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Original

Comparison Between Conventional EEG and Amplitude Integrated EEG in Neonates

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Background: We aimed to determine the optimal method for evaluating brain function in babies at risk for neurological complications using both conventional electroencephalography (cEEG) and amplitude integrated EEG (aEEG). **Methods:** Between January 2007 and March 2009, 28 newborns were enrolled in this comparative study of aEEG and cEEG. As soon as possible after the infants had been admitted, simultaneous aEEG and cEEG recordings were started. We analyzed 65 recordings at post-conceptional ages (PCA) ranging from 25 weeks 5 days to 44 weeks 2 days, including serial EEG recordings from 11 infants. The aEEGs were evaluated using 3 classifications and cEEGs were graded according to suppression pattern or chronic phase abnormalities based on previous reports. **Results:** cEEG showed 41 abnormalities in 65 recordings. On the other hand, with aEEG, only 11, 15 and 19 cases were evaluated as abnormal by the al Naqeeb, Hellstrom-Westas and Burdjalov methods, respectively. Cases with the suppression pattern on cEEG showed relatively high consistency with the aEEG evaluation. However, in those with chronic phase abnormalities on cEEG, there were no abnormal findings on aEEG. **Conclusions:** The aEEG method appears to be very useful for monitoring acute phase brain function while in the chronic phase it is more appropriate to use cEEG. The aEEG is a more powerful tool when used in conjunction with cEEG as well as neurological examinations.

Key Words: conventional EEG, amplitude integrated EEG, perinatal medicine, neurological examination, neurological sequelae

Introduction

The recent development of perinatal medicine has reduced the mortality rate of newborns, especially premature babies. On other hand, the incidence of neurological sequelae such as periventricular leukomalacia and intracranial hemorrhage has not apparently decreased. Thus, elucidation of the mechanisms underlying perinatal brain damage and preventive measures are urgently needed.

To examine the brain functions of babies at risk for neurological sequelae, conventional electroencephalography (cEEG) has been used and appears to be a very powerful tool, providing neurological prognoses[1)2)], demonstrating brain functional states and degrees of maturation, revealing cerebral lesions and identifying the presence and number of electrographic seizures. Experimentally, EEG serves as an indicator of neuronal organization and differentiation, as well as depicting the level of functional maturity[3)4)], and has thus been used to examine brain maturation as the infant grows in the first year of life, and also to identify abnormalities in cerebral electrographic activity which appear to correlate with neurological insults[5)].

These evaluations require serial EEG recordings in the neonatal intensive care unit (NICU), although artifact-free recordings are difficult to obtain in this setting. Under these circumstances, neonatologists have sought a reliable tool that is readily applicable, with easily interpreted results, for real-time assessment of brain function. The use of amplitude integrated EEG (aEEG), which meets these needs, has thus become widespread.

However, is aEEG always a good alternative to the standard cEEG? If aEEG is not equivalent to cEEG in terms of accuracy in evaluating maturational changes or in sensitivity for detecting abnormalities, what are the major advantages of aEEG and how readily applicable is this method in the actual NICU setting? What is the optimal method for evaluating brain function in babies at risk for neurological complications using both cEEG and aEEG?

Thus, we designed this study to clarify the differences between aEEG and cEEG, and to determine the most appropriate use of each method in the clinical NICU setting.

Patients and Methods

1. Patients

Between January 2007 and March 2009, 28 newborns were enrolled in this comparative study of aEEG and cEEG. They were admitted to our NICU because of moderate or severe asphyxia, extremely premature birth, and so on. There were 19 males and 9 females, including 12 extremely premature babies. They all had gestational ages of at least 25 weeks and 5 days. As soon as possible after the infants had been admitted, simultaneous aEEG and cEEG recordings were started. Serial EEG recordings were obtained for 11 infants. Both aEEG and cEEG traces of the simultaneous recordings were analyzed off-line and independently classified by each method, as described below. Informed consent was obtained from the parents of all 28 patients.

2. Recordings

The cEEG recordings were performed on an 8 channel EEG and Electrocardiogram (ECG), with electrodes placed at Fp1, Fp2, P3, P4, O1, O2, T3 and T4 based on the 10-20 system as modified for newborns, and aEEG of C3 and C4 were derived from these EEG data using a Nicoletone® monitor (Viasys). The post-conceptional ages (PCA) at the time of recording ranged from 25 weeks 5 days to 44 weeks 2 days.

3. Analysis

We adopted 3 classification systems for aEEG and that reported by Watanabe for cEEG[6]. The method of al Naqeeb[7] is based only on the upper and lower amplitudes (Table 1-1). The Hellstrom-Westas classification[8] is based on the recording pattern, as well as the lower and upper amplitudes (Table 1-2). The Burdjalov maturational score is calculated based on cyclicity, continuity, lower amplitude and bandwidth[9] (Table 1-3). Using the al Naqeeb and Hellstrom-Westas methods, we directly adopted 2 criteria for abnormality. While for Burdjalov's score, we adopted the established method. We had previously investigated the reliability of Burdjalov's score[10], and thus utilized the equation from our previous study for the expected value and defined the score as abnormal if the score was 2.5 below the expected value as calculated by this equation. The Watanabe classification of cEEG is pattern-based, including the suppressive pattern representing acute phase abnormalities, as well as other features such as immature or disorganized patterns indicating chronic phase abnormalities (Table 2). Suppression patterns were identifiable by the degree of discontinuity, changes in frequency and varying degrees of amplitude range lowering, based on which the pattern was graded from 1 to 5 (G1 to G5, G1 is mildest, and G5 is most severe). Abnormalities seen in the chronic phase refer to EEG abnormalities without definite findings of acute depression and consisted mainly of immature and disorganized patterns. Immature patterns are defined as an EEG with some immature patterns for PCA, meaning the persistence of premature patterns including very high amplitude ultra-slow delta waves, temporal theta bursts or brushes, and so on, as well as the absence or poor development of a mature high voltage slow pattern. A disorganized pattern refers to abnormal, deformed background activity without definite findings of acute depression. We compared the detection rate of abnormalities and findings of aEEG and cEEG findings using Mann-Whitney's U test.

Results

The cEEG showed 41 abnormalities in 65 recordings. On the other hand, on the aEEG, only 11, 15 and 19 cases were evaluated as abnormal using the al Naqeeb, Hellstrom-Westas and Burdjalov methods, respectively, and evaluations of aEEG and cEEG findings revealed significant differences (Table 3). However, in 3 cases, we could not evaluate the aEEG traces using the Hellstrom-Westas method because they had been affected by body movements or instability of the electrodes, though we were able to evaluate the cEEG pattern from other unaffected electrodes. To precisely investigate the differences between abnormalities on cEEG and aEEG, we compared both types of EEG findings in cases showing abnormalities on cEEG. Cases with the suppression pattern on cEEG showed relatively high consistency with the aEEG evaluation, especially the more severe cases graded as greater than G2. However, those with an immature or disorganized pattern on cEEG that had not been evaluated as abnormal by aEEG, showed significant differences by the Mann-Whitney U test (Table 4, Fig. 1). It thus appears to be difficult to identify cases with chronic cEEG abnormalities such as dysmature or disorganized patterns based only on aEEG findings.

Table 1-1 The classification proposed by al Naqeeb

	Upper band margin	Lower band margin
Normal (NN)	>10 μV	>5 μV
Moderately abnormal (MA)	>10 μV	5 μV
Suppressed (S)	<10 μV	<10 μV

As noted above, several cases showed discordant aEEG and cEEG findings. Figure 2 shows EEG findings recorded sequentially once a week in the same neonate. First, the lower margin of the aEEG recording is slightly depressed and shows no cyclicity, and then slight cyclicity appears with persistently low voltage at the lower margin. Next, the voltages of the lower margin gradually increase, suggesting maturational change on the aEEG. These recordings showed no abnormalities. However, on the cEEG, a few abnormalities such as sharp spikes or mechanical brushes, findings identifiable as a disorganized pattern, can be seen.

Discussion

Recent advances in neonatal medicine have allowed very premature babies to survive and inno-

Table 1-2 The classification proposed by Hellstrom-Westas

		Lower band margin	Upper band margin	pattern	
Normal	N1	5-10 μV	10-25 μV	Continuous pattern	SWC developed
	N2				Immature SWC
	N3				No SWC
Moderately abnormal (D)		<5 μV	<10 μV	Discontinuous pattern	
Severely abnormal	BS	0-2 μV	25 μV<	Absence of variability, discontinuous pattern	
	CLV	<5 μV	5 μV<	Continuous low voltage pattern	
	FT	<5 μV	<5 μV	Isoelectric pattern	

BS: burst suppression, CLV: continuous low voltage, FT: Inactive flat, SWC: sleep wake cycle.

Table 1-3 CFM (cerebral function monitoring) scoring system (Burdjalov)

score	Continuity	Cyclicity	Lower margin	Bandwidth and lower
0	Discontinuous	None	<3 μV	low voltage (≦15 μV) low voltage (5 μV)
1	Somewhat continuous	Waves first appear	3-5 μV	high span>20 μV or moderate span (15-20 μV) and low voltage (5 μV)
2	Continuous	Not definite, somewhat cycling	>5 μV	high span (>20 μV) and high voltage (>5 μV)
3		Definite cycling, but interrupted		moderate span (15-20 μV) and high voltage (>5 μV)
4		Definite cycling, non interrupted		low span (<15 μV) and high voltage (>5 μV)
5		Regular and mature cycling		

vations such as hypothermic therapy for protecting the brain have been adopted in the field of the neonatology[11]. Thus, efforts are now focused on decreasing neurological complications. It would appear to be both important and necessary to obtain EEG recordings which directly represent brain activity. There has been a great deal of research on neonatal EEG, especially the relationship with prognosis in premature infants[2)12)~14)]. Serial EEG recordings beginning immediately after birth are very useful for assessing the timing and mechanism of brain injuries and for predicting the outcomes of infants[6)12)].

On the other hand, however, EEG recording has been regarded as difficult and somewhat troublesome in the NICU, where there are already numerous medical devices such as respirators, heart and respiratory monitors, and so on. Moreover, the evaluation of neonatal EEG can be difficult because it is rather different from EEG of babies at 3-4 months of age or older, and it changes continually with maturation[15]. Therefore, the EEG has not often been utilized in actual clinical situations. For practical application in the NICU, devices that can be used easily are needed. For this reason, aEEG has gained popularity in the field of neonatology.

Douglas Maynard designed early aEEG formats in the 1960s and Pamela Prior evaluated the main clinical applications[16]. Initially, aEEG was used to monitor adults during anesthesia or for monitoring the patient's state after cardiac arrest. In Europe, the use of aEEG in the NICU had already become widespread in the 1980s[17]. In Japan, however, aEEG has only recently been introduced in the NICU.

Generally, EEG measures the difference in electrical potential between 2 scalp locations. This alternating signal, which reflects the ebb and flow of current between different regions of the cortex, contains both positive and negative values of voltages that fluctuate over time. The raw microvolt EEG signal is first amplified, and then narrowly filtered to attenuate electrical activity of less than 2 Hz and more than 15 Hz, minimizing artifacts from sources such as sweating, muscle activity and environmental electrical interference. These filtered signals are rectified and the peak to peak amplitudes are measured in microvolts. These amplitudes are biased to emphasize alpha frequencies over theta or delta frequencies, and are smoothed using a moving average of 0.5 seconds. The final result is plotted on a semi-logarithmic scale to emphasize the lower voltage activity. The aEEG tracing is thereby viewed on a highly compressed time scale, historically at a rate of 6 cm/hr. These views enable us to ascertain the time course of changes in EEG amplitude, one of the most useful features of aEEG. Thus, aEEG is now more frequently used for monitoring brain function. Numerous studies have shown the clinical utility of aEEG, for example, in demonstrating the timing of intracranial bleeding or the progression of hydrocephalus[8)18)~20)].

Although reading an aEEG depends primarily on subjective visual pattern recognition of a record's continuity, bandwidth, the presence of a cycling pattern, and the occurrence of epileptiform activity, we can easily identify the sleep-awake cycle of neonates, the maturational level and abnormal neurological activities. Herein, we adopted three methods for aEEG classification, an approach suggested to increase the accuracy of the assessment. These are the methods reported by al Naqeeb, Hellstrom-Westas and Burdjalov.

With al Naqeeb's method, only the amplitudes of

Table 2 The Watanabe classification of cEEG

Acute stage abnormalities			
	Continuity	Frequency	Voltage
Grade1 (G1)	Prolonged inter-burst interval	Attenuated $\beta/\alpha/\theta$	—
Grade2 (G2)	—	—	Mildly low voltage
Grade3 (G3)	Decreased continuous pattern	—	—
Grade4 (G4)	Absent continuous pattern	Delta activity only	Moderately low voltage
Grade5 (G5)	—	—	Very low voltage/flat

Chronic stage abnormalities	
Pattern	Characteristics of the pattern
Disorganized (DO)	Abnormal, deformed background activity without acute depression
Immature (IM)	Immature pattern for chronological age

Table 3 The rate of detection of abnormalities by each method

criteria	aEEG			cEEG
	Naqeeb	Hellstrom-Westas	Burdjalov	
Number of abnormalities	11	15	19	41
The rate of abnormalities (%)	16.9※	24.2※, ※※	29.2	63.1

※p<0.01.
※※3 cases could not be classified due to artifacts.

Table 4 aEEG evaluation in patients with abnormal cEEG findings

The findings of cEEG	PCA at the recording	al Naqeeb	Hellstrom-Westas	Budrjalov
G1	39w1d	NN	N1	N
	40w1d	NN	N1	N
	42w4d	NN	N1	N
G2	25w5d	NN	D	N
	41w2d	NN	D	A
	41w3d	NN	N1	N
G3	35w4d	S	CLV	A
	35w5d	MA	CLV	A
	36w3d	S	CLV	N
	36w5d	MA	D	A
	36w5d	S	CLV	A
	36w6d	MA	D	N
	36w6d	S	BS	A
	40w3d	S	CLV	A
	41w4d	MA	CLV	A
G4	41w0d	S	CLV	A
	41w2d	S	FT	A
DO	32w2d	NN	N3	N
	33w2d	NN	D	N
	34w2d	NN	N2	N
	34w3d	NN	N1	N
	34w4d	NN	N2	N
	35w2d	NN	N1	N
	35w4d	NN	N2	N
	36w2d	NN	N1	N
	38w5d	NN	N2	N
	39w2d	NN	N2	N
	41w6d	NN	D	A
	42w5d	NN	D	A
	43w0d	NN	N2	N
	43w6d	NN	N1	A
	45w1d	NN	N3	A
	47w2d	NN	N3	A
IM	37w2d	NN	N2	N
	38w2d	NN	N1	N
	38w5d	NN	N2	N
	40w3d	NN	N2	N
	40w4d	NN	N1	N
	41w4d	NN	N1	N
	42w0d	NN	N2	A
	42w5d	NN	N1	A

N: normal, A: abnormal.

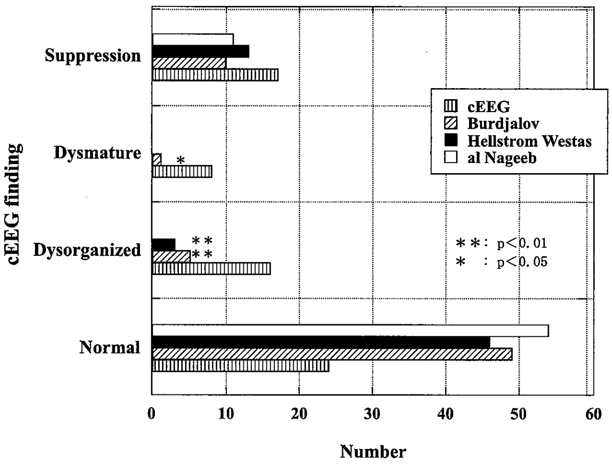

Fig. 1 This graph shows each case, as evaluated by cEEG based on the abnormalities detected by aEEG
The cases showing a immature or disorganized pattern on cEEG in the chronic phase had not been evaluated as abnormal by aEEG despite the high coincidence between cEEG and aEEG findings in the acute phase.

the lower and upper margins are considered, making it a very simple technique. With the Hellstrom-Westas method, patterns of traces other than the amplitudes of the lower and upper margins are considered. The maturational score for Burdjalov is calculated based on the cyclicity, continuity, lower amplitude and bandwidth. We previously investigated the reliability of the Burdjalov score in our laboratory and obtained results similar to those of Burdjalov's report. Therefore, in this study, we used our equation to determine the expected maturation score. This appeared to improve sensitivity for detecting abnormalities.

The abnormality detection rate with aEEG was lowest with the al Naqeeb method. It has showed the importance of the evaluation for the continuity and cyclicity of the tracing of the EEG, which has been evaluated by the method of Hellstrom-Westas or Burdjalov.

The abnormalities found on aEEG tended to co-

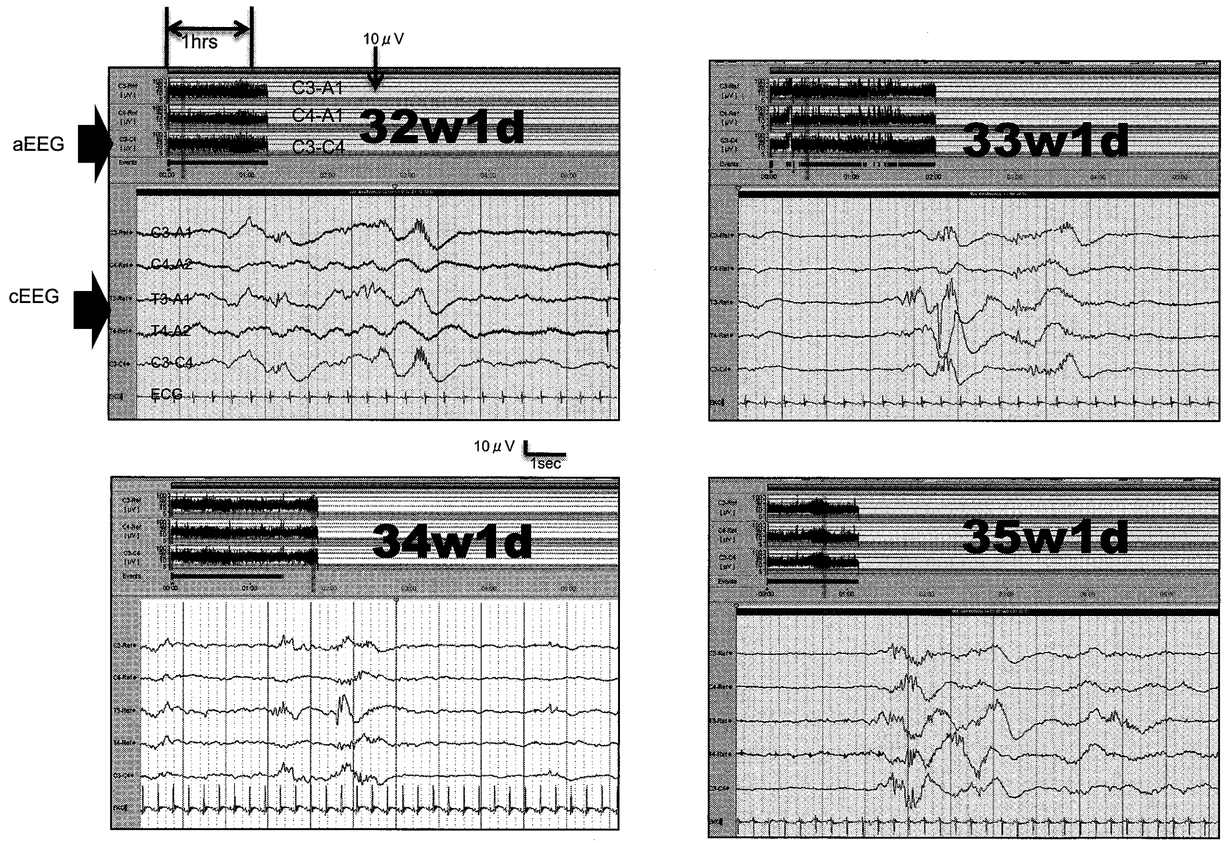

Fig. 2 Serial aEEG findings in this study
The aEEG showed maturational changes such as the appearance of clear cyclicity with no definite abnormalities. However, on the cEEG, sharp spikes or mechanical brushes, findings indicative of a disorganized pattern, can be seen.

incide with those on cEEG in the acute phase, indicating suppression of the background on cEEG.

Though the sleep-awake cycle, which reflects maturation, had been identified in some cases on aEEG with the pattern of recordings, i.e. continuity and cyclicity, as read using the Hellstrom-Westas or Burdjalov methods, these observations couldn't be made even in some cases with abnormal brain function. Thus, maturation could not be judged accurately by aEEG alone. It was also difficult for only aEEG to detect a disorganized pattern, a finding which appears to reflect white matter injury. This can easily be understood because the aEEG reflects time course fluctuation in amplitude, not the configuration of EEG waves. Thus, severe suppression in the acute phase was detectable with aEEG, while chronic phase abnormalities such as a dysmature or disorganized pattern were not detectable with aEEG alone.

Based on these results, aEEG may only be highly useful for monitoring brain function during the acute phase, because it might enable us to detect the inhibitory changes due to events such as intracranial bleeding or infarction immediately after onset of the events.

Furthermore, ictal change could easily be recognized by detecting an acute increase in the lower margin of long-term aEEG recordings, a situation in which abnormalities are often quite difficult to be detect[21)22)] by cEEG. It has thus been recommended that aEEG be used as a monitoring device and that other intermittent or simultaneous cEEG recording is also needed, as previously reported[23)24)]. To obtain good recordings and evaluate aEEG appropriately, several factors must be considered. The aEEG can be recorded using only 2 electrodes, possibly making it very convenient for placement on the heads of very small infants in the NICU and reducing the burden on these infants. For the same reason, however, aEEG would tend to be more affected by artifacts. If we use only 2 electrodes for a prolonged period, it is necessary to minimize these effects. By using 6 or 8 electrodes, not only can we obtain detailed information relating to the localization of electrical brain activity but also these multiple electrodes might compensate for the effects of artifacts on the trace.

In this study, we used the NicoletOne® monitor, which is compact enough for the NICU, and allows recording of both aEEG and cEEG simultaneously, which is the most important advantage of this device.

Although accurate evaluation of aEEG appears to be relatively easy for most neonatalogists with a little experience in EEG readings, the aEEG alone is not sufficient. Recording aEEG and cEEG simultaneously is essential for evaluating brain function accurately. With both, we can easily evaluate the brain state of infants during the acute phase from the aEEG, and detect maturational changes in detail or the quality of electrical activity in the brain using the information provided by the precise cEEG configuration.

Conclusion

The aEEG method appears to be very useful only for monitoring acute phase brain function while in the chronic phase the cEEG is more appropriate. The ready availability and ease of use of the aEEG by bedside staff make it an attractive method for monitoring brain functions in neonates. Thank to the progress of a new machine which enable us to get the aEEG and cEEG simultaneously, we can obtain more useful information of neonatal brain activity by this equipment. Thus this simultaneous record of aEEG and cEEG become more powerful tool to evaluate neonatal brain function as well as neurological examination.

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新生児における従来型脳波と amplitude integrated EEG 所見の比較

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〔背景〕我々は従来型の脳波（cEEG）と amplitude integrated EEG（aEEG）の両者を用いて神経学的合併症のリスクのある新生児の脳機能を評価し，その有効性を検討した．

〔方法〕2007 年 1 月から 2009 年 3 月までに 28 人の新生児を aEEG と cEEG の比較研究の対象とした．これらの児の NICU 入院後できるだけ早期に aEEG と cEEG の同時記録を開始した．記録時期は受胎後 25 週 5 日から 44 週 2 日までで，延べ 65 回の同時記録を行った．この中の 11 人では経時的な記録を行った．aEEG は al Naqeeb, Hellstrom-Westas，Burdjalov の 3 つの判定基準を使い評価，cEEG は急性期パターンの分類と慢性期異常の分類を使って判定した．

〔結果〕cEEG は 65 記録のうち 41 記録が異常を示した一方 aEEG ではそれぞれ al Naqeeb 法で 11 記録，Hellstrom-Westas 法で 15 記録，Burdjalov 法で 19 記録に異常を認めた．cEEG で抑制パターンが認められた 17 症例では aEEG と cEEG の結果が一致する傾向を認めた．それに対し cEEG で慢性異常が認められた 24 症例では aEEG において異常と判定されなかったものが多かった．

〔結論〕aEEG は急性期の脳機能のモニターには非常に有効であったが，慢性期には cEEG による評価が必要と思われた．神経学的検査法に合わせて，aEEG と cEEG の同時施行がより有用な脳機能評価法と思われた．