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Auditory Evoked Potentials in Schizophrenic Patients Before and During Neuroleptic Treatment

Relationship to Psychopathological State

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Summary. The auditory evoked potential (AEP) components N1 and P2 were investigated under a no-task condition in a group of 14 acutely ill unmedicated schizophrenic patients and compared with the findings in an age- and sex-matched control group. In the patients, N1 latency was significantly increased, P2 latency and N1-P2 interpeak latency were reduced. There were significant relationships between AEP parameters and the psychopathological state evaluated by means of the brief psychiatric ratings scale (BPRS). The N1 and P2 latencies were negatively correlated with the BPRS subscore "anergia" and positively correlated with "agitation". In 8 of the patients, a standardized neuroleptic treatment was started with 10 mg haloperidol/day. After 2 weeks of treatment, BPRS scores and N1 amplitude had significantly decreased. However, there was no relationship between BPRS improvement and N1 amplitude reduction. N1 latency in the unmedicated state was negatively correlated with subsequent therapeutic response measured as proportional improvement of the BPRS score within 2 weeks. Thus, N1 latency may be seen as a psychophysiological measure with prognostic applications.

Key words: Schizophrenia – Auditory evoked potentials – Neuroleptics – Psychopathology – Prognosis

Introduction

A variety of alterations of evoked potential parameters has been reported in schizophrenic patients. However, apart from often rather speculative relationships with cognitive impairment, attentional dysfunction or altered level of psychophysiological arousal, little clinically useful information related to psychopathological state, diagnosis or prognosis can be deduced. Clinically meaningful evoked potential research in schizophrenic patients has to consider two aspects: 1. evoked potential parameters have to be related to clinical parameters such as history, psychopathological state, course of illness and therapeutic response; 2. effects of pharmacological treatment may obscure evoked potential alterations related to schizophrenia. In evoked potential studies in acutely psychotic patients, in our view a no-task condition of stimulus presentation is preferable to a task condition, in order to avoid variance produced by nonpredictable interpretation of task instructions. On the actual background of evidence, under a no-task condition of stimulus presentation, the auditory evoked potential (AEP) components N1 and P2 appear to be most promising for the search for evoked potential alterations in schizophrenic patients. Thus, we investigated the AEP components N1 and P2 in a group of acutely ill unmedicated schizophrenic patients and related the AEP findings to patient history, psychopathological state and clinical course under a standardized neuroleptic treatment.

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Subjects and Methods

The study was performed in 14 newly admitted schizophrenic patients according to DSM-III-R criteria (9 men, 5 women; age: 24–43 years), who had not been under neuroleptic treatment for at least 1 week. Eleven of them had not been under neuroleptic treatment for at least 1 month; four of these were drug-naive. At admission, before starting neuroleptic therapy, the psychopathological state was evaluated by means of the brief psychiatric rating scale (BPRS) and an AEP investigation was performed. A detailed patient history was obtained, providing information on duration of illness, duration of the current episode, number and duration of stationary treatments, previous medication and family history.

In eight of the patients admitted to our research ward, a standardized treatment was given, with 10 mg haloperidol/day. There were no significant differences with respect to patient history, demographic and psychopathological parameters between these patients and the entire patient group.

The AEP findings in the patients were compared with those obtained in a group of 14 healty age- and sex-matched controls.

AEP were elicited by 1-kHz tones of 50 ms duration and an intensity of 70 dB SL presented binaurally through headphones at a

stimulation frequency of 0.3/Hz. Recordings were performed from Cz using linked mastoids as reference. Filter settings were 1–100 Hz. Electrooculographic activity was monitored with electrodes placed diagonally above and below the right eye, in order to detect eyeblinks as well as lateral and vertical eye movements. For the EOG channel, artifact rejection level was individually adjusted in order to exclude trials with eyeblinks and eye movements from averaging; for the EEG channel, trials with amplitudes exceeding 150 μV were excluded from averaging. Latency measurements were referred to stimulus onset; amplitude measurements were referred to the prestimulus baseline.

AEP findings in the unmedicated schizophrenic patients and controls were compared by means of unpaired *t*-tests ($f = 26$); the effects of neuroleptic treatment in the subgroup of 8 patients were evaluated by paired *t*-tests ($f = 7$). Relationships between AEP parameters and BPRS scores were studied by linear regression analyses.

Results

Psychopathological and AEP Findings at Admission (N = 14)

The mean BPRS score in the patients was 61 (range: 50–73). Mean duration of illness was 90 months; mean duration of the actual episode before admission was 5 weeks. The patients had had 2.4 stationary treatments (mean) with a total duration of 94 days (mean). In the patients, N1 latency was significantly increased ($P < 0.05$), P2 latency was significantly reduced ($P < 0.01$). Consequently, there was a highly significant reduction of N1-P2 interpeak latency in the schizophrenic patients ($P < 0.001$). N1-P2 interpeak latency was the AEP parameter separating most clearly unmedicated schizophrenic patients from controls. There was no significant difference between unmedicated patients and controls for the N1 and P2 amplitudes. N1 and P2 latencies for the individual patients and controls are plotted in Fig. 1; means and standard deviations are given in Table 1. Recordings from one of the control subjects and one of the schizophrenic patients are shown in Fig. 2.

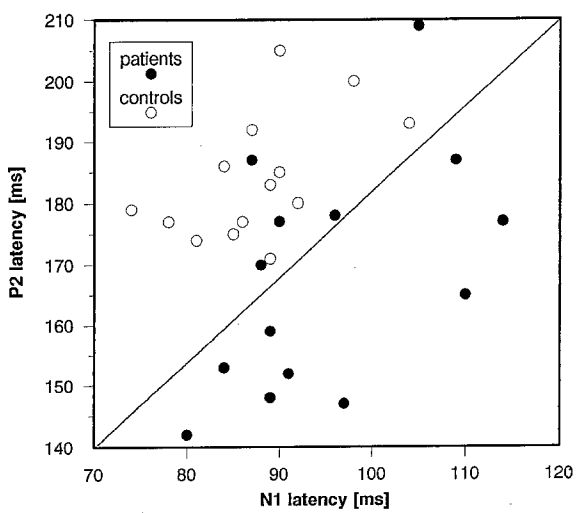

Fig. 1. N1 and P2 latencies are distributed differently in schizophrenic patients and controls. In this diagram, the N1 and P2 latencies of the 14 drug-free schizophrenic patients and of their age- and sex-matched controls are plotted against each other. In the schizophrenic patients, N1 latency was increased, P2 latency was decreased. By this method, a fairly good discrimination between patients and controls can be achieved

Table 1. N1- and P2-latency alterations in schizophrenic patients. The N1- and P2-latencies and the N1-P2 interpeak latency are given as means, SD for the 14 drug-free schizophrenic patients and for their age- and sex-matched controls. *P*-values were calculated by unpaired *t*-tests. In the schizophrenic patients, N1 latency was increased, P2 latency and N1-P2 interpeak latency were reduced

		Patients	Controls
N1 latency	Mean	94.9	87.6
	SD	10.6	7.6
	P	<0.05	
P2 latency	Mean	167.9	184.1
	SD	19.1	10.1
	P	<0.01	
N1-P2 interpeak latency	Mean	73.0	96.5
	SD	16.4	8.7
	P	<0.001	

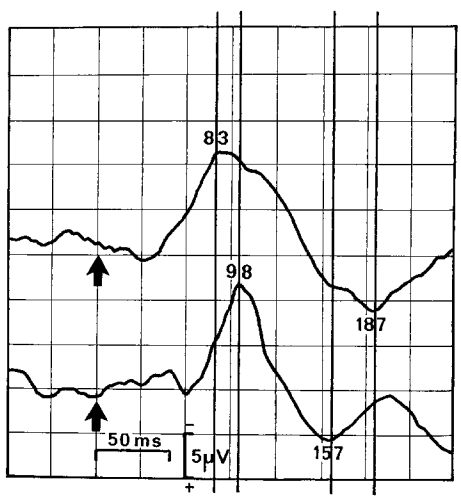

Fig. 2. AEP alterations in schizophrenic patients. AEP recordings in one of the control subjects *(top curve)* and one of the schizophrenic patients *(bottom curve)*. Negativity is plotted upwards. *Arrows* indicate stimulus onset. N1 and P2 latencies are given in milliseconds

Regarding relationships between AEP parameters and BPRS scores, N1 and P2 latencies were negatively correlated with "anergia" and positively correlated with "agitation" (Fig. 3). "Anergia" and "agitation" were negatively correlated with each other, but at a lower degree than with AEP latencies ($r = 0.31$; $P < 0.10$). There were no other significant correlations between AEP parameters and BPRS scores or history parameters.

Findings in the Patients Under Standardized Neuroleptic Treatment (N = 8)

Initial AEP findings in the 8 schizophrenic patients who underwent a standardized neuroleptic treatment did not

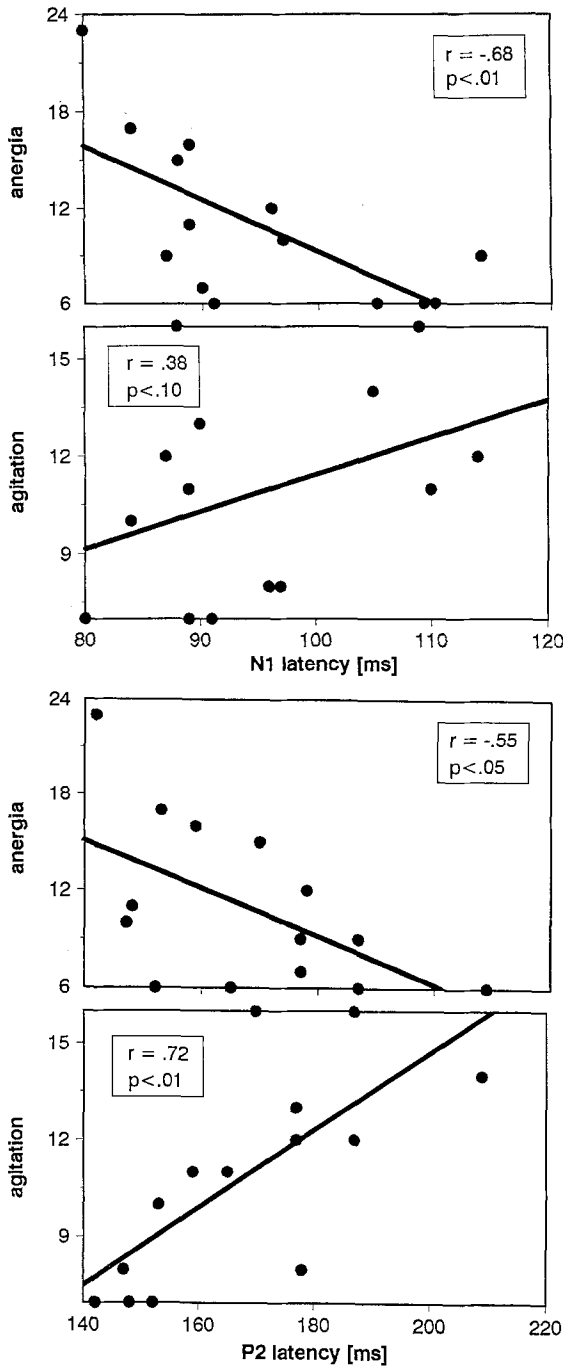

Fig. 3. N1 and P2 latencies are related to BPRS subscores. In these diagrams, the N1 and P2 latencies (in ms) are plotted against the values of the BPRS subscores "anergia" and "agitation" in the 14 drug-free schizophrenic patients studied. Both N1 and P2 latencies were negatively correlated with "anergia" and positively correlated with "agitation"

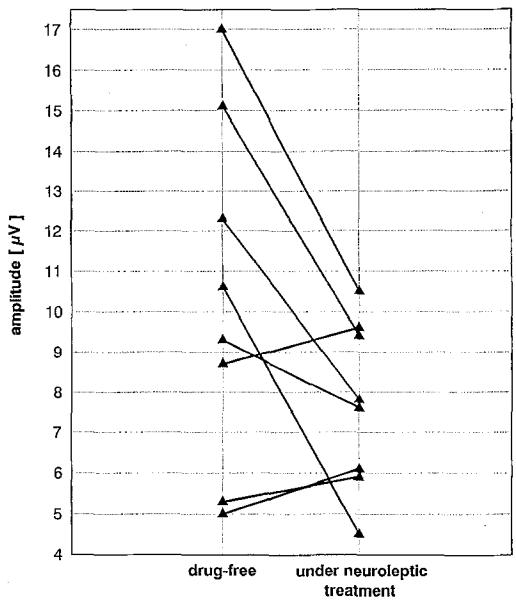

Fig. 4. N1 amplitude decreases under neuroleptic treatment. N1 amplitudes before and during neuroleptic treatment are plotted for 8 schizophrenic patients treated with 10 mg haloperidol/day for 2 weeks. Under neuroleptic therapy, there was a significant decrease of mean N1 amplitude. In the individual subjects, high N1 amplitudes decreased, whereas small N1 amplitudes slightly increased

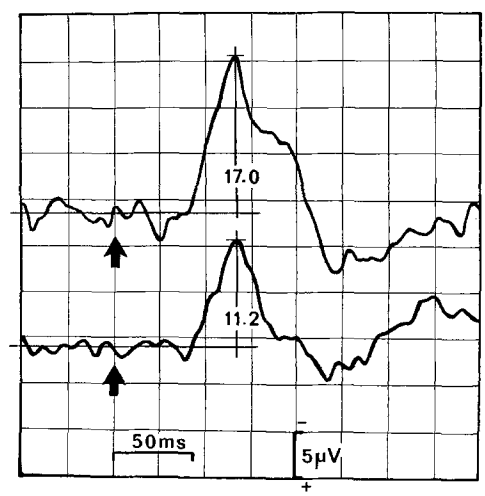

Fig. 5. AEP changes under neuroleptic treatment. AEP recordings in one of the schizophrenic patients before *(top curve)* and after 2 weeks of neuroleptic treatment *(bottom curve)*. Negativity is plotted upwards. *Arrows* indicate stimulus onset. N1 amplitudes are given in microvolts

differ significantly from those of the entire patient group. After 2 weeks of neuroleptic treatment, the BPRS score had decreased from 60.3 ± 8.4 (means ± SD) to 38.3 ± 11.4 ($P < 0.003$). In the same period, N1 amplitude decreased from 10.4 ± 4.3 μV (mean ± SD) to 7.7 ± 2.1 μV ($P < 0.05$). N1 amplitude changes followed a differential pattern: high baseline N1 amplitudes decreased clearly, whereas low amplitudes slightly increased (Fig. 4). Thus, N1 amplitude changes under neuroleptic treatment show the pattern of a regression to the mean. N1 amplitude changes were not related to psychopathological improvement. P2 amplitude and N1 and P2 latencies did not change significantly. Recordings from one of the schizophrenic patients before and after 2 weeks of neuroleptic treatment are shown in Fig. 5.

N1 latency in the unmedicated state was negatively correlated with short-term therapeutic response measured as absolute and percent improvement of the baseline BPRS score within 2 weeks of neuroleptic treat-

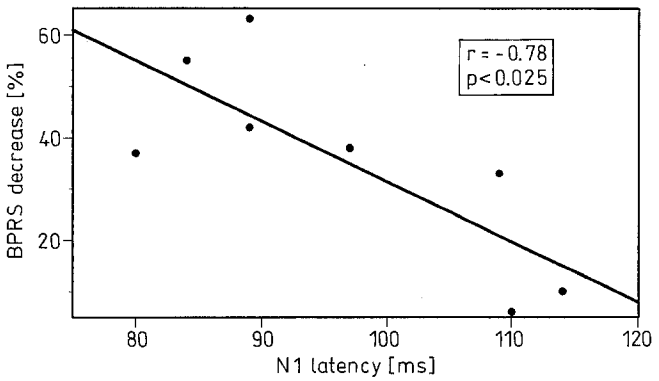

Fig. 6. N1 latency is related to therapeutic response. In this diagram, therapeutic response, measured as percent improvement of the BPRS score within 2 weeks under 10 mg haloperidol/day, is plotted against N1 latency in the unmedicated state for 8 schizophrenic patients. BPRS improvement was negatively correlated with N1 latency

ment (Fig. 6). Thus, a shorter N1 latency predicted a better therapeutic response. There was no other significant correlation between initial BPRS scores or AEP parameters and psychopathological improvement under neuroleptic treatment.

Discussion

Our finding of increased N1 latency in schizophrenic patients has already been described in the literature (Roth et al. 1981; Sandman et al. 1987; Adler et al. 1990). This finding contrasts with the report of a reduced N1 latency in unmedicated schizophrenic patients that normalizes under neuroleptic treatment (Schlör et al. 1985). A reduction of P2 latency has also been reported in schizophrenic patients (Roth et al. 1981, 1982) and in healthy subjects showing conceptual loosening on an object sorting test (Catts et al. 1986). Thus, the N1 latency increase and P2 latency reduction observed in unmedicated schizophrenic patients in this study are in accordance with previous findings. The reduced N1-P2 interpeak latency proved to be the AEP parameter with the best discrimination between schizophrenic patients and controls.

With respect to the N1 and P2 amplitudes in unmedicated schizophrenic patients, our results seem to be in contradiction to the findings reported by various authors. An N1 amplitude reduction has been reported in medicated schizophrenic patients (Pfefferbaum et al. 1989), in mixed groups of medicated and unmedicated schizophrenic patients (Shagass et al. 1977, 1978; Pfefferbaum et al. 1980, 1984; Roth et al. 1980, 1981) and in unmedicated schizophrenic patients (Brecher and Begleiter 1983; Connolly et al. 1985; Kessler and Steinberg 1989; Michie et al. 1990). In order to rule out effects of neuroleptic medication, at this point we will only discuss the studies performed in unmedicated schizophrenic patients. The crucial difference between these studies and our own is the condition of stimulus presentation. Two of these studies were performed under task conditions (Brecher and Begleiter 1983; Michie et al. 1990). It is well known that direction of attention towards the stimuli and cognitive processing enhance the N1 component (Hillyard et al. 1973) by the involvement of additional generators (reviewed by Näätänen and Picton 1987). Thus, studies on the N1 component under task and no-task conditions can hardly be compared. The study of Connolly et al. (1985) refers to the N120 wave recorded from temporal electrode locations that is supposed to differ from the centrally recorded N1, in terms of the component structure (Wolpaw and Penry 1975; Adler and Adler 1989) as well as of the underlying generators (Näätänen and Picton 1987). Moreover, the selected mode of stimulus presentation (pseudorandomly to left and right ears) is suited to elicit a mismatch negativity. With respect to the study of Kessler and Steinberg (1989), the application of stimulation conditions producing maximum habituation of the N1 component (high stimulation frequency, long runs of stimuli) and an unmatched control group including patients with clinically relevant personality and adjustment limit comparability. Our results are in accordance with those presented by Roth et al. (1991), who did not find N1 amplitude alterations in unmedicated schizophrenic patients.

Previous studies on relationships between AEP parameters and psychopathological variables referred to the N1 amplitude (Lifshitz et al. 1987; Kessler and Steinberg 1989). Lifshitz et al. (1987) reported an inverse relationship between psychopathology and N1 amplitude. Kessler and Steinberg (1989) found an N1 amplitude reduction in schizophrenic patients of the paranoid type, not in those of the residual or undifferentiated type. We could not confirm a relationship between N1 amplitude and psychopathological state. However, we found consistent correlations between the N1 and P2 latencies and the BPRS subscores "agitation" and "anergia". As the correlations between AEP latencies and BPRS subscores are stronger than the one between "anergia" and "agitation", the former do not seem to be artifactual. However, the sign of the correlations is somewhat surprising. In healthy subjects, diazepam administration increases N1 latency, whereas the application of amphetamine decreases N1 latency (Herrmann et al. 1981). Thus, sedation in normals and "anergia" in schizophrenic patients or amphetamine-induced over-alertness in normals and "agitation" in schizophrenic patients might be rather opposite than corresponding in terms of AEP. On the other hand, the BPRS subscore "agitation" comprises symptoms that reflect paranoid suspiciousness and thinking disorder (tension, mannerisms and posturing, excitement), whereas the symptoms contributing to "anergia" (emotional, withdrawal, motor retardation, blunted affect, disorientation) are more closely related to a depressive syndrome (Overall 1972). Thus, it might be suggested that patients with high "agitation" in terms of BPRS and increased N1 and P2 latencies are more severely involved in pathophysiological processes specifically related to schizophrenia. There were no significant correlations between AEP parameters and parameters of the patient history. This may be at least in part

attributed to the relative homogeneity of the patient sample investigated.

A decrease of N1 amplitude under neuroleptic medication, as we observed it, has already been described (Pfefferbaum et al. 1989, Roth et al. 1991). It may also be reflected by an apparent amplitude reduction in studies of mixed groups of medicated and unmedicated schizophrenic patients (Shagass et al. 1977, 1978; Pfefferbaum et al. 1980, 1984; Roth et al. 1980, 1981). This decrease of N1 amplitude under neuroleptic medication was unrelated to the evolution of the psychopathological state. It may be related to the sedative effect of the neuroleptic, because sedation produced by ethanol or diazepam and distraction of attention also lead to an amplitude reduction of N1 (Gross et al. 1966; Picton and Hillyard 1974; Pfefferbaum et al. 1979; Herrmann et al. 1981). In contrast to the observations of Schlör et al. (1985), we found no correlation between changes in the psychopathological state and changes of the AEP parameters investigated.

A correlation between N1 latency and therapeutic response as we observed it in our patients has not yet been reported. The sign of the correlation is as expected: patients with a higher degree of AEP abnormality showed a poorer recovery. In the unmedicated patients, N1 latency correlated significantly with BPRS subscores. After neuroleptic treatment, N1 latency remained unchanged, whereas BPRS psychopathology improved significantly. Thus, N1 latency may be seen as a relatively stable psychophysiological measure in schizophrenic patients with prospective diagnostic and prognostic applications.

References

Adler G (1991) Die Hyperarousal-Hypothese: Neue Aspekte eines neurophysiologischen Konzeptes der endogenen Psychosen. Fortschr Neurol Psychiatr 59:203–206

Adler G, Adler J (1989) Influence of stimulus intensity on AEP components in the 80- to 200-millisecond latency range. Audiology 28:316–324

Adler G, Adler J, Schneck M, Armbruster B (1990) Influence of stimulation parameters on auditory stimulus processing in schizophrenia and major depression: an auditory evoked potential study. Acta Psychiatr Scand 81:453–458

Brecher M, Begleiter H (1983) Event-related potentials to high-incentive stimuli in unmedicated schizophrenic patients. Biol Psychiatry 20:293–303

Callaway E, Naghdi S (1982) An information processing model for schizophrenia. Arch Gen Psychiatry 39:339–347

Catts SV, Armstrong MS, Ward PB, McConaghy N (1986) Reduced P200 latency and allusive thinking: an auditory evoked potential index of a cognitive predisposition to schizophrenia. Int J Neurosci 30:173–179

Connolly JF, Manchanda R, Gruzelier JH, Hirsch SR (1985) Pathway and hemispheric differences in the event-related potential (ERP) to monaural stimulation: a comparison of schizophrenic patients with normal controls. Biol Psychiatry 20:293–303

Freedman R, Adler LE, Waldo MC, Pachtman E, Franks RD (1983) Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. Biol Psychiatry 18:537–551

Gross MM, Begleiter H, Tobin M, Kissin B (1966) Changes in auditory evoked response induced by alcohol. J Nerv Ment Dis 143:152–156

Herrmann WM, Hofmann W, Kubicki S (1981) Psychotropic drugs induced changes in auditory averaged evoked potentials: results of a double-blind trial using an objective fully automated AEP analysis method. Int J Clin Pharmacol Ther Toxicol 19:56–62

Hillyard SA, Hink RF, Schwent VL, Picton TW (1973) Electrical signs of selective attention in the human brain. Science 182: 177–180

Kessler C, Steinberg A (1989) Evoked potential variation in schizophrenic subtypes. Biol Psychiatry 26:372–380

Lifshitz K, Lee KL, Susswein S (1987) Long-term replicability of EEG spectra and auditory evoked potentials in schizophrenic and normal subjects. Neuropsychobiology 18:205–211

Michie PT, Fox AM, Ward PB, Catts SV, McConaghy N (1990) ERP indices of selective attention and cortical lateralization in schizophrenia. Psychophysiology 27:209–227

Näätänen R, Picton TW (1987) The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Int J Psychophysiol 24:375–425

Overall JE (1972) The brief psychiatric rating scale in psychopharmacology research. Psychometric Laboratory Reports 29, University of Texas, Galveston

Pfefferbaum A, Roth WT, Tinklenberg JR, Rosenbloom MS, Kopell BS (1979) The efffects of alcohol and meperidine on auditory evoked potentials. Drug Alcohol Depend 4:371–380

Pfefferbaum A, Horvath TB, Roth WT, Tinklenberg JR, Kopell BS (1980) Auditory brain stem and cortical evoked potentials in schizophrenia. Biol Psychiatry 15:209–223

Pfefferbaum A, Wenegrat BG, Ford JM, Roth WT, Kopell BS (1984) Clinical application of the P3 component of event-related potentials. II. Dementia, depression, and schizophrenia. Electroencephalogr Clin Neurophysiol 59:104–124

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

Picton TW, Hillyard SA (1974) Human auditory evoked potentials. II. Effects of attention. Electroencephalogr Clin Neurophysiol 36:191–199

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

Roth WT, Goodale J, Pfefferbaum A (1991) Auditory event-related potentials and electrodermal activity in medicated and unmedicated schizophrenics. Biol Psychiatry 29:585–599

Roth WT, Horvath TB, Pfefferbaum A, Kopell BS (1980) Event-related potentials in schizophrenics. Electroencephalogr Clin Neurophysiol 48:127–139

Roth WT, Pfefferbaum A, Kelly AF, Berger PA, Kopell BS (1981) Auditory event-related potentials in schizophrenia and depression. Psychiatry Res 4:199–212

Sandman CA, Gerner R, O'Halloran JP, Isenhart R (1987) Event-related potentials and item recognition in depressed, schizophrenic and alcoholic patients. Int J Psychophysiol 5:215–225

Schlör KH, Moises HW, Haas S, Rieger H (1985) Schizophrenia, psychoticism, neuroleptics, and audiotry evoked potentials. Pharmacopsychiatry 18:293–296

Shagass C, Straumanis JJ, Roemer RA, Amadeo M (1977) Evoked potentials of schizophrenics in several sensory modalities. Biol Psychiatry 12:221–235

Shagass C, Roemer RA, Straumanis JJ, Amadeo M (1978) Evoked potential correlates of psychosis. Biol Psychiatry 13: 163–184

Wolpaw JR, Penry JK (1975) A temporal component of the auditory evoked response. Electroencephalogr Clin Neurophysiol 39:609–620