ORIGINAL

Differences in waveforms of cerebral evoked potentials among healthy subjects, schizophrenics, manic-depressives and epileptics

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Abstract : The differences in the waveform of Cerebral EP (Evoked Potential)s ; SEP, VEP and AEP, among healthy subjects, schizophrenics, manic-depressives and epileptics were investigated. In 585 subjects of both sexes comprising these diagnostic groups, 6 channels of EPs, each 2 channels for each sensory modality, were recorded simultaneously/parallelly from each subject, without assigning a mental task. Then, waveforms of the g-m (group mean) EPs of each diagnostic group were superimposed for inspection. Peak latencies and inter-peak amplitudes of individual EPs were statistically tested among (ANCOVA) and between (Scheffe's multiple comparison test) these diagnostic groups for each channel (modality), and for each sex. The waveforms of g-m EPs of each diagnostic group differed from each other. The differences of latencies and inter-peak amplitudes among these diagnostic groups attained to the significant level ($P<0.05$), with more significant differences between healthy subjects and each of these pathological diagnostic groups than between each of these pathological diagnostic groups, for each sex. Thus the differences in the waveform of EPs among these diagnostic groups were confirmed even taking the effect of medication on EPs into consideration. These results might suggest the existence of a waveform for individual EPs specific to each of these diagnostic groups, for each sex. J. Med. Invest. 54 : 303-315, August, 2007

Keywords **:** *waveforms of evoked potentials, healthy subjects, schizophrenics, manic-depressives, epileptics*

INTRODUCTION

Originally, each of cerebral EP (Evoked Potential) s ; SEP (somatosensory EP), VEP (visual EP) or AEP (auditory EP), was recorded by repeatedly administering identical sensory stimuli to the subject, and averaging the responses to the stimuli to delineate the waveforms of the individual (averaged) EP. However, the inter-individual diversity in the waveform of the individual EP was very large, and it was therefore difficult to assume the general waveform of a human EP.

However, it was confirmed in 1980 that the g-m (group mean) SEP of 200 healthy subjects of both sexes converged to a given waveform different, beyond its 98% confidence belt, from the flat horizontal baseline (1). Then, it was shown in 1982 that the g-m SEPs of each sex converged to waveforms that were significantly different (MANOVA (multivariate analysis of variance)) from each other (2). Prior to that, in 1974, in a total of 245 subjects, different waveforms of the g-m SEP among healthy

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subjects, schizophrenics, and epileptics had been reported for each sex without a statistical test (3). Furthermore, differences of the waveform of g-m EPs ; g-m SEP, g-m VEP and g-m AEP, and significant differences ($P<0.05$) in peak latencies and inter-peak amplitudes of individual EPs, between healthy control subjects and each of schizophrenics (4-6), manic-depressive illness (7-9), and epileptics (10, 11) were confirmed by ANCOVA (analysis of covariance) (4-6, 10, 11) and by Mann-Whitney U-test (7-9), respectively for each channel (modality), for each sex, in the previous studies from our Department in 1998.

In this study, using EPs data recorded until 1998 in our Department, we intended to confirm the differences in the waveform of EPs among healthy subjects, schizophrenics, manic-depressives and epileptics, respectively, for each sex.

SUBJECTS AND METHODS

Subjects

The 585 subjects in this study comprised healthy subjects, schizophrenics, manic-depressives and epileptics of both sexes, with no sensory disturbances. They were widely dispersed in age distribution at the time of EPs recording, within and among these diagnostic groups, and for each sex, except for healthy subjects (Table 1). All of these patients had been treated as in/out patients in the Department of Neuropsychiatry, School of Medicine, University of Tokushima, over a period of up to 40.9 y (mean 6.2 ± SD 7.2 y) until EPs recording, and their diagnoses were definitely confirmed retrospectively according to the course of their illness. These patients met the diagnostic categories F20.0-20.6 of schizophrenia, F30.1-30.2, 31.0-31.7, 32.0-32.3 and 33.0-33.4 of affective disorder, and G40.0 and 40.3 of epilepsy in ICD-10 (12). Schizophrenics had been treated with neuroleptics ; mainly phenothiazines and butyrophenones, manic-depressives with anti-manics, antidepressants and mood stabilizers ; lithium carbonate (Li), carbamazepine (CBZ), tri- and tetra-cyclics and sulpiride, and epileptics with anti-epileptics ; sodium valproate (VPA), CBZ, diphenylhydantoin (PHT) and phenobarbital (PB). EPs were recorded from these patients while they were on concomitant medication, but EPs in 21 (11 males and 10 females) patients were recorded prior to medication at their initial visit to the Department, and those in 2 male patients and 1 female patient were recorded after an accidental unmedicated period of more than 2 weeks. The healthy subjects of both sexes were unpaid volunteers (young medical doctors in the Department) and paid volunteers (students in the University) with normal EEG. In all of these subjects, EPs were recorded with informed consent.

Methods of EPs recording

During the EPs recording, the subjects were reclining in a chair, with eyes closed, in a dark shielded room, air conditioned at 24-25°C. The subjects were not assigned any mental task, but were only instructed to relax.

EPs were evoked by, 1) electric shock stimulation of square wave current with 0.5 ms pulse duration, at the voltage of twitching threshold of the thumb (mean 88± SD 11V), delivered from a constant voltage source, percutaneously to the median nerve at the right wrist (electronic stimulator SEN-3201 with isolator SS -102J. Nihon Kohden. The same hereinafter if not specified), for SEP : 2) flash stimulation of 0.6 J intensity, from a sound-shielded xenon tube (Retinograph MSP-2R), delivered 30 cm in front of the closed eyes, for VEP : and 3) binaural click stimulation of 110 dB (acoustic stimulator SSS-3100) through a pair of speakers (SH10, 8Ω. Fostex), 80 cm distant from the ears, for AEP.

During recording, each subject was repeatedly

Table 1. Numbers and age(y) distribution of 585 subjects at the time of EPs recordings for healthy subjects (HEL), schizophrenics (SCH), manic-depressives (MDI) and epileptics (EPI), and for males (M), females (F) and both sexes (M+F)

	HEL		SCH		MDI		EPI	
Number (M+F)	200		181		40		164	
	M	F	M	F	M	F	M	F
Number	100	100	100	81	20	20	99	65
Mean(y)	25.4	21.6	33.6	37.1	40.5	46.6	35.9	36.0
SD(y)	3.1	2.6	10.4	13.7	13.8	16.5	13.1	15.0
Range(y)	20-34	19-36	17-75	15-67	20-69	20-79	9-78	12-77

stimulated by a single 1) electric shock, 2) flash and 3) click in cyclical order. A shock was followed 1 s later by a flash, the flash was then followed 2 s later by a click, and then the click was followed 2 s later by the next electric shock, so that the ISI (interstimulus interval) between the stimuli of the same sensory modality was always 5 s. Consequently, SEP, VEP and AEP were recorded simultaneously/parallelly from each individual subject in about 8 min 20 s (13).

Recording electrodes were placed on the subject's scalp on their left hemisphere, according to the 10-20 international electrode system (14). SEP was derived from the derivation (C3'-F 3') and (C 3'-A1). F3' is 5 cm anterior and C3' is 2 cm posterior to the midcoronal line, on the parasagittal line 6.5 cm left of the vertex (1). VEP and AEP were derived from each 2 derivations (O1-A1), (O1-Cz) and (Cz-A1), (Cz-T5) (15, 16). Recording electrode resistances were kept around 5 kΩ.

EEGs containing EPs were derived from the 6 derivations into each corresponding (1st to 6th) channel of an EEG amplifier (3 sets of AB-622M), with band pass filter settings of 0.1-100Hz, time constant 0.1 s and a gain of 20,000. These amplified EEGs were recorded into the corresponding channel of magnetic tape using a data recorder (XR-50L, TEAC), together with each of the trigger pulses for SEP, VEP and AEP into each of another channel. Reproducing the magnetic tape, the 6 channels of EPs of 1024 ms of analysis time were triggered by each corresponding trigger pulse, and averaged 100 times, by the 6 channels of EP recording equipment (3 sets of ATAC-210) at 1024 Hz sampling rate, by visually monitoring and manually avoiding the contamination of noise. Thus, 6 channels of individual (averaged) EPs ; Ch(channel)1·SEP(C3'-F3'), Ch 2·VEP(O1-A1), Ch3·AEP(Cz-A1), Ch4·SEP(C3'-A 1), Ch5·VEP(O1-Cz) and Ch6·AEP(Cz-T5) were recorded simultaneously/parallelly from each of the subjects.

These EPs data were recorded as a waveform plotted by a X-Y plotter, and as a time series of 1024 digital data recorded into an 8-inch floppy disk using a universal computer (U-1100, PANAFACOM), and subjected to further data analysis.

Methods of data processing

To avoid the interference of sex factor (2, 17-20), EPs data were analysed separately for each sex.

The axis of each individual EPs waveform was adjusted by the method of least squares, to eliminate the tendency to be biassed by the conditions in the recording system.

Inter-individually averaging the individual (averaged) EPs on 1024 data points, the waveforms of the g-m (group mean) EPs (21) ; g-m SEP, g-m VEP and g-m AEP were delineated respectively for each channel (modality), for each diagnostic group ; healthy subjects (HEL), schizophrenics (SCH), manic-depressives (MDI) and epileptics (EPI), respectively, for each sex. Then the waveforms of g-m EPs of the 4 diagnostic groups were superimposed on the same coordinate plane, and compared with each other for each channel (modality), for each sex.

Superimposing on the CRT display, the peaks in the g-m EPs in each diagnostic group were identified referring to those in the schematic average profile of EPs (22) of healthy subjects in our Department, respectively, for each channel, for each sex. Similarly, the peaks in each individual EPs were identified by referring to those in the schematic average profile of EPs of the corresponding diagnostic group, respectively, for each channel, for each sex. Next, the differences of peak latencies and inter-peak amplitudes between the main peaks of opposite polarity were tested among the 4 diagnostic groups by ANCOVA after eliminating the effect of age, respectively, for each channel, for each sex. Furthermore, the differences between peak latencies and inter-peak amplitudes were tested by Scheffe's multiple comparison test between each 2 (a pair) of these among the 4 diagnostic groups, for 6 pairs ; HEL : SCH, HEL : MDI, HEL : EPI, SCH : MDI, SCH : EPI and MDI : EPI, respectively for each channel, for each sex.

RESULTS

Large diversity in the waveform of individual EPs

The diversity in the waveform of individual (averaged) EPs was very large among the subjects. Therefore, it was difficult to assume the general waveform of human EPs, even those of healthy adults of very close age distribution ; males mean 25.4±SD 3.1 y, females 21.6±2.6 y, and even with EP of identical sensory modality ; SEP (Fig 1).

Differences in the waveform of the group mean EPs among the 4 diagnostic groups

In the waveform of the g-m (group mean) EPs, each of 8 positive (P1-8) and negative (N1-8) peaks were identified with 1024 ms latency, which was in

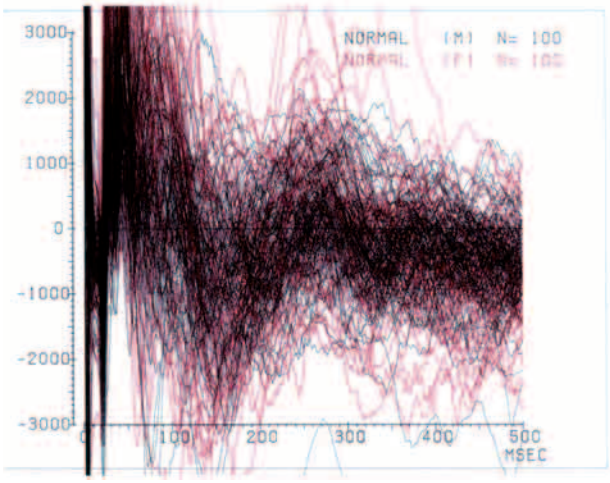

Fig. 1 Large diversity in the waveforms among 200 individual SEPs of healthy adults of both sexes, with close age distribution. Waveforms of 200 individual (averaged) SEPs of 100 each males (mean 25.4±SD 3.1 y, black lines) and females (21.6±2.6 y, red lines), superimposed on the same coordinate plane at regular time intervals, up to 500 msec in latency. Scales of amplitude are comparative, 2570 corresponds to 10μV.

agreement with the previous studies in our Department (4-11, 17-20). The g-m EPs ; g-m SEP, g-m VEP and g-m AEP, superimposed on the same coordinate plane, had different waveforms among the 4 diagnostic groups ; healthy subjects, schizophrenics, manic-depressives and epileptics for each channel (sensory modality), for each sex (Fig. 2, 3).

The waveforms of g-m SEP were complicated, consisting of 2 main positive peaks P3 and P6 with preceeding and intervening negative peaks N1 and N3. The average latencies of SEP peaks in Ch4·SEP (C3'-A1) of healthy males were N1 ; mean 19.9±SD 1.8 ms, P3 ; 45.2±4.0 ms, N3 ; 69.5±9.1 ms and P6 ; 270.5±20.4 ms.

The waveforms of g-m VEP were rather simple, consisting of the main positive peak, which tended to split into P4, 5 and 6, with preceding and following negative peaks N3 and N7. The average latencies of the VEP peaks in both Ch2·VEP(O1-A1) and Ch5·VEP(O1-Cz) of healthy subjects of both sexes showed the following rangs N2 ; 37.2-44.7 ms, P3 ; 48.6-53.1 ms, N3 ; 68.5-73.1 ms, P4 ; 96.8-106.8 ms, N4 ; 111.8-126.2 ms, P5 ; 135.0-155.2 ms and N7 ; 340.3-351.5 ms.

The waveforms of g-m AEP were the most simple, consisting of the main positive peak P5, with preceding and following negative peaks N4, N5 and N7. The average latencies of AEP peaks in both Ch3·AEP (Cz-A1) and Ch6·AEP(Cz-T5) of healthy subjects of both sexes showed the following rangs P3 ; 55.8-57.1 ms, N4 ; 103.3-110.0 ms, P5 ; 161.4-179.5 ms, N5 ; 271.5-275.5 ms, P7 ; 425.4-451.8 ms and N7 ; 465.0-489.3 ms.

Differences in peak latencies in EPs among the 4 diagnostic groups

The differences in the 16 peak latencies in EPs waveforms when tested by ANCOVA after eliminating the effect of age among the 4 diagnostic groups, for each channel (modality), for each sex attained to the significant level ($P<0.05$). The differences were more significant for N2 and P3 in SEP, P3, N3 and P5 in VEP, and P3, N4 and P5 in AEP. The numbers and ratios of the peak latencies with significant differences were lower among males 31% (32/96) than among females 47% (45/96) (Table 2).

The differences in the 16 pairs of peak latencies in EPs waveforms between any 2 (a pair) among the 4 diagnostic groups, 6 pairs, when tested by Scheffe's multiple comparison test, for each channel (modality), for each sex attained to the significant level ($P<0.05$). The numbers and ratios of pairs with significant differences were higher between healthy subjects and each of these pathological diagnostic groups (males : 13% (38/288), females : 19% (56/288)), than between each of these pathological diagnostic groups (males : 4.5% (13/288), females : 7.3% (21/288)), and finally lower between males 8.9% (51/576) than between females 13% (77/576) (Table 3).

Differences in inter-peak amplitudes in EPs among the 4 diagnostic groups

Differences of 7 inter-peak amplitudes, including main peaks of EPs waveforms tested by ANCOVA after eliminating the effect of age among the 4 diagnostic groups, for each channel (modality), for each sex attained to the significant level ($P<0.05$). The numbers and ratios of the inter-peak amplitudes with significant differences were higher among males 76% (32/42) than among females 64% (27/42) (Table 4).

The differences in 20 inter-peak amplitudes, including the main peaks, between any 2 (a pair) among the 4 diagnostic groups, 6 pairs, when tested by Scheffe's multiple comparison test, for each channel (modality), for each sex attained to the significant level ($P<0.05$). The numbers and ratios of the pairs with significant differences were higher between healthy subjects and each of the pathological diagnostic groups (males : 16% (57/360), females : 30% (108/360)) than between each of the pathological diagnostic groups (males : 10% (36/360), females : 6.7% (24/360)), and lower between males 13% (93/720) than between females 18% (132/720) (Table 5).

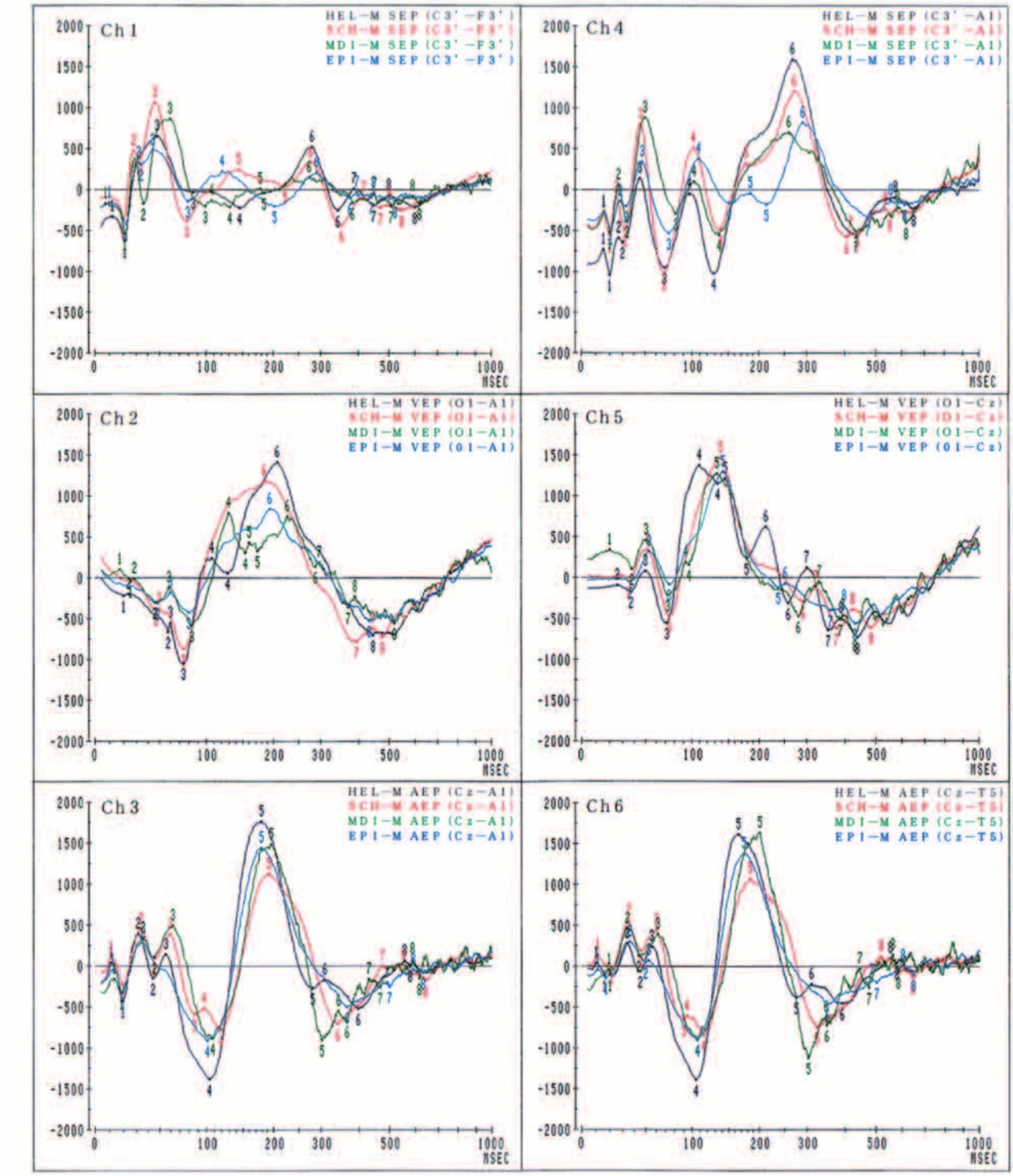

Fig. 2 Different waveforms of group mean EPs among healthy subjects, schizophrenics, manic-depressives and epileptics for each channel (modality), for males

Waveforms of group mean EPs ; of healthy subjects (HEL, black line), schizophrenics (SCH, red line), manic-depressives (MDI, green line) and of epileptics (EPI, blue line), superimposed on the same coordinate plane at logarithmic time intervals up to 1024 ms in latency, for each Ch (modality) in males. Ch represents channel. Scales of amplitude are comparative, 2570 corresponds to 10μV. Left panels are Ch1·SEP (C3'-F3'), Ch2·VEP (O1-A1) and Ch3·AEP (Cz-A1), and right panels are Ch4·SEP (C3'-A1), Ch5·VEP (O1-Cz) and Ch6·AEP (Cz-T5) from top to bottom. Upward deflections are positive, and downward ones are negative peaks, suffixed by the arabic ordinal numeral of the same color as the peak, indicating N4, P5, etc.

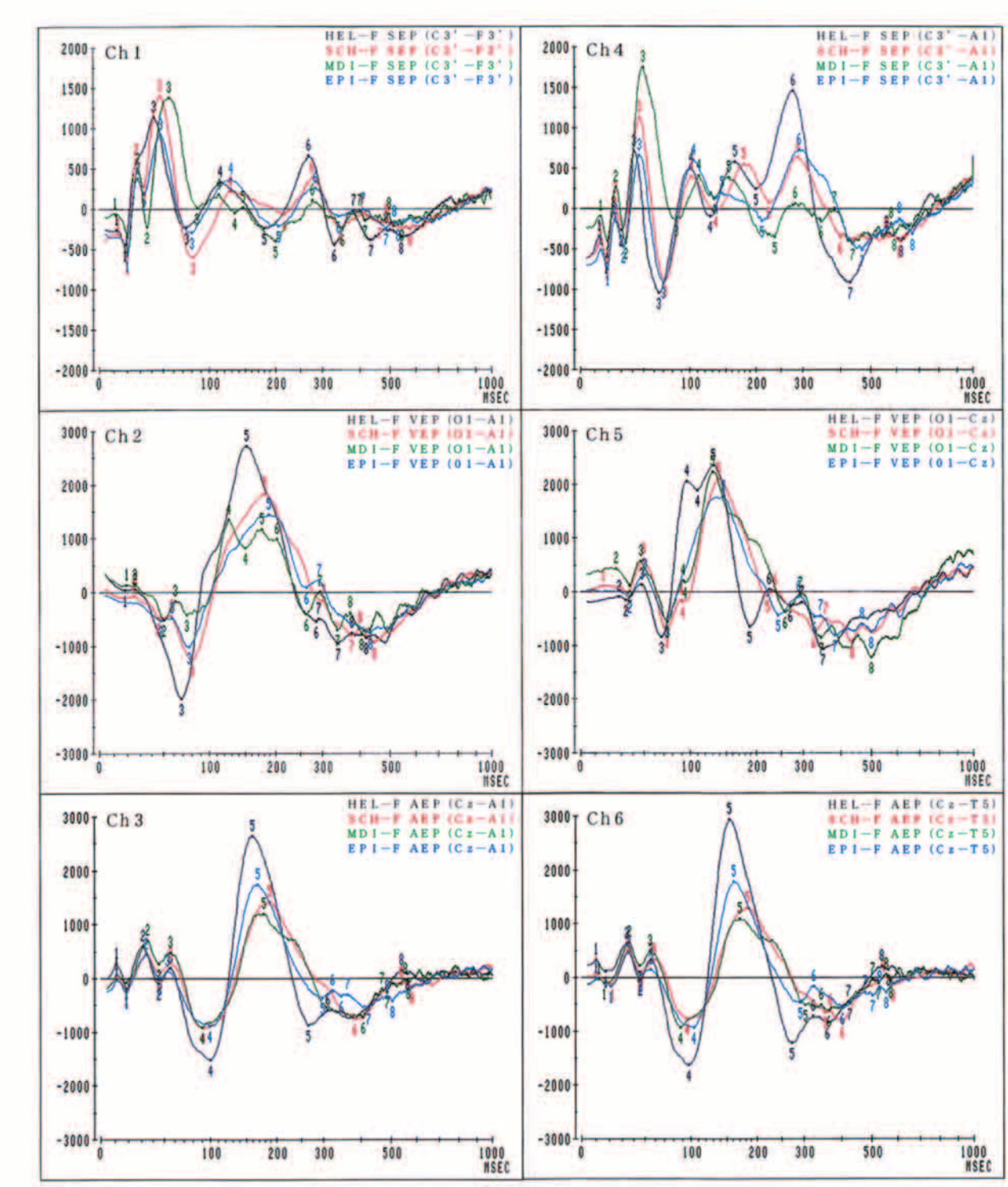

Fig. 3 Different waveforms of group mean EPs among healthy subjects, schizophrenics, manic-depressives and epileptics for each channel (modality), for females

Waveforms of group mean EPs ; of healthy subjects (HEL, black line), schizophrenics (SCH, red line), manic-depressives (MDI, green line) and of epileptics (EPI, blue line), superimposed on the same coordinate plane at logarithmic time intervals up to 1024 ms in latency, for each Ch (modality) in females. Ch represents channel. Scales of amplitude are comparative, 2570 corresponds to 10 μV. Left panels are Ch1·SEP (C3'-F3'), Ch2·VEP (O1-A1) and Ch3·AEP (Cz-A1), and right panels are Ch4·SEP (C3'-A1), Ch5·VEP (O1-Cz) and Ch6·AEP (Cz-T5) from top to bottom. Upward deflections are positive, and downward ones are negative peaks, suffixed by the arabic ordinal numeral of the same color as the peak, indicating N4, P5, etc.

Table 2. Differences in 16 peak latencies in EPs waveforms tested by ANCOVA after eliminating the effect of age, among the 4 diagnostic groups ; healthy subjects (HEL), schizophrenics (SCH), manic-depressives (MDI) and epileptics (EPI) for each channel (modality), for each sex.

Males	P1	N1	P2	N2	P3	N3	P4	N4	P5	N5	P6	N6	P7	N7	P8	N8	No.(Ratio)	No.(Ratio)
Ch1·SEP(C3'− F3')	**	ns	ns	*	**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	3/16(19%)	9/32(28%)
Ch4·SEP(C3'− A1)	ns	ns	*	ns	ns	ns	ns	**	ns	ns	**	ns	*	**	ns	**	6/16(38%)	
Ch2·VEP(01− A1)	ns	ns	**	ns	**	**	**	**	**	**	ns	ns	ns	**	**	**	10/16(63%)	13/32(41%)
Ch5·VEP(O1− Cz)	ns	ns	ns	ns	**	*	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	3/16(19%)	
Ch3·AEP(Cz − A1)	ns	ns	**	ns	**	ns	ns	ns	ns	ns	*	ns	ns	ns	*	*	5/16(31%)	10/32(31%)
Ch6·AEP(Cz − T5)	**	**	ns	ns	**	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	*	5/16(31%)	
Sum	2	1	3	1	5	2	1	3	2	1	2	0	1	2	2	4		32/96(31%)

Females	P1	N1	P2	N2	P3	N3	P4	N4	P5	N5	P6	N6	P7	N7	P8	N8	No.(Ratio)	No.(Ratio)
Ch1·SEP(C3'− F3')	*	**	ns	**	**	**	ns	ns	ns	ns	ns	ns	**	*	ns	ns	7/16(44%)	11/32(34%)
Ch4·SEP(C3'− A1)	ns	ns	ns	**	**	ns	ns	ns	ns	**	*	ns	ns	ns	ns	ns	4/16(25%)	
Ch2·VEP(01− A1)	ns	**	ns	**	**	**	*	*	ns	ns	ns	ns	ns	ns	ns	*	7/16(44%)	17/32(53%)
Ch5·VEP(O1− Cz)	**	**	ns	ns	ns	ns	ns	ns	*	**	**	**	**	**	**	**	10/16(63%)	
Ch3·AEP(Cz − A1)	ns	ns	**	ns	**	**	**	**	**	ns	ns	ns	*	ns	ns	ns	7/16(44%)	17/32(53%)
Ch6·AEP(Cz − T5)	ns	*	**	*	ns	ns	ns	**	**	ns	ns	*	**	**	*	*	10/16(63%)	
Sum	2	4	2	4	4	3	2	3	3	2	2	2	4	3	2	3		45/96(47%)

Numbers and ratios (%) of peak latencies with significant differences (**P<0.01, *P<0.05, ns=not significant) in each Ch (channel) among the 4 diagnostic groups, for males (above) and females (below).

Table 3. Differences in 16 pairs of peak latencies in EPs waveforms tested by Scheffe's multiple comparison test, between any 2 (a pair) among the 4 diagnostic groups ; healthy subjects (HEL), schizophrenics (SCH), manic-depressives (MDI) and epileptics (EPI) for each channel (modality), for each sex.

Males	HEL : SCH	HEL : MDI	HEL : EPI	SCH : MDI	SCH : EPI	MDI : EPI	No.(Ratio)	No.(Ratio)
Ch1·SEP(C3'−F3')	1/16	1/16	0/16	1/16	0/16	1/16	4/96(4.2%)	15/192(7.8%)
Ch4·SEP(C3'−A1)	0/16	1/16	5/16	0/16	4/16	1/16	11/96(11%)	
Ch2·VEP(01−A1)	4/16	1/16	4/16	0/16	4/16	0/16	13/96(14%)	20/192(10%)
Ch5·VEP(O1−Cz)	1/16	2/16	4/16	0/16	0/16	0/16	7/96(7.3%)	
Ch3·AEP(Cz−A1)	4/16	0/16	2/16	0/16	0/16	0/16	6/96(6.3%)	16/192(8.3%)
Ch6·AEP(Cz−T5)	2/16	4/16	2/16	1/16	0/16	1/16	10/96(10%)	
	12/96	9/96	17/96	2/96	8/96	3/96		
Sum	38/288(13%)			13/288(4.5%)				51/576(8.9%)

Females	HEL : SCH	HEL : MDI	HEL : EPI	SCH : MDI	SCH : EPI	MDI : EPI	No.(Ratio)	No.(Ratio)
Ch1·SEP(C3'−F3')	3/16	3/16	5/16	1/16	2/16	1/16	15/96(16%)	26/192(14%)
Ch4·SEP(C3'−A1)	4/16	3/16	4/16	0/16	0/16	0/16	11/96(11%)	
Ch2·VEP(01−A1)	0/16	2/16	3/16	0/16	2/16	0/16	7/96(7.3%)	29/192(15%)
Ch5·VEP(O1−Cz)	10/16	1/16	4/16	2/16	3/16	2/16	22/96(23%)	
Ch3·AEP(Cz−A1)	5/16	4/16	1/16	1/16	3/16	2/16	16/96(17%)	22/192(11%)
Ch6·AEP(Cz−T5)	2/16	0/16	2/16	0/16	2/16	0/16	6/96(6.3%)	
	24/96	13/96	19/96	4/96	12/96	5/96		
Sum	56/288(19%)			21/288(7.3%)				77/576(13%)

Numbers and ratios (%) of each pair of peak latencies with significant differences (P<0.05), between each pair among the 4 diagnostic groups, respectively for each Ch (channel), for males (above) and females (below).

Table 4. Differences in 7 main inter-peak amplitudes in EPs waveforms tested by ANCOVA after eliminating the effect of age, among the 4 diagnostic groups ; healthy subjects (HEL), schizophrenics (SCH), manic-depressives (MDI) and epileptics (EPI) for each channel (modality), for each sex.

Males	N1−P3	P2−N2	N2−P3	P3−N3	N3−P6	P3−N7	P6−N6	No.(Ratio)	No.(Ratio)
Ch1・SEP(C3'−F3')	**	**	**	**	ns	**	**	6/7(86%)	13/14(93%)
Ch4・SEP(C3'−A1)	**	**	**	**	**	**	*	7/7(100%)	
	N2−P3	P3−N3	N3−P4	N3−P5	P5−N7	N3−P6	P6−N6		
Ch2・VEP(01−A1)	**	**	**	**	*	**	ns	6/7(86%)	10/14(71%)
Ch5・VEP(O1−Cz)	ns	**	**	**	*	ns	ns	4/7(57%)	
	N1−P5	N2−P3	N2−P5	N3−P4	P5−N5	N4−P5	P5−N7		
Ch3・AEP(Cz−A1)	*	**	**	ns	ns	*	*	5/7(71%)	9/14(64%)
Ch6・AEP(Cz−T5)	*	*	**	ns	ns	*	ns	4/7(57%)	
Sum									32/42(76%)

Females	N1−P3	P2−N2	N2−P3	P3−N3	N3−P6	P3−N7	P6−N6	No.(Ratio)	No.(Ratio)
Ch1・SEP(C3'−F3')	*	**	ns	ns	**	ns	ns	3/7(43%)	10/14(71%)
Ch4・SEP(C3'−A1)	**	**	**	**	**	**	**	7/7(100%)	
	N2−P3	P3−N3	N3−P4	N3−P5	P5−N7	N3−P6	P6−N6		
Ch2・VEP(01−A1)	ns	ns	ns	**	**	*	ns	3/7(43%)	4/14(29%)
Ch5・VEP(O1−Cz)	**	ns	ns	ns	ns	ns	ns	1/7(14%)	
	N1−P5	N2−P3	N2−P5	N3−P4	P5−N5	N4−P5	P5−N7		
Ch3・AEP(Cz−A1)	*	**	**	ns	*	**	*	6/7(88%)	13/14(93%)
Ch6・AEP(Cz−T5)	**	**	**	**	**	**	**	7/7(100%)	
Sum									27/42(64%)

Numbers and ratios (%) of inter-peak amplitudes with significant differences (**P<0.01, *P<0.05, ns=not significant) in each Ch (channel) among the 4 diagnostic groups, for males (above) and females (below).

Table 5. Differences in 20 pairs of inter-peak amplitudes in EPs waveforms tested by Scheffe's multiple comparison test, between any 2 (a pair) among the 4 diagnostic groups ; healthy subjects (HEL), schizophrenics (SCH), manic-depressives (MDI) and epileptics (EPI) for each channel (modality), for each sex.

Males	HEL : SCH	HEL : MDI	HEL : EPI	SCH : MDI	SCH : EPI	MDI : EPI	No.(Ratio)	No.(Ratio)
Ch1・SEP(C3'−F3')	5/20	2/20	3/20	2/20	6/20	2/20	20/120(17%)	49/240(20%)
Ch4・SEP(C3'−A1)	8/20	4/20	4/20	0/20	9/20	4/20	29/120(24%)	
Ch2・VEP(01−A1)	0/20	1/20	6/20	0/20	5/20	1/20	13/120(11%)	24/240(10%)
Ch5・VEP(O1−Cz)	5/20	1/20	3/20	0/20	1/20	1/20	11/120(9.2%)	
Ch3・AEP(Cz−A1)	4/20	3/20	4/20	1/20	2/20	2/20	16/120(13%)	20/240(8.3%)
Ch6・AEP(Cz−T5)	2/20	1/20	1/20	0/20	0/20	0/20	4/120(3.3%)	
	24/120	12/120	21/120	3/120	23/120	10/120		
		57/360(16%)			36/360(10%)			93/720(13%)

Females	HEL : SCH	HEL : MDI	HEL : EPI	SCH : MDI	SCH : EPI	MDI : EPI	No.(Ratio)	No.(Ratio)
Ch1・SEP(C3'−F3')	6/20	6/20	4/20	1/20	2/20	1/20	20/120(17%)	52/240(22%)
Ch4・SEP(C3'−A1)	10/20	9/20	2/20	1/20	2/20	8/20	32/120(27%)	
Ch2・VEP(01−A1)	2/20	3/20	4/20	2/20	1/20	2/20	14/120(12%)	30/240(13%)
Ch5・VEP(O1−Cz)	8/20	5/20	1/20	0/20	1/20	1/20	16/120(13%)	
Ch3・AEP(Cz−A1)	11/20	4/20	7/20	0/20	1/20	0/20	23/120(19%)	50/240(21%)
Ch6・AEP(Cz−T5)	8/20	7/20	11/20	0/20	1/20	0/20	27/120(23%)	
	45/120	34/120	29/120	4/120	8/120	12/120		
		108/360(30%)			24/360(6.7%)			132/720(18%)

Numbers and ratios (%) of each pair of inter-peak amplitudes with significant differences (P<0.05), between each pair among the 4 diagnostic groups for each Ch (channel), for males (above) and females (below).

DISCUSSION

In order to confirm the differences of waveforms of EPs among healthy subjects, schizophrenics, manic-depressives and epileptics, a large number of 3510 (585 subjects×6 channels) EPs data from individuals with definite clinical diagnoses were collected for this study. The EPs were recorded simultaneously/parallelly with SEP, VEP and AEP from each subject, repeatedly stimulating with a shock, flash and click in cyclical order. A shock was followed 1 s later by a flash, the flash was then followed 2 s later by a click, and then the click was followed 2 s later by the next electric shock, so that the ISI (inter-stimulus interval) for the stimuli of identical modality was always 5 s, and each 2 channels of SEP, VEP and AEP was recorded separately, in about 8 min 20 s (13). Longer ISI results in a reduced rate of habituation (23). The cross-modality depression of the amplitude of EP (15%) when stimuli of different modality are repeated alternatively is smaller than identical modality depression (28% on average) when identical stimuli are repeated, with ISI of 2.5 s (24). Thus, the simultaneously/parallelly recorded EPs from each subject under his identical physical and mental condition, used in this study, enabled comprehensive data processing for all of SEP, VEP and AEP (13). This method differs from the multimodality evoked potentials reported by Greenberg (25), in which SEP, VEP and AEP were each recorded in different time sessions.

Regarding the peak latencies, the SEP peaks of healthy males in this study, N1, P3 and N3, correspond respectively to those of Lüders(26), N1 ; mean 17.6±standard error 0.23 ms, P2 ; 42.0± 0.35 ms, and probably to N3 ; 53.5±0.85 ms recorded from Japanese healthy male adults aged 19-29 y, as inferred from the similar derivation to that in this study ; 2 cm posterior to the midcoronal line on the parasagittal line 7 cm from the vertex, contralateral to the median nerve stimulated. VEP peaks of healthy subjects of both sexes in this study, N2, P3, N3, P4, N4, P5 and N7, correspond respectively to those of Cigánek (27), peak I ; negative, mean 39.12±SD 4.18 ms, II ; positive, 53.40±4.42 ms, III ; negative, 73.33 ± 6.36 ms, IV ; positive, 94.19±7.13 ms, V ; negative, 114.00±7.41 ms, VI ; positive, 134.6±9.92 ms and to VII ; negative, around 300 ms in the figure, by flash-VEP, recorded from Oz-Pz, with the subjects not specified sex and age. AEP peaks of healthy subjects of both sexes in this study, P3, N4, P5, N5 and P7, nearly correspond respectively to those of Picton and Hillyard (28), P1 ; mean 50±SD 4 ms, N1 ; 83±7 ms, P2 ; 161±17 ms, N2 ; 290±47 ms and P3 ; 450±26 ms, recorded between the vertex and mastoid electrodes by clicks with students of unspecified sex. Thus, the reliability and usefulness of the method, simultaneous/parallel EPs recording, applied in this study was verified by getting EPs peaks corresponding to those of previous reports by other researchers.

To make the differences in the waveform of EPs as conspicuous as possible among the 4 diagnostic groups, non-pathological factors affecting EPs were reduced or removed as much as possible throughout the recording and processing of EPs data. EPs were recorded without assigning any mental task to the subjects. Flash stimulation to closed eyes eliminated the need for subjects of making an effort to gaze at pattern reversal stimulation. The interference of sex factors (2, 17-20), in which different waveforms of g-m EPs with larger amplitudes and a tendency for shorter latencies are seen in females than in males, was avoided by processing all EPs data separately for each sex.

Dysfunctions (disorganization) of hyper-activated dominant hemisphere were reported in neuropsychological investigations, including EEG, in schizophrenics. Also, schizophrenic and paranoid symptomatology is related to dominant temporal limbic dysfunction in epilepsy, whereas manic-depressive syndromes reflect non-dominant limbic dysfunction (29, 30). Regarding the waveform stability of EPs, lower stability than in normal subjects, and lower stability in the left than in the right hemisphere in both schizophrenia and psychotic depression, indicate dysfunctions of the left hemisphere (31). Also, a significant positive correlation between the severity of positive thought disorder and left regional cerebral blood flow measured by PET (32), and localized reduction in the volume of gray matter of the posterior superior temporal lobe related to the degree of the total thought disorder score were observed by MRI in the left temporal lobe in schizophrenics (33). Because more than 85% of our subjects were right-handed (34), all EPs used in this study were recorded from the left hemispheres of the subject. SEP was derived from the derivation (C3'-F3') and (C3'-A1), modifying those of Shagass and Schwartz (35). VEP was derived from (O1-A1) and (O1-Cz), and AEP from (Cz-A1) and (Cz-T5). Each 2 derivations for VEP and AEP were selected according to the ratio of "deviation" between VEP and AEP, so as to record each of them as selectively as

possible, including their long latency components of up to 1000 ms latency. The "deviation" is the value of the area encircled by the waveform and baseline (15, 16), after adjusting the axis of the EPs waveform against baseline so that the value is minimum (36). Finally, these derivations confirmed that stimulus intensities of 0.6 J for flash-VEP and 110 dB for click-AEP were optimal (37).

Long latency SEP components, more than 20 ms latency, are generated in the somatosensory cortex (38). Early flash VEP components arise in the primary visual cortex, while the later flash components, including P2 (120 ms), are generated in the secondary visual cortex or visual association areas (39). Middle latency components of AEP up to 50 ms in latency originate from the mid-brain and primary cortical projection area, and later components, 50-600 ms in latency, originate from secondary, 3rd and 4th cortical projection areas (40). Early EP components, up to 100 ms in latency, are thought to be concerned with transmission of information, and later components are thought to reflect information-processing and to be related to attentive activity (41), and possibly to psychiatric events. Furthermore, a positive peak with about 800 ms latency was reported in deep sleep (42). Therefore, in this study, EPs including later components with up to 1024 ms latency were recorded and subjected to data analysis.

Although the differences of latencies and amplitudes of the components of EPs between psychotics and healthy subjects had been reported to vary for each sensory modality and for different researchers, and even between subgroups within each major diagnostic group. In general, the latencies of the long latency components, more than 80 ms latency, tend to increase and their amplitudes to decrease in psychotics, and there is higher waveform variability in the later components in psychotics than in healthy subjects (21, 43). Prolonged latencies of EPs were also reported in epileptics (44).

Furthermore, in this study, differences in the waveform of EPs among healthy subjects, schizophrenics, manic-depressives and epileptics were confirmed by the results that 1) The different waveforms of g-m EPs among the 4 diagnostic groups for each channel (modality), for each sex, by inspection. 2) The differences in latencies and inter-peak amplitudes among the 4 diagnostic groups attained to the significant level by ANCOVA after eliminating effect of age for each channel (modality), for each sex. 3) The numbers and ratio of pairs of latencies and inter-peak amplitudes with significant differences by Scheffe's multiple comparison test, which were higher between healthy subjects and each of these pathological diagnostic groups than between the pathological diagnostic groups, for each sex.

Almost all patients in this study were on medication. Medications alter EPs in various ways. Minor tranquillizers tend to increase latencies of early components and decrease the amplitudes. Psychoexcitants such as amphetamine shorten latencies and increase amplitudes. Antipsychotics tend to increase latencies and decrease amplitudes of early components. Antidepressants tend to decrease latencies and amplitudes of early components, and increase latencies of later components (21). Antiepileptics also tend to increase the latencies of EPs (44).

However, in the previous studies in our Department, less significant ($P<0.05$) differences of latencies and inter-peak amplitudes of EPs in schizophrenics medicated with neuroleptics, between those taking more than and less than 600 mg/day of chlorpromazine equivalent, than between those patients and healthy subjects were confirmed by ANCOVA after eliminating the effect of age, for each sex (4-6). No dose-related effect of neuroleptics on AEP was found in schizophrenics in a study including unmedicated patients by Jones and Callaway (45). In manic-depressives on concomitant medications, no or less significant differences in latencies and inter-peak amplitudes in EPs between the patients taking and not taking each of Li or CBZ, than between each of these patients and healthy subjects was found by U-test, for each sex (7-9). Similarly, in epileptics on concomitant medications, less significant differences in latencies and inter-peak amplitudes in EPs between these patients taking and not taking each of these anti-epileptics ; CBZ, PB, VPA or PHT, than between each of these patients and healthy subjects were confirmed by ANCOVA after eliminating the effect of age, for each sex (10, 11). Furthermore, the relevant peaks were mostly different between healthy subjects and these patients and between medicated and not medicated patients (4-11). These results were in accord with the results obtained by Scheffe's multiple comparison test in this study, in which the numbers and ratio of pairs of latencies and inter-peak amplitudes with significant differences were higher between healthy subjects and these pathological diagnostic groups than between each of these pathological diagnostic groups, for each sex. Therefore, the differences in the waveforms of EPs, including those of latencies and inter-peak amplitudes, among these diagnostic groups confirmed in this

study can not be attributed entirely to the effects of medication, but must also be attributed to the pathological factor of each diagnostic group.

Differences in the waveforms of EPs among healthy subjects, schizophrenics, manic-depressives and epileptics were confirmed in this study, without dividing the diagnostic groups into their subtypes or different conditions of the subject groups, such as manic or depressive. The 3 pathological diagnostic groups subjected to this study correspond to the previous rough concept of the 3 circles of major psychoses by Jaspers, 1948 (46) ; genuine (idiopathic (47)) epilepsy, schizophrenia and manic-depressive illness. This might suggest the existence of a waveform for individual EPs specific to each of these major diagnostic groups, for each sex. Further it suggests the possibility of making an objective neuropsychiatric diagnosis based on the waveform of EPs.

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