

PSYCHOLOGICAL MANIPULATION OF P300 AMPLITUDE
ABNORMALITIES IN SCHIZOPHRENICS :
RECONFIRMATION AND EXTENSION OF OUR PREVIOUS RESULT #

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INTRODUCTION

Efforts to ameliorate the psychological and psychophysiological abnormalities in schizophrenic patients through psychological intervention are quite intriguing and may prove to be therapeutically valuable in aiding schizophrenic patients. For example, Holzman et al.6) reported saccadic movements in eye-tracking tasks were reduced by altering verbal instructions. Kashima et al.7) and Goldberg et al.4) reported that poor performance levels on the Wisconsin Card Sorting Test were ameliorated by employing a verbal coaching-procedure. So far, however, there has been no study reported that has addressed the issue of whether psychological intervention can influence P300 abnormalities in schizophrenia, although P300 amplitude reduction has been widely found in schizophrenic patients.

In a previous preliminary study (Fukuda et al.3)), we investigated the possible effects of psychological intervention upon P300 in schizophrenic patients by coaching schizophrenic subjects while they were engaged in performing rather difficult auditory target-detection tasks. Results of the study indicated that psychological intervention can partly enhance reduced P300-amplitudes as well as improve performance level in schizophrenics. Here, we report an expanded study with more subjects and more detailed analyses.

SUBJECTS

The subjects consisted of fourteen medicated DSM-III schizophrenic outpatients (10 males, 4 females). The age of the

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patients ranged from 25 to 60 years (mean age : 33.9 years). Their scaled-expanded BPRS 1) scores were distributed within a range from 4 to 23 (mean score :13.6).

METHOD

We employed a three-tone discrimination task for the P300-evoking paradigm, which consisted of a series of 200 tone bursts of 150 msec duration delivered at 2 sec intervals. The series included tones at 950Hz, 1000 Hz, and 1053 Hz in random sequence. The 1000 Hz tone occurred with a probability of 0.66, and each of the 950 Hz and 1053 Hz tones with one of 0.17. Tones were delivered at 50 dB SL binaurally through headphones.

Subjects went through six sessions. In all the sessions, the subjects were required to press a lever upon detecting the targets as accurately and quickly as possible. The target tone was one of the two infrequent tones, and it was not changed during any of the six sessions for each subject. However, one of the infrequent tones was the target for half of the group, and the other infrequent tone was the target tone for the other half of the group.

In the third and fourth sessions, a buzzer ("coaching buzzer") was sounded about 1100 msec after each designated target tone, indicating the occurrence of the target tone (the "intervention" sessions). Coaching-buzzer sounds were delivered after recording the EEG-segments for averaging as well as measuring reaction-times to the target tones. Therefore, delivery of the buzzer sounds had no influence on EEGs, performance levels, or reaction times.

EEGs were derived from the Pz region with Ag/AgCl electrodes referenced to linked earlobe electrodes (with a band-pass filter of 0.15-300 Hz). Trials in which EEG-amplitudes exceeded 100 μ V were automatically rejected from the averaging. EEG data were then digitized on-line with a sampling frequency of 500 Hz, from 128 msec preceding stimulus-onset to 896 msec post-stimulus. Each type of stimulus was averaged separately. Data with incorrect responses (omission errors or commission errors) were rejected in the averaging. These averaged waveforms were smoothed with a digital filter (moving-average method; width of data window, 50 points) to minimize any alpha activity in the record. The baseline was determined as the mean voltage over the 128 msec period before the stimulus onset.

RESULTS

Data were analyzed in the following two ways. First, the data for all the subjects were analyzed as a whole; and secondly, analyses were conducted separately in the two patient sub-groups obtained after breaking them down into groups based on the P300-amplitudes in the first and second sessions.

The six sessions were divided into three blocks. We designated the block of the first and second sessions as the "before intervention" block, the third and fourth sessions as the "during intervention" block, and the fifth and sixth sessions as the "after intervention" block. We then compared the "before", "during" and "after" data.

(1) Results of data analyses for all the subjects as a whole

Table 1 and Figure 1 show the results obtained through the analyses for all the subjects as a whole. As shown in Table 1, the reaction times tended to be shortened in the "during intervention" blocks as compared to the "before intervention" block; however, the performance levels showed no significant difference among the three blocks.

In the upper half of Figure 1, two comparisons of the grand-averaged ERP waveforms for the target stimuli derived from the Pz region in the three blocks are shown, each comparing two waveforms out of the three; and the lower half of the figures demonstrate the results of the paired t-test between the corresponding two waveforms. The paired t-tests revealed no significant difference in these ERP waveforms.

(2) Results of separate analyses in the two sub-groups

We determined the subgroups by dividing the subjects according to whether the P300-peak amplitude exceeded 5uV in the first and second sessions. The group of subjects with P300 amplitudes of greater than 5 uV was designated as the "larger P300-amplitude group", with the other group of less than 5 uV being designated as the "smaller P300-amplitude group". The smaller P300-amplitude group consisted of six patients and the larger P300-amplitude group of eight patients.

In the smaller P300-amplitude group, performance levels tended to be improved in the "after intervention" blocks, and reaction times tended to be shortened in the "during intervention" block as compared to the "before intervention" block (Table 2). Furthermore, P300 amplitudes increased significantly in the "during intervention" block (peak amplitude 4.4uV) compared to the "before intervention" block (peak amplitude 1.6uV), and was sustained in the "after intervention" block (peak amplitude 3.9uV) (Figure 2). Four subjects of this sub-group reported that they felt to be the task easier in the "during and after intervention" blocks than in the "before intervention" block, and two reported no subjective change.

In the larger P300-amplitude group, no significant difference was found in either the performance levels or the reaction times in the comparisons among the "before", "during" and "after" intervention blocks (Table 3). However, the P300 amplitudes decreased significantly in both the "during" and "after" intervention blocks (peak amplitude : 5.2uV, 6.0uV,

respectively) over the "before intervention" block (peak amplitude : 9.1uV) (Figure 3). Concerning the subjective difficulties of the task, two out of eight subjects reported that the subjective task difficulties increased in the "during" and "after" intervention blocks, four reported no subjective change, and two reported feeling easier.

Sub-group comparisons between the smaller and larger P300-amplitude groups demonstrated no significant differences in performance levels on reaction times for the "before", "during", and "after" intervention blocks.

DISCUSSION

Summarizing the results obtained in this study, it was found that a psychological intervention (coaching by means of sounding buzzers to help subjects perform an auditory discrimination task) was effective in augmenting P300 amplitudes of schizophrenic patients. The effects, however, proved to differ among subjects depending upon their original P300 amplitudes. Coaching was effective in augmenting P300s and improving performance levels in the originally smaller P300-amplitude subjects; on the other hand, coaching produced a P300 reduction in the originally larger P300-amplitude subjects. These changes in the P300s were almost consistent with the changes in task-difficulty judgments subjectively reported by the patients. Summing up the changes in the two sub-groups, the analyses of all the subjects as a whole revealed no significant changes before and after the intervention.

It could be inferred that the observed P300 amplitude changes were not specific changes brought about by "coaching" but rather non-specific changes caused by changing the arousal level of the subjects. Other researchers using alcohol (Hasama 5)) and sulphiride (Ogura et al. 9)) have obtained similar results in inducing changes in P300 amplitude in normal subjects. They noted that through drug administration P300 amplitude increased in subjects who showed low amplitudes; whereas P300 amplitude decreased in high P300 amplitude subjects. They speculated that arousal level changes played an important role in these changes. Three lines of evidence, however, demonstrate that the observed P300 amplitude changes in the present study are not solely due to changes in arousal level.

First, we discovered that by comparing the ERP waveforms session by session rather than block by block, the timing of the amplitude change between the two P300 subgroups was different (Figure 4, upper half). In the smaller P300-amplitude group, only the comparison between the third and fourth sessions showed a significant P300-amplitude change. In other words, this change occurred during the latter half of the intervention period. However, in the larger P300-amplitude group the change occurred only between the second and third sessions, during the first half of the intervention period. Moreover, superimposed individual

ERP waveforms show that the observed P300-amplitude changes were not due to noticeable changes in only a few subjects, but due to changes in most subjects (Figure 4, lower half).

Second, we found that the P300s elicited by non-target infrequent tones also changed in the course of the intervention, with the pattern of this change differing between the two subgroups. In the larger P300-amplitude group, a P300-amplitude reduction was observed for infrequent non-targets (Figure 5); however, in the smaller P300-amplitude group, no significant amplitude change was observed for infrequent non-targets (Figure 6). Thus, the smaller P300-amplitude group displayed an amplitude increase for target tones but no change for non-target tones; while the larger P300-amplitude groups showed decreases for both target tones and non-target tones.

Third, we examined eight normal subjects and found no significant P300 amplitude changes when the group was analyzed as a whole (Figure 7) as well as when it was broken into two groups based on the subjects' original P300 amplitudes.

P300 amplitude reduction is a widely found electrophysiological abnormality in schizophrenia. Recently, however, some researchers have reported that, as clinical symptoms improve with antipsychotic drug medication, P300 amplitudes increase to some degree. Matsubayashi et al.6) reported that P300-amplitude increase was observed in patients whose symptoms had been improved with medication. Duncan et al.2) also reported similar results. These studies suggest that P300 amplitudes vary somewhat due to therapeutic modifications rather than remain unchanged in the same schizophrenic subjects when repeatedly measured. The results of the present study suggest that P300 amplitudes in schizophrenic patients can be influenced not only through antipsychotic medication but also through psychological intervention. However, this does not mean that P300 amplitude reduction in schizophrenia is "normalized." It should be noted that, first, P300 amplitudes in the "during and after intervention" blocks in the smaller P300-amplitude subgroup were much less than, for example, those of the larger P300-amplitude subgroup in the "before intervention" block. Second, a P300-amplitude increase was observed in some of the subjects.

Although the authors of this report investigated possible differences in clinical characteristics including symptoms and behavior patterns between the smaller and larger P300-amplitude sub-groups, so far they have not found any differences in clinical characteristics between the two sub-groups. It can be speculated that the difference in P300 responses to the intervention employed in this study might be related to different responses to actual clinical psychological interventions (psychotherapy, behavior therapy, cognitive-behavioral therapy).

Reproduction of the results obtained here will enhance the clinical utility of P300 measurements, which it may have value in

the choice of psychological and behavioral therapeutic approaches and in the assessment of the efficacy of a particular treatment. Moreover, they may shed further light on the role brain mechanisms play in effective psychological and behavioral treatments.

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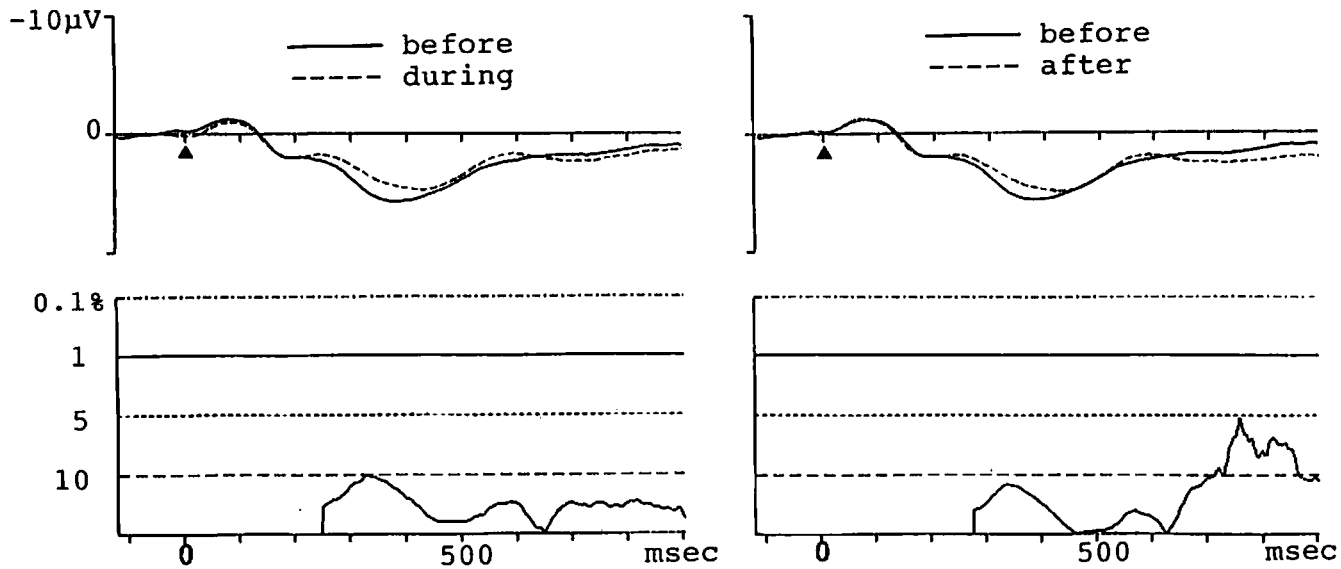


Figure 1

ERP waveforms and results of paired t-tests for all the subjects as a whole. The upper half of the figure shows comparisons of the grand-averaged ERP waveforms for the target stimuli derived from the Pz region in the three blocks, each comparing two waveforms out of the three. The lower half shows the results of the paired t-test between the corresponding two waveforms.

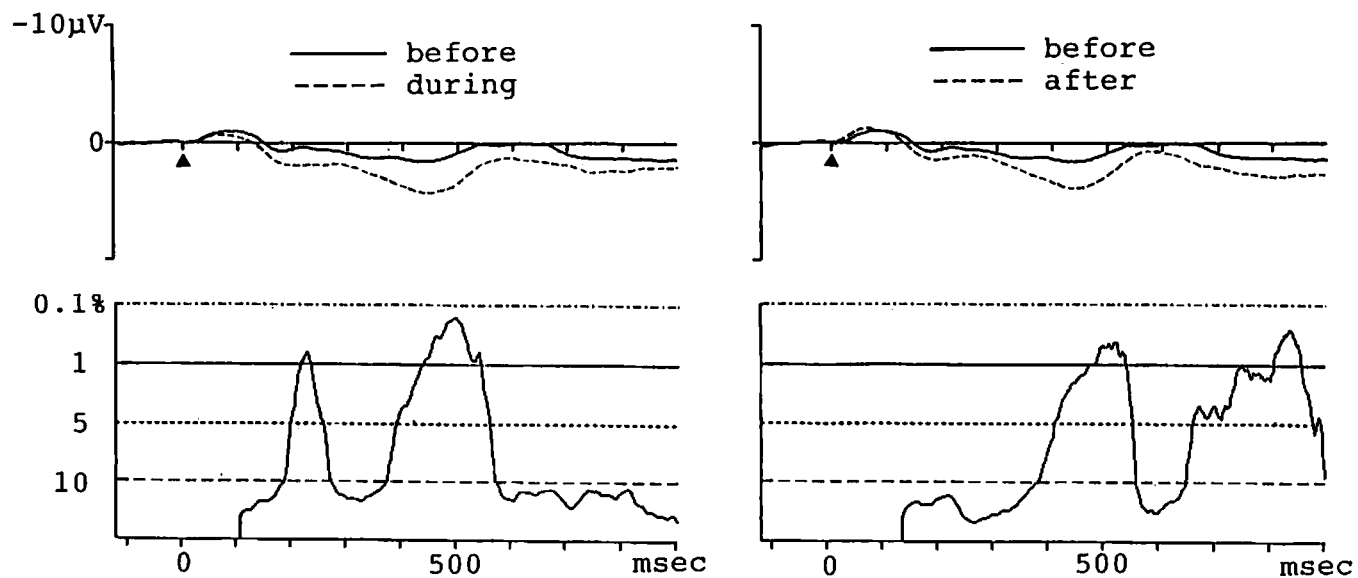


Figure 2

ERP waveforms for the target stimuli and results of paired t-tests for the smaller P300-amplitude group as given in figure 1.

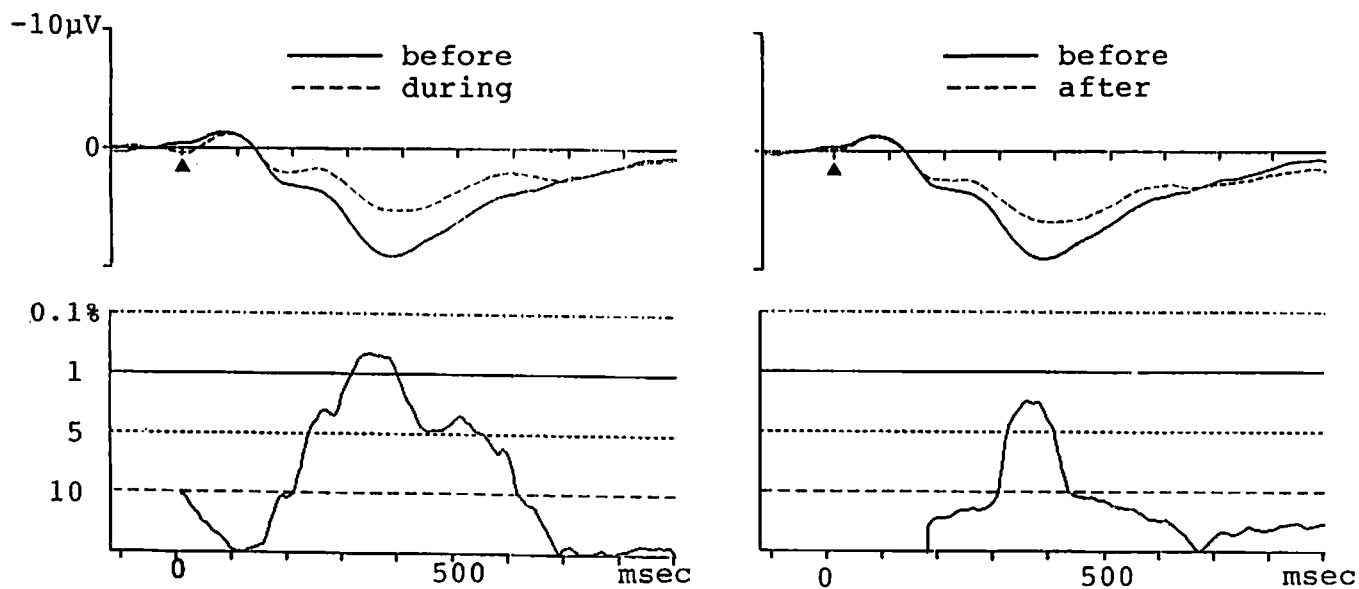


Figure 3

ERP waveforms for the target stimuli and results of paired t-tests for the larger P300-amplitude group as given in figure 1.

SMALL P300 GROUP

LARGE P300 GROUP

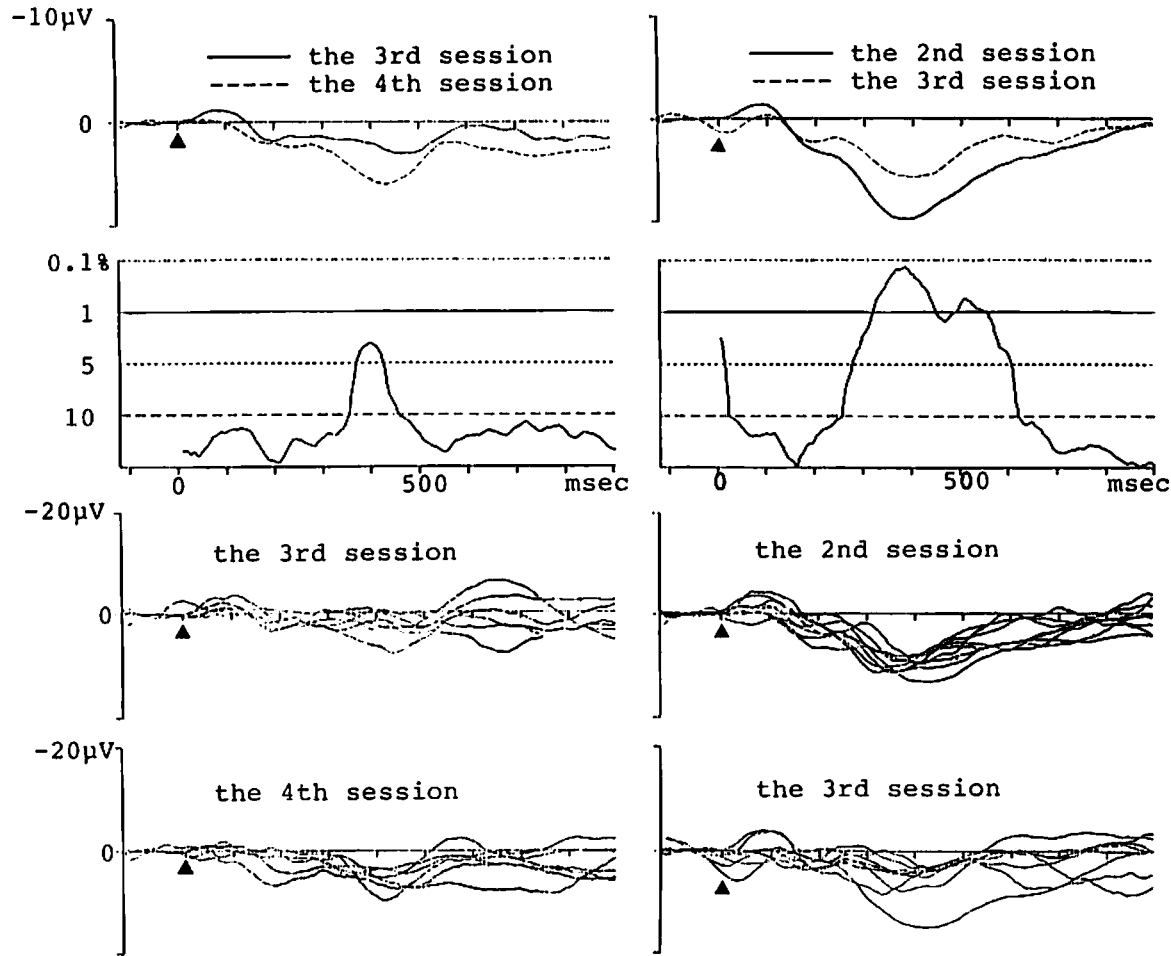


Figure 4

ERP waveforms for the target stimuli and results of paired t-tests for the smaller and the larger P300-amplitude group (session by session analyses). Upper half : same as figure 1. Lower half : superimposed individual ERP waveforms.

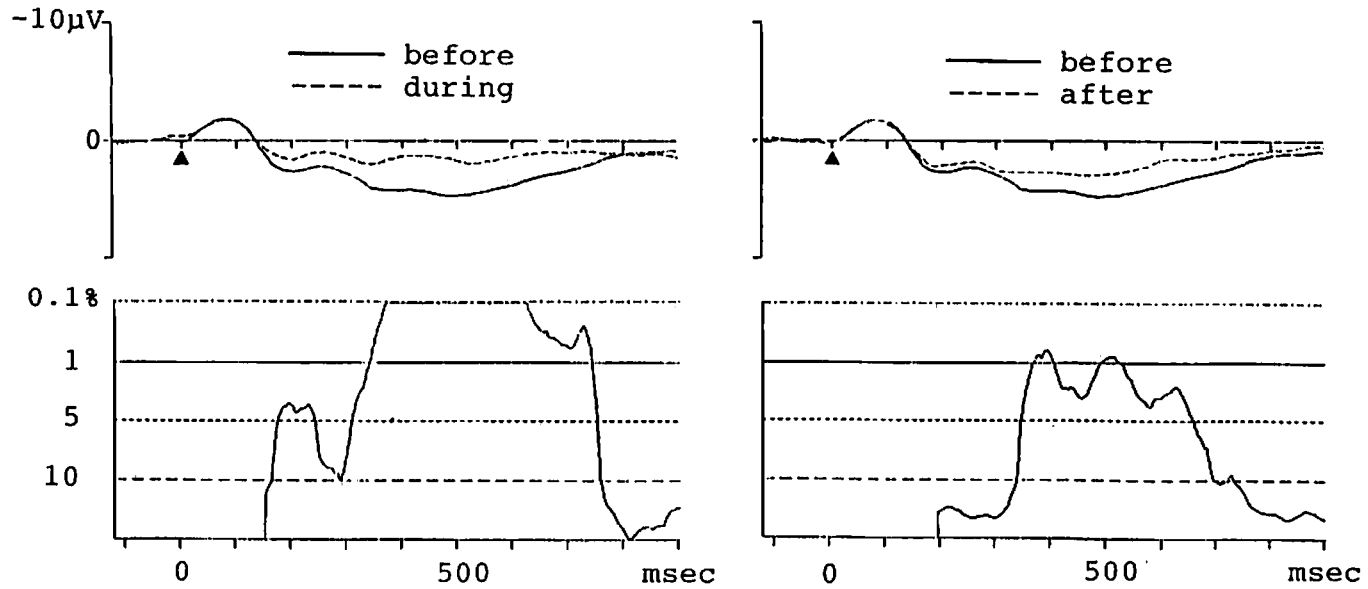


Figure 5

ERP waveforms for the infrequent non-target stimuli and results of the paired t-test for the larger P300-amplitude group. Detailed explanation is same as given in figure 1.

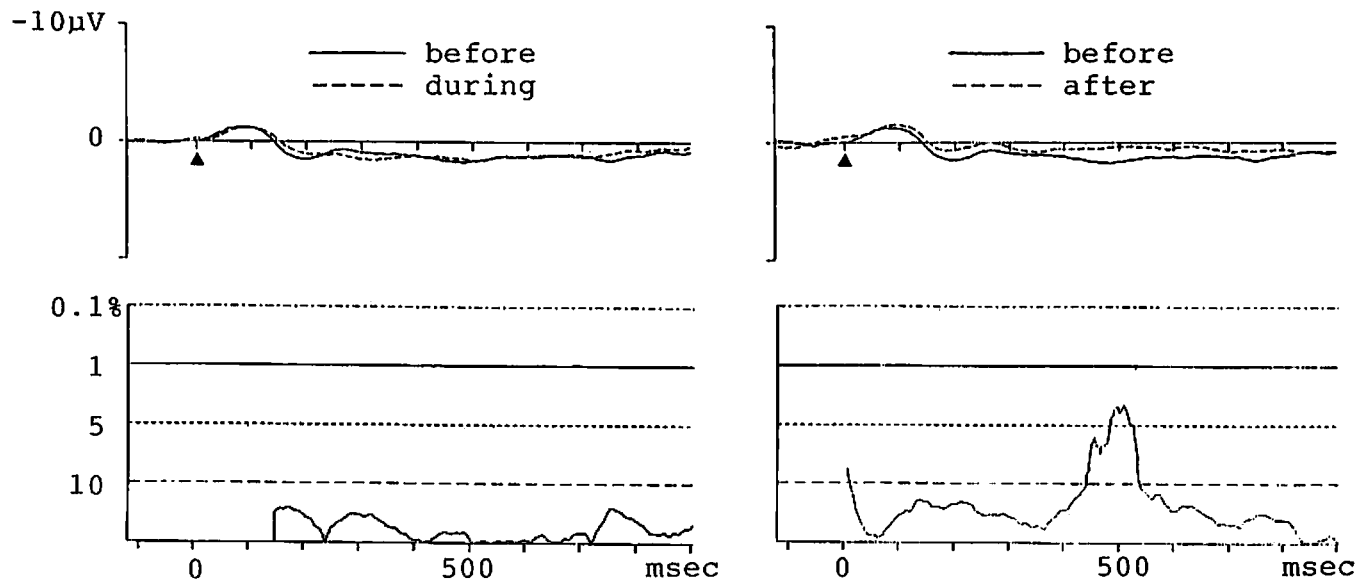


Figure 6

ERP waveforms for the infrequent non-target stimuli and results of the paired t-tests for the smaller P300-amplitude group as given in figure 1.

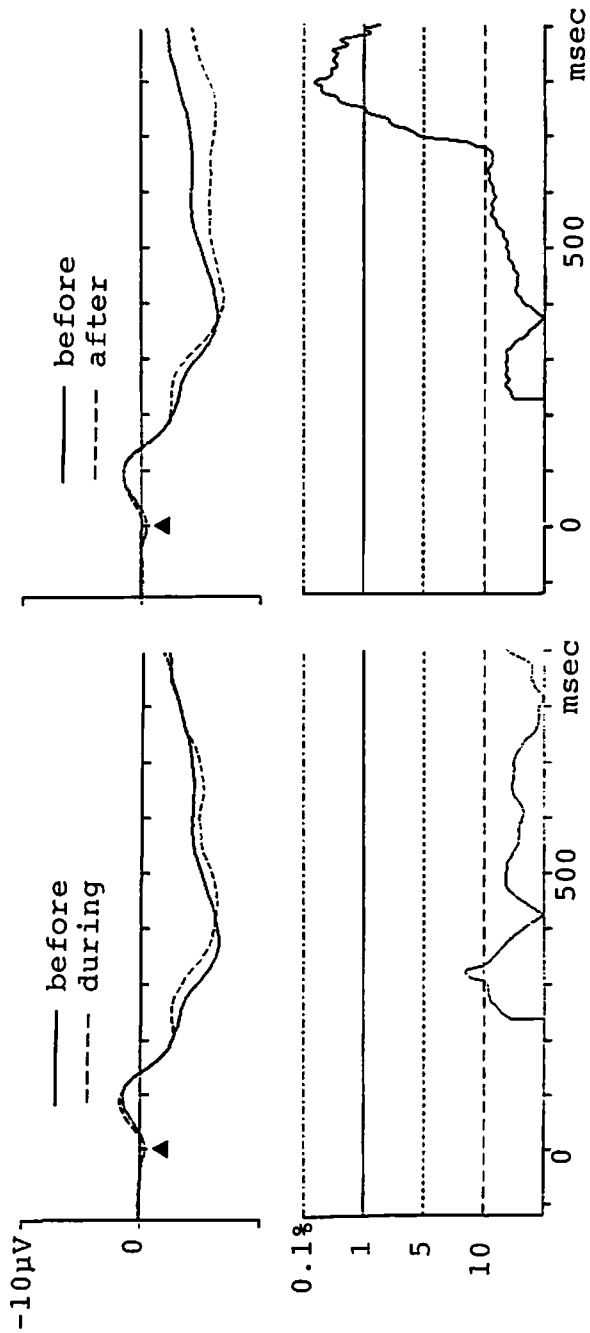


Figure 7

ERP waveforms for the target stimuli and results of the paired t-tests for normal controls as given in figure 1.

Table 1 Behavioral data for all the schizophrenics as a whole

	hit rate (%)	reaction time (msec)
before coaching	64.1 ± 21.5	628 ± 96
during coaching	67.2 ± 21.2	601 ± 86
after coaching	69.1 ± 23.1	622 ± 89

* : p < 0.1

Table 2 Behavioral data for the smaller P300-amplitude group

	hit rate (%)	reaction time (msec)
before coaching	60.3 ± 23.8	657 ± 54
during coaching	65.0 ± 19.4 *	628 ± 43
after coaching	70.6 ± 22.0	629 ± 61

* : p < 0.1

Table 3 Behavioral data for the larger P300-amplitude group

	hit rate (%)	reaction time (msec)
before coaching	67.1 ± 19.9	606 ± 115
during coaching	68.9 ± 22.9	580 ± 105
after coaching	68.0 ± 24.6	616 ± 107

* : p < 0.1

Table 4 Behavioral data for normal controls

	hit rate (%)	reaction time (msec)
before coaching	87.3 ± 9.3	548 ± 56
during coaching	92.6 ± 5.9 **	580 ± 54 *
after coaching	89.9 ± 7.7	580 ± 73 **

* : p < 0.1 ** : p < 0.05