis to try to confirm the observation made using conventional methods that there is an attenuation of N100, N200 and P300 amplitudes in schizophrenia. The differential analysis of ERP subcomponent latency and reaction time was carried out in order to clarify which ERPs are prolonged in schizophrenia and to delineate changes in input-related and central deviant or task-related processes.

Subjects and methods

Thirty-five schizophrenic subjects (mean age 29.9 ± 8.1 years) from the psychiatric hospital of Ludwig-Maximilians University in Munich were studied. Psychiatric diagnoses were determined by the consensus of at least two psychiatrists who concurred on a diagnosis of DSM-IV. All patients had received neuroleptic medications. Eleven patients had typical neuroleptics (2 haloperidol, 2 perphenazine, 3 perazine, 1 ziprasidone, 1 pimozide, 1 fluphenazine, 1 flupentixol), whereas 24 patients had atypical neuroleptics (16 clozapine, 8 olanzapine). They were treated between 2 and 3 weeks in the hospital. The illness duration ranged from 3 months to 30 years and the number of hospitalisations from 1 to 22.

For comparison, 35 unmedicated healthy controls (mean age 29.4 ± 6.5 years) from the hospital staff and Munich population underwent the same procedure. They did not differ from the schizophrenic patients according to age ($t = 0.29$; $p = 0.77$). Neither the healthy controls nor their first-degree relatives had a history of neurological or mental illness. Patients and control subjects gave their informed consent prior to their inclusion in the study. The examination was approved by the local ethics committee and was therefore in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki.

ERP method

Event-related potentials were recorded using an oddball paradigm. Sinus tones (80 dB SPL, 40 ms duration, 10 ms rise/fall time using fixed 1.5-s interstimulus interval) were presented binaurally via earphones in pseudo-randomised order. Twenty percent of these tones were targets (100 sinus tones, 1000 Hz), and 80% were standards (400 sinus tones, 500 Hz).

Subjects were seated with closed eyes in a reclining chair. They had to press a button with their dominant hand after target stimuli. All subjects were instructed to recognise the target stimuli and then to press the button fast.

EEG recording and averaging

Evoked responses were recorded with 31 channels (29 Zn electrodes of an electro cap and three additional Zn electrodes at nasion and the mastoids, all referenced to Cz). Most of the electrodes were positioned precisely according to the international 10–20 system. A coronal line of four electrodes was added between frontal and central electrode locations, and another coronal line of four electrodes was added between central and parietal electrode locations and one electrode at the inion. Electrode impedance was maintained at less than 5 kOhm. The EEG was amplified with bandpass filters of 0.16–70 Hz (sampling rate of 256 Hz).

The EOG was recorded with electrodes above the eyes and lateral to the eyes and at the nasion. For artefact suppression all trials were excluded, if their voltage exceeded (50 μV in any one of the 31 channels at any time point during the averaging epoch (from 200 ms pre stimulus to 800 ms post stimulus).

Dipole source analysis

Dipole source analysis was performed with BESA (Scherg and von Cramon 1985; Scherg and von Cramon 1986), which can be used to distinguish temporally overlapping activities recorded with the scalp electrodes. The scalp data were transformed in the dipole source activity of dipoles using a four-shell head model. The dipoles are thought to represent activity of circumscribed cortical areas; therefore, they change strength over time, but not location or orientation. The optimal location and orientation of the dipoles are found by an iterative process (simplex algorithm) optimising the residual variance (variance of the measured scalp data unexplained by the dipole model), whereas the dipole source potentials are determined by the direct linear approach, as described by Scherg and Picton (1991).

The potential distribution at the scalp at the time range of the N100/P200 component can be explained by the activity of two dipoles per hemisphere: the activity of a tangential dipole located in the superior temporal plane (including primary auditory cortex) and the later activity of a radial dipole located near the lateral temporal cortex (secondary auditory cortex; Scherg et al. 1989). A dipole model of the auditory P300 can decompose the overlapping subcomponents of P300 (Hegerl and Frodl-Bauch 1997). Each dipole pair is suggested to represent a subcomponent of the auditory P300. The temporo-basal dipoles reflect parietal P300 and the temporo-superior dipoles reflect frontal P300 and negative slow wave as well as the previous negative deflection N200. With two dipoles per hemisphere a considerable model has been found that enhances the test-retest reliability and the validity of P300 measurements.

Dipole source analysis of N100/P200 is performed with the dipole model described by Scherg et al. (1989) and the dipole procedure of Hegerl et al. (1994; Fig. 1). The N100/P200 interval was assessed between 70 and 238 ms. N200 and P300 dipole source analysis was carried out with the dipole model described in Hegerl and Frodl-Bauch (1997; Fig. 2). N200 was determined between 180 and 250 ms after stimulus onset. The individual P300 data were analysed starting with the grand average dipole model and determining the dipole parameters without fitting the dipole configurations. The P300 interval was started 40 ms after the individual P200 peak and had a duration of 166 ms.

The dipole amplitudes and latencies were defined as the most negative or positive point of the dipole activities in the ERP interval. The magnitude of the dipole activity (source potential) were measured in units of nano-ampere-meters (nAm).

Results

Analysis of variance was performed on the amplitudes of ERP components with Group (schizophrenics and healthy controls) as within-subject factor. The results are presented in Table 1. Significant amplitude reductions between schizophrenic patients and healthy controls were found for the amplitudes of the tangential N100 (Fig. 3), radial

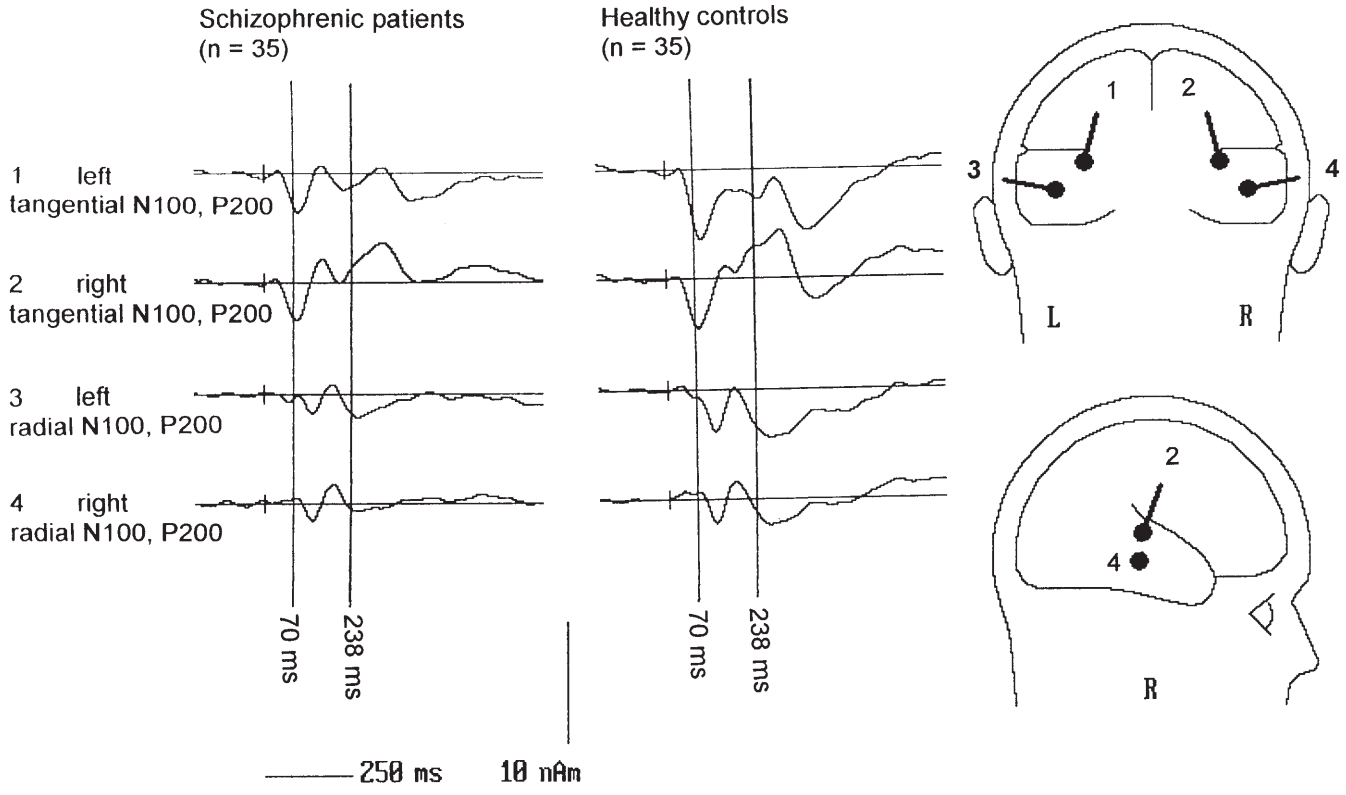

Fig. 1 Dipole model of the N100. Two pairs of dipoles, a tangential and a radial, represent the N100, P200. A tangential N100, P200 component reflects activity of the primary auditory cortex and a radial N100, P200 component reflects activity of the secondary auditory cortex

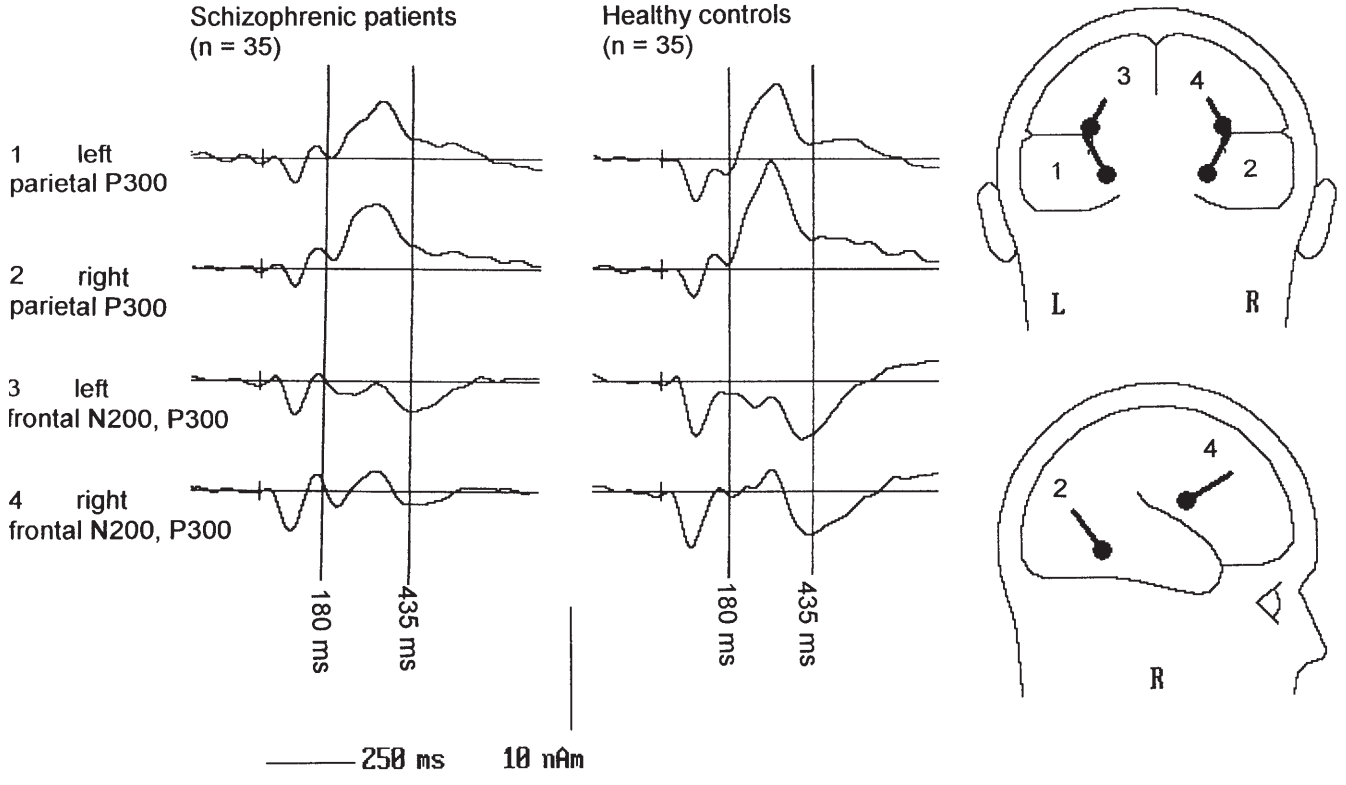

Fig. 2 Dipole model of P300: a temporo-basal dipole pair represents the parietal P300, whereas a temporo-superior dipole pair represents the N200 and frontal P300

Table 1 Mean amplitudes of ERP components from healthy controls (n = 35) and schizophrenic patients (n = 35). Significance of ANOVA for Group effects (controls vs patients)

Component	Controls	Patients	ANOVA F value	Sign
N1 amplitude: tangential dipole	–5.66 ± 1.8	–4.05 ± 1.6	15.85	0.000
N1 amplitude: radial dipole	–3.34 ± 2.0	–2.05 ± 1.6	9.1	0.004
P2 amplitude: tangential dipole	1.29 ± 3.0	2.02 ± 2.6	1.2	n.s.
P2 amplitude: radial dipole	1.5 ± 2.0	1.80 ± 1.6	0.5	n.s.
N2 amplitude	–3.3 ± 2.6	–3.01 ± 2.4	0.26	n.s.
P3a amplitude	2.85 ± 4.2	2.61 ± 3.4	0.07	n.s.
P3b amplitude	9.21 ± 3.9	6.62 ± 2.9	9.87	0.002

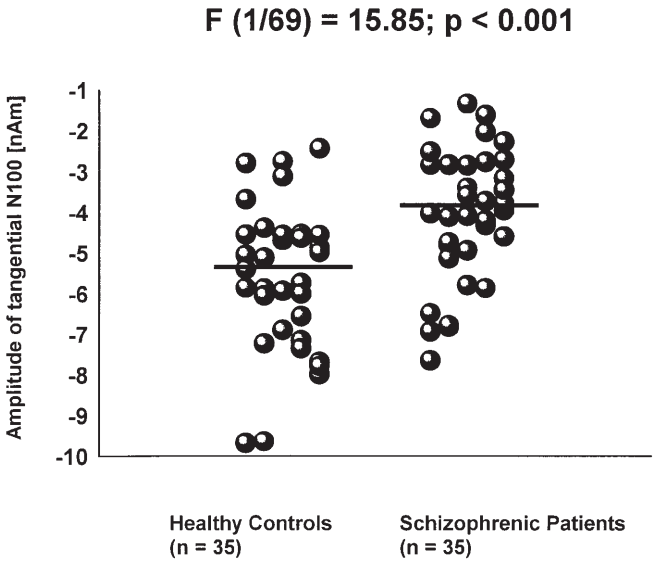

Fig. 3 Amplitudes of tangential N100 (nano-ampere-meters) from schizophrenic patients (n = 35) in comparison with healthy controls (n = 35)

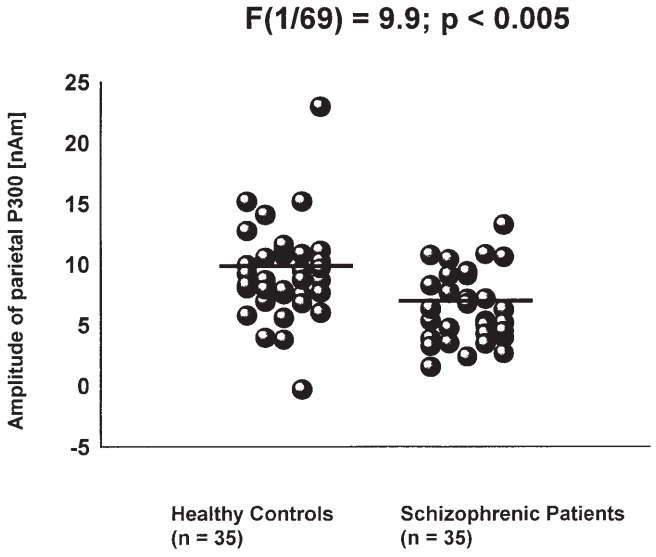

Fig. 4 Amplitudes of parietal P300 (nAm) from schizophrenic patients (n = 35) and healthy controls (n = 35)

N100 as well as for parietal P300 amplitudes (Fig. 4). Mean amplitudes of tangential P200 were higher for the patients group, but this result was not significant ($F(1/69) = 1.2$; $p = 0.27$). Subtraction of tangential N100 from tangential P200 did not reveal significant differences between patients and controls. The activities from radial P200, N200 and frontal P300 were not significantly different.

Latency analysis using simple ANOVA revealed significant differences in N200 ($F(1/69) = 5.2$; $p = 0.025$), frontal P300 ($F(1/69) = 14.4$; $p = 0.000$) and parietal P300 ($F(1/69) = 8.5$; $p = 0.005$). Latencies of tangential and radial N100, as well as latencies of tangential and radial P200, were not significantly longer in schizophrenics in comparison with healthy controls. However, total central processing time (reaction time minus N100 latency; $F(1/69) = 3.9$; $p = 0.05$) as well as reaction time ($F(1/69) = 4.0$; $p = 0.05$) was significantly longer for schizophrenics in comparison with healthy controls (Fig. 5).

In the present data there were no significant interactions with gender. Moreover, concerning medication effects, significant differences were found between typical and atypical neuroleptics. Amplitudes of frontal P300 were higher for patients receiving typical neuroleptics ($F(1/34) = 5.5$; $p = 0.025$), whereas those patients had higher amplitudes of radial P200 ($F(1/34) = 4.2$; $p = 0.047$). Furthermore, they had shorter latencies of N200 ($F(1/34) = 4.3$; $p = 0.046$) and prolonged latencies of radial N100 ($F(1/34) = 5.1$; $p = 0.031$) and tangential P200 ($F(1/34) = 4.2$; $p = 0.049$). The other components are not significantly influenced by the type of medication.

Discussion

Dipole source analysis was used to separate overlapping ERP subcomponents from the scalp data. Tangential and radial N100–P200 components, as well as N200, frontal P300 and parietal P300 components, were investigated. Decrements of N100 (Jones and Callaway 1970; Saletu et al. 1971; Cohen et al. 1973; Eichert et al. 1993) and of P300 (Pritchard 1986; Duncan 1988; Ford et al. 1994) in schizophrenic patients have been reported to be one of the most robust biological findings in schizophrenic subjects. The present results are in line with these findings. The

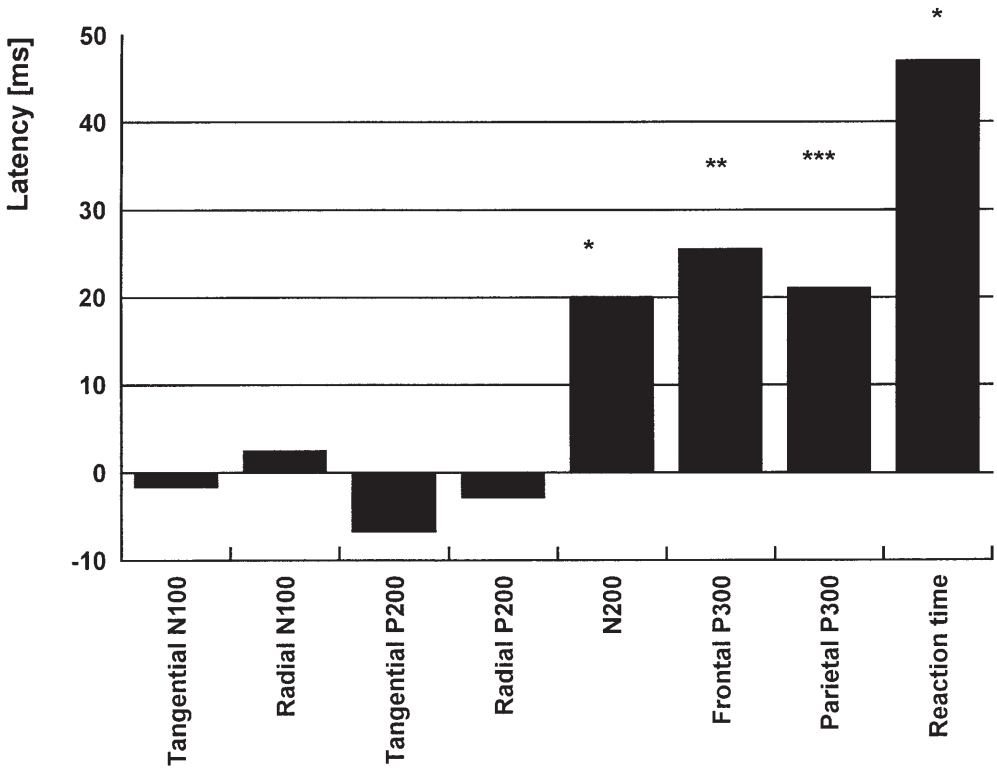

Fig. 5 Differences from mean latencies and reaction times of schizophrenic patients and of healthy controls (milliseconds). The difference is equal to the latency prolongation of schizophrenic patients in comparison with healthy controls. The significance of the prolongations is included (*$p < 0.05$; **$p < 0.01$; ***$p < 0.005$)

parietal P300 component in accordance with conventional measurements of the parietal P300 was diminished as were the tangential as well as the radial N100 components in accordance with changes in the conventional N100 component. Important is that tangential P200 is higher for the patient group and that subtraction of tangential N100 from P200 did not obtain differences between groups. This finding has several possible explanations. It might point to a higher negativity in the N100–P200 interval for the healthy controls in comparison with schizophrenic patients, so that the N100–P200 processes are not attenuated, whereas they are overlaid by a slow potential. On the other hand, it can be that N100 is really diminished, whereas P200 is enhanced in schizophrenic patients.

They suggest that N100 and the parietal P300 are both affected in schizophrenia. Cognitive disturbances of schizophrenic patients do not seem to be specific to a single ERP component. Significantly, the activity of the obligatory input-related N100 as well as the non-obligatory task-dependent parietal P300 are both diminished in schizophrenia. Therefore, disturbances in schizophrenics might include input-related registration processes as well as task-related central processes. On the other hand, N200 and the frontal P300, which have been related to stimulus evaluation processes, were not reduced in the present study. This finding is in agreement with others, who found neither alterations of N200 in target data waveforms (Roth et al. 1980; Barett et al. 1986) nor alterations in the frontal P300 (Michie et al. 1990; Frodl-Bauch et al., in press). Thus, stimulus evaluation processes do not seem to be attenuated in schizophrenics. The fact that N200 was not altered in the schizophrenic patients in the present study can be explained. No subtraction of target minus non-target waveforms was made, in order to measure N100, P200 components as well as N200, frontal P300 and parietal P300. Subtracting waveforms would cause N100 and P200 components to appear attenuated. Furthermore, cognitive operations reflected by N200, presumably compromised by damaged/dysfunctional neuronal substrates in schizophrenics, can be compensated for if the task is relatively easy (Salisbury et al. 1994).

While the findings on the amplitudes of ERP in schizophrenia were solid, latency measurements of the ERP components revealed inconsistent results (Rist and Cohen 1987; Roth et al. 1980). A significant prolongation of N200, frontal P300 and parietal P300 latency and reaction time was found in the present study, whereas the latencies of the other components were not changed. Therefore, central cognitive processes reflecting stimulus categorisation/evaluation (N200), stimulus evaluation (frontal P300) and reorientation of attention (parietal P300) as well as motor execution (reaction time) were prolonged. On the other hand, input-related processes, such as N100 and P200, were not altered. This result is in line with the finding that post-acute schizophrenics needed 1.8 times longer than the healthy controls for central processing time and more time for motor execution time, but not for input-related processes, reflected in N100 latency (Eichert et al. 1993). Moreover, the results can be related to the finding of Kraepelin (1913), who described intact passive

attention abilities but impaired active or directed attention. The intact passive attention reflects the existence of robust input-related processes, which underlie N100 and P200, whereas the impaired active or directed attention reflects the prolongation of central processes which underlie N200, frontal P300, parietal P300 and reaction time. Thus, cognitive disturbances in schizophrenics are more pronounced in processes that are related to effortful, active attention, causing those components to be prolonged, which indicate cognitive stages under the effortful control of the subject.

An interesting finding, however, of minor importance in the present study, is that patients receiving typical neuroleptics had reduced amplitudes of frontal P300, enhanced amplitudes of radial P200 as well as shortened latencies of N200 and prolonged latencies of radial N100 and tangential P200. Such a medication effect can be investigated in a double-blind randomised study.

Taken together, these findings indicate that the functions of the N100 and the parietal P300 components are clearly attenuated in schizophrenics. Concerning latencies, the later components related to central, active or effortful attention processes, such as N200, frontal P300, parietal P300 and reaction time, are prolonged, whereas previous input-related components such as N100, P200 are not altered.

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