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Event-related Potentials in Methamphetamine Psychosis During an Auditory Discrimination Task

A Preliminary Report

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Summary. Auditory event-related potentials (ERPs) during a syllable discrimination task were recorded from 15 patients suffering from methamphetamine (MAP) psychosis after the remission of acute psychotic symptoms, and from 15 normal age-matched controls. Subjects were instructed to press a button in response to the target syllables applied to one designated ear. In MAP psychotics, the attention-related negative components (Nd) area was reduced and P300 latency was delayed compared with normal controls. MAP psychotics and controls did not differ significantly in P300 amplitude. These findings suggest that MAP psychotics show some impairment in the auditory information processing.

Key words: Methamphetamine psychosis – Event-related potential – Nd – P300 – Selective attention

Introduction

Methamphetamine (MAP) psychosis, which is characterized by paranoid symptoms very similar to those of schizophrenia, has been considered to be a model of schizophrenia [1, 2, 8, 21]. In Japan, an epidemic of methamphetamine abuse broke out in the post-war period, but gradually subsided around 1957 [23]. However, since the early 1970s up to the the present, a 'second epidemic' of methamphetamine abuse has dramatically unfolded on a large scale. Consequently the increase in the number of patients with MAP psychosis has turned into a grave psychiatric problem [16, 20]. Contrary to Connell's opinion that patients with amphetamine psychosis generally recover within a week [4], Japanese researchers have often noted that MAP use may result in psychotic symptoms lasting more than several months [7, 23]. In addition, Sato et al. reported that MAP psychosis has a remarkable tendency toward recurrence [20]. These clinical features in MAP psychotics indicate the possibility that MAP psychotics experience some biological changes in their central nervous systems, even after the disappearance of the direct pharmacological effect of MAP.

Event-related potentials are considered to be physiological indices which reflect attentional and cognitive functioning. The attention-related negative components (Nd) refer to negative potentials of ERPs as have been reported by Hillyard et al. [9] and Näätänen et al. [15], which start at approximately 70–100 ms, peaking at approximately 200 ms after the onset of stimulus. They are thought to emerge on the occasions of differential discrimination beween task-relevant and task-irrelevant stimuli, thus implicating selective attentional functioning. The P300 component of event-related potentials, which is elicited by infrequent, task-relevant stimuli, reflects a variety of psychological processes such as attention, effort, and memory function. Sutton et al. [22] first explained the possible cognitive meaning of P300 component as the resolution of uncertainties. Later, Donchin et al. [6] hypothesized that the P300 would reflect context updating or stimulus evaluation. In this study, to examine the hypothesis that MAP psychotics experience some biological changes in their central nervous systems, we investigated auditory event-related potentials of MAP psychotics performing a syllable discrimination task utilizing Nd and P300 as indices.

Subjects and Methods

Subjects

Fifteen right-handed MAP psychotics (11 men, 4 women), who were willing to provide informed consent, were included in this study. All patients were in the residual state following the remission of acute psychotic symptoms. MAP psychotics (aged 20–58 years, mean 33.8, SD 12.3) met the DSM-III-R criteria for "am-

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phetamine or similarly acting sympathomimetic delusional disorder". Exclusion criteria included meeting the DSM-III-R criteria for schizophrenia, major mood disorders, other substance use disorders and having other neurological disorders. All of the MAP psychotics were receiving antipsychotic medication, and the mean daily dosage in chlorpromazine equivalents [5], was 684 mg (SD 549). Symptoms present on the day of testing were rated with the Brief Psychiatric Rating Scale (BPRS). Total scores of BPRS ranged from 4 to 24 (mean 11.1, SD 4.2), indicating that the symptoms of the patients were mild. Fifteen healthy volunteers (11 men, 4 women), serving as the control group, had no history of psychiatric or neurological illness (aged 21–56 years, mean 35.8, SD 9.7).

Event-Related Potential Recordings

Event-related potentials were recorded during a syllable discrimination task similar to that employed by Kamayama et al. [11]. Two consonant-vowel (CV) syllables (/te/ and /ga/), said in a male voice were presented monaurally as stimuli to the subjects through headphones. The frequency ratio in appearance of /te/ and /ga/ was 1:2. The stimuli were presented in a random and alternative pattern to one side or to the other. The subjects were required to press a button as quickly as possible in response to the target syllable, which was the syllable /te/ applied to one designated ear. The duration of each stimulus was 200 ms, the stimulus-intensity being set at approximately 60 dBSL. The inter-stimulus intervals varied randomly between 1200 and 1300 ms. The number of total stimuli was 240. All subjects performed two runs; that is, one run using the left ear and another the right ear. The order of the two runs was randomized among subjects. In Fig. 1, an illustration of a run using the left ear in this syllable discrimination task is shown.

The subjects were seated in an sound-proof room with eyes closed. According to the International 10–20 Electrode System, scalp EEGs were recorded with Ag-AgCl disc electrodes from the midline frontal (Fz), central (Cz), and parietal (Pz) monopolarly referred to linked ear-lobe electrodes. Bandpass was set to 0.15–120 Hz. Vertical and horizontal electro-oculograms were recorded from electrodes placed below and on the outer canthus of the right eye. EEGs were sampled every 4 ms from 100 ms before the onset of stimulus to 924 ms after the onset of stimulus. EEGs contaminated by peak-to-peak potentials of more than 100 μV or accompanied by EOGs of more than 75 μV were eliminated from averaging. Trials in which subjects displayed correct reactions were averaged separately into four categories: 1) target syllables in the attended (chosen) ear; 2) non-target syllables in the attended ear; 3) target syllables in the non-attended ear; 4) non-target syllables in non-attended ear.

Nd was defined as the negative component of a difference wave, spanning the period of 0–400 ms after the onset of stimulus, between ERPs elicited by non-target syllables in the attended ear and those for non-target syllables in the non-attended ear. For the index to represent Nd, Nd areas were employed which were defined as the negative areas appearing 0–400 ms after the onset of stimulus in the difference wave described above. P300 was defined as the most positive peak between 250 and 600 ms after the onset of stimulus. P300 amplitude and latency for targets in the attended ear were employed as the indices representing P300. Amplitudes were measured with respect to an average voltage applied during the 100 ms prestimulus period.

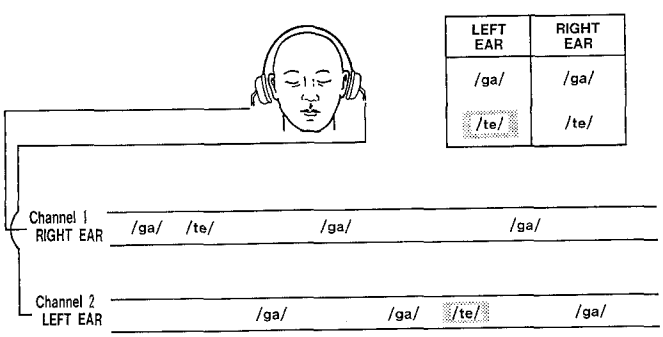

Fig. 1. Illustration of a run in the syllable discrimination task

Statistical Methods

In the following analyses, the means of the two runs (one attended to the left ear and one attended to the right ear) were used. Group differences in Nd area, P300 latency, and P300 amplitude were analysed using analysis of variance (ANOVA), with repeated measures (electrode position). Greenhouse-Geisser corrections were applied when appropriate. Post-hoc comparisons of the means were carried out using Student's t test, if the ANOVA effects were significant. Reaction time and detection accuracy were analysed using t test.

Results

Behavioural Data

Mean reaction time and detection accuracy of the two groups are reported in Table 1. Mean reaction time for MAP psychotics was delayed, in comparison with the controls ($t = 3.24$, $P < 0.01$). MAP psychotics and controls did not differ significantly in detection accuracy.

ERP Components

The grand average ERP waveforms of the two groups are presented in Fig. 2, in which waveforms for the four stimulus categories are shown separately. For both groups, P300 is most clearly elicited by the targets in the attended ear at the Pz region. Figure 3 shows the difference waves for both groups, between ERPs elicited by non-target syllables in the attended ear and those by non-target syllables in the non-attended ear, and the t graph indicating t value for each 4 ms point between both groups. Nd waves for MAP psychotics were reduced, in comparison with the controls. The difference of the Nd waves for the two groups is most clearly observed at Fz and Cz approximately from 100 ms to 300 ms after the onset of stimulus.

Repeated measures of ANOVAs revealed the following results. For the Nd area, there was a group effect ($F = 4.60$, $P < 0.05$) and an electrode position effect ($F = 5.96$, $P < 0.05$). The interaction effect between group and electrode position was not significant. For P300 amplitude, the group effect was not significant, but the electrode position effect was significant ($F = 89.78$, $P < 0.001$). The interaction effect between group and

Table 1. Means (SD) for reaction time and detection accuracy

	MAP psychotics	Controls
RT (ms)	551.8 (93.0)	456.0 (75.4) *
Detection accuracy (%)	98.5 (3.1)	99.3 (2.3)

* $P < 0.01$

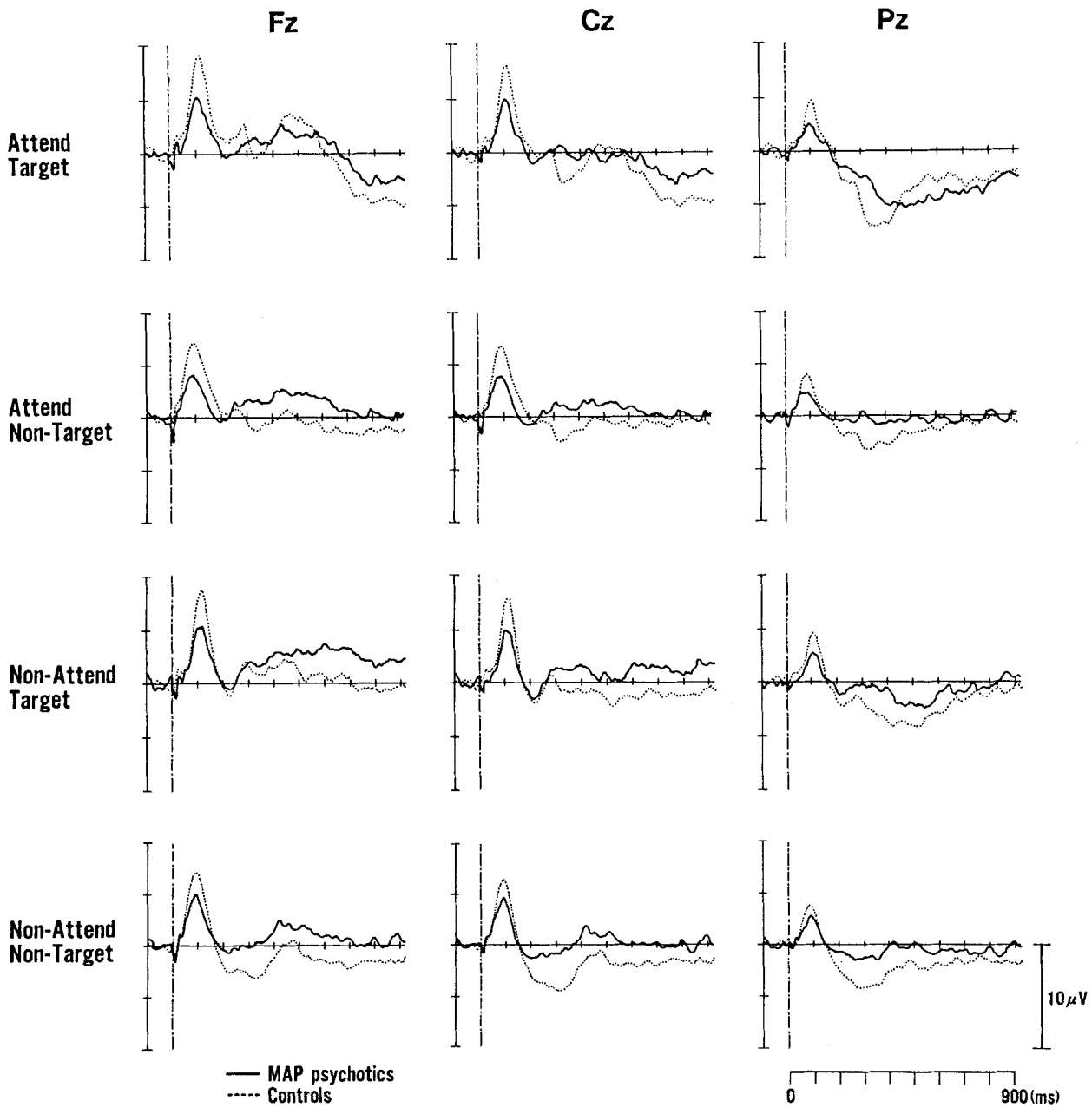

Fig. 2. Grand average ERP wave-forms for each region and stimulus category. "Attend Target": target stimuli presented to the attended ear; "Attend Non-target"; non-target stimuli presented to the attended ear; "Non-Attend Target"; target stimuli presented to the non-attended ear; "Non-Attend Non-Target": non-target stimuli presented to the non-attended ear

electrode position was not significant. For P300 latency, the group effect was significant ($F = 18.17$, $P < 0.001$), but the electrode position effect and the interaction effect were not significant. Table 2 shows the means and standard deviations of Nd area, P300 amplitude, and P300 latency for the two groups.

In both groups, age did not correlate significantly with Nd area, P300 latency, and P300 amplitude at the three electrode positions. In MAP psychotics, the degree of psychopathology (as reflected in the BPRS total scores) did not correlate significantly with Nd area, P300 latency, and P300 amplitude at the three electrode positions.

Effect of Medication

In MAP psychosis, Pearson's product moment correlations for Nd area, P300 latency, and P300 amplitude at the three electrode positions with medication dosage (daily dosage in chlorpromazine equivalents) were calculated. P300 amplitude at Pz correlated negatively with medication dosage ($r = -0.591$, $P < 0.05$). To clarify the effect of antipsychotic medication on ERP indices in MAP psychotics, we divided patients into two groups, namely "Low-dosage group" and "High-dosage group", and compared ERP indices between the two groups.

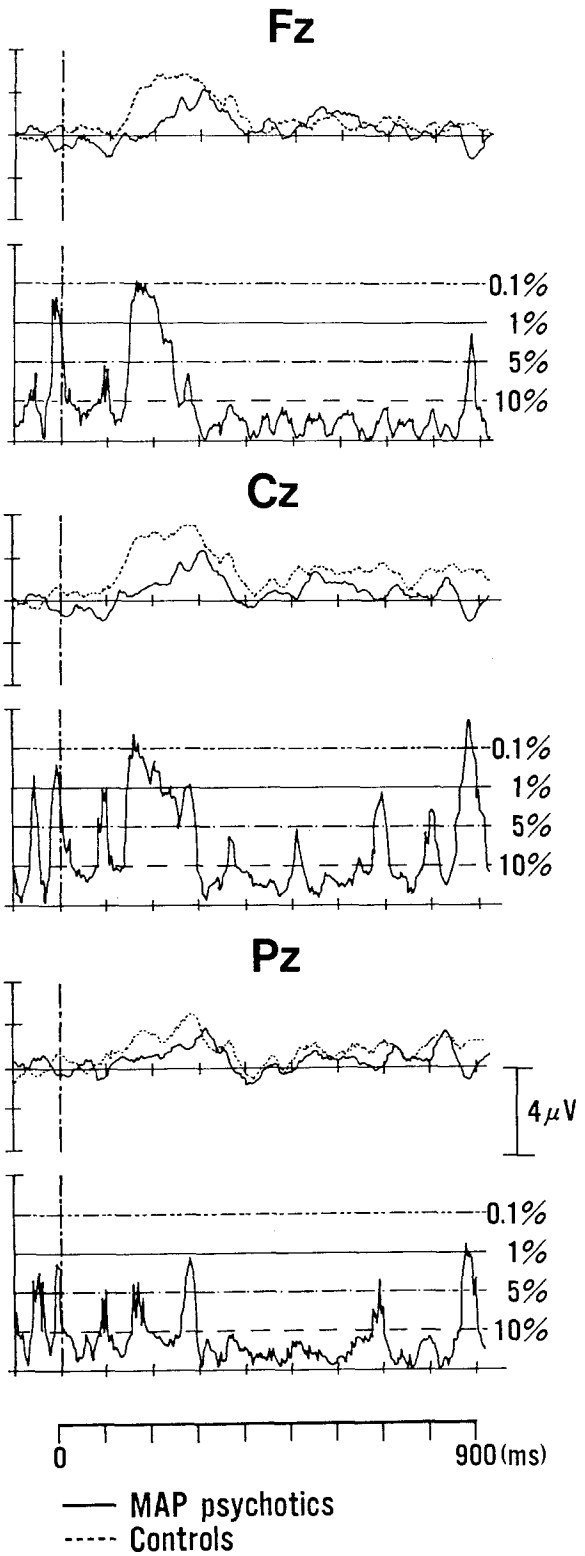

Fig. 3. Difference wave. Upper: Grand average of difference wave for each region (Attend Non-Target minus Non-Attend Non-Target) Lower: t graph indicating t value for each 4 ms point

"Low-dosage group" included 10 patients whose daily dosage was less than 684 mg (mean daily dosage of the 15 patients). "High-dosage group" included 5 patients whose daily dosage was more than 684 mg. The two groups did not differ significantly in age and the degree of psychopathology. The mean daily dosage in "High-dosage group" (1335 mg) was larger (t test: $t = 4.132$, $P < 0.05$) than that in "Low-dosage group" (359 mg). The results were indicated in Fig. 4. P300 amplitudes at Pz region was significantly different in the two groups (t-test: $t = 2.229$, $P < 0.05$).

Table 2. Means (SD) for Nd area (μV × ms), P300 latency (ms), and P300 amplitude (μV)

	MAP psychotics	Controls	
Nd area			
Fz	525.8 (278.1)	883.2 (628.4)	+
Cz	539.9 (304.8)	989.4 (626.0)	*
Pz	488.1 (284.7)	679.7 (362.9)	
P300 latency			
Fz	429.3 (60.0)	358.1 (31.8)	**
Cz	425.5 (50.5)	362.3 (29.8)	**
Pz	428.5 (46.3)	369.6 (30.7)	**
P300 amplitude			
Fz	1.5 (4.1)	2.3 (3.7)	
Cz	3.9 (4.3)	5.2 (4.4)	
Pz	8.2 (5.0)	9.8 (4.8)	

+ $P < 0.1$, * $P < 0.05$, ** $P < 0.001$

Discussion

In this study, MAP psychosis showed reduced Nd area in comparison with controls. Some researchers have reported that both medicated and unmedicated schizophrenics show an attenuated enhancement of N100 (actually superimposed Nd), in response to stimuli presented in an attended channel using selective attention paradigms similar to those employed in this study [3, 11, 14, 19]. Reduced Nd area in MAP psychotics indicated the possibility that MAP psychotics show impairment in auditory information processing similar to that of schizophrenics. Concerning the effect of antipsychotic medication on the Nd area, Kameyama et al. [11] reported that an enhancement of N100 associated with channel selection was not observed in schizophrenics before antipsychotic medication but that it became apparent during the course of antipsychotic medication. They concluded that the deficit in selective attention of schizophrenics is alleviated by antipsychotic medication. Accordingly, it seems reasonable to suppose that reduced Nd area in MAP psychotics in this study is not due to antipsychotic medication.

Kutas et al. [12] reported that P300 latency reflects stimulus evaluation time. Some researchers have noted that P300 latency was delayed when taking antipsychotic medicine [13, 17, 18]. Consequently, delayed P300 latency in MAP psychotics may be in some degree due to the effect of antipsychotic medication. However, no significant correlation was found between medication dosage and P300 latency, and the "Low-dosage group" and the "High-dosage group" did not differ significantly in

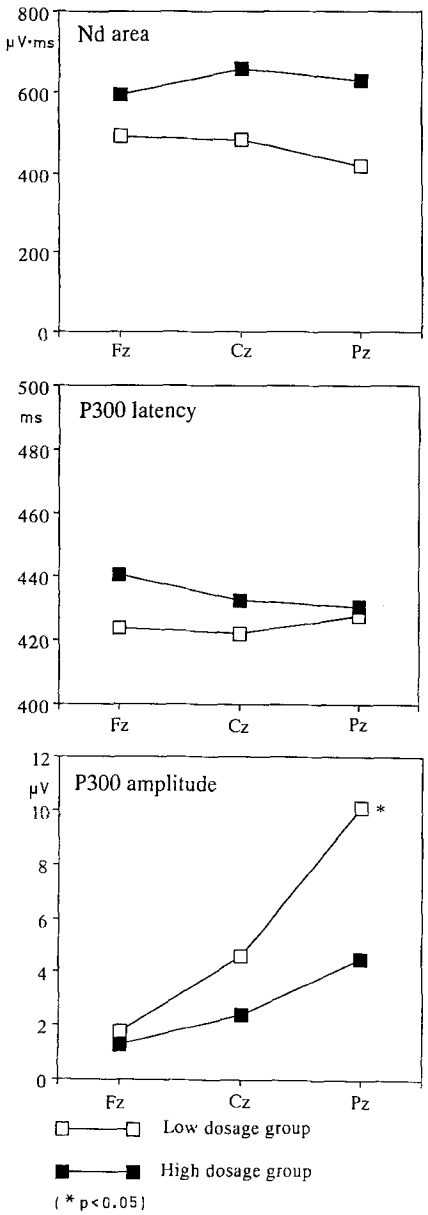

Fig. 4. Means of Nd area, P300 latency, and P300 amplitude for "Low-dosage group" and "High-dosage group"

P300 latency. Consequently, the possibility that delayed P300 latency in MAP psychotics may reflect an impairment of the process of stimulus evaluation can not be denied.

P300 amplitude did not differ significantly between MAP psychotics and controls. This result suggests that MAP psychotics have less cognitive impairment than schizophrenics. In our previous study using an oddball paradigm, P300 amplitude in MAP psychotics was smaller than that of normal controls at Fz and Cz region, but did not vary at Pz [10]. In this study, since the larger Nd area in the controls make the P300 amplitude at Fz and Cz region seem small, P300 amplitude may not differ in the two groups at the three electrode positions. P300 amplitude at Pz correlated negatively with medication dosage in MAP psychosis.

One possible explanation of this finding is to assume that P300 amplitude is affected by antipsychotic medication, which is not in agreement with previous reports [11, 17, 18]. Another possibility is that to assume that MAP psychotics with small P300 amplitude need high dosage of antipsychotic medicine because of their severe cognitive impairment. Further investigations are necessary to clarify the relationships between antipsychotic medication and P300 amplitude.

In the present investigation, MAP psychosis shows reduced Nd area, delayed P300 latency, and normal P300 amplitude. These results suggest that MAP psychotics show some impairment in auditory information processing. However, it is debatable whether these abnormalities of ERPs are entirely due to MAP psychosis since all the patients in this study received antipsychotic medication. Further investigations are in progress to verify the results in this study in an extended sample including unmedicated patients.

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