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A Confirmatory Study on the Mechanisms Behind Reduced P300 Waves in Depression

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A single-trial analysis of event-related potentials (P300) of 21 depressives was performed in comparison with matched controls. The purpose was to confirm previous results revealing an overall reduction of the single-trial P300 amplitude in depression despite fewer elicited single-trial P300 waves in schizophrenics. The result of the present study is in line with our previous investigation implicating a general reduced P300 amplitude on single trials of depressive patients. Therefore, it appears possible to differentiate depressives and schizophrenics by measuring event-related potentials and applying a single-trial analysis of them.
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INTRODUCTION

It is a well-known phenomenon that there are manifest alterations of the P300 potential in several psychiatric disorders. Both schizophrenic and depressive patients present a significant reduction of P300 amplitude. Especially for schizophrenics this could be confirmed in several investigations (Roth *et al*, 1980a, b; Brecher and Begleiter, 1983; Pfefferbaum *et al*, 1984; Ford *et al*, 1994). For depressives, the majority of studies also report a reduced P300 amplitude (Roth *et al*, 1981; Pfefferbaum *et al*, 1984; Diner *et al*, 1985; Blackwood *et al*, 1987; Gandaghar *et al*, 1993).

These alterations are found in averaged signals and do not give any information about alterations of event-related activity in single trials. In two recent studies (Röschke *et al*, 1996a, c), a new method of single-trial analysis of event-related potentials based on signal detection theory (Banks, 1970) was proposed. In a defined time window, the maximum positive deflections were measured in digitally filtered single trials separately for target and nontarget conditions. The results of an exploratory study revealed a reduction of the single-trial P300 amplitude in depressives and a combination of amplitude reduction along with fewer elicited single-trial P300 waves in schizophrenia (Röschke *et al*, 1996c).

In the present paper, we describe the investigations of a new sample of depressive inpatients using the same experimental setup and identical analyzing methods as in the former studies (Röschke *et al*, 1996a–c). Based on these previous findings, we tested the hypothesis that depressives depict smaller P300 amplitudes in their single evoked responses than control subjects.

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METHODS

Subjects

We investigated 21 patients suffering from a major depressive episode according to the DSM-III-R criteria who did not take an antidepressant medication for at least 4 weeks before admission (13 females, eight males; mean age = 39 years, SD = 11.9 years) and compared with healthy controls ($n = 21$) matched in gender and age (mean age = 38.1 years, SD = 12.4 years).

Diagnosis was confirmed according to the DSM-III-R criteria by the consensus of two experienced senior psychiatrists. Exclusion criteria were psychiatric comorbidity (eg addictive diseases), hearing deficits, any psychotropic medication in the last three months before admission and any serious physical illness. Written consent was obtained from all participants. The experiment was performed on the first day after the patients' admissions, between 10 am and noon. During ERP recording the subjects were instructed to close their eyes and to count the infrequent stimuli as well as to press a button in response to them.

Experimental Design

The experimental paradigm consisted of 300 stimuli with 90% nontarget (1500 Hz sine wave tone) and 10% target stimuli (2000 Hz). The intensity of both stimuli was 80 dB SPL with a duration of 500 ms. Stimuli were presented randomly in a constant sequence across subjects. The interstimulus intervals were randomly distributed between

1.0 and 1.5 s. The sequence of pauses between stimuli were fixed across subjects. The electroencephalogram was recorded from Cz and Pz. A2 served as the reference electrode. Additionally, both horizontal EOG (between outer canthi of right and left eye) and vertical EOG (above and below the right eye) were recorded. Electrode impedances were all below 5 kΩ. Analogue recording band pass was 0.16 Hz (time constant = 1.0 s) to 70 Hz (3dB/Oct). For further analysis, the data were digitized with a sampling frequency of 1000 Hz (200 Hz low-pass filter 48 dB/Oct; 1024 data points pre- and poststimulus).

P300 Measurement and Single-Trial Analysis

P300 was obtained by averaging all artifact-free ERPs (off-line rejection of trials showing a saturation of the ADC or EOG amplitude exceeding 75 μV) following target stimuli. There was no significant difference between counted and presented targets between groups. Individual baseline was obtained by computing the prestimulus (1.024 s) DC component of each single trial. The P300 latency (t_{lat}) of the averaged ERPs was determined visually by a clinician who was blind for diagnosis and not engaged in the recruitment of the patients. Consecutively, each single trial was digitally filtered in the frequency range between 1 and 30 Hz (Basar, 1980; Basar and Stampfer, 1985; Basar-Eroglu *et al*, 1992, Röschke *et al*, 1996a, c). For target and nontarget conditions, identical time and frequency windows were used. A computer algorithm calculated the maximum positive deflection of each single trial within a time window $t_{lat}-50\,ms \leqslant t_{lat} \leqslant t_{lat}+50\,ms$. From the distribution of the positive deflections' amplitudes of the targets and non-targets around t_{lat}, we calculated the corresponding density functions by dividing the interval ranging from −5 to 31 μV into 18 bins ($x\,\mu V$, $x+2\,\mu V$). After applying a moving average procedure, we obtained two overlapping density functions for each subject that revealed an individually defined point of intersection '*S*' (see Figure 1).

The point of intersection *S* served as an individual threshold for a given subject, enabling us to differentiate operationally whether a P300 was elicited or not. Single-trial ERPs with an amplitude lower than *S* under target conditions were considered as 'false negative' and potentials with an amplitude greater than *S* under nontarget conditions were considered as 'false positive' responses and so on.

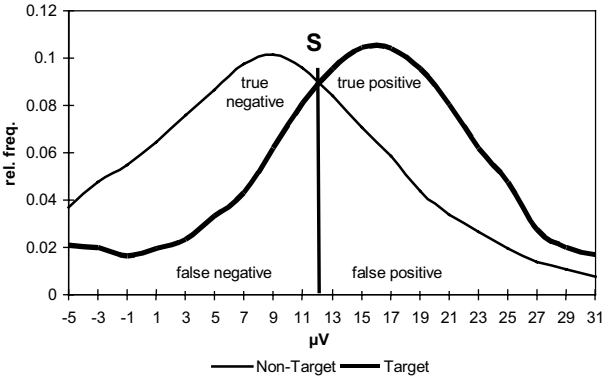

Figure 1 P300 amplitude distributions of target and nontarget single trials for a single subject. The point of intersection 'S' marks the point of discrimination between presence or absence of a P300 wave in single trials.

We averaged separately all single trials that were classified as 'true positives', 'false positives', or 'false negatives' as mentioned above. For the averaged potentials, we estimated the P300 amplitude relative to the DC component of the prestimulus baseline.

Statistics

Normal distribution of the data was demonstrated with the Shapiro–Wilk W-test. The numbers and the magnitudes of 'true' and 'false positive' responses were subjected to an analysis of variance (ANOVA) with repeated measurement design. The factor 'group' (levels: patients and controls) was regarded as a 'between-subject' factor, whereas the lead position (levels: Cz and Pz) was regarded as a 'within-subject' factor. All statistics were performed according to the general linear model by standard software (SPSS™). A *p*-value of <0.05 was regarded as statistically significant.

RESULTS

Figure 2 presents the results of the depressives *vs* matched controls.

The depressives revealed a small, nonsignificant decrease in the *number of true positive responses* when compared to their matched controls ($F1,40 = 2.98$; $p = 0.092$). In the same way no clear difference was found concerning the *number of false positive responses* ($F1,40 = 1.34$; $p = 0.255$). In both cases, the interaction 'group × lead position' ($F1,40 = 0.03$; $p = 0.871$ for true positive responses and $F1,40 = 1.46$; $p = 0.234$ for false positive responses) was not significant.

There was a marked effect observable in the *mean amplitudes of true positive responses* ($F1,40 = 12.20$; $p = 0.001$). The amplitudes of *false positive responses* appeared markedly reduced in depressives compared to their controls. ($F1,40 = 8.22$; $p = 0.007$). The depressive patients showed significantly smaller mean amplitudes in the averaged signals for both categories without exhibiting a significant interaction 'group × lead position' ($F1,40 = 0.30$, $p = 0.589$ for true positive responses; $F1,40 = 0.17$, $p = 0.681$ for false positive responses).

DISCUSSION

The present investigation was performed in order to replicate the findings concerning different functional mechanisms underlying the reduced P300 in depressives and schizophrenics (Röschke *et al*, 1996c), which has been reported for the averaged signals in previous studies (Roth *et al*, 1980a, b, 1981; Brecher and Begleiter, 1983; Pfefferbaum *et al*, 1984; Diner *et al*, 1985; Blackwood *et al*, 1987; Gandaghar *et al*, 1993). In a former study, we reported the replication of a reduced number of 'true positive' P300 waves in schizophrenics (Wagner *et al*, 2000).

In accordance with these previous findings (Röschke *et al*, 1996c), we found a statistically significant reduction of the averaged P300 amplitude for both depressives and schizophrenics compared to healthy controls. Concerning

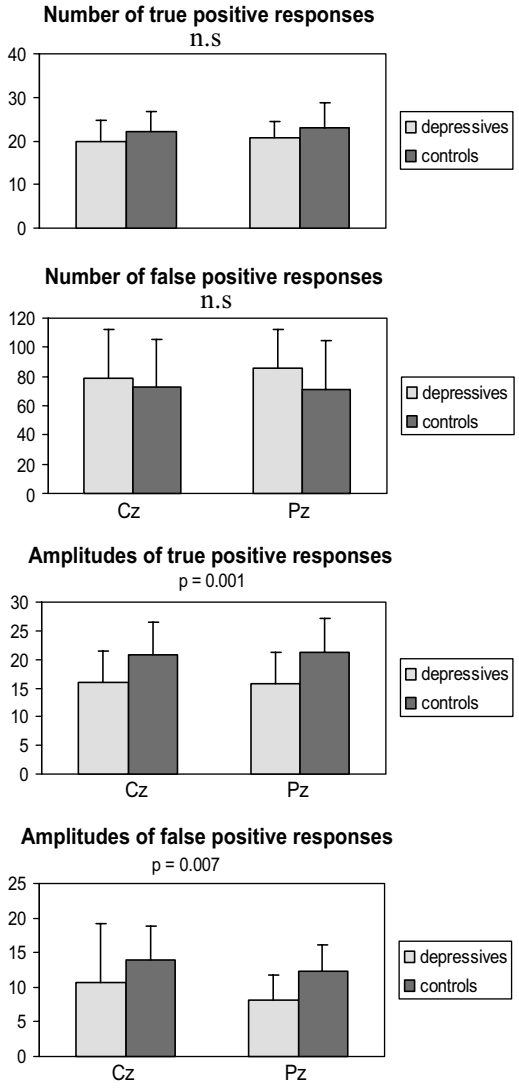

Figure 2 Number and amplitudes of true and false positive and negative responses for depressives (*vs* matched controls; $n = 21$).

single-trial analysis the following results could be confirmed:

a. Depressive patients revealed smaller P300 amplitude responses both in the category of 'true positive' and 'false positive' reactions when compared to matched controls. Depressives did not differ in the number of responses.
b. Schizophrenics depicted a significant decrease in the number of 'true positive' responses. Moreover, the magnitude of 'true positive' responses was nonsignificantly reduced, whereas 'false positive' responses did not differ from controls concerning amplitudes (Wagner *et al*, 2000).

The clearest difference between schizophrenics and depressives occurred in the amplitudes of false positive responses where depressives exhibited an impressive decrement compared to their controls (which was not the case for schizophrenics). Taken together, the single-trial analysis of event-related potentials enabled a differentiation between depressives and schizophrenics in terms of single-trial P300 waves. This differentiation could not be achieved regarding the averaged P300 potential being the common standard in investigations of event-related processes. Here 'grand average P300 ERPs' showed reduced P300 amplitudes in the classical analysis without significant differences between the groups.

Up to now, it is an open question if (and how) these P300 alterations are correlated to psychopathology. There is some evidence reported in the literature that brain function of schizophrenic patients shows an increased variability and instability (Anderson *et al*, 1995) possibly leading to a reduced attentiveness to external stimuli (Wagner *et al*, 1996). Increased variability of central nervous processes are in accordance with the finding of seldom-elicited P300 waves in single trials of schizophrenics. This could be interpreted as attentional deficits in schizophrenics.

For depressive patients, the generalized attenuation of single-trial P300 amplitude might be an electrophysiological equivalent to cognitive impairments indicating a lack of available resources. It is interesting to notice that even for 'false positive' responses, that is, when irrelevant stimuli were presented, depressives elicited smaller amplitudes in their electrophysiological responses which was opposite in schizophrenics. In conclusion, it might be briefly stated that information processing in schizophrenics is mainly disturbed by misallocation of resources and attentional deficits, whereas in depressives a general deficit of resources—regardless of relevance of stimuli—is observed.

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