Enhancement of Behavior and P3 Amplitude of Event-Related Potentials in Schizophrenia Following Feedback Training

フィードバック訓練を用いた精神分裂病における行動障害・事象関連電位P３成分振幅増強の改善の試み

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フィードバック訓練を用いた精神分裂病における行動障害・事象関連電位Ｐ３成分振幅減衰の改善の試み

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INTRODUCTION

Schizophrenia

Schizophrenia is one of the most common psychiatric disorders. Its prevalence is estimated to be as high as 0.5–1.5% in the general population, and it severely interferes with the daily and social lives of patients. Many patients suffer hallucinations and delusions, and schizophrenia affects more than three-fourths of inpatients in psychiatric hospitals in Japan. Schizophrenia is a problem not only for the patients and their families but also for society in general because the treatment and social costs of schizophrenia are estimated to be 33 billion dollars per year in the United States, for example: 18 billion dollars for direct costs and 17 billion dollars for indirect costs (The National Advisory Mental Health Council 1993).

The signs and symptoms of schizophrenia cover many domains of higher brain function such as sensation, cognition, thinking, language, affect and motivation. Antipsychotic drugs are effective in reducing hallucinations and delusions, and their introduction into clinical treatment has greatly improved the ability of patients to function normally in society. However, antipsychotic drugs are not fully effective in eliminating so-called positive symptoms such as hallucinations and delusions and moreover are generally ineffective for many symptoms of cognition, affect and motivation, the so-called negative symptoms. Hence, the negative symptoms are mainly treated in clinical settings not with antipsychotic drugs but by nonpharmacological procedures, which include psychotherapy, behavioral therapy, and cognitive therapy.

Although brain mechanism underlying the effectiveness of antipsychotic drugs has been attributed to their antagonism of D_2 dopamine receptors, brain mechanisms underlying the effectiveness of the nonpharmacological treatments have not been intensively investigated and hence have not yet been clarified. The effects of nonpharmacological treatment on schizophrenic patients are usually explained in terms of psychological or behavioral aspects but not of brain mechanisms. Elucidation of such brain mechanisms would be important for the improvement of nonpharmacological treatment methods and the improvement in therapeutic assessment of nonpharmacological treatment.

Event-related potential (ERP)

Event-related potentials (ERPs) are scalp recorded potentials which reflect cognitive aspects of information processing in the brain. Brain potentials occurring within 100msec following stimulus onset are generally called "evoked potentials" and are assumed to reflect sensory information processing in the brain, whereas potentials appearing after 100msec following stimulus onset are ERPs and reflect more complex information processing. ERPs include several components, each of which corresponds to a specific psychological function: contingent negative variation (CNV) to expectation (Walter et al. 1964), movement-related potential to motor preparation (Gliden et al. 1965), P3 to cognition (Sutton et al. 1965), and negative difference (Nd) to selective attention (Davis 1964).

Among these components P3 has been investigated intensively in psychiatric disorders because its amplitude and latency vary with cognitive dysfunction. For example, in normal subjects P3 latency decreases with age before adolescence is reached (Mullis et al. 1985) and increases with age in adulthood (Goodin et al. 1978; Polich et al. 1985). P3 latency is markedly prolonged in demented patients (Goodin et al. 1978). The observed prolongation of P3 latency is interpreted as indicating the slowing of information processing in the brain in infants, the aged and demented subjects. The P3 component has also been investigated in schizophrenic subjects, and its amplitude reduction has been one of the most consistently observed findings as described below.

ERP study in schizophrenia

The most consistently reported finding regarding ERPs in schizophrenia is abnormality of the P3 component. Reduction of P3 amplitude has been observed especially in auditory tasks (Pritchard 1986; Pfefferbaum et al. 1989) and prominently in the tasks where normal control subjects show larger P3 amplitude (Brecher et al. 1987), and P3 amplitude reduction has been replicated irrespective of task type used. The findings are consistently observed for both acute and chronic patients (Blackwood et al. 1987; Eikmeier et al. 1992), and for patients receiving and not receiving medication (Pfefferbaum et al. 1989; Ford et al. 1994) irrespective of their schizophrenia subtype (St. Clair et al. 1989). Some researchers reported that P3 amplitude reduction was most prominent in the left temporal regions (Faux et al. 1988, 1990).

P3 amplitude reduction is interpreted as "a trait marker" of schizophrenia because it has been observed in patients' siblings (Saitoh et al. 1984; Steinhauer et al. 1991) and other relatives (Kidogami et al. 1992), in children at high risk of developing schizophrenia (Friedman et al. 1982; Schreiber et al. 1992), and in normal subjects with thought disorders of the schizophrenic type (Ward et al. 1992). The relationships between P3 amplitude and clinical psychiatric symptoms are unclear, because coefficients of correlation between them are significant in some but are nonsignificant in other studies, and longitudinal studies comparing the subjects before and after antipsychotic medication also yielded inconsistent results (Blackwood et al. 1987; Duncan et al. 1987). Hence, P3 amplitude reduction in schizophrenia is assumed to reflect cognitive dysfunction of schizophrenia which is stable across clinical status and underlies vulnerability to schizophrenia. Prolongation of P3 latency has been reported to occur in schizophrenia but less consistently than reduction of P3 amplitude (Blackwood et al. 1990) and is also interpreted as a trait marker of schizophrenia.

Remediability of schizophrenic deficit

Schizophrenic patients have been demonstrated to show abnormally deteriorated performance in a variety of psychological and psychophysiological experiments (Steinhauer et al. 1991). Some of these findings, called "state markers", are observed only in patients with psychotic exacerbation and vary with psychiatric symptom amelioration by antipsychotic drug medication. Other findings, called "trait markers" are observed consistently irrespective of psychiatric status (Nuechterlein & Dawson 1984; Dawson & Nuechterlein 1984; Spring et al. 1990; Spring 1992), and include increased saccadic movements in eye-tracking tasks (Holzman 1991), poor performance in the Wisconsin Card Sorting Test (Goldberg & Seidman 1989), and deficits in other neuropsychological test performances (Goldberg & Weinberger 1986; Goldstein 1991).

Recently, however, several studies in schizophrenic patients revealed some remediation of the deficits in these trait markers by nonpharmacological intervention. The frequency of saccadic movements in eye-tracking tasks was decreased by altering verbal instructions or target characteristics (Holzman et al. 1976; Shagass et al. 1976; Levin et al. 1981; Levin 1984), performance in the Wisconsin Card Sorting Test was improved using a verbal coaching procedure and/or by providing reinforcement (Kashima et al. 1987; Goldberg et al. 1987;

Bellack et al. 1990; Green et al. 1992; Delahunty et al. 1993; Vollema et al. 1995; Young & Freyslinger 1995; Bellack et al. 1996), and neuropsychological test performance was improved by cognitive training (Olbrich et al. 1990; Corrigan et al. 1995; Corrigan & Addis 1995; Tompkins et al. 1995), although all improvements were partial. Most of these studies were intended to clarify the basic mechanism of the effectiveness of rehabilitation, such as cognitive rehabilitation (Spaulding 1994), for schizophrenic patients and to help develop more effective treatment procedures.

As described in the preceding section, reduction of P3 amplitude in the ERPs, particularly in an auditory task, is assumed to be an electrophysiological trait marker of schizophrenia (Pritchard 1986; Ford et al. 1992). Although P3 amplitude reduction is generally considered to be observed consistently irrespective of the patients' psychiatric state at the ERP examination, partial remediation of P3 amplitude reduction in schizophrenia was demonstrated with improvement of psychotic symptoms by antipsychotic medication in some studies (Matsubayashi et al. 1984; Duncan 1988; Mintz et al. 1995). These findings suggest that P3 amplitude reduction in schizophrenia can be remediated by pharmacological treatment, although to a limited extent, and observed increases in P3 amplitude might reflect some change in the brain function due to pharmacological treatment.

To date, except for our preliminary report (Fukuda et al. 1989), no study has examined whether P3 amplitude reduction in schizophrenia can be remediated by nonpharmacological intervention in experimental settings. In our preliminary report, we investigated the effects of intensive training upon P3 amplitude in schizophrenics, and demonstrated partial remediation of P3 amplitude reduction in the grand averaged ERP waveforms and a moderate increase in the hit rate in some patients. The results suggested that some improvement had occurred in brain function as a result of the training at least in some patients, and hence provided empirical evidence that cognitive deficits in schizophrenia revealed by P3 amplitude reduction could be partially remediated by nonpharmacological intervention, as well as pharmacological treatment.

The preliminary study included many limitations: 1) only schizophrenic patients were included; 2) the subject number was only seven; and 3) P3 amplitude was analyzed in a grand averaged ERP waveform across all subjects. I expanded the study reported here so that more schizophrenic subjects were included, a comparison was made between schizophrenic and normal control subjects, and P3 amplitude was measured for individual subjects using peak

identification. The results obtained are presented and their implications on the biological basis for effective nonpharmacological treatment in schizophrenics will be discussed.

STUDY 1

Methods

Subjects

Fourteen schizophrenic subjects and twelve normal controls were included in the study. The schizophrenic group consisted of fourteen outpatients of the Tokyo University Hospital (10 males, 4 females). Their diagnoses were made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, the third edition revised (DSM-III-R; American Psychiatric Association 1987), and their subtypes were as follows: 10 residual type, 2 paranoid type, 1 disorganized type, and 1 undifferentiated type. The ages of the patients ranged from 25 to 60 years (mean 37.4±10.1 years). Their psychiatric symptoms were stable for at least three months prior to the examination, and their scores on the Psychiatric Symptom Assessment Scale (PSAS; Bigelow & Berthot 1989) were distributed within a range from 4 to 23 (mean 12.7±7.2 points), indicating mild to moderate severity of their illnesses and dominance of negative symptoms. All but one of the subjects were full- or part-time workers, housewives, or college students. All of them were on antipsychotic medication at the time of examination, with dosages ranging from 100 to 1175 mg chlorpromazine equivalents (360+269 mg/day). No abnormal findings were observed in 10 schizophrenic subjects who underwent computerized tomographical brain scans or magnetic resonance imaging brain scans.

The control group consisted of twelve healthy volunteers (8 males, 4 females; age 33.0±10.3 years), who had no history of psychiatric disease, had taken no medication for at least one week prior to the ERP examination, and were functioning well as office workers or college students. Although the mean age of the normal control group was 4.4 years smaller than that of the schizophrenic group, the difference was statistically nonsignificant. Prior to ERP examination, written informed consent was obtained from all subjects participating in the study, and the absence of hearing loss was ascertained for them.

Experimental paradigm

A three-tone discrimination task was employed for ERP recording. Each experiment consisted of six sessions conducted in the same day, and each session consisted of a series

of 200 tone bursts of 150msec duration, delivered at 2000msec interstimulus intervals and 50dBSL binaurally through headphones. The series included three types of tone bursts at 950Hz, 1000Hz, and 1053Hz in quasi-random sequence, with probabilities of 0.17, 0.66 and 0.17, respectively. The frequencies of tone bursts were determined so that the ratio of 950Hz to 1000Hz was equal to that of 1000Hz to 1053Hz.

In the six sessions conducted, either of two infrequent tones was designated as the target, and the subjects were required to press a lever as accurately and quickly as possible upon detecting the targets. Target designation was unchanged in the six sessions for each subject, and was balanced among the schizophrenic and normal control groups. Hit rate, number of commission errors, and reaction times were determined from lever responses. The lever responses were used for analyses when they occurred between 200 and 1000 msec poststimulus, while the responses outside this period were rejected as omission errors.

During the third and fourth of the six sessions, intensive training called "coaching" was offered for improving target detection by the subjects; a buzzer of 300msec duration ("coaching buzzer") was sounded 1100msec after each target tone, indicating the occurrence of the target tone. On hearing this coaching buzzer, the subjects ascertained the occurrence of the target tone after the period of reaction time sampling. Detailed instructions were given and practice sessions were conducted during the interval between the second and third sessions, until a complete understanding of the meaning of the coaching buzzer was attained. After the fourth and sixth sessions, the subjects were asked to judge the change in task difficulty due to coaching using three categories: easier, no change, and more difficult.

EEG recording and ERP processing

Electroencephalograms (EEGs) were derived from the Fz, Cz, and Pz regions with Ag/AgCl electrodes referenced to linked earlobe electrodes, and were amplified with band-pass filter down 6dB at 0.15 and 300 Hz. Electrooculogram (EOG) was also recorded between the electrodes 2cm above and lateral to the outer canthus of the right eye for monitoring eye movements or blinks.

After being processed through an antialiasing filter of 95Hz, EEG data were digitized on-line with a sampling frequency of 500 Hz, from 128 msec preceding onset of the stimulus to 896 msec poststimulus. Digitized EEG data, excluding those with EEG amplitudes over 100 microvolts, EOG amplitudes over 150 microvolts, or incorrect responses or omission

errors, were averaged separately for each type of tone burst. The averaged waveforms were smoothed using a digital filter with a window width of 100msec (50 data points) to minimize any alpha activity in the record. The baseline was determined as the mean voltage over the 128msec period before the onset of the stimulus. In the ERP waveforms thus obtained, the P3 component was identified as the most positive deflection within the period between 260 and 600 msec poststimulus for each electrode. The amplitude, latency, and area, which was defined as positive area between 260 and 600msec poststimulus, of the P3 component were determined and analyzed.

Data analysis

The six sessions conducted were divided into three blocks (pre-, mid-, and post-coaching blocks), each consisting of two sessions. Behavioral and ERP data in the mid-coaching block were excluded from data analyses because the use of the coaching buzzer during the mid-coaching block was considered to have a great influence on the data: for example, ERP waveforms were thought to be affected with overlapping negative potential such as contingent negative variation (CNV) preceding the coaching buzzer. Thus, three behavioral measures, that is hit rate, number of commission errors, and reaction time, were analyzed with repeated measure of analysis of variance (RM-ANOVA) using the MANOVA program in the statistical program package SPSS-X, with "block" (the pre- and post-coaching block) and "session" (the former and the latter session within a block) factors as within-subject factors of independent variables, and "group" (schizophrenic and normal control groups) and "target" (950Hz and 1053Hz) factors being intersubject factors of independent variables. The "electrode" factor (Fz, Cz, and Pz) was also incorporated into the RM-ANOVA analysis as another within-subject factor when P3 amplitude, P3 latency, and P3 area were analyzed.

Results

Subjective change in task difficulty

Seven of the fourteen schizophrenic group and seven of the twelve control group reported that the task was easier after coaching, while three of the schizophrenic group and six of the control group reported there was no change in the task difficulty, and two from

each group reported that the task was more difficult.

Behavioral indices (Fig.1)

The main effect of "group" was significant for all three behavioral indices: the schizophrenic group showed a lower hit rate ($F[1,22]=15.21$; $P=0.001$), more commission error responses ($F[1,22]=4.77$; $P=0.040$), and longer reaction times ($F[1,22]=7.64$; $P=0.011$) than the normal control group. The means and standard deviations (SDs) of these indices in the four sessions analyzed were as follows for the schizophrenic and normal control groups, respectively: hit rate, 66.6±22.3% and 90.1±7.8%; number of error responses, 10.9±16.0 and 1.9±3.0; and reaction time, 625±79msec and 536±85msec. The main effects of the factors "block" and "target" were nonsignificant for hit rate ($F[1,22]=1.26$, $P=0.275$ and $F[1,22]=2.40$, $P=0.136$, respectively), number of error responses ($F[1,22]=2.41$, $P=0.135$ and $F[1,22]=3.34$, $P=0.081$), or reaction time ($F[1,22]=2.21$, $P=0.152$ and $F[1,22]=2.37$, $P=0.138$). The main effect of the factor "session" was also nonsignificant for hit rate ($F[1,22]=1.19$, $P=0.287$) or number of error responses ($F[1,22]=1.51$, $P=0.233$), but was significant for reaction time ($F[1,22]=10.10$, $P=0.004$), indicating that the subjects' reactions were slower in the latter session (633±80msec for the schizophrenic group, 556±77msec for the normal control group) than in the former session (616±93, 516±78) within a block. All interactions between any two factors were nonsignificant.

P3 indices

Examples of ERP waveforms before and after the auditory coaching for three schizophrenic and one normal control subject are presented in Fig. 2. In the case of the normal control subject (subject N1) the ERP waveforms before the auditory coaching did not differ markedly from those after the auditory coaching. In the case of the schizophrenic subjects the P3 amplitude was larger (subject S1), unchanged (subject S2), or smaller (subject S3) after the auditory coaching compared with before it.

When analyzed using ANOVA (Fig. 3), the main effect of the factor "electrode" was significant for P3 amplitude ($F[1,22]=27.88$; $P<0.001$) and P3 area ($F[1,22]=23.62$; $P<0.001$), but was nonsignificant for P3 latency ($F[1,22]=0.63$; $P=0.536$), showing that the P3 appeared predominantly in the Pz region (7.16±3.79microvolt) with the decreasing order of Cz (3.92±4.39) and Fz (1.88±5.50) without significant change of latency. The main effect of the

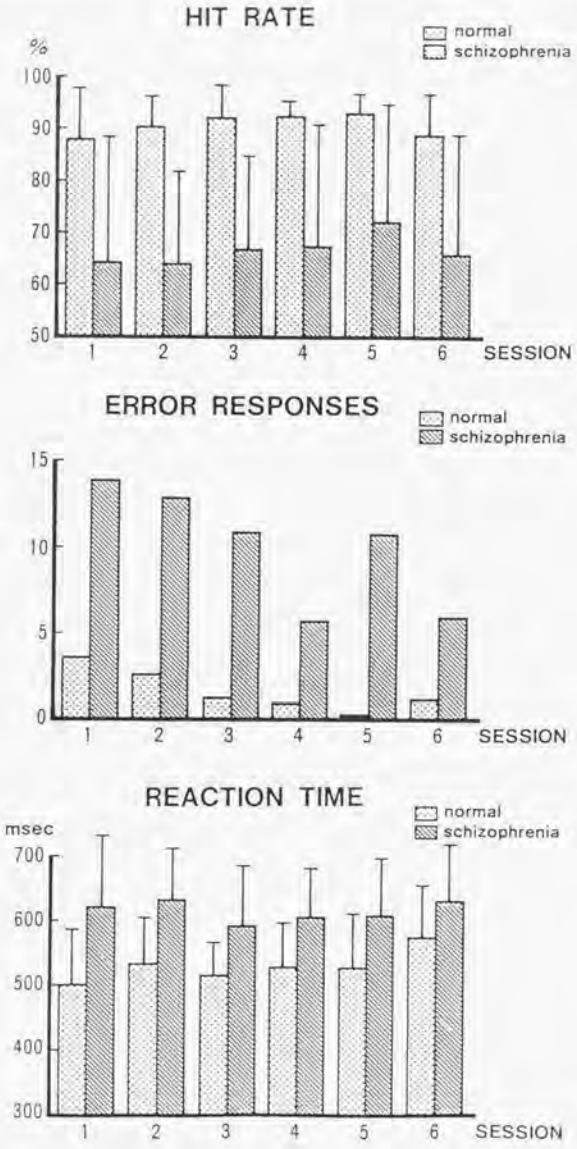

Fig. 1
Mean and SD of hit rate (top), number of commission error responses (center), and reaction time (bottom) in normal (left bar) and schizophrenic (right bar) subjects in the auditory coaching task (study 1).

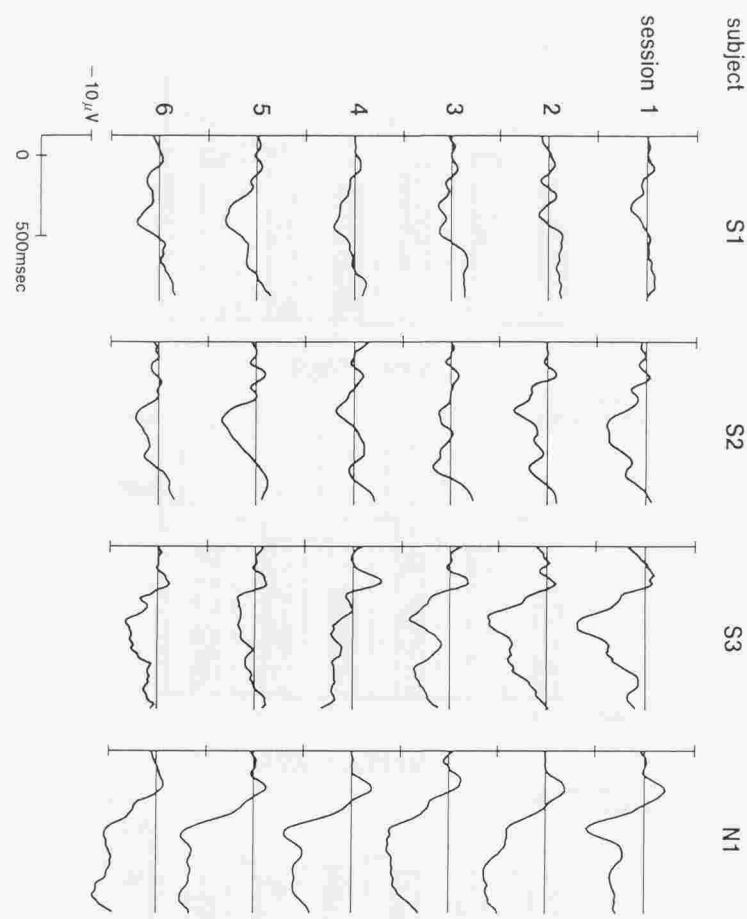

Fig. 2
Examples of ERP waveforms in the auditory coaching task (study 1) for three schizophrenic and one normal control subject. In the schizophrenic subjects P3 amplitude was larger (subject S1), unchanged (subject S2), or smaller (subject S3) after the auditory coaching compared with before it. In the case of the normal control subject (subject N1) the ERP waveforms showed no marked change due to the auditory coaching.

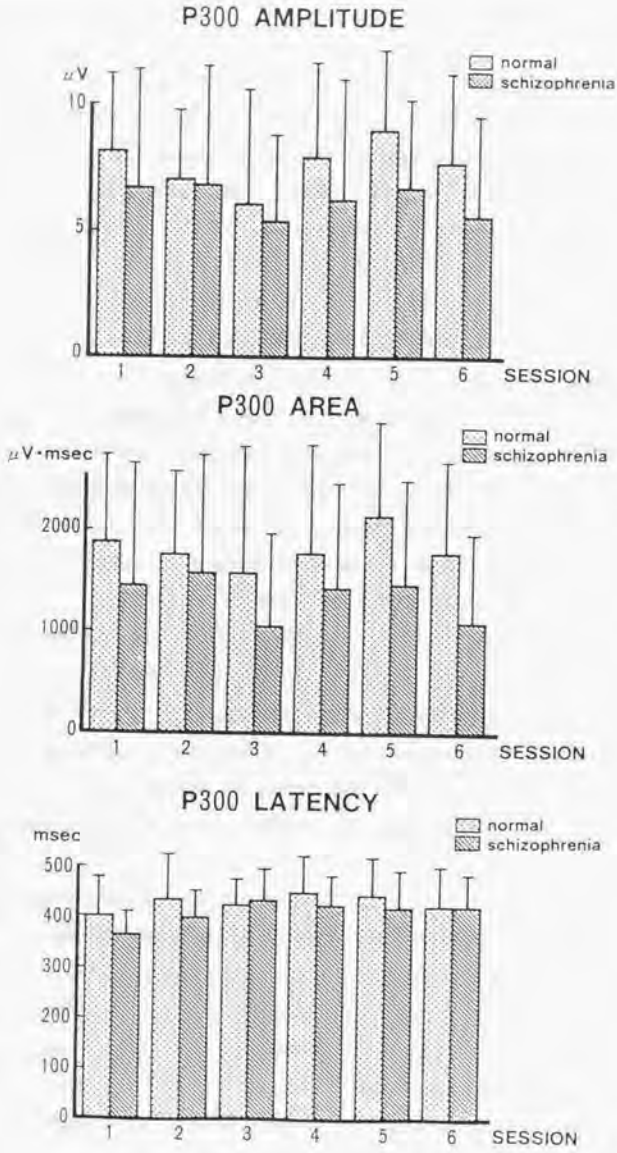

Fig. 3
Mean and SD of amplitude (top), area (center), and latency (bottom) of P3 component in the Pz region in normal (left bar) and schizophrenic (right bar) subjects in the auditory coaching task (study 1).

factor "group" was nonsignificant for P3 amplitude ($F[1,22]=0.01$; $P=0.916$), P3 area ($F[1,22]=0.64$; $P=0.434$, or P3 latency ($F[1,22]=1.17$; $P=0.291$), although the mean amplitude and the mean area were smaller in the schizophrenic group (6.47±4.18microvolt and 1404±1076 microvolt-msec, respectively both in Pz) than in the normal control group (7.96±3.14, 1896±878) and the latency was shorter in the schizophrenic group (403±66msec) than in the normal control group (428±79). The main effect of the factor "block" was nonsignificant for P3 amplitude ($F[1,22]=0.19$; $P=0.670$) and P3 area ($F[1,22]=0.33$; $P=0.569$) but significant for P3 latency ($F[1,22]=6.08$; $P=0.022$), showing that P3 latency was longer in the post-coaching block (425±68msec) than in the pre-coaching block (397±76msec). All the main effects of "session" and "target" were nonsignificant.

Significant two-way interactions were observed in "electrode" and "block" for P3 amplitude ($F[2,44]=4.96$; $P=0.011$) and in "target" and "session" for P3 area ($F[1,22]=4.92$; $P=0.037$). The former significant interaction reflects that the mean P3 amplitude in all subjects was unchanged in the Pz region both in the pre-coaching (7.16±3.89 microvolt) and in the post-coaching block (7.16±3.72 microvolt), but was reduced in Fz and Cz regions in the post-coaching block (1.14±5.29 and 3.60±4.63 microvolt, respectively) compared with that in the pre-coaching block (2.61±5.65 and 4.24±4.16). The latter significant interaction indicates that the mean P3 area was greater in the former session (1215±1116 microvolt-msec) than in the latter session (926±906 microvolt-msec) when the 950Hz tone burst was designated as the target whereas the reverse was the case (1013±1023 and 1054±1058 microvolt-msec, respectively) when a 1053Hz tone burst was the target.

Behavioral and P3 change due to coaching

The changes in behavioral and P3 indices due to coaching were nonsignificant as revealed by the absence of the main effect of the "block" factor in the RM-ANOVA, and the differences in these indices between the schizophrenic and the normal control groups were also nonsignificant as revealed by the absence of any interactions between the factors "group" and "block", as described above. In fact, the changes in behavioral and P3 indices due to coaching were small when averaged within the schizophrenic and normal control groups respectively: hit rate changed +1.8±16.0% and +4.9±7.1%; number of commission errors −2.3±14.0 and −5.0±2.6; reaction time −6±59 and 36±52 msec; P3 amplitude −0.61±4.05 and +0.73±2.30 microvolts; P3 area −237±1028 and +144±760 microvolt-msec; and P3 latency

+38±66 and +14±48 msec. The variances of the changes due to coaching were significantly greater in the schizophrenic group than in the normal control group for the hit rate ($F[11,13]=4.98$; $P=0.0016$), the number of error responses ($F[11,13]=27.80$; $P<0.0001$), and P3 amplitude ($F[11,13]=3.07$; $P=0.0071$),, but not for reaction time ($F[11,13]=1.26$; $P=0.71$), P3 latency ($F[11,13]=1.87$; $P=0.31$), or P3 area ($F[11,13]=1.81$; $P=0.33$).

When the relationship between the changes of behavioral and P3 indices due to coaching was examined individually, significant correlations were obtained between P3 amplitude and behavioral indices in the schizophrenic group. In the schizophrenic group, hit rate improvement ($r=0.60$, $P=0.011$; Fig.4, top), reaction time shortening ($r=-0.58$, $P=0.015$; Fig.4, center), and P3 amplitude recorded from Pz in the pre-coaching block ($r=-0.68$, $P=0.004$; Fig.4, bottom) were significantly correlated with increase in P3 amplitude recorded from Pz due to coaching. Similar relationships were also observed for P3 amplitude recorded from Cz and Fz although the correlation coefficients were smaller. In the normal control group, however, no significant correlation with increase in P3 amplitude recorded from Pz due to coaching was found in the hit rate improvement ($r=0.022$, $P=0.95$, Fig.5, top), in the reaction time shortening ($r=-0.37$, $P=0.24$, Fig.5, center), or in the P3 amplitude recorded from Pz in the pre-coaching block ($r=-0.32$, $P=0.31$, Fig.5, bottom). The correlations were also nonsignificant for P3 amplitude recorded from Cz and Fz. Correlations of P3 area with other indices were also significant in the schizophrenic group but nonsignificant in the normal control group similar to P3 amplitude, whereas correlations for P3 latency were nonsignificant both in the schizophrenic and the normal control groups.

Although changes in these indices due to coaching were not different among subjects who felt that the task was easier (circles in Fig. 4, 5), unchanged (squares in Fig. 4, 5), or more difficult (triangles in Fig. 4, 5) after coaching when examined by ANOVA, visual inspection suggests a weak relationship. In the schizophrenic group, P3 amplitudes in the pre-coaching block were small and P3 amplitude increases due to coaching were large for those who felt the task was easier after coaching, except for one subject represented in the lowest right corner in the bottom figure of Fig.4. Two schizophrenic subjects who felt that the task was more difficult after coaching showed large P3 amplitudes in the pre-coaching block and P3 reduction due to coaching. Such a trend was not observed in the normal group.

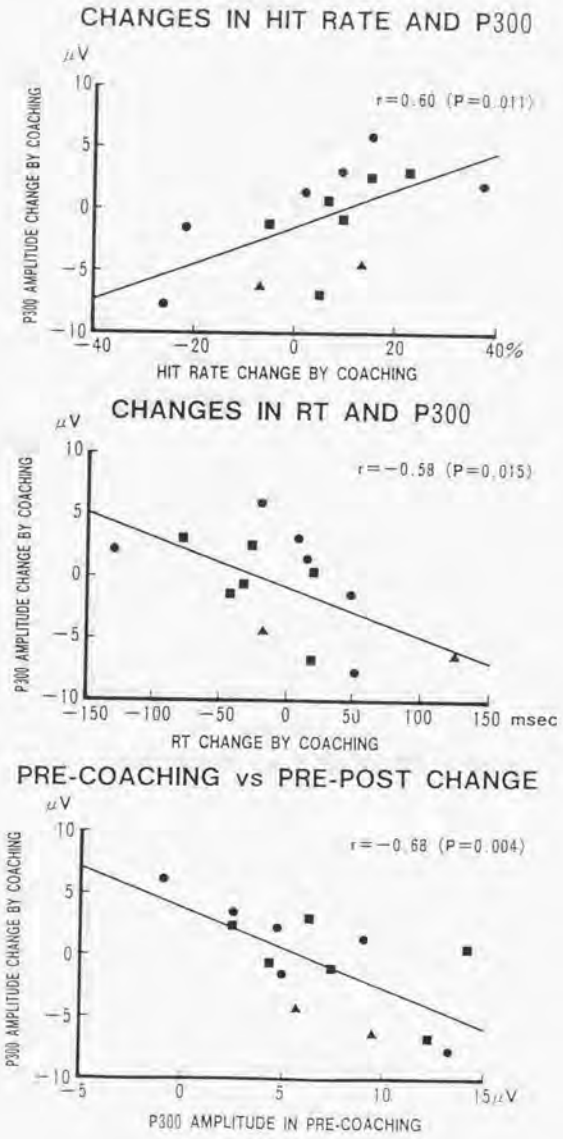

Fig. 4

Relationship between changes in hit rate and those in P3 amplitude in the Pz region due to coaching (top), changes in reaction time and those in P3 amplitude in the Pz region due to coaching (center), and P3 amplitude in the Pz region in the pre-coaching block and P3 amplitude change in the Pz region due to the auditory coaching (bottom) in the schizophrenic patients. Symbols represent changes in the subjective difficulty of the task due to coaching; circles, easier, squares, unchanged, and triangles, more difficult.

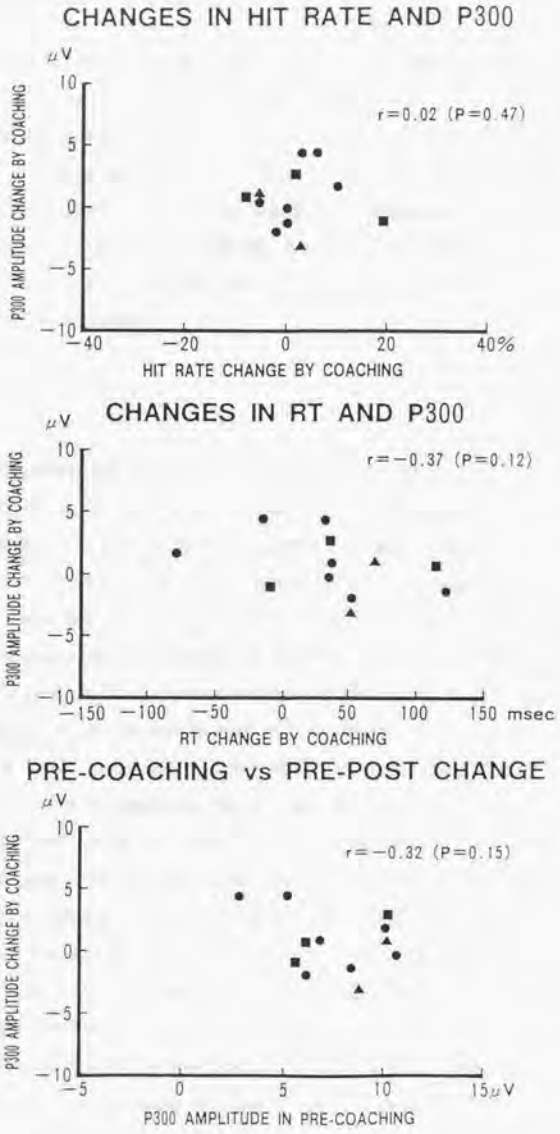

Fig. 5
Results in the normal control subjects in the auditory coaching task. Details are the same as in Fig. 4.

Relationship between changes due to coaching and clinical indices

In the schizophrenic group, the relationship between behavioral and P3 amplitude changes due to coaching and clinical symptoms was investigated. The scores in five symptom clusters of the PSAS scores, behavior positive, anxiety-depression, deficit symptoms, paranoia, and verbal positive, showed no significant correlation with behavioral and P3 indices in the pre-coaching block or with the changes in behavioral and P3 indices due to coaching. P3 amplitude changes due to coaching were also not correlated with the antipsychotic medication dosage.

Discussions

Before discussing the main finding of the study, one point should be mentioned: P3 amplitude and P3 area in the schizophrenic group were not significantly decreased compared with those in the normal control group. The finding is inconsistent with most of the findings of previous ERP studies on schizophrenia demonstrating the P3 amplitude reduction in the auditory oddball paradigm (Pritchard 1986; Ford et al. 1992). Two reasons can be given for the unreduced P3 amplitude in the schizophrenic group in this study. Firstly, the subjects in the schizophrenic group suffered from a mild form of the illness; they were all outpatients, were functioning well socially except for one, and showed mild to moderate psychopathology as assessed using PSAS. Some schizophrenic patients with mild symptomatology have been reported to show normal P3 amplitude (Ward et al. 1991; Stirk et al. 1993). Secondly, the auditory paradigm used to record ERPs was difficult to perform because the frequency difference between the target and the frequent tone bursts was quite small, and such difficult tasks are reported to obscure P3 amplitude reduction in schizophrenic patients (Brecher et al. 1987). These two reasons are assumed to contribute to the absence of significant differences in P3 amplitude between the schizophrenic and the normal control groups. These reasons are also assumed to contribute to the shorter, although nonsignificant, P3 latency in the schizophrenic group than in the normal control group, which is in clear contrast to prolonged P3 latency reported for schizophrenic patients (Blackwood et al. 1990).

The most impressive results obtained in this study were significant correlations between P3 amplitude increase and hit rate increase and reaction time decrease due to coaching in the schizophrenic group. The results duplicated and expanded our preliminary

ones (Fukuda et al. 1989) using more subjects and peak identification in individual ERP waveforms instead of the grand averaged ERP waveforms. The changes in behavioral and P3 indices due to coaching were all nonsignificant when they were analyzed as a whole group of schizophrenic or normal control subjects. This means that the changes due to coaching were not even across all the subjects but were variable interindividually. Hence, the obtained results indicate that 1) behavioral deficits in schizophrenics, such as poor performance and slowed response, can be remediated by means of intensive training at least in some patients, and 2) such behavioral improvement by nonpharmacological intervention corresponded with improvement of brain function as reflected in the P3 amplitude increase. A significant negative correlation between increase in P3 amplitude due to coaching and P3 amplitude in the pre-coaching block offers a clue to understand the more precise meaning of the above results. According to the assumption in some studies (Pfefferbaum et al. 1989; Ward et al. 1991) that the degree of P3 amplitude reduction reflects the severity of cognitive impairment in schizophrenics, intensive training should be more effective for schizophrenic patients with severe cognitive impairment, and its efficacy should be reflected as improvement in both behavioral performance and increase in P3 amplitude.

We examined the possibility that the correlation between the increase in P3 amplitude due to coaching and the P3 amplitude in the pre-coaching block might be an artifact due to the effect called "regression toward the mean" or to a nonspecific change such as in the subjects' attention or motivation level. The former possibility postulates that random variances of P3 amplitude both in the pre- and the post-coaching block was the cause of the apparently significant correlation. This possibility is inconsistent with the fact that significant correlations were observed not only between the increase in P3 amplitude due to coaching and the P3 amplitude in the pre-coaching block, but also between the changes in behavioral indices and the increase in P3 amplitude due to coaching. The latter possibility cannot be completely ruled out based on the results obtained in the present study. However, two facts argue against it: first, visual inspection of background alpha activity in EEG during the task revealed no difference in the level of this activity between the pre- and the post-coaching block; second, all the subjects were rather tired in the post-coaching block because they had already performed the task for more than forty minutes. Therefore, we do not attribute the correlation to the effect of regression toward the mean or to a nonspecific change such as in the subjects' attention or motivation levels.

Lack of such significant correlations in normal controls was in clear contrast to the results in schizophrenics. Although this discrepancy might be partially explained by a smaller variance of hit rate change due to coaching and a smaller variance of P3 amplitude in the pre-coaching block in the normal control group than in the schizophrenic group, such an explanation would not be applicable to the different results observed in reaction time change, because the variance of reaction time change due to coaching was not different between the schizophrenic and normal control groups. Another possible explanation is, therefore, that behavioral performance in schizophrenics might be coupled more directly and more tightly with brain electrophysiological activity than in normal controls; in other words, schizophrenics might have reduced flexibility and redundancy in response behavior.

Two points need to be mentioned regarding the significance of P3 amplitude change in the schizophrenic group due to coaching. Firstly, the above results do not indicate *normalization* of poor performance, slowed response, and P3 amplitude reduction in schizophrenics. The means of hit rate, reaction time and P3 amplitude of the schizophrenic group in the post-coaching block were lower, longer, and smaller, respectively, than those in the normal control group. Secondly, hit rate and P3 amplitude increase and reaction time decrease was observed only in *some* of the schizophrenic subjects. As described in "Subjects", the schizophrenic patients participated in this study were all outpatients with mild to moderate severity of the illness and were able to perform the rather difficult task used in this study. Therefore, improved patients could be characterized as poor performers in spite of their less severe illness, and behavioral and electrophysiological improvement was observed only in such patients. However, it is unclear which variables are responsible for the remediability of P3 amplitude reduction. Clinical symptoms, morphological changes in the brain, and antipsychotic drug dosage were not related to P3 amplitude in the pre-coaching block or to P3 amplitude increase due to coaching.

Although P3 amplitude reduction in schizophrenia is generally reported to be observed consistently irrespective of clinical state or medication status (Blackwood et al. 1987; Pfefferbaum et al. 1989), some papers report remediation of P3 amplitude reduction in schizophrenics to some degree with clinical improvement using antipsychotic medication. Matsubayashi et al. (1984), Duncan (1988), and Mintz et al. (1995) reported P3 amplitude increase in schizophrenic patients who responded well to antipsychotic medication. These studies suggest that P3 amplitude reduction in schizophrenics can be remediated by

antipsychotic medication at least in some patients who respond to clinical treatment. Combining these results of pharmacological treatment with the present result obtained using nonpharmacological intervention, P3 amplitude reduction in schizophrenics could be conceptually divided into two aspects according to their consistency; one is a consistent aspect stemming from the biological changes in the brain, and the other a remediable aspect reflecting secondary aberrant information processing. P3 amplitude change observed in this study as well as antipsychotic medication studies is speculated to represent the latter.

STUDY 2

Methods and Materials

Subjects

Twelve of both schizophrenic and normal control subjects were included in the study. The schizophrenic group consisted of twelve outpatients of the Tokyo University Hospital (7 males, 5 females). Their diagnoses were made according to the criteria of the DSM-III-R, and their subtypes were as follows: 6 residual type, 3 paranoid type, and 3 disorganized type. The ages of the patients ranged from 27 to 54 years (mean 35.7±8.8 years). Their psychiatric symptoms were stable for at least three months prior to the examination, and their scores on the Psychiatric Symptom Assessment Scale (PSAS; Bigelow & Berthot 1989) were distributed within a range from 3 to 41 (mean 21.6±5.4 points), indicating mild to moderate severity of their illnesses and dominance of negative symptoms. All the subjects were full- or part-time workers, housewives, or college students. All of them were on antipsychotic medication at the time of examination, with dosages ranging from 37 to 415 mg chlorpromazine equivalents (182.4±63.7 mg/day).

The control group consisted of twelve healthy volunteers (9 males, 3 females; age 31.1±8.0 years), who had no history of psychiatric disease, had taken no medication for at least one week prior to the ERP examination, and were functioning well as office workers or college students. Although mean age of the normal control group was 4.6 years smaller than that of the schizophrenic group, the difference was statistically nonsignificant. Five subjects of the schizophrenic group and none of the normal control group were also included in Study 1. Prior to ERP examination, written informed consent was obtained from all subjects participating in the study, and the absence of hearing loss was ascertained for them.

Experimental paradigm

A three-tone discrimination task was employed for ERP recording. Each experiment consisted of five sessions, and each session consisted of a series of 200 tone bursts of 150msec duration, delivered at 2000msec interstimulus intervals and 50dBSL binaurally through headphones. The series included three types of tone bursts at 950Hz, 1000Hz, and 1053Hz in quasi-random sequence, with probabilities of 0.17, 0.66 and 0.17, respectively.

The frequencies of tone bursts were determined so that the ratio of 950Hz to 1000Hz was equal to that of 1000Hz to 1053Hz.

In the five sessions conducted, the 950Hz tone was designated as the target, and the subjects were required to press a lever as accurately and quickly as possible upon detecting the targets. Hit rate, number of commission errors, and reaction times were determined from lever responses. The lever responses were used for analyses when they occurred between 200 and 1000 msec poststimulus, while the responses outside this period were rejected as omission errors.

During the second and fourth of five sessions, intensive training called "visual coaching" was offered for improving the stimulus discrimination ability of the subjects. On a CRT situated in front of the subjects, one of the following three figures ("coaching figures") was displayed between 1000msec and 1300msec after each tone burst: an inverted triangle for the 950Hz tone burst, a square for the 1000Hz one, and a triangle for the 1053Hz one. On seeing the figure presented on the CRT, the subjects ascertained the type of tone after the period of reaction time sampling. Detailed instructions were given and practice sessions were conducted during the interval between the first and second sessions, until a complete understanding of the meaning of the figures on the CRT was attained.

EEG recording and ERP processing

Electroencephalograms (EEGs) were derived from the T_3, T_4, and Pz regions with Ag/AgCl electrodes referenced to linked earlobe electrodes, and were amplified with band-pass filter down 6dB at 0.15 and 300 Hz. Electrooculogram (EOG) was also recorded between the electrodes 2cm above and lateral to the outer canthus of the right eye for monitoring eye movements or blinks.

After being processed through an antialiasing filter of 95Hz, EEG data were digitized on-line with a sampling frequency of 500 Hz, from 128 msec preceding onset of the stimulus to 896 msec poststimulus. Digitized EEG data, excluding those with EEG amplitudes over 100 microvolts, EOG amplitudes over 150 microvolts, or incorrect responses or omission errors, were averaged separately for each type of tone burst. The averaged waveforms were smoothed using a digital filter with a window width of 100msec (50 data points) to minimize any alpha activity in the record. The baseline was determined as the mean voltage over the 128msec period before the onset of the stimulus. In the ERP waveforms thus obtained, the

P3 component was identified as the most positive deflection within the period between 260 and 600 msec poststimulus. The amplitude, latency, and area, which was defined as positive area between 260 and 600msec poststimulus, of the P3 component were determined and analyzed.

Data analysis

Behavioral and ERP data obtained in the second and fourth sessions were excluded from data analyses because the use of the coaching figures during the sessions was considered to have a great influence on the data: for example, ERP waveforms were thought to be affected with overlapping negative potential such as contingent negative variation (CNV) preceding presentation of the coaching figures. The remaining three sessions, for which the data obtained were analyzed, were designated as follows: the first session as the pre-training session, the third session as the once-trained session, and the fifth session as the twice-trained session. Four behavioral parameters, that is, hit rate (HR), number of commission errors (false alarm rate; FAR), d' calculated as 2arcsin of the square root of (1/2 + (HR-FAR)(1+HR-FAR)/4HR(1-FAR)) and reaction time, were analyzed with repeated measures of analysis of variance (RM-ANOVA) using the MANOVA program in the statistical program package SPSS-X, with "session" factor (the first, third, and fifth session) being an intraindividual factor of independent variables and "group" factor (schizophrenic and normal control groups) an interindividual factor of independent variables. The "region" factor (Pz, T_3, T_4) was also incorporated into the RM-ANOVA as another intraindividual factor of independent variables when P3 amplitude, P3 latency, and P3 area were analyzed.

Results

Subjective change in task difficulty

Eleven of the 12 patients in the schizophrenic group and nine of the twelve subjects in the normal control group reported that the task was easier during the visual coaching because they could confirm the type of each auditory stimulus by the type of figure which appeared on the CRT soon after. One of the subjects in the normal control group reported no change in the task difficulty between during the coaching and the noncoaching sessions. One of the patients in the schizophrenic group and two of the subjects in the normal control

group reported that the task was more difficult during the visual coaching because they were distracted by the visual stimuli which appeared soon after the auditory stimuli.

Behavioral indices (Fig.6)

The main effect of the "group" factor was significant for hit rate and reaction time; the schizophrenic group showed lower hit rates ($F[1,22]=11.48$; $P=0.003$) and longer reaction times ($F[1,22]=12.83$; $P=0.002$) than the normal control group, while its main effect was nonsignificant for the number of error responses ($F[1,22]=2.22$; $P=0.150$). The means and standard deviations of hit rate were 77.0±20.7%, 71.3±23.1% and 71.8±26.0% for the first, third, and fifth session, respectively, in the schizophrenic group, and 92.4±7.6%, 94.6±5.9%, and 96.1±5.8% in the normal control group. Those of reaction times were 585±103msec, 595±102msec, and 617±126msec in the schizophrenic group, and 504±69msec, 469±54msec, and 446±61msec in the normal control group.

The main effect of the "session" factor was nonsignificant for hit rate ($F[2,44]=0.19$, $P=0.832$) or reaction time ($F[2,44]=1.36$, $P=0.268$), but was significant for the number of error responses ($F[2,44]=4.23$, $P=0.021$), indicating that the subjects committed more errors in the first session (8.3±14.4 for the schizophrenic group, 3.0±7.6 for the normal control group) than in the third (4.3±6.7, 0.6±0.9) and the fifth session (2.3±4.3, 0.5±0.9). Two-way interaction was significant only for "group" and "session" in the reaction time; the reaction time significantly increased with the number of sessions in the schizophrenic group ($F[2,22]=2.90$, $P=0.076$; session 1 585±103msec, session 3 595±102msec, session 5 617±126msec) but significantly decreased in the normal control group ($F[2,22]=13.72$, $P<0.001$; session 1 504±69msec, session 3 469±54msec, session 5 446±61msec). The calculated d' was significantly smaller ($F[1]=27.1$; $P=0.0001$) for the schizophrenic group (d'=2.61±0.33) than for the normal control group (d'=2.94±0.16). However, the main effect of "session" ($F[2]=0.30$; $P=0.74$) and the two-way interaction of "group" by "session" ($F[2]=0.20$; $P=0.82$) were nonsignificant for d'.

P3 indices

Examples of ERP waveforms along the visual coaching for schizophrenic (subjects S1 and S2) and normal control subjects (subjects N1 and N2) are presented in Fig. 7. Visual inspection reveals that the P3 amplitude tended to increase with progression of the visual

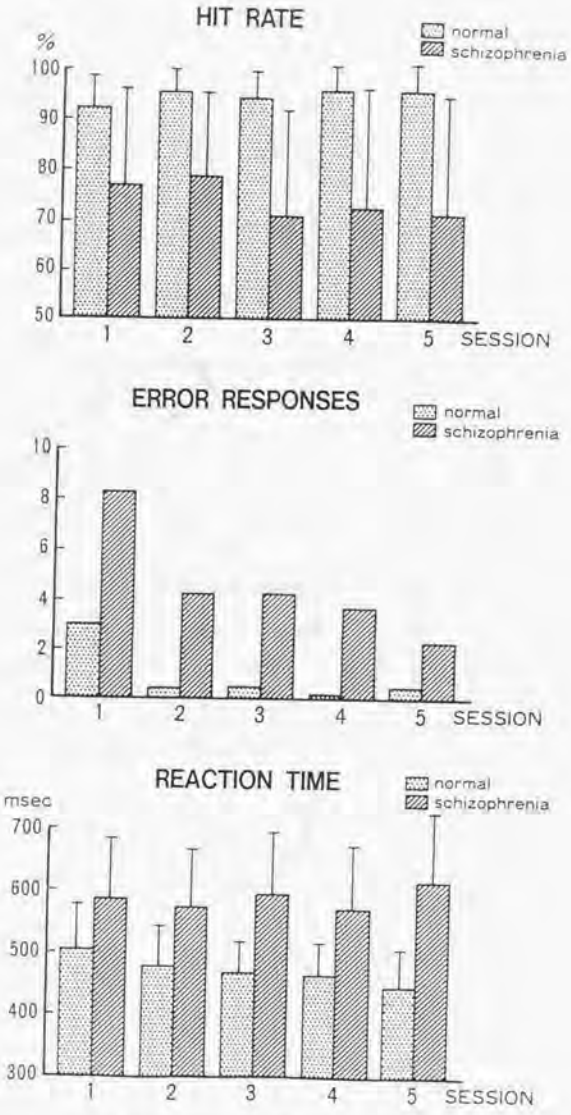

Fig. 6
Mean and SD of hit rate (top), reaction time (center), and number of comission error responses (bottom) in normal (left bar) and schizophrenic (right bar) subjects in the visual coaching task (study 2).

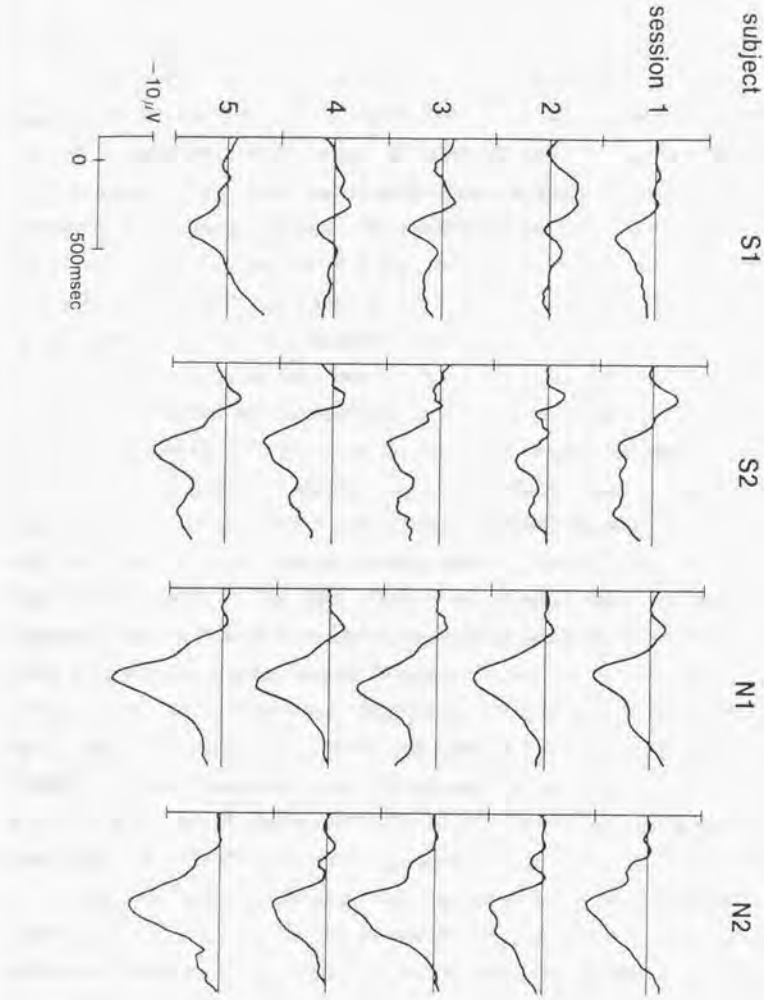

Fig. 7
Examples of ERP waveforms in the visual coaching task (study 2) for schizophrenic (subjects S1 and S2) and normal control subjects (subjects N1 and N2). In both the schizophrenic and normal contorl subjects P3 amplitude tended to increase along the visual coaching procedures progressed.

coaching procedures progressed in both the schizophrenic and the normal control subjects.

When analyzed using MANOVA (Fig. 8), the main effect of the "electrode" factor was significant for P3 amplitude ($F[1,22]=27.88$; $P<0.001$) and P3 area ($F[2,44]=42.38$; $P<0.001$), but was nonsignificant for P3 latency ($F[2,44]=0.32$; $P=0.729$), showing that the P3 component appeared was predominant in the Pz region compared with the T_3 and T_4 regions, without significant change of latency. The main effect of the "group" factor was significant for P3 amplitude ($F[1,22]=12.40$; $P=0.002$) and P3 area ($F[1,22]=9.91$; $P=0.005$) but nonsignificant for P3 latency ($F[1,22]=2.84$; $P=0.106$), demonstrating that P3 was smaller for the schizophrenic group than for the normal control group.

The main effect of the "session" factor was nonsignificant for P3 latency ($F[2,44]=0.17$; $P=0.842$) but was significant for P3 amplitude ($F[2,44]=3.27$; $P=0.047$) and P3 area ($F[2,44]=4.22$; $P=0.021$). The "session" effect demonstrated that P3 amplitude increased with the number of sessions (session 1, 7.98±4.68 microvolt and 1797±1164 microvolt-msec; session 3, 9.54±4.17 and 2223±1146; session 5, 10.26±4.73 and 2453±1337) when the schizophrenic and the normal control groups were combined. When the two groups were analyzed separately, the main effect of the "session" factor reached statistical significance only for P3 in the Pz region for the normal control group. In the normal control group, P3 amplitudes recorded from the Pz region in session 1, 3, and 5 were 10.42±4.20, 12.11±3.49, and 12.95±3.92microvolt ($F[2,22]=3.84$; $P=0.037$), respectively, and P3 areas in the Pz region were 2360±1042, 2910±904, and 3204±1203 microvolt-msec ($F[2,22]=6.57$; $P=0.006$). In the schizophrenic group, P3 amplitudes in the Pz region were 5.54±3.90, 6.97±3.14, and 7.56±3.95 microvolt ($F[2,22]=2.47$; $P=0.108$), and P3 areas in the Pz region were 1235±1029, 1537±950, and 1702±1029 microvolt-msec ($F[2,22]=2.27$; $P=0.127$).

Significant two-way interaction was observed in "group" and "electrode" for P3 amplitude ($F[2,44]=4.39$; $P=0.018$) and P3 area ($F[2,44]=5.14$; $P=0.010$), indicating that P3 differences between the Pz region and the T_3 and T_4 regions were significantly larger for the normal control group than for the schizophrenic group.

Behavioral and P3 change due to the visual coaching

When the relationships between the changes of behavioral and P3 indices due to the visual coaching were examined individually, all correlations were found to be nonsignificant for both the schizophrenic group and the normal control group (top and middle in Fig. 9 and

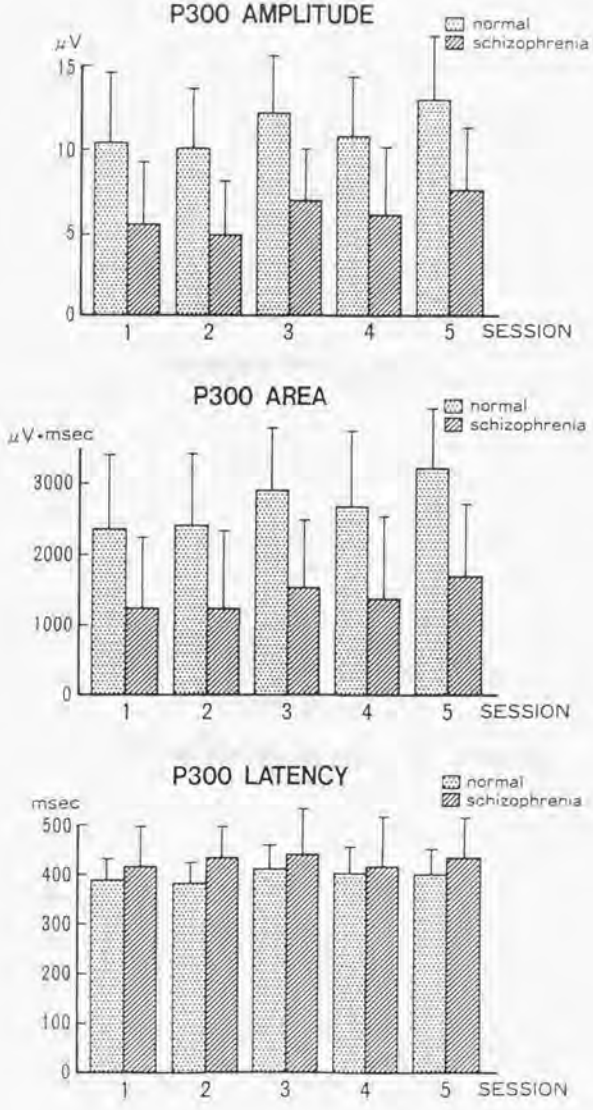

Fig. 8
Mean and SD of amplitude (top), area (center), and latency (bottom) of P3 component in the Pz region in normal (left bar) and schizophrenic (right bar) subjects in the visual coaching task (study 2).

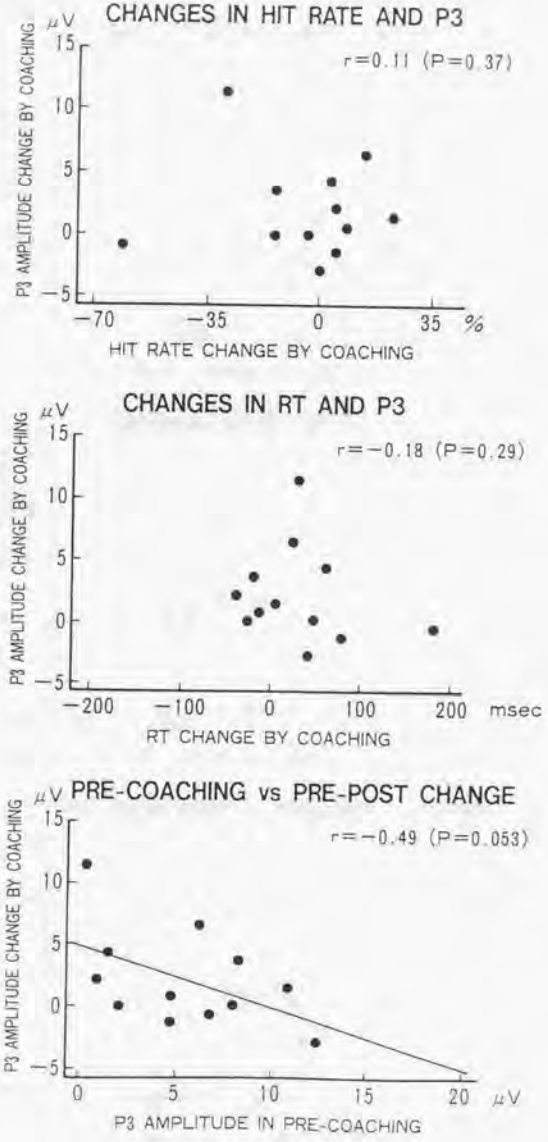

Fig. 9

Relationship between changes in hit rate and those in P3 amplitude in the Pz region due to coaching (top), changes in reaction time and those in P3 amplitude in the Pz region due to coaching (center), and P3 amplitude in the Pz region in the pre-coaching block and P3 amplitude change in the Pz region due to the visual coaching (bottom) in the schizophrenic patients.

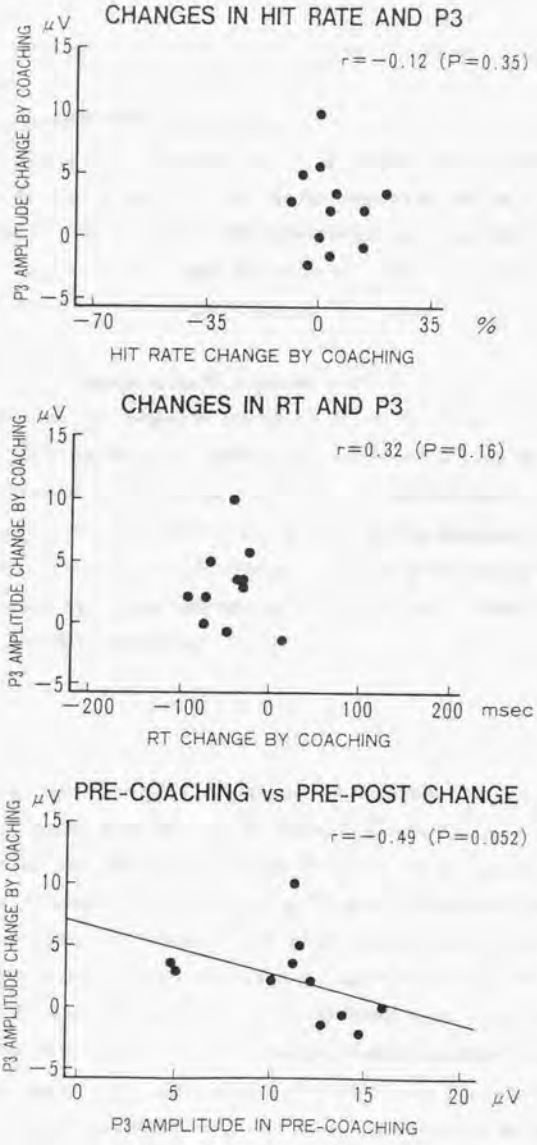

Fig. 10
Results in the normal control subjects in the visual coaching task. Details are the same as in Fig. 9.

10). The Pearson's correlation coefficients between the hit rate and the P3 amplitude in the Pz region were r=0.18 (P=0.29) for the schizophrenic group and r=0.07 (P=0.42) in the normal control group for the changes between the first and third sessions, and were r=0.11 (P=0.37) and r=−0.12 (P=0.35), respectively, for the changes between the first and the fifth sessions. The correlation coefficients between the reaction time and the P3 amplitude in the Pz region were r=−0.05 (P=0.44) for the schizophrenic group and r=0.01 (P=0.49) in the normal control group for the changes between the first and the third sessions, and r=−0.18 (P=0.29) and r=0.32 (P=0.16), respectively, for the changes between the first and fifth sessions.

However, the changes in the P3 amplitude in the Pz region due to the visual coaching correlated significantly or marginally with the P3 amplitude in the first session for both the schizophrenic group and the normal control group (bottom in Fig. 9 and 10). The correlation coefficients between the P3 amplitudes in the first session and their changes between the first and third sessions were r=−0.61 (P=0.017) for the schizophrenic group and r=−0.59 (P=0.021) for the normal control group, and the correlation coefficients between the P3 amplitudes in the first session and their changes between the first and fifth sessions were r=−0.49 (P=0.053) and r=−0.49 (P=0.052), respectively.

Discussion

The main result obtained in this study was the significant main effect of the "session" factor on the P3 amplitude in the Pz region, indicating that the P3 amplitude increased with the number of sessions. The absence of a significant two-way interaction for "session" and "group" in the P3 amplitude indicated that the P3 amplitude increased similarly with the number of sessions in both the schizophrenic group and the normal control group although the P3 amplitude increase did not reach statistical significance in the schizophrenic group. The observed P3 amplitude increase could be attributed either to the effect of session repetition or that of the visual coaching. Although a definite conclusion cannot be drawn as to which is the case from the results, the result of reaction time supports the latter possibility. The reaction time increased significantly with the number of sessions for the schizophrenic group, whereas it decreased significantly along sessions for the normal control group. The reaction time changes in the opposite directions for the schizophrenic group and the normal

control group, with the same direction change of P3 amplitude for both groups, imply that the observed changes along sessions cannot be attributed to the effect of session repetition, but can be due to the effect of visual coaching.

The P3 amplitude changes due to the visual coaching were not correlated with the changes of behavioral indices such as hit rate and reaction time. The absence of significant correlations could be interpreted to indicate that the observed P3 amplitude changes did not directly reflect the behavioral changes but reflected the change in subjective certainty of stimulus discrimination; most subjects reported that the task seemed easier after visual coaching because they could confirm the type of auditory stimulus by the type of figure appearing on the CRT soon after. The P3 amplitude increase due to such certainty increment was consistent with the finding that P3 amplitude increased as subjects were more convincing of stimulus discrimination (Squires et al. 1975). If this interpretation is correct, the P3 amplitude increase can be interpreted as reflecting cognitive improvement in the normal control subjects because the reaction times were shortened due to visual coaching. On the other hand, the P3 amplitude increase in the schizophrenic subjects can be interpreted as reflecting a shift towards a more cautious response manner because the reaction times were lengthened due to the visual coaching.

The significant correlation between the P3 amplitude change due to the visual coaching and the P3 amplitude in the first session could be interpreted as a result known as "the regression towards the mean". However, such an interpretation is unlikely because the correlation between the P3 amplitude in the third session and the P3 amplitude change from the third to fifth session was nonsignificant for both the schizophrenic group ($r=-0.08$; $P=0.40$) and the normal control group ($r=-0.10$; $P=0.32$). Thus, the significant positive correlation between the P3 amplitude change due to visual coaching and the P3 amplitude in the first session suggests that the P3 amplitude increase was more marked in the subjects whose original P3 amplitudes were small.

GENERAL DISCUSSION ON STUDIES 1 AND 2

There are three methodological limitations in this study. First, no experiments under control conditions in which behavioral and P3 changes due to simple repetition of ERP recording sessions without any coaching were conducted. This prevented us from determining whether the results were due to the coaching during the training sessions or simply to the repetition of the sessions. Second, the coaching session timing among the ERP recording sessions differed between the auditory and the visual coaching tasks: in the auditory coaching task two coaching sessions were interposed between the pre- and post-coaching sessions, whereas in the visual coaching task the two coaching sessions were conducted alternately with the non-coaching sessions. Third, the types of stimuli in response to which the coaching cues were delivered differed between the auditory and the visual coaching tasks: the coaching cues were delivered only for the target stimuli in the auditory coaching task whereas they were delivered for all three types of stimuli in the visual coaching task. The second and the third points prevented us from comparing directly the effectivenesses of the auditory and visual coaching procedures.

Under the limitations described in the preceding paragraph, the results obtained in the above studies are summarized as follows. 1) Due to the auditory coaching, the changes in hit rate and reaction time correlated significantly with the P3 amplitude change in the schizophrenic group but not in the normal control group, and the P3 amplitude change also correlated with the P3 amplitude prior to the coaching only in the schizophrenic group. 2) Due to the visual coaching, P3 amplitude increased similarly in the schizophrenic and the normal control groups, but P3 amplitude changes were not correlated with the changes in behavioral indices. These results demonstrate that P3 amplitude reduction in schizophrenia is not fixed but can be ameliorated through intensive training.

The visual coaching was more effective in ameliorating P3 amplitude reduction than the auditory coaching for schizophrenic patients. There are three possibilities to explain the difference in effectiveness between the two coaching procedures. First, the modalities through which the coaching cues were delivered, auditory and visual, were different. The visual coaching may have been more effective than the auditory coaching in improving P3 amplitude reduction because the subjects could confirm the type of auditory task stimulus more clearly through visual coaching, the different modality coaching, than through auditory coaching, the

same modality coaching. Second, the orders of the coaching sessions and the non-coaching sessions were different between the auditory and the visual coaching tasks. In the auditory coaching task two coaching sessions were interposed between the pre- and post- coaching sessions, whereas in the visual coaching task the two coaching sessions were conducted alternately with the non-coaching sessions. The subjects could experience the coaching twice in the visual coaching task whereas only once in the auditory coaching task. This may have led to the visual coaching being more effective than the auditory coaching for ameliorating P3 amplitude reduction. Third, the coaching cues were delivered only for the target stimuli in the auditory coaching task whereas they were delivered for all three types of stimuli in the visual coaching task. Hence, the visual coaching was speculated to be more effective than the auditory coaching for the discrimination of the three types of stimuli. The above mentioned three points may explain the greater effectiveness of the visual coaching in ameliorating the reduction of P3 amplitude in schizophrenia.

The effects of the auditory and visual coaching procedures were also different in that significant correlations between the changes of P3 amplitude and behavioral indices due to the coaching were observed only in the auditory coaching task but not in the visual coaching task for the schizophrenic group. This difference might be explained by a difference in the coaching procedures. In the auditory coaching task, response to the target tone bursts was promoted because the coaching cues were delivered only for the target stimuli and no coaching cues were sounded for the nontarget stimuli. In the visual coaching task, however, the subjects hesitated to respond to the target stimuli because the visual coaching cues delivered for the nontarget stimuli clearly informed them of the incorrect commission responses. The overall increase in the reaction time in the visual coaching task along sessions for the schizophrenic group supports this interpretation. These differences in response tendency due to the coaching procedures could explain the presence and absence of significant P3-behavioral correlations in the auditory and the visual coaching tasks, respectively.

Although some differences existed in the results of studies 1 and 2 as described above, the most important finding in the two studies was that P3 amplitude reduction in schizophrenia is not fixed but can be ameliorated to some extent through intensive training. This finding might seem to be incongruous if one considers that P3 amplitude reduction in schizophrenia is one of the most consistently observed findings and is a trait marker of schizophrenia. However, P3 amplitude reduction in schizophrenia does not necessarily mean

that the reduction cannot be ameliorated by any means. In fact, other biological abnormalities in schizophrenia such as increased degree of saccadic eye movements and impaired neuropsychological test performances have been demonstrated to be ameliorated by nonpharmacological intervention as described in the introduction. These ameliorations are assumed to reflect an improvement in the brain function through nonpharmacological intervention. A similar improvement in brain function may underlie the observed amelioration in P3 amplitude reduction.

Such remediability of P3 amplitude reduction in schizophrenia is important in the following two respects. First, studies on remediability of P3 amplitude reduction in schizophrenia are helpful for elucidating more precisely the nature of P3 amplitude reduction in schizophrenia. Although P3 amplitude reduction has been detected consistently in schizophrenic patients, its clinical correlates are not clear: the degree of P3 amplitude reduction cannot be explained by severity of psychiatric symptoms, schizophrenic subtypes, or medication status at the time of examination. Detailed investigation of the remediability of P3 amplitude reduction may offer some clues to its clinical significance in schizophrenia. Second, the remediability of P3 amplitude reduction in schizophrenia is helpful for elucidating the brain mechanisms underlying the effectiveness of clinical nonpharmacological treatments. In this study the auditory and visual coaching procedures were employed to decrease the severity of behavioral and P3 amplitude deficits in schizophrenic subjects. Although the two procedures were not directly related to behavioral and cognitive training conducted in clinical settings and were used for each subject for only a short period of time during the experiments, they were intended to imitate the actual repeated training conducted over a long period of time in a clinical setting. Hence, the results obtained in this study indicate possible brain mechanisms that underlie the effectiveness of nonpharmacological treatments administered clinically, such as behavioral and cognitive training. More direct evidence for the brain mechanisms could be obtained if the results obtained here were replicated in ERP experiments conducted before and after such actual behavioral and cognitive training.

In summary, ERP measurements are expected to provide valuable data for elucidating the biological mechanisms underlying behavioral remediation of schizophrenic deficits because ERP indices reflect brain function more directly than behavioral outputs. It can be speculated that the difference in behavioral and P3 responses to the coaching procedures employed in this study might be related to differences in responses to actual clinical

nonpharmacological treatments. Reproduction and confirmation of the results obtained in the present study, using control experiments without coaching intervention, will enhance the clinical utility of ERP measurements, which may influence the choice of psychological, behavioral, and cognitive therapeutic approaches and the assessment of the efficacy of a particular treatment. Moreover, the results may shed further light on the role that brain mechanisms play in effective psychological, behavioral, and cognitive treatments.

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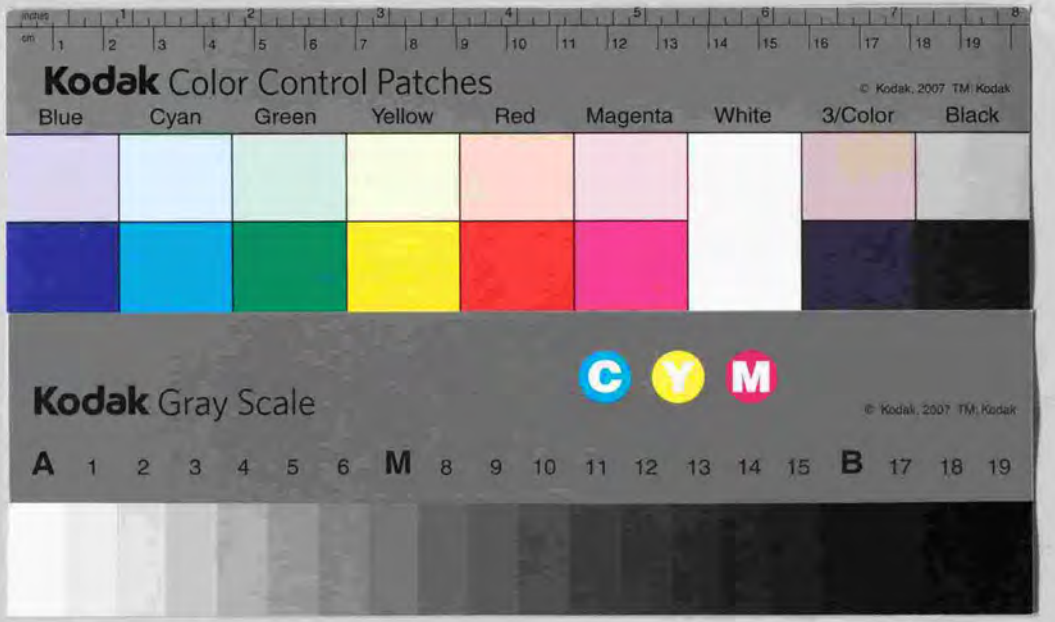
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