Eur Arch Psychiatry Clin Neurosci (1991) 241:61–64

European Archives of Psychiatry and Clinical Neuroscience

Visual Dysfunction in Treated Schizophrenia Suggested by Visual Evoked Potentials from Pattern-Reversal Stimulation

Itsuki Jibiki[1], Yuko Takizawa[2], and Nariyoshi Yamaguchi[1]

[1]Department of Neuropsychiatry, Kanazawa University School of Medicine, 13-1 Takaramachi, Kanazawa, Japan 920
[2]Department of Central Clinical Laboratory, Kanazawa University Hospital, Kanazawa, Japan

Received May 24, 1990

Summary. Steady-state visual evoked potentials (steady-state VEPs) from pattern-reversal stimulations were compared in treated schizophrenic patients and normal subjects matched for sex and age. The VEP amplitudes were more variable in the patients than in the controls. Furthermore, the VEP amplitudes of the patients mostly showed little or no change when the check size was varied, in contrast to the controls who showed a marked check size effect. These results suggest that schizophrenics receiving drugs have dysfunction of the visual system, especially an inability to respond adequately to changes of visual information.

Key words: Visual evoked potential (VEP) – Steady-state VEP – Pattern-reversal stimulation – Schizophrenia – Haloperidol

Introduction

There has been general agreement about the higher reliability or sensitivity of pattern-reversal stimulations in visual evoked potential (VEP) studies (Kuroiwa and Celesia 1981). However, we are aware of no studies of pattern-reversal VEPs in schizophrenics, although there have been VEP studies in schizophrenics with light flash stimulations (Ishikawa 1968; Jutai et al. 1984; Kirpichenko and Ladik 1984; Rodin et al. 1964; Shagass and Schwartz 1965; Speck et al. 1966) and pattern flash stimulations (Roemer et al. 1978; Straumanis et al. 1982). In the present study, we measured steady-state VEPs elicited by pattern-reversal stimulations at high stimulus frequencies in schizophrenic patients receiving drugs in comparison with normal subjects matched for sex and age, to investigate whether the patients had deficits in the visual system. Although it is difficult in this kind of study to determine in treated patients whether the results obtained depend on the illness itself or on the drug effects, the present study may be of clinical significance in schizophrenic patients.

Offprint requests to: I. Jibiki

Subjects and Methods

The schizophrenic subjects, who were diagnosed according to DSM-III-R criteria, consisted of 10 adult patients of either sex. The mean age of the men was 27.0 years with a standard deviation (SD) of 0.7 years, and 26.7 years, SD 4.9 years in the women. All of the 20 patients had a clinical history of more than 2 years (mean 8 years, SD 4.4 years). Patients using only haloperidol and biperiden were selected at the time of the VEP tests, because these drugs were the most commonly used to treat schizophrenia in our hospital, and because we wanted to avoid patients with polypharmacy, so as to facilitate the interpretation of the results obtained. The haloperidol dose was 9.6, SD 6.9 mg/day (range; 3–25 mg/day) and the biperiden dose was 4.1, SD 1.8 mg/day (range; 2–9 mg/day). At the time of the VEP tests, all of the patients were either in incomplete remission soon after recovery from the active phase of the illness or on the way to recovery, showing relatively minor auditory hallucinations or delusions. The severity of these psychiatric symptoms was evaluated by two senior psychiatrists using the Brief Psychiatric Rating Scale (BPRS).

The normal subjects consisted of 20 adults; 10 males (23.9, SD 3.9 years old) and 10 females (20.7, SD 0.7 years old). The age of the schizophrenic and normal subjects in either sex did not differ significantly on the two-tailed *t*-test. None of the women were menstruating at the time of the VEP tests.

The VEP examinations were carried out in a dark room, with the subjects seated comfortably in a chair positioned 1 m from a TV monitor. Three recording electrodes with a resistance below 5000 Ω were placed on the scalp in the midline occipital area (MO) at 5 cm above the inion, and in the right and left occipital areas (RO and LO) at 5 cm lateral to the MO. These occipital electrodes were referred to a midfrontal electrode (MF) at 12 cm above the nasion. The input from these electrodes was fed into preamplifiers adjusted to a bandwidth of 2–100 Hz. The output was fed to a minicomputer.

Pattern reversal of a black and white checkerboard was presented on a TV screen. The entire stimulus field of the TV screen subtended 17.2° to the subject's eye. The subjects were instructed to fixate the centre of the screen with the dominant eye, with the other eye covered with a patch. To check the eye fixation, EOG monitoring was performed simultaneously using conventional EEG equipment, and when the eye fixation was not well maintained, the VEP data were omitted, and the test performed again.

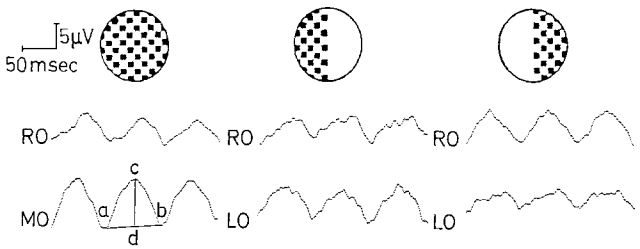

Fig. 1. Typical examples of steady-state visual evoked potentials (VEPs) to pattern-reversal stimulations at the standard check size in a control subject. VEPs recorded simultaneously in midline occipital area (MO) and right occipital area (RO) under full-field stimulations, and those in RO and left occipital area (LO) under right and left half-field stimulations are demonstrated by the partial presentation of only three waves following stimulations. Each amplitude of the three waves was measured (height of "c–d") and the mean value was regarded as the VEP amplitude

In patients with anomalies of refraction, corrective lenses were used. Right and left half-field stimulations were applied in this order at the pattern-reversal rate of 10 Hz. The check size in the checkerboard employed in these stimulations was a standard one, i.e. 18.0 mm length 23.0 mm width (1.0° visual angle) based on the guidelines of the American Electroencephalographic Society (1984). In a VEP recording, 128 sweeps during the analysis time of 500 ms after reversal of the checkerboard pattern were averaged. The averager (MEB 5100, Nihon Kohden, Tokyo, Japan) had only two channels. Thus, VEPs under these half-field stimulations were simultaneously recorded from RO and LO for the purpose of determining lateralized hemispheric dominance in the VEP amplitudes (Barrett et al. 1976; Kuroiwa and Celesia 1981). Next, full-field stimulations at 10 Hz were applied using four different check sizes. These check sizes were used in the following order: 9.0 mm length × 11.5 mm width (31° visual angle), 18.0 × 23.0 mm (1.0°), 36.0 × 46.0 mm (2.1°) and 72.0 × 92.0 mm (4.1°). The VEPs were simultaneously recorded from MO and RO, placing greater weight on the MO recording, because it is known that VEPs under full-field stimulation show higher amplitudes in MO than in the other two recording sites (Kuroiwa and Celesia, 1981). All of the VEP recordings were performed only once. These VEPs were composed of a train of sine waves with almost constant amplitudes. Only the amplitude of each wave was measured, and the average amplitude of three waves after the reversal stimulus was considered as the VEP amplitude (Fig. 1). The peak latency or duration was excluded from analysis because it always corresponded to the stimulus frequency at 10 Hz in all subjects. In addition, there were no significant differences in vision between the controls and schizophrenics of either sex (two-tailed *t*-test).

Statistical Analyses

The VEP amplitude differences were examined by two-way analysis of variance (ANOVA) with designs as below; "diagnosis" (two subfactors; control and patient groups) and "recording site" (two subfactors; RO and LO recordings under half-field stimulations, or MO and RO recordings under full-field stimulations at the standard check size), and "diagnosis" and "check size" (four subfactors; MO recordings under full-field stimulation at the above mentioned four check sizes). The ANOVA with these designs was performed separately on data from both sexes. The ANOVA for the "diagnosis" and "check size" was followed by Dunnett's multiple comparison test. In addition, two-way ANOVA for the "diagnosis" and "sex" was performed on data from each recording site under the half-field stimulations or full-field stimulations at the standard check size.

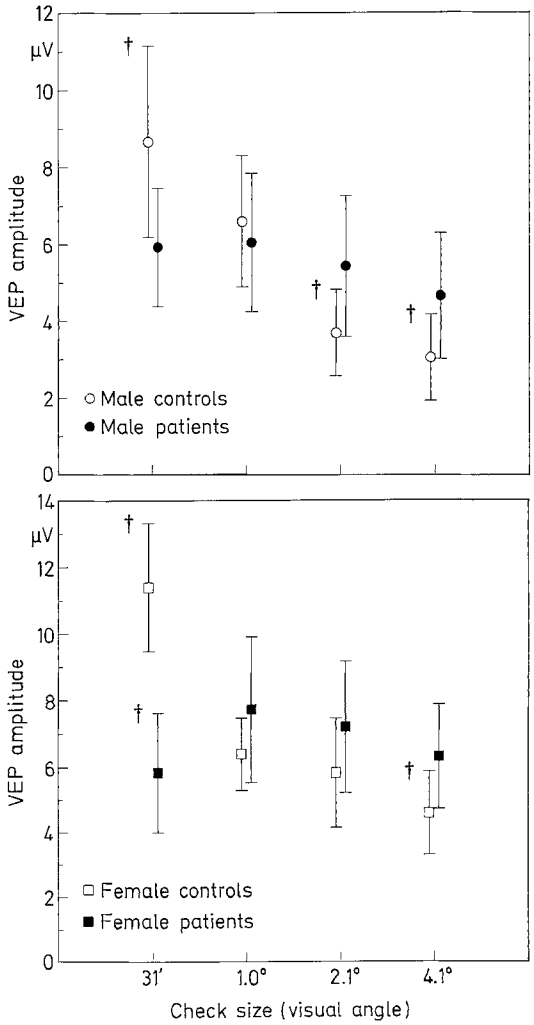

Fig. 2. Changes of visual evoked potential (VEP) amplitudes by varying the check size. VEP amplitudes recorded in midline occipital area (MO) under full-field stimulations are presented with mean values and SDs. † $P < 0.05$ by two-way analysis of variance (ANOVA), and Dunnett's test for multiple comparisons with the VEP amplitude at the standard check size (1.0°) in each of control and patient groups

The difference in a variance of the VEP amplitudes between the patient and control groups in each of the sexes was examined by *F*-test, using SD values of the VEP amplitudes at the standard square size under identical stimulus and recording conditions (SD_1^2/SD_2^2).

The relations between drugs and the VEPs were examined by two-way ANOVA with designs as "haloperidol dose" and "recording site" or "check size", and designs as "biperiden dose" and "recording site" or "check size". The ANOVA was also performed separately on data from both sexes. The haloperidol dose and biperiden dose factors were divided into two subfactors each, composed of patient groups receiving high and low doses respectively. The critical doses were 15 mg/day for haloperidol and 6 mg/day for biperiden. In both the male and female groups, 3 and 7 patients had haloperidol doses above and below the critical value, respectively. Four and 6 male patients had biperiden doses above and below the critical value, respectively, as did 3 and 7 female patients. The analyses for these uneven samples were performed by the Tukey-Kramer procedure (Hochberg and Tamhane 1987).

In addition, the relations between psychiatric symptoms and the VEPs were examined by two-way ANOVA with designs as "severity of symptom" and "recording site" or "check size", also

Table 1. Visual evoked potential (VEP) amplitudes under full-field and half-field stimulations at a standard check size (1.0° visual angle) in the patient and control groups

MALE

	FULL-FIELD STIMULATION	
	MO	RO
CONTROLS	6.6±2.4μV	4.9±1.2μV
PATIENTS	6.1±2.5μV	5.0±3.6μV

MALE

	RIGHT HALF-FIELD STIMULATION	
	RO	LO
CONTROLS	5.1±1.4μV	3.4±1.1μV
PATIENTS	4.4±3.9μV	3.2±1.7μV

MALE

	LEFT HALF-FIELD STIMULATION	
	RO	LO
CONTROLS	3.6±1.2μV	4.9±1.2μV
PATIENTS	3.6±2.5μV	3.9±2.0μV

FEMALE

	EULL-FIELD STIMULATION	
	MO	RO
CONTROLS	6.3±1.5μV	6.5±3.5μV
PATIENTS	7.7±3.1μV	5.1±3.5μV

FEMALE

	RIGHT HALF-FIELD STIMULATION	
	RO	LO
CONTROLS	5.5±1.4μV	4.2±1.0μV
PATIENTS	4.1±1.2μV	4.6±3.5μV

FEMALE

	LEFT HALF-FIELD STIMULATION	
	RO	LO
CONTROLS	4.0±1.0μV	5.6±2.5μV
PATIENTS	5.0±4.2μV	4.9±2.2μV

Each numerical value expresses the mean (SD) in ten subjects. MO, RO, LO: the midline, right and left occipital areas as recording sites of VEPs. Although differences in the VEP amplitudes were examined by two-way ANOVA with a design as "diagnosis" and "recording site" (refer to text) separately on six sets of data from both sexes shown in this table, there were no significant differences in either factor on any of the six sets. Each underlined amplitude indicates a significant difference in the variance of VEP amplitudes under identical stimulus and recording condition between the patient and control groups on F-test $[SD_1^2/SD_2^2 > F_9^9 (0.05) = 3.18]$

separately on data from the male and female patients. This analysis was performed regarding each of the 16 psychiatric symptoms listed on the BPRS. The severity factor was divided into two subfactors composed of patient groups with high and low BPRS scores on each of these symptoms. The Tukey-Kramer procedure was used also for these analyses.

Results

The data from MO recordings under full-field stimulation at four check sizes are shown in Fig. 2. With regard to the data from either sex, the two-way ANOVA for the "diagnosis" and "check size" showed no significant differences in "diagnosis" but a significant difference in "check size" [F-value (7.833 and 5.634 in male and female data, respectively) > $F(3,72)$ (0.05) = 2.74]. Further, as shown in Fig. 2, Dunnett's tests following the analyses showed significant differences between the four subfactors in "check size" on the data from both sexes in the control group; the VEP amplitudes to stimulations with the larger square size were significantly lower than those to stimulations with the smaller size. In contrast, these tests did not show any significant differences in the data from the patient groups, showing that in most schizophrenic patients the VEP amplitudes showed little or no change when the check size was varied, except for a significant difference showing a change opposite to that of the controls between 31′ and 1.0° in the data from the female group.

The data under the full-field and half-field stimulations at the standard square size are given in Table 1, which show that, in the response to the right and left half-field stimulations in the controls, the VEP amplitudes in the recording site ipsilateral to the visual field of the stimulations tended to be higher than those in the contralateral recording site. However, the two-way ANOVA for the "diagnosis" and "recording site" showed no significant differences in either factor in the data from either sex. On the other hand, the F-test showed that the VEP amplitude variance was significantly higher in the patient group than in the control group when these data were compared under the same stimulus and recording conditions (Table 1, underlined), showing that the VEP amplitudes are more variable in the patients than in the controls.

In addition, there were no significant differences in the ANOVA for the "diagnosis" and "sex", "haloperidol dose" and "recording site" or "check size", and "biperiden dose" and recording site" or "check size". Further, all of the 16 symptoms on the BPRS were observed in the patients of either sex, and six symptoms, i.e. anxiety, tension, suspiciousness, hallucinatory behaviour, unusual thought content and blunted affect were found in a large number of patients of both sexes. No significant differences were seen in the ANOVA for the "severity of psychiatric symptoms" and "recording site" or "check size" in any of the 16 symptoms.

Discussion

It has been reported that transient VEP amplitudes to light flash stimulations at low stimulus frequencies are lower in untreated schizophrenics than in normal subjects (Ishikawa 1968; Jutai et al. 1984; Rodin et al. 1964), although conflicting results have also been reported (Speck et al. 1966). On the other hand, Ishikawa (1968) pointed out that treated schizophrenics showed higher amplitudes in the later components of the transient VEPs to light flash stimuli than did untreated patients. Conversely, Straumanis et al. (1982) reported that the transient VEP amplitudes to checkerboard pattern flash stim-

ulations showed a reduction when antipsychotic drugs were administered. In the present study, the VEP amplitudes in the schizophrenic patients were neither significantly lower nor higher than those in the normal subjects. However, the results of the present study on steady-state VEPs to pattern-reversal stimulations indicate that the VEP amplitudes in treated schizophrenics were more variable than those in the controls, and further that in the schizophrenic patients of either sex there was little or no change of the VEP amplitudes when the check size was varied, whereas in the controls there was a marked effect due to changes of the check size. The presence of the check size effect in the controls is consistent with that of a previous study, in which the effect of check size on transient VEPs to checkerboard pattern flash stimulations was examined in normal subjects (Harter and White 1970). Further, the virtual absence of the effect in the schizophrenic patients may be similar to the finding that schizophrenics exhibited a decreased reactivity to changes of the intensities of light flash stimulations (Landau et al. 1975). It is not known whether the present abnormalities result from medication or the illness itself. It has been reported that the latency of the transient VEPs to pattern-reversal stimulations is prolonged by the intravenous injection of haloperidol in patients with an acute paranoid state, presumably because this drug directly modifies dopaminergic function in the retina (Onofrj et al. 1988). It is possible that the present findings are attributable to the direct effects of haloperidol on the retina.

In conclusion, the present study suggests that schizophrenics receiving drugs have a dysfunction of the visual system especially an inability to respond adequately to changes of visual information. These findings may be of clinical significance in schizophrenics.

Acknowledgement. We thank Prof. Kazuo Hashimoto (Department of Hygienics, Kanazawa University School of Medicine) for his help with the statistical analyses.

References

American Electroencephalographic Society (1984) Guidelines for clinical evoked potential studies. J Clin Neurophysiol 1:3–53

Barrett G, Blumhardt L, Halliday AM, Halliday E, Kriss A (1976) A paradox in the lateralization of the visual evoked response. Nature 261:253–55

Harter MR, White CT (1970) Evoked cortical responses to checkerboard patterns. Effect of checksize as a function of visual acuity. Electroencephalogr Clin Neurophysiol 28:48–57

Hochberg Y, Tamhane AC (1987) Multiple comparison procedures. Wiley, New York, pp 91–93

Ishikawa K (1968) Studies on the visual evoked responses to paired light flashes in schizophrenics. Kurume Med J 15:153–167

Jutai JW, Gruzelier JH, Connolly JF, Manchanda R, Hirsch SR (1984) Schizophrenia and spectral analysis of the visual evoked potential. Br J Psychiatry 145:496–501

Kirpichenko AA, Ladik BB (1984) Dynamics of evoked potentials in the course of progressive schizophrenia. Neurosci Behav Physiol 14:489–492

Kuroiwa Y, Celesia GG (1981) Visual evoked potentials with hemifield pattern stimulation. Their use in the diagnosis of retrochiasmatic lesions. Arch Neurol 38:86–90

Landau SG, Buchsbaum MS, Carpenter W, Strauss J, Sacks M (1975) Schizophrenia and stimulus intensity control. Arch Gen Psychiatr 32:1239–1245

Onofrj M, Ghilardi MF, Basciani M, Gambi D (1986) Visual evoked potentials in parkinsonism and dopamine blockade reveal a stimulus-dependent dopamine function in humans. J Neurol Neurosurg Psychiatry 49:1150–1159

Rodin E, Zacharopoulos G, Beckett P, Frohman C (1964) Characteristics of visually evoked responses in normal subjects and schizophrenic patients. Electroencephalogr Clin Neurophysiol 17:458

Roemer R, Shagass C, Straumanis JJ, Amadeo M (1978) Pattern evoked potential measurements suggesting lateralized hemispheric dysfunction in chronic schizophrenics. Biol Psychiatry 13:185–202

Shagass C, Schwartz M (1965) Visual cerebral evoked response characteristics in a psychiatric population. Am J Psychiatry 121:979–987

Speck LB, Dim B, Mercer M (1966) Visual evoked responses of psychiatric patients. Arch Gen Psychiatry 15:59–63

Straumanis JJ, Shagass C, Roemer RA (1982) Influence of antipsychotic and antidepressant drugs on evoked potential correlates of psychosis. Biol Psychiatry 17:1101–1122