Eur Arch Psychiatry Clin Neurosci (1994) 244:247–251

ORIGINAL PAPER

Yuji Wada · Yuko Takizawa · Saeko Kitazawa
Jiang Zheng-Yan · Nariyoshi Yamaguchi

Quantitative EEG analysis at rest and during photic stimulation in drug-naive patients with first-episode paranoid schizophrenia

Received: 5 January 1994 / Accepted: 13 June 1994

Abstract In the present study, quantitative EEG analysis was performed at rest and during 10 Hz photic stimulation in 14 drug-naive paitents with first-episode paranoid schizophrenia and 20 sex- and age-matched control subjects. Compared with the normal controls, the patients had significantly lower alpha-2 band amplitude in the resting EEG over all recording regions. No significant group differences were found in other frequency bands. In addition, EEG analysis during photic stimulation demonstrated that the patients had a rather uniform topographic profile in EEG amplitude for the alpha band, with significant group differences being confined to the posterior regions in the left hemisphere. There were no significant group differences in the amplitude for the frequency bands harmonically related to the stimulus frequency. These findings provide further evidence that schizophrenic patients have abnormal EEG activity in both non-stimulus and stimulus conditions, and suggest a dysfunction in the mechanisms underlying EEG alpha generation in schizophrenia.

Key words Quantitative EEG · Schizophrenia · Photic stimulation

Introduction

Recent advances in computerized EEG have made possible the sophisticated analysis of a large amount of EEG data, and numerous studies have dealt with quantitative EEG analysis of schizophrenic patients. Although there is agreement that a significant portion of schizophrenic patients have abnormal EEGs such as alpha reduction and an increase in slow activity (reviews in Morihisa 1986; Shagass 1991), differences in such abnormalities among subgroups of schizophrenics have not been well documented. In addition, the possible influence of neuroleptic treatment on these results is still debated.

Photic driving responses (PDRs) refer to synchronization of the EEG rhythm with the frequency identical or harmonically related to the frequency of photic stimulation. Although PDRs are commonly conducted in routine EEG examinations and have been validated as a useful tool to investigate neurological disorders (Takahashi 1987), few PDR studies have been conducted in schizophrenic patients. Recently, Rice et al. (1989) and Jin et al. (1990) conducted spectral EEG analysis during photic stimulation and showed attenuated PDRs in schizophrenic patients. However, these studies used patients who had been withdrawn from neuroleptic medication. Human and animal studies have shown that neuroleptic drugs can affect various aspects of PDRs (Wilson and Glotfelty 1958; Jörgensen and Wulff 1958; Killam et al. 1968). It is also reported that neuroleptic medication can cause neurochemical changes which persist for several months after drug withdrawal (Clow et al. 1980). These findings raise the possibility that the results of the previous PDR studies may have been influenced by medication withdrawal effects. In addition, the previous studies assessed PDRs at the limited recording sites (Rice et al. 1989; Jin et al. 1990), and the topographic PDR abnormality was unclear.

In the present study, therefore, quantitative EEG analysis was performed at rest and during photic stimulation at 16 electrode sites in never-medicated patients with first-episode paranoid schizophrenia, and showed that schizophrenics had abnormal EEG activity in both conditions.

Yuji Wada (✉) · Jiang Zheng-Yan · Nariyoshi Yamaguchi
Department of Neuropsychiatry,
Kanazawa University School of Medicine,
13-1 Takara-machi, Kanazawa 920, Japan

Yuko Takizawa · Saeko Kitazawa
Central Clinical Laboratory, Kanazawa University Hospital,
Kanazawa 920, Japan

Subjects and methods

Subjects

The patient group consisted of 14 patients (7 men and 7 women) who consulted the psychiatric outpatient clinic of Kanazawa University Hospital for the first time and fulfilled DSM-III-R criteria

for paranoid schizophrenia. None of the patients had ever been treated with neuroleptic drugs or had a history of neurological disorder or substance abuse. Their mean age (± S.D.) was 23.3 ± 4.15 years (range, 19–29 years); the mean duration of illness, 1.7 ± 1.69 years (range 0.5–4 years); and the mean age at onset, 18.8 ± 3.11 years (range, 16–24 years). All patients were in the first episode of psychosis and showed predominantly positive symptoms such as delusional ideas and auditory hallucination for 7.1 ± 5.8 months (range, 1–19 months).

The control group consisted of 20 healthy volunteers (10 men and 10 women) with no personal or family history of psychiatric or neurologic abnormality. Their mean age was 23.1 ± 2.51 years (range, 19–26 years). Patients were not significantly different from controls in age or gender.

All patients and control subjects were right-handed. They agreed to participate in the study with full knowledge of the experimental nature of the research.

EEG recording and analysis

All subjects were studied while seated within a soundproof, light controlled recording room. Standard scalp electrodes were attached to the scalp with paste, according to the International 10–20 System. The EEG was recorded with an 18-channel electroencephalograph (EEG-4418, Nihon Kohden, Tokyo) at the following 16 electrode sites: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, Fz, Pz, T5, T6. In addition, movements of the eye and of the lid were monitored by bipolar EOG derivations. Monopolar derivation with linked ear lobe reference was used with low and high cut filters set at 0.3 sec and 60 Hz, respectively. Impedance of electrode-skin conductance was kept below 5,000 Ω. Ten to 15 minutes of EEG were recorded for each subject in the eyes closed-alert condition. Selection of EEG segments was done by visual inspection of EEG and EOG recordings, and segments containing eye movements, blinks, or muscle activity were excluded from the analyses. The process of eliminating contaminated data was performed blind to diagnosis. Quantitative EEG analysis was performed using a Signal Processor 7T18A (Nihon Denki San-ei, Tokyo). An artifact-free epoch of 5-sec duration was subjected to spectral analysis by a fast Fourier transformation, to yield a spectrum over the range of 2–30 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).

Photic driving responses (PDRs)

After a routine EEG examination, a photic stimulation was given to each subject for 30 sec to obtain PDRs. The photic stimulation used was a white flicker at 10 flashes/sec with flash intensity of 5023 cd/m^2, which was 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. Three artifact-free 5-sec epochs were selected. EEG power during photic stimulation was analyzed using the same procedure described above for the non-stimulus condition. In order to evaluate fundamental PDRs elicited by 10 Hz photic stimulation, we calculated the EEG power of the alpha band from 9.8 to 10.2 Hz. The EEG power of the theta (4.8–5.2 Hz) and beta frequency bands (19.8–20.2 Hz) were also calculated to evaluate PDRs harmonically related to the stimulus frequency (Rice et al. 1989; Wada et al. 1994).

Statistics

The square root of absolute power was calculated to yield the band amplitude of each frequency band. Differences between control subjects and schizophrenic patients were analyzed using a two-way analysis of variance (ANOVA) with repeated measures, followed by two-tailed Student's t-test. Statistical significance was defined as $P < 0.05$.

Results

EEG activity in non-stimulus condition

The repeated measures ANOVA showed no significant diagnosis-related differences in the EEG amplitude for the delta, theta, beta-1 and beta-2 bands, although the patients tended to show a higher delta amplitude than the controls over the frontal regions. In addition, no significant Diagnosis × EEG Lead interactions were found in these frequency bands. In the amplitude for the alpha-2 band, however, there was a significant main effect of Diagnosis (F = 13.464; df = 1.32; $P < 0.001$) and Diagnosis × Lead interaction (F = 5.266; df = 15.32; $P < 0.005$). Figure 1 shows the mean amplitude for the alpha-2 band at each of the 16 electrode sites. Although the topographic profile of the alpha-2 band amplitude was almost identical in the two groups, the patients showed a significantly lower alpha-2 amplitude than the controls over all brain regions. Al-

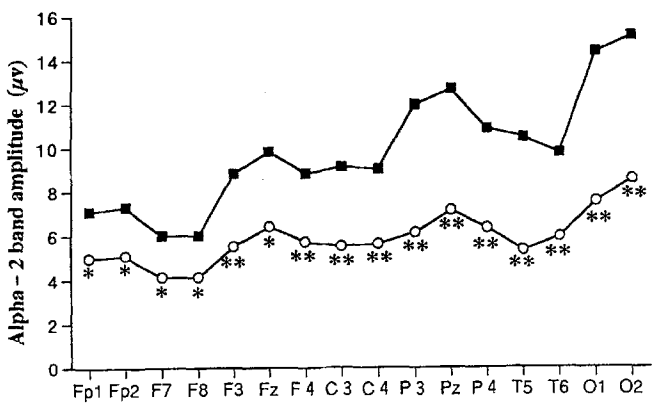

Fig. 1 Topographic profile of mean amplitude for alpha-2 band (9.0–12.8 Hz) in resting EEG of schizophrenic patients (○) and controls (■). $*P < 0.05$, $**P < 0.01$ compared with control group

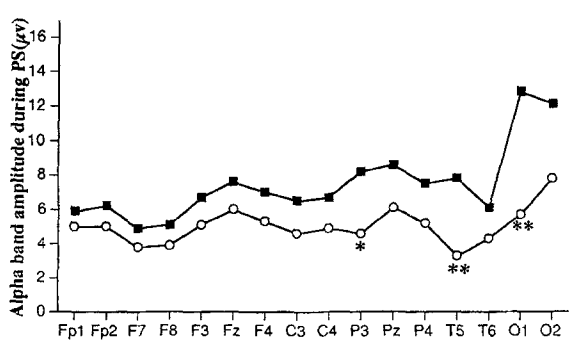

Fig. 2 Topographic profile of mean amplitude for the frequency band (9.8–10.2 Hz) corresponding to the stimulus frequency in schizophrenic patients (○) and controls (■). $*P < 0.005$, $**P < 0.001$ compared with control group. PS, photic stimulation

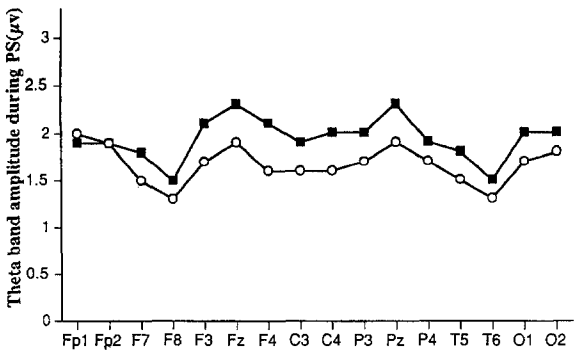

Fig. 3 Topographic profile of mean amplitude for the frequency band (4.8–5.2 Hz) harmonically related to the stimulus frequency in schizophrenic patients (○) and controls (■). PS, photic stimulation

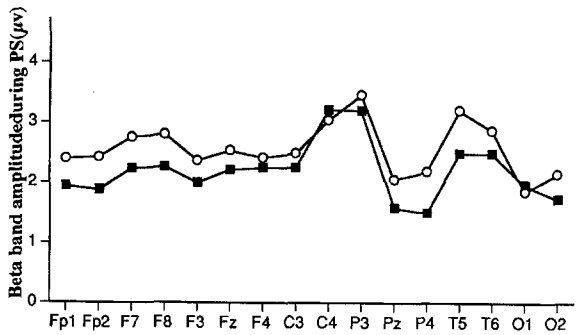

Fig. 4 Topographic profile of mean amplitude for the frequency band (19.8–20.2 Hz) harmonically related to the stimulus frequency in schizophrenic patients (○) and controls (■). PS, photic stimulation

though the patients tended to show a lower alpha-1 amplitude over the posterior regions, neither significant diagnosis-related difference nor Diagnosis × Lead interaction was observed in this band amplitude.

EEG activity during photic stimulation

The analysis of the stimulus data showed a significant main effect of Diagnosis ($F = 7.699$; df = 1.32; $P < 0.01$) and Diagnosis × Lead interaction ($F = 5.043$; df = 15,32; $P < 0.005$) in the EEG amplitude for the frequency band (9.8–10.2 Hz) corresponding to the stimulus frequency. As shown in Fig. 2, the control subjects showed a differentiated topographic pattern in the amplitude for this alpha band, which was characterized by elevated amplitude predominantly at the occipital regions. In contrast, the schizophrenic patients showed a rather uniform topographic profile and were found to have a significantly lower EEG amplitude over the posterior regions in the left hemisphere (P3, $P < 0.005$; T5, $P < 0.001$; O1, $P < 0.001$; t-test). Figures 3 and 4 show the mean amplitude for the frequency bands harmonically related to the stimulus frequency. In contrast to the alpha band amplitude, there was no significant main effect of Diagnosis or Diagnosis × Lead interaction in the EEG amplitude for the theta (4.8–5.2 Hz) or beta frequency band (19.8–20.2 Hz).

Discussion

In the present study quantitative analysis of the resting EEG was performed for a 2-min period for each subject, and showed that the schizophrenic patients had a significantly lower alpha-2 band amplitude than sex- and age-matched normal controls (Fig. 1). Our findings are consistent with those of earlier studies showing reduced alpha activity in schizophrenic patients (reviews in Morihisa 1986; Shagass 1991). A number of previous studies have also demonstrated that schizophrenics have more slow activity as compared with normal controls (reviews in Morihisa 1986; Shagass 1991). In the present study, however, no significant difference was found between the patients and normal controls in EEG amplitude for delta and theta bands. The clinical background seems to be an important factor contributing to the differences between this and previous studies. Our subjects consisted mainly of patients in the acute phase, whereas previous studies have largely investigated chronic schizophrenic patients. Miyauchi et al. (1990) have recently suggested that progress of the disease may cause increased slow activity in schizophrenia. In fact, Fenton et al. (1980) demonstrated that in contrast to the pronounced delta activity in chronic hospitalized patients, acute schizophrenics showed only reduced alpha activity. Williamson and Mamelak (1987) also reported no significant difference in delta activity between acute schizophrenic patients and healthy controls. In addition, all our patients were diagnosed as having paranoid schizophrenia which has been reported to show less marked EEG abnormality as compared with other schizophrenic subtypes (Kessler and Kling 1991; Nagase et al. 1992). Finally, most previous studies have examined medicated patients or patients off medication for a short period time, whereas none of our patients had previously received neuroleptic medication. Since pharmaco-EEG studies demonstrate an increase in slow activity in healthy subjects after neuroleptic medication (Fink 1974), it is possible that neuroleptic medication influenced the results of the previous studies.

The present study also demonstrated that the schizophrenic patients had a significantly lower EEG amplitude during 10 Hz photic stimulation for the alpha band (9.8–10.2 Hz), but not theta (4.8–5.2 Hz) or beta band (19.8–20.2 Hz), as compared with the controls (Figs. 2–4). These findings are consistent with those of previous studies showing diminished EEG reactivity of schizophrenics to external stimuli (Blum 1957; Salamon and Post 1965; Albus et al. 1982). The present results are also consistent with those of the recent PDR studies (Rice et al. 1989; Jin et al. 1990). These studies conducted quantitative EEG analysis on the basis of average PDR amplitude (Rice et al. 1989) and relative EEG power (Jin et al. 1990), and demonstrated that PDRs to frequencies within the alpha range were selectively decreased in schizophrenic patients. Since PDR production has been suggested to relate to mechanisms underlying alpha rhythm generation (Barlow 1960; Inouye et al. 1980), the present data, together

with reduced alpha amplitude in the resting EEG, support the view of Rice et al. (1989) that schizophrenics have a dysfunction in the mechanisms involved in the pacing of EEG alpha activity. In the previous PDR studies, however, EEG analysis was performed only at three regions (Fz, Cz and Pz), and topographic abnormality of PDRs was unclear (Rice et al. 1989; Jin et al. 1990). In the present study, therefore, quantitative EEG analysis was performed during photic stimulation at 16 electrode sites, and the control subjects showed a marked increase in the posterior EEG amplitude. This is in line with the well-demonstrated evidence that PDRs are provoked predominantly over the posterior regions. In contrast, the schizophrenic patients were found to show a uniform topographic profile in the EEG amplitude (Fig. 2), and significant group differences were observed over the posterior regions. Since Matsue et al. (1982) reported that normal subjects failed to show posterior PDR predominance when they performed a task causing distraction of attention, our findings may reflect attention disturbance in schizophrenia. In addition, the present study demonstrated that the significant group differences in EEG activity during photic stimulation were confined to the left hemispheric regions, supporting the hypothesis of left hemisphere dysfunction in schizophrenia (reviews in Morihisa 1986; Nasrallah 1986).

The previous PDR studies of schizophrenics were conducted after medication washout periods of 2 weeks (Jin et al. 1990) and at least 8 days (Rice et al. 1989). It has been shown, however, that neuroleptic drugs can influence EEG responses to photic stimulation in humans (Jörgensen and Wulff 1958; Wilson and Glotfelty 1958) and in the baboon (Killam et al. 1968). In addition to these direct effects of neuroleptic drugs, some effects of long-term medication, such as the increased stimulation of striatal adenylate cyclase by dopamine, are shown to persist unchanged throughout 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 EEG responses to photic stimulation did not result from the direct action of drugs or effects following drug withdrawal.

Although EEG segments containing eye movements, blinks and muscle activity were carefully screened out in this study, the effects of these artifacts need to be considered. In the present study, however, the patients showed deviant EEG activity in the alpha frequency range in both stimulus and non-stimulus conditions. Considering that the frequency range of ocular and muscle artifacts is not generally in the alpha range (reviews in Shagass 1991), it is unlikely that these artifacts influenced the present findings, although methods for correcting EOG artifacts should be used in future studies (Gasser et al. 1992).

Although caution must be exercised in drawing any conclusion from the small number of patients studied here, the present results suggest that paranoid schizophrenics have abnormal EEG activity within the alpha range in both non-stimulus and stimulus conditions. Further studies are necessary to define the relationships between these EEG abnormalities and the clinical symptomatology of schizophrenic patients.

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