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ABNORMALITIES IN THE LATE POSITIVE COMPONENTS OF ERPs MAY REFLECT A GENETIC PREDISPOSITION TO SCHIZOPHRENIA*

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Abstract

Event-Related Potentials (ERPs) were recorded in the Cz region during syllable discrimination tasks in siblings of schizophrenic probands. ERPs in these siblings were compared to those of normal controls and schizophrenics. The siblings, like the normal controls, displayed an increase in N100 amplitudes according to the allocation of their attention between two different channels (ears). However, the siblings, unlike the normal controls, failed to demonstrate an augmentation of late positive components upon detection of the target stimuli in the attended channel. The mean amplitudes of the late positive components elicited by the target stimuli in the attended channel for the siblings were nearly equal to those of non-medicated schizophrenics, with these values in siblings being significantly smaller compared to those of the normal controls.

Based on the results of the present study, it was concluded that abnormalities of late positive components in siblings may reflect a genetic predisposition to schizophrenia.

Introduction

It has been noted that auditory Event-Related Potentials (ERPs), especially N100 and P300 components, correlate with selective attentional functioning (Donchin, 1979; Hillyard et al., 1973; Hillyard and Picton, 1979). Accordingly, ERP measurements are considered a useful method of clarifying the pathophysiological bases underlying those diseases that display disturbed attentional functioning as a cardinal symptom. Included among such diseases is schizophrenia; and, a number of studies measuring ERPs in schizophrenics have already been reported (Roth and Cannon, 1972; Levit et al., 1973; Shagass et al., 1977, 1978; Roth et al., 1981; Saitoh et al., in press). These reports concerning ERPs in schizophrenics are nearly consistent in that in all of them schizophrenics demonstrate a reduction in P300 amplitudes.

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We (Hiramatsu et al., in press) reported the results of our investigation in which ERPs were recorded in schizophrenics during syllable discrimination tasks such as those employed by Hink et al. (1978). The schizophrenics employed in our investigation exhibited neither an increase in the N100 amplitudes elicited by stimuli presented to the attended ear, nor an augmentation of the P300 component elicited by target stimuli. From these results, we speculated that schizophrenics demonstrate deficits in "stimulus set" as well as "response set" as defined by Broadbent (1958, 1971).

In recent years, there have been several controversies concerning whether "state" or "trait" is reflected in schizophrenic disorders in this reduction of the P300 component. It is necessary to examine ERPs in biological relatives of schizophrenic probands so as to gain insight into this issue. Previous to this study, however, only Friedman et al. (1982) have reported on whether abnormalities in the P300 reflect a genetic predisposition to schizophrenia. According to Friedman et al., "high-risk children" for schizophrenia showed smaller amplitudes of the late positive components (P350 and P400) as compared to control group children.

Recently, we succeeded in measuring ERPs in siblings of schizophrenic probands —specifically, during the same syllable discrimination tasks employed in our previous study (Hiramatsu et al., in press). In the present report, results for siblings of schizophrenic probands concerning exclusively ERPs derived from the Cz region will be described, in comparison to those of schizophrenics and normal controls.

Method

Subjects

The schizophrenic subjects consisted of 12 medicated patients (6 males and 6 females; ages, 19–39 years; mean ± SD, 29.8 ± 5.6) and 10 non-medicated patients (5 males and 5 females; ages, 24–34 years; mean ± SD, 28.2 ± 3.1). These were the same subjects as used in our previous study (Hiramatsu et al., in press). All of the schizophrenics met the diagnostic criteria of DSM-III for schizophrenic disorders. All of the non-medicated patients had not received any drugs for at least 4 weeks prior to the experiments.

Twenty siblings of schizophrenic probands participated in this study. They consisted of 10 males and 10 females (ages, 18–40 years; mean ± SD, 28.5 ± 6.0). They were selected from among the siblings of a group of schizophrenics treated at the Out-Patient Clinic of the Department of Neuropsychiatry, Tokyo University Hospital, with one sibling only for each proband. This group of schizophrenic probands included 12 of the schizophrenic subjects described above (9 medicated patients, 3 non-medicated patients). All of the twenty siblings of schizophrenic probands (here-after abbreviated as siblings) had no history of psychiatric or neurological disease.

Twenty volunteers with no family history of psychiatric disorders (10 males and 10 females; ages, 20–38 years; mean ± SD, 29.1 ± 4.8) served as the normal control group. These volunteers were the same control subjects also used in our previous study. They had no history of psychiatric or neurological disease.

All of the subjects were free from any hearing disability. There was no difference among the four categories of groups regarding male/female ratios or age.

Procedure

Syllable discrimination tasks were employed in this experiment. Four CV-syllables (/ba/, /da/, /ga/, /za/) by a male voice were presented to one ear, with the same four CV-syllables by a female voice presented to the other ear through headphones monaurally. The four CV-syllables by both the male and the female voice were digitized and stored in a mini-computer (DEC, LSI-11/2) and were modified in waveshape into a duration of 150 msec. Each of the eight stimuli was presented randomly with an equal a priori probability of 0.125. The syllables by the male voice were placed in one channel (ear) and those by the female voice in another channel and presented through stereo-headphones (TEAC, HP102) monaurally, with an intensity of approximately 60 dBSL. The interstimulus intervals ranged between 800–1,000 msec.

The subjects were seated in an anechoic room with eyes closed. They were informed that a male voice would be presented to one ear, and a female voice to the other ear, and were asked to silently count the number of occurrences of a particular target syllable in a given ear in each run. All of the subjects performed 16 runs: that is, four target syllables x two voices (male or female) x two attended channels (left or right ear). The order of the 16 runs was randomized for all subjects, with the number of the target syllables for each run being set between 18–26. After the conclusion of each run, the subjects were asked to give the number of target stimuli detected.

EEG Recording and Data Analysis

EEGs were recorded in the Cz, T3, and T4 regions monopolarly, utilizing linked earlobe electrodes as references (electrodes: Ag/AgCl). The EEGs were then amplified using DC pre-amplifiers (bandpass down 6 dB at 1.5 and 300 Hz) (YHP, 8811A) and recorded on FM analog tape along with the stimulus signals (data recorder: TEAC, R-252). After the experiment, the EEGs without artifacts were passed through a bandpass filter set at 1.5 to 25 Hz, and digitized at a sampling rate frequency of 250 Hz/CH. Subsequently, the EEGs were averaged using a laboratory mini-computer (DEC, LSI-11/2). The averaging period began 20 msec before each stimulus onset and lasted for 620 msec thereafter. A total of 56 or 112 EEG data was averaged for each ERP, and printed out by an X-Y plotter.

Each of the ERP components was labeled as follows. N100 was the most negative peak in the 56–156 msec period after a stimulus onset. P200 was the most positive peak in the 40–120 msec period after the N100 peak. The late positive component (including the P300 component) was a component of the ERP in the 50–330 msec period after the P200 peak. Hereafter, the mean amplitude of the late positive component (summated amplitudes during a given period/length of time) will be abbreviated as "LPC." The amplitudes of the N100 and LPC were measured employing a mini-computer and printed out by a line printer. Each amplitude of the ERP components was measured with respect to a 20 msec pre- and post-stimulus baseline used as the zero level.

Statistical Analysis

Statistical analysis was performed on the data concerning the amplitudes of the N100 component as well as the LPC derived from the Cz region using an analysis of variance (ANOVA, Statistical Package for the Social Sciences, 8th Edition).

In the ANOVA, AGE (years) was employed as a covariate, with CHANNEL (attend/non-attend), SYLLABLE (target syllable/non-target syllable), EAR (left/right) and SEX (male/female) as independent variables. When the data were compared between two groups out of the four category groups, GROUP (medicated schizophrenia/non-medicated schizophrenia/sibling/normal control) was added to the independent variables.

Results

Only the results concerning the N100 component and the LPC derived from the Cz region will be reported here. The data for the normal controls and the schizophrenics are cited in part from our previous study (Hiramatsu et al., in press).

Amplitudes of the N100 Component

The data concerning amplitudes of the N100 component were first analyzed within each category group using the ANOVA. The results of this analysis revealed a main effect for CHANNEL significant in the siblings [$F(1,143) = 6.575$, $p < 0.02$] as well as the normal controls [$F(1,143) = 4.609$, $p < 0.04$] (Normal controls: attended channel, $4.07 \pm 1.88\ \mu V$; non-attended channel, $3.53 \pm 1.40\ \mu V$/siblings: attended channel, $3.60 \pm 1.57\ \mu V$; non-attended channel, $3.02 \pm 1.45\ \mu V$). However, the main effect for CHANNEL was not significant in either the medicated or non-medicated schizophrenics. (Medicated schizophrenics: attended channel, $3.46 \pm 2.21\ \mu V$; non-attended channel, $3.24 \pm 2.30\ \mu V$/non-medicated schizophrenics. attended channel, $3.59 \pm 1.59\ \mu V$; non-attended channel, $3.30 \pm 1.51\ \mu V$.)

In the next step, the data concerning the amplitudes of the N100 component for the siblings were compared with those of the other three category groups separately using the ANOVA. The results of this analysis revealed a main effect for GROUP which was significant in the comparison between the siblings and the normal controls [$F(1,287) = 6.312$, $p < 0.02$].

The results described above can be summarized as follows. Although the siblings displayed smaller amplitudes of the N100 component as compared to the normal controls, both the siblings and the normal controls demonstrated an increase in the amplitudes of the N100 component elicited by stimuli presented to the attended channel (ear). On the other hand, the medicated as well as the non-medicated schizophrenics failed to show such an increase in the amplitudes of the N100 component due to channel-selective attention (see Fig. 1).

Mean Amplitudes of the Late Positive Component (LPCs)

As in the case of the amplitudes of the N100 component, the data concerning the LPCs were first analyzed within each category group using the ANOVA. The results of this analysis revealed a main effect for SYLLABLE significant only in the

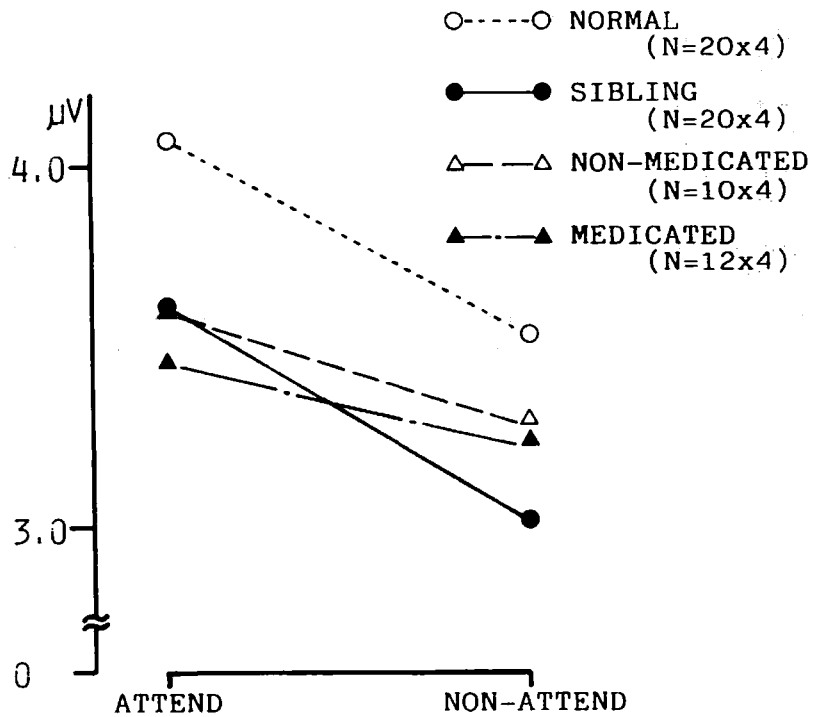

Fig. 1 *Mean amplitudes of the N100 component in the Cz region elicited by stimuli presented to the attended, as well as non-attended, channel (ear) for each category group.*

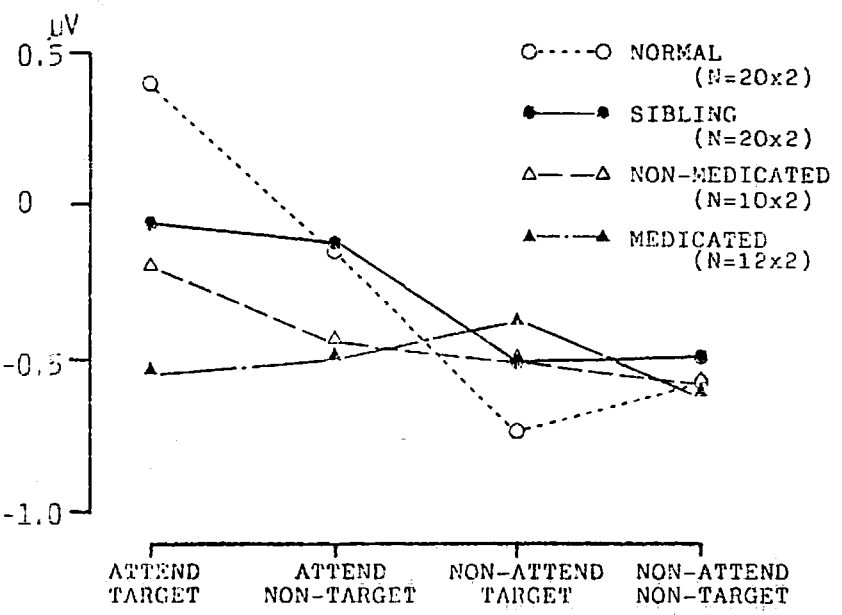

Fig. 2 *Mean LPCs in the Cz region for each category group and condition. Attend Target: Target stimuli in the attended channel; Attend Non-Target: Non-Target stimuli in the attended channel; Non-Attend Target: The same syllables as the target stimuli in the non-attended channel; Non-Attend Non-Target: different syllables from the target stimuli in the non-attended channel.*

normal controls [$F(1,71) = 7.628$, $p < 0.007$] (see Fig. 2).

In the next step, the LPCs elicited by the target stimuli presented to the attended channel (ear) in the siblings were compared to those of the other three category groups separately using the ANOVA. The results revealed a main effect for GROUP significant in the comparison between the siblings and the normal controls [$F(1,75) = 6.087$, $p < 0.02$]. (Normal controls. $0.40 \pm 0.97\ \mu V$; siblings. $-0.06 \pm 0.72\ \mu V$. See Fig. 3). The results also revealed that the main effect for GROUP was significant in the comparison between the siblings and the medicated schizophrenics [$F(1,55) = 4.754$, $p < 0.04$]. (Medicated schizophrenics: $-0.53 \pm 0.83\ \mu V$. See Fig. 3.) However, this main effect for GROUP was not significant in the comparison between the siblings and the non-medicated schizophrenics. (Non-medicated schizophrenics: $-0.19 \pm 0.71\ \mu V$. See Fig. 3.)

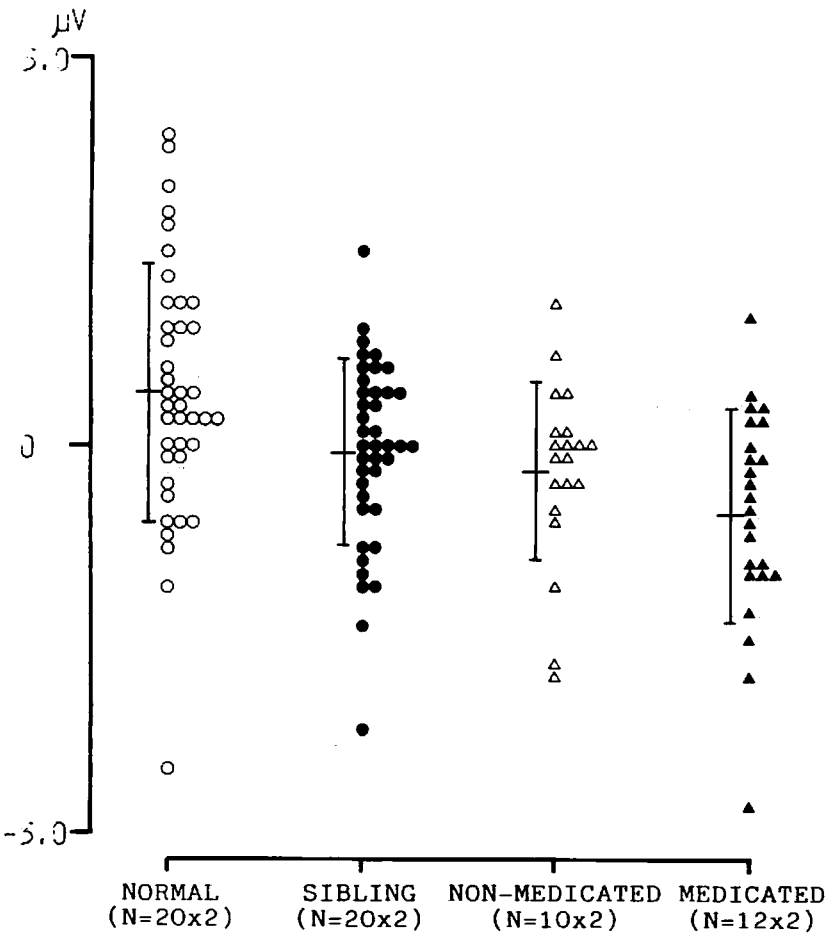

Fig. 3 *LPCs in the Cz region elicited by the target stimuli in the attended channel for each category group. The LPCs for both sides of the attended channel are plotted for each subject.*

Summarizing the results described above, the following can be said. The siblings, as well as both groups of schizophrenics, failed to demonstrate an augmentation in LPCs for the target stimuli in the attended channel (ear). However, the normal controls alone exhibited such an augmentation in LPCs. In addition, the LPCs

for the target stimuli presented to the attended channel (ear) in the siblings were nearly equal to those of the non-medicated schizophrenics. The siblings displayed significantly smaller LPCs to the target stimuli in the attended channel as compared to the normal controls.

Discussion

Syllable discrimination tasks such as those employed in this study require subjects to activate two sets of selective attention. In performing these tasks, subjects first pay attention to one channel (ear), ignoring stimuli presented to the other channel (ear). That is, channel-selective attention is activated in the first step. Next, subjects must discriminate the target syllables from the non-target syllables among the stimuli presented to the attended channel (ear). The processes of stimulus evaluation, decision making and response organization comprise the second step of selective attention. According to Broadbent (1958, 1971), the former step corresponds to the "stimulus set", with the latter step corresponding to the "response set".

Based on the results of their experiment employing syllable discrimination tasks, Hillyard in collaboration with Hink (Hink et al., 1978) hypothesized that the "stimulus set" was reflected in the N100 component, with the "response set" being reflected in the P300 component. However, this hypothesis of Hink et al., specifically concerning the relationship between the "stimulus set" and the N100 component, was challenged by the work of Näätänen and Michie (1979a, b) who reported the existence of an endogenous negative shift reflecting an orienting to, and processing of, relevant input.

Later, Hillyard and his associates (Hansen and Hillyard, 1980; Hillyard, 1981) also found that an endogenous, prolonged negative shift summated algebraically with the evoked N100 component, with the amplitude of this negativity varying according to subjects' allocation of their attention among several different channels.

On the other hand, the cognitive implications of the P300 component have also been inferred differently from Hillyard and his associates. Donchin and his colleagues (Kutas et al., 1977; Donchin, 1979; Donchin and Isreal, 1980) related the P300 component to a stimulus evaluation process as well as a context-revision process. In addition, Kutas et al. (1977) suggested a dissociation of the P300 component from the response selection or initiation processes. Desmedt (1980) has speculated that the P300 component reflects the post-decisional "closure" of cognitive activity.

Although these interpretations regarding the functional significance of the P300 component by several different investigators are not mutually consistent, they are all similar in that the P300 is thought to correlate with the later stages of information processing, specifically with the processes of stimulus evaluation, decision making, and context-updating.

As was described above, our normal controls demonstrated an increase in the amplitudes of the N100 component due to channel-selective attention. Moreover, the normal controls exhibited an augmentation in LPCs upon detection of the targets. Therefore, it can be concluded that the results of Hink et al. (1978) have

been replicated in our study.

Based on the results described above for the normal controls, it seems reasonable to assume that the N100 component relates to channel-selective attention (the "stimulus set"), with the P300 component relating to stimulus evaluation as well as decision making (the "response set"), though other controversies will probably persist regarding the complete functional significance of the N100 as well as the P300 components.

What can be deduced from the results obtained in the present study for the siblings of schizophrenic probands? It is well known that siblings of schizophrenic probands have a greater predisposition to schizophrenia (e.g., Kety et al., 1968 Slater and Cowie, 1971). Furthermore, the siblings of schizophrenic probands employed in this study had no history of psychiatric or neurological disease. Hence, the differences in the ERP findings between the siblings and the normal controls, as well as the similarlities in the ERPs between the siblings and the schizophrenics, can be regarded as reflections of a genetic predisposition to schizophrenia.

The siblings in the present study demonstrated an increase in the N100 component due to channel-selective attention. This result was similar to that for the normal controls, but different from the results for both schizophrenic groups. On the other hand, the siblings, similar to both of the schizophrenic groups, failed to demonstrate an augmentation in LPCs upon detection of the target stimuli. This result was different from that for the normal controls. Although not described in detail in the present report, the performance levels in the syllable discrimination tasks for the siblings, as expressed by their Error Indexes (EIs), were higher than those of both schizophrenic groups. However, the differences between the siblings and the schizophrenics did not reach statistical significance. The EIs were calculated according to the following formula.

$$EI = \frac{|\text{number of targets} - \text{subject's answer}|}{\text{number of targets}} \times 100$$

The exact value of the EI for each category group is shown below. Normal controls: 5.6 ± 12.9 (mean ± SD)/siblings: 18.0 ± 28.2/non-medicated schizophrenics: 31.9 ± 51.9/medicated schizophrenics. 21.4 ± 28.8. These figures seem to indicate that the siblings as well as the schizophrenics were rather motivated and concentrated fairly well on the required tasks, since the mean EIs of the siblings and the schizophrenics were far smaller than the expected EI value if they had counted the number of target stimuli in a random manner, that is approximately 300.

Therefore, it can be concluded that the abnormalities of the LPCs in the siblings, particularly the reduction in the LPCs and the lack of augmentation in the LPCs upon detection of target stimuli, may reflect a genetic predisposition to schizophrenia. In other words, disturbances in "response set" may be genetically determined. This conclusion also seems consistent with that of Friedman et al. (1982), who measured ERPs in "high-risk children". They found that abnormalities in the late positive components of ERPs suggest a high risk for schizophrenia.

Mednick and Schulsinger (1968) and Venables (1977) reported abnormalities of skin conductance responses in high-risk children for schizophrenia. Holzman et al. (1974, 1977) reported abnormal smooth-pursuit eye movements in biological relatives of schizophrenics. At the present time, however, the literature concerning

the possible physiological markers of a predisposition to schizophrenia is relatively small. Hence, further studies employing ERP measurements in biological relatives of schizophrenics can be expected to privide valuable information for clarifying the pathogenesis of schizophrenia.

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