Abnormal Photic Driving Responses in Never-Medicated Schizophrenia Patients

by Yuji Wada, Yuko Takizawa, and Narlyoshi Yamaguchi

Abstract

The present study was conducted to compare electroencephalogram (EEG) driving responses to 10 hertz photic stimulation in 14 drug-naive schizophrenia patients and 16 sex- and age-matched control subjects. The amplitude of photic driving responses (PDRs) recorded from the occipital region was significantly lower in schizophrenia patients than in controls. In eight schizophrenia patients (vs. none in the control group) the PDR amplitudes recorded at the frontal region were higher than those at the occipital region, and frontal to occipital PDR ratios were significantly larger in schizophrenia subjects than in controls. Quantitative analysis of the resting EEG showed that the patients also had a significantly lower amplitude for the alpha frequency band. These findings suggest that the PDRs of schizophrenia patients are abnormal in their amplitude and distribution.


Photic driving responses (PDRs), which refer to synchronization of the electroencephalogram (EEG) rhythm with the frequency of photic stimulation, have commonly been recorded in routine EEG examinations (Takahashi 1989). Although numerous EEG abnormalities have been reported in schizophrenia (for reviews, see Morihisa 1986; Shagass 1991), only a few studies have focused on PDRs in this disorder. Previous PDR studies of schizophrenia patients have used both patients who were currently taking medication (Matsue et al. 1982) and patients who had been withdrawn from neuroleptic medication (Jin et al. 1990). Human and animal studies have shown, however, that neuroleptic drugs can affect various aspects of PDRs (Jørgensen and Wulff 1958; Wilson and Glotfelty 1958; Killam et al. 1967). In addition, neuroleptic medication has been reported to cause neurochemical changes that persist for several months after drug withdrawal (Clow et al. 1980). These findings raise the possibility that the results of previous PDR studies may have been influenced by neuroleptic medication or medication withdrawal effects. In the present study, therefore, we assessed PDRs in neuroleptic-naive schizophrenia subjects by means of averaging techniques, which have been shown to be useful in this regard (Matsue et al. 1982; Wada et al. 1992).

Methods

Subjects. The subjects were 14 schizophrenia patients (7 men and 7 women) who were diagnosed according to DSM-III-R criteria (American Psychiatric Association 1987). Thirteen patients met DSM-III-R criteria for paranoid type and one for undifferentiated type. None of the patients had ever been treated with neuroleptic drugs. Their mean age (± standard deviation [SD]) was 22.8 ± 3.95 years (range = 19–29 years); the mean duration of illness, 1.8 ± 1.54 years (range = 0.5–4 years); and the mean age at onset, 18.5 ±

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3.10 years (range = 16–24 years). The control group consisted of 16 healthy volunteers (8 men and 8 women) with no personal or family history of psychiatric or neurologic abnormality. Their mean age was 22.1 ± 2.41 years (range = 19–26 years). Patients were not significantly different from controls in age and gender.

Procedure. Subjects were seated in a soundproof, darkened recording room. Electrodes were attached to the scalp with paste, according to the International 10-20 System. Monopolar derivation with linked ear lobe reference was used with low and high cut filters set at 0.3 second and 60 hertz (Hz), respectively. Impedance of electrode/skin conductance was kept below 5,000 Ω. A 10- to 15-minute resting EEG was recorded for each subject in the eyes closed–alert condition, followed by a 30-second photic stimulation to obtain PDRs. The photic stimulation used was a white flicker at 10 flashes/second delivered by a photostimulator and a stroboscopic lamp placed 25 cm from the subject’s eyes. All subjects were instructed to relax and keep their eyes closed throughout the testing period. Great care was taken to minimize eye movements and blinks, and movements that did occur were monitored by bipolar electrooculogram derivations. The PDRs were analyzed on the EEGs recorded from the frontal (Fz), central (Cz), and occipital (Oz) leads. The analysis time was 500 ms, and fifty 500-ms epochs were averaged using a Signal Processor 7T18A (Nihon Denki San-ei, Tokyo). The computer sampling rate was 2,048 data points/second for PDR measurements. Since the initial part of the recording was occasionally contaminated by artifacts, we started to analyze PDRs 2 seconds after the beginning of photic stimulation. During the test period, every effort was made to keep the subject alert, and EEG recording contaminated by eye movements, blinks, or muscle activity were excluded from the data analysis. The amplitude of each PDR was measured (i.e., height of “a–b” in figure 1A), and their mean value was regarded as the PDR amplitude.

Quantitative analysis of the resting EEG was also performed at the Fz, Cz, and Oz using a Signal Processor 7T18A. An artifact-free epoch of 5-second duration was subjected to spectral analysis by a fast Fourier transform to yield a spectrum over the range of 2 to 30 Hz. A total of 24 epochs per subject were processed. To calculate absolute EEG power, the frequency spectrum was divided into 0.2 Hz bands and collapsed into EEG frequency bands of delta (2.0–3.8 Hz), theta (4.0–7.8 Hz), alpha 1 (8.0–8.8 Hz), alpha 2 (9.0–12.8 Hz), beta 1 (13.0–19.8 Hz), and beta 2 (20.0–29.8 Hz). The square root of absolute power was then calculated to yield the band amplitude of each frequency band.

The Mann-Whitney U test was used to compare the two groups. Statistical significance was defined as p < 0.05.

Results

Figure 1 shows examples of averaged PDRs provoked by 10-Hz white flicker stimulation in a control subject and a schizophrenia patient. The PDRs were easily discernible and well sustained for 500 ms, and they could be accurately assessed and quantified. As shown in table 1, the mean amplitude of PDRs recorded from the occipital region was significantly lower in the schizophrenia subjects than in the controls (U = 58, p < 0.05). No significant difference was
Table 1. Photic driving responses (PDRs) in schizophrenia patients and normal subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PDR amplitude (µV)</th>
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<th>FO ratio</th>
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<tr>
<td></td>
<td>Fz</td>
<td>Cz</td>
<td>Oz</td>
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<tr>
<td>Schizophrenia</td>
<td>10.0 ± 3.7</td>
<td>10.3 ± 3.5</td>
<td>10.5 ± 5.1</td>
<td>1.11 ± 0.58</td>
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<tr>
<td>Controls (n = 16)</td>
<td>11.1 ± 3.9</td>
<td>11.9 ± 4.5</td>
<td>14.5 ± 3.9</td>
<td>0.69 ± 0.20</td>
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Note.—Values are mean ± standard deviation. Fz = frontal; Cz = central; Oz = occipital.

1p < 0.05.
2p < 0.02.

found between the two groups in PDR amplitudes at the Fz or Cz. In this study, frontal to occipital PDR ratios (FO ratios) were calculated in each subject by dividing the PDR amplitude at the Fz by that at the Oz. Eight of the 14 patients showed FO ratios above 1.0 (vs. none in the control group), and the schizophrenia patients had significantly greater FO ratios when compared with the controls (U = 50.5, p < 0.02). There were no significant gender differences in PDR amplitude in either the schizophrenia or control groups, although the females in both groups tended to show a higher PDR amplitude than the males at the Oz.

As shown in figure 2A, the schizophrenia patients had a significantly lower alpha 2 amplitude in the resting EEG than the controls at the three electrode sites evaluated. There were also significant group differences in the alpha 1 amplitude at the Cz and Oz (figure 2B). In contrast, no significant differences were found between the two groups in the amplitude for delta, theta, beta 1, or beta 2 band.

Discussion

The present study shows that PDR amplitudes recorded from the occipital area are significantly lower in drug-naïve schizophrenia subjects than in sex- and age-matched controls. This finding is consistent with the recent PDR study of Jin et al. (1990), who conducted spectral analysis of EEGs during photic stimulation in schizophrenia patients after a medication washout period of 2 weeks and found that schizophrenia subjects showed significantly reduced PDRs in the alpha range compared with normal subjects. Shetty (1971) has reported that in hyperkinetic children PDRs are inhibited by the administration of amphetamine, which is known to produce or exacerbate schizophrenic symptoms. Conversely, it has been shown that neuroleptic drugs can enhance various aspects of PDRs in humans (Jorgensen and Wulff 1958; Wilson and Glotfelty 1958) and in the baboon (Killam et al. 1967). Although the exact mechanism of the PDR generation is unclear, these findings suggest that the lower PDR amplitudes of schizophrenia patients seen in the present study may relate to neurochemical dysfunction in schizophrenia.

In addition to reduced PDR amplitudes in the occipital region, the present study shows that FO ratios are significantly larger in schizophrenia patients than in controls. PDRs are known to be provoked predominantly in the occipital area. In eight of our schizophrenia patients (57.1%), however, PDR

Figure 2. Mean (±) standard deviation amplitude for alpha 2 (A) and alpha 1 (B) bands in the resting EEG of schizophrenia patients (○, n = 14) and controls (●, n = 16)

A

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<thead>
<tr>
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<th>Alpha 2 band amplitude (µV)</th>
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<tbody>
<tr>
<td>Fz</td>
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<tr>
<td>Cz</td>
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<td>Oz</td>
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B

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<tr>
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<th>Alpha 1 band amplitude (µV)</th>
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<tr>
<td>Fz</td>
<td>*</td>
</tr>
<tr>
<td>Cz</td>
<td>**</td>
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<td>Oz</td>
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*p < 0.01, **p < 0.001. EEG = electroencephalogram; Fz = frontal; Cz = central; Oz = occipital.
amplitudes recorded in the frontal region were higher than those in the occipital region, indicating the absence of occipital PDR predominance in these patients. Matsue et al. (1982) reported a similar result. They found that schizophrenia subjects tended to show larger FO ratios compared with normal controls, although their patients were receiving long-term antipsychotic medications. They also reported that FO ratios in normal controls became larger when they performed a task that distracted attention, suggesting that abnormal PDR distribution may reflect attention disturbance in schizophrenia. In addition to the direct effects of neuroleptic drugs on PDRs, some effects of long-term medication, such as the increased stimulation of striatal adenylate cyclase by dopamine, have been shown to persist unchanged for 6 months after drug withdrawal (Clow et al. 1980). Korpi et al. (1984) have reported that haloperidol and its active metabolite can be detected in the postmortem brain 72 days after the last administration of this drug. However, since no patients in our study had previously received neuroleptic medication, the reduced PDR amplitudes and abnormal PDR distribution do not result from the direct action of drugs or the effects of drug withdrawal.

It has been demonstrated that PDR production relates to mechanisms underlying alpha rhythm generation in the resting EEG (Barlow 1960; Inouye et al. 1980). In the present study, therefore, quantitative analysis of the resting EEG was also performed for a 2-minute period for each subject. The analysis showed that the schizophrenia patients had a significantly lower alpha band amplitude than the control subjects (figure 2). Our findings are consistent with those of earlier studies showing reduced alpha activity in schizophrenia patients (Morihisa 1986; Shagass 1991). Although previous studies have also demonstrated that schizophrenia subjects have more slow activity than normal controls (Morihisa 1986; Shagass 1991), the present study showed no significant group differences in EEG amplitude for delta and theta bands. This discrepancy may relate to differences in the clinical background of the patients. Most of our subjects were patients in the acute phase, whereas previous studies have almost exclusively investigated chronic schizophrenia patients. Our findings are consistent with those of Fenton et al. (1980), who demonstrated that patients with acute schizophrenia showed only reduced alpha activity. Williamson and Mamelak (1987) also reported no significant difference in delta activity between acute schizophrenia subjects and healthy controls. In addition, most of our patients were diagnosed as paranoid type, which has been reported to show less marked EEG abnormality than other schizophrenia subtypes (Kessler and Kling 1991; Nagase et al. 1992).

Because of the small number of patients, caution must be exercised in drawing any conclusion from this study. However, our findings do suggest that the PDRs of schizophrenia patients are abnormal in their amplitude and distribution. A full exploration of the confused variables, such as subtypes of diagnosis and clinical symptomatology, will require a much larger sample. Further studies are also necessary to determine the neural mechanism underlying PDR abnormalities in schizophrenia.

References


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