



## Event-Related Potentials for Cognitive Assessment of Patients with Epilepsy

Yoshimi Kaga<sup>1,2\*</sup>, Hideaki Kanemura<sup>1</sup>, Sayaka Ishii<sup>2</sup>, Shigeaki Kaga<sup>3</sup> and Masao Aihara<sup>4</sup>

<sup>1</sup>Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

<sup>2</sup>National Hospital Organization Kofu National Hospital, Yamanashi, Japan

<sup>3</sup>Department of Surgery, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

<sup>4</sup>Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan

### Abstract

Event-related potentials (ERPs) are very useful for evaluating cognitive function in patients with neurological and psychiatric disorders. The method is noninvasive, economical, and offers a certain level of temporal resolution. This review focuses on cognitive functions in epilepsy patients using various ERPs, such as P300, mismatch negativity, NoGo potentials, cognitive negative variation and working memory paradigms. Patients with epilepsy show impaired cognitive functions in the form of selective attention, pre-attentive cognitive function, working memory and frontal inhibitory functions. These impairments come from either the epileptogenic focus or the effects of therapy. Anti-epileptic drugs (AEDs) influence cognitive functions. These influences may be dose-dependent and can improve after discontinuation. By assessing various ERPs, the clinician can evaluate cognitive functions, differential diagnoses and the effects of AEDs in patients with epilepsy. Furthermore, these evaluations can lead to improved quality of life for patients.

### Introduction

An event-related potential (ERP) is a measured brain response that is the direct result of a specific sensory, cognitive, or motor event. ERPs are measured by electroencephalogram (EEG), and represent any stereotyped electrophysiological response to a stimulus. The study of the brain in this way provides a noninvasive means of evaluating brain function in patients with psychological, neurological and cognitive dysfunctions.

Several investigators have studied the cognitive changes that appear in epilepsy. A decline in cognitive functions is seen in epilepsy, particularly in terms of memory, attention, concentration and speed of mental processing, and these abnormalities may be caused by the process of epileptogenesis itself, the seizures, and/or antiepileptic drug (AED) therapy.

This review gives a brief overview of cognitive functions in patients with epilepsy using various kinds of ERP, discusses recent research findings, and assesses the influence of epileptogenesis itself and AEDs on cognitive functions.

### P300: The Clinical Aspects of Epilepsy

Sutton et al. first reported ERPs associated with cognitive activity in 1965 [1]. The major positive component with latency of 300 ms is reported to be related to cognitive functions. The P300 latency is considered to reflect stimulus evaluation time, the process of selective attention, and/or the updating of working memory. The P300 is a late component of ERP occurring at a latency of approximately 300 ms after presentation of the target stimulus, and has provided a useful tool for noninvasively assessing cognitive functions in humans. The most common method of obtaining P300 is the oddball paradigm. Although two different frequencies of auditory stimulus are presented, the subject is required to count rare target stimuli. P300 tasks generally use auditory stimulation, but are sometimes designed with visual or somatosensory stimulations. Various theories have been put forward regarding the origin of P300, which may include the temporal lobe, centro-parietal lobe, frontal lobe, thalamus and hippocampus.

Many P300 studies for patients with epilepsy have been reported, as shown in Table 1 [2-22]. Most previous studies have described prolonged P300 latencies and no significant reductions in P300 amplitude among patients with epilepsy. Regarding type of epilepsy, patients with symptomatic partial epilepsy (PE) or cryptogenic PE

showed significantly prolonged P300 latency compared to idiopathic generalized epilepsy (IGE) [10,11,15]. Furthermore, patients with temporal lobe epilepsy (TLE) displayed prolonged P300 latencies compared to patients with IGE [2,12]. In contrast, Sunaga showed significant differences in P300 latency with IGE, but not with TLE [3]. He speculated that dysfunction of the mesencephalic reticular formation and thalamus may contribute to prolongation of P300 in children with IGE [3]. On the other hand, Shimono [9], Chayasirisobhon [18] and Bocquillon [22] showed no significant difference in P300 latency with SPE or TLE. These differences may be due to the different ages of subjects or the different timings of examination in the epileptic period. Various studies have revealed a negative correlation between age and P300 latency in normal children with development, and a positive correlation in normal adults with aging [23-25]. Furthermore, the prolongation for P300 latencies correlated strongly with increasing age in controls, but not in epilepsy patients [11,12]. Accordingly, developmental and aging aspects must be considered for P300 analysis.

In patients with IGE, particularly in absence epilepsy, Duncan compared auditory and visual P300 between absence epilepsy and patients with complex partial seizures (CPS) [21]. P300 latencies in both groups were normal, but a significant reduction in the amplitude of visual P300 was seen in both groups, and auditory P300 were only observed in absence epilepsy [21]. They concluded that auditory processing depended on intact mechanisms in the brainstem, which were dysfunctional in patients with absence seizures. On the other hand, P300 latency in idiopathic PE showed no significant difference from that in normal controls [5-7,11]. Despite these findings, other studies have reported that patients with benign childhood epilepsy with

**\*Corresponding author:** Yoshimi Kaga, Department of Pediatrics, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, Chuo City, Yamanashi 409-3898, Japan, Tel: +81-55-273-9606; Fax: +81-55-273-6745; E-mail: [yoshi3st@gmail.com](mailto:yoshi3st@gmail.com)

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Subjects, n	Age Range, years	Task	Response	Target (%)	Non-target (%)	P300 Latency	P300 Amplitude	Reference
Epi, 68	15-60	A	C	2000 Hz (20)	1000 Hz (80)	Prolonged in TLE>FLE>IGE	N.S.	Triantafyllou NI, 1992
IGE, 32; TLE, 18	6-15	A	K	2000 Hz (20)	1000 Hz (80)	Prolonged in IGE	N.D.	Sunaga Y, 1994
BCECTS, 23	7-16	A	C	2000 Hz (20)	1000 Hz (80)	Prolonged in BCECT	N.D.	Naganuma Y, 1994
IPE, 26; SPE, 47; IGE, 25	5-16	A	C	2000 Hz (20)	1000 Hz (80)	Prolonged in SPE, IGE	N.D.	Konishi T, 1995
IPE, 26; SPE, 46	5-16	A	C	2000 Hz (20)	1000 Hz (80)	Prolonged in SPE	N.D.	Naganuma Y, 1997
Epi, 50	15-64	A	N.D.	2000 Hz/1000 Hz (20)	1000 Hz/2000 Hz (80)	Prolonged	N.D.	Wu X, 1997
Epi with IQ 100, 6; epi with IQ 52, 6	16-23	A	K	2000 Hz (12)	1000 Hz (88)	N.S.	N.S.	Shimono M, 1997
CPE, 64; IGE, 52	12-54	A	C	1000 Hz (15)	8000 Hz (85)	Prolonged in CPE	N.S.	Soysal A, 1999
IGE, 23; IPE, 2; CPE, 54; SPE, 29	6-74	A	C	2000/1000 Hz (20)	1000/2000 Hz (80)	Prolonged in SPE	N.S.	Caravaglios G, 2001
IGE, 27; TLE, 13	IGE 30.59 ± 12.50 TLE 40.91 ± 15.11	A	C	750 Hz (10)	125 Hz (90)	Prolonged in TLE	N.S.	Chen R, 2001
Epi with abnormal MRI, 32; epi with normal MRI, 18	7-20	A/V	C	8 kHz (15-20), check 64'	1 kHz (80-85), check 16'	Prolonged in patients with abnormal MRI	N.S.	Turkdogan D, 2003
Intractable TLE, 10	20-59	A	K	2000 Hz (20)	1000 Hz (80)	N.D.	Reduced at postictal intervals	Abubakr A, 2003
PE, 55; GE, 45; intractable Sz, 20	9-20	A	C/K	1000 Hz (15)	8000 Hz (85)	Prolonged in PE, intractable Sz	N.D.	Celebisoy N, 2005
CEOP, 30	5-17	A	C/K	1000 Hz (15)	8000 Hz (85)	Prolonged	N.S.	Gokcay A, 2006
Epi, 73	35.64±11.89	A	C	2000 Hz (20)	1000 Hz (80)	Prolonged	N.S.	Soyuer F, 2006
Pretreated TLE, 30	11-78	A	C	2000 Hz (20)	1000 Hz (80)	N.S.	N.S.	Chayasirisobhon WV, 2007
IGE, 9; SGE, 31	18-70	A	C	2000 Hz (20)	1000 Hz (80)	Prolonged in IGE	N.D.	Ozmenek OA, 2008
Patients with centrotemporal spikes, 21	7-12.2	A	C/K	2000 Hz (20)	1000 Hz (80)	N.S.	Reduced	Duman O, 2008
Absence, 9; CPS, 13	absence 29.3±8.7, CPS 34.5 ± 8.2	A/V	K	1500Hz (25), X (25)	600 Hz/1050 Hz (75), non X (75)	N.S.	V; reduced in absence, CPS A; reduced in absence	Duncan CC, 2009
TLE, 10	18-49	A/V	K	1500 Hz (15), light blue rectangles (15)	1000 Hz (85), dark blue rectangles (85)	N.S.	Reduced at temporal area	Bocquillon P, 2009

epi: Epilepsy; IGE: Idiopathic Generalized Epilepsy; TLE: Temporal Lobe Epilepsy; BCECTS: Benign Childhood Epilepsy With Centrottemporal Spikes; IPE: Idiopathic Partial Epilepsy; SPE: Symptomatic Partial Epilepsy; IQ: Intelligence Quotient; CPE: Cryptogenic Partial Epilepsy; PE: Partial Epilepsy; GE: Generalized Epilepsy; Sz: Seizures; CEOP: Childhood Epilepsy with Occipital Paroxysms, SGE: Secondary Generalized Epilepsy; CPE: Complex Partial Seizures; A: Auditory; V: Visual; C: Count; K: Key press; N.D: Not Described; N.S: Not Significant

**Table 1:** Previous P300 Epilepsy Studies.

centrottemporal spike (BCECTS) show significantly prolonged P300 latency [4] and decreased P300 amplitude [20]. Moreover, patients with childhood epilepsy with occipital paroxysms also had prolonged P300 latency [16]. Interestingly, these abnormalities of P300 improved after complete recovery of epilepsy [4]. As noted above, several researchers have suggested that patients with epilepsy, even as idiopathic PE and IGE, showed a possibility of cognitive dysfunction in the form of inattention and delays in updating working memory. In particular, these abnormalities of P300 in most patients with SPE may originate from the process of epileptogenesis.

Some researchers examined the relationship between P300 and psychological evaluations such as the Wechsler Adult Intelligence Scale (WAIS) or Wechsler Intelligence Scale for Children (WISC) [8,26]. Wu found that prolonged P300 latencies did not correlate with full-scale IQ from the WAIS [8]. However, P300 peak latency was closely related with specific items in WAIS such as “arithmetic”, “digit symbol”, and “picture arrangement”. For children with epilepsy, Naganuma reported that age-corrected P300 latency showed an inverse correlation with the total scale of the WISC-R and that of the Wechsler Memory Scale (WMS). As

specific items in the WISC-R, “comprehension”, “picture completion”, and “coding” correlated with P300 latencies [26]. These findings suggest that P300 latency reflects psychogenic functions.

### P300: Effects of AEDs

A few reports have examined P300 latency and the effects of AEDs. Comparing monotherapy and polytherapy, Ozmenek evaluated differences in P300 latency among patients with epilepsy showing different seizure types of IGE and secondary generalized epilepsy (SGE) [19]. They found no significant difference in P300 latency between monotherapy and polytherapy [19]. In contrast, Triantafyllou reported that patients on AED monotherapy had shorter P300 latencies compared with patients taking a combination of two or more AEDs [2]. In terms of individual AEDs, P300 latencies were significantly increased in children receiving phenobarbital (PB), but not in children receiving carbamazepine (CBZ) or valproate sodium (VPA) [27]. However, the changes in P300 latencies may improve after discontinuation of AEDs. On the other hand, Panagopoulos examined the effect of VPA on P300 latency in patients with IGE [28]. P300

latency was significantly prolonged in the VPA group, but not in the CBZ group or healthy controls. Misra reported the effects of phenytoin (PHT) monotherapy on P300 latency [29]. With serum PHT levels in the therapeutic range (10.2-17.7 µg/ml), P300 latency was normal in all patients. They concluded that PHT seems not to produce significant cognitive dysfunction in the therapeutic range. In contrast, Enoki recorded P300 from children receiving high-dose AEDs [30]. P300 latency was prolonged in five of eight patients in the CBZ group and in four of seven patients in the PHT group, but normal in all patients in the VPA group. In particular, P300 latency was extremely prolonged when PHT level exceeded 30 µg/ml. This prolongation was described as dose-dependent. Naganuma also reported that age-correlated P300 latency showed a significant positive correlation with serum concentration of CBZ [4]. In summary, their results suggest that AEDs may have effects on cognitive function, especially PB, and occasionally CBZ, VPA and PHT. The effects can show dose-dependence and may improve after discontinuation of AEDs.

### Mismatch Negativity (MMN)

MMN is early ERP elicited when infrequent (“deviant”) stimuli occur in a sequence of repetitive (“standard”) stimuli [31]. MMN is elicited as a negative wave with a latency of about 100-250 ms from stimulus onset in the fronto-central region. In general, these tasks are used with auditory stimulus as tone or speech sounds, but MMN is observed with visual stimulus as colors [32]. It reflects a pre-attentive cognitive function that acts automatically in comparisons with consecutively presented stimuli. MMN, calculated as the deviant-standard difference, is considered a reliable index of pre-attentive sensory memory [33]. MMN can be elicited even in the absence of attention, and effects of motivation are minimal. As a result, MMN has been examined under physiological conditions in newborns, infants, and patients with neurological disorders such as schizophrenia, Alzheimer’s disease, and mental retardation, who are unable to perform traditional cognitive tasks.

Previous MMN studies for patients with epilepsy have been very limited. Gene-Cos compared MMN between subjects with non-epileptic seizures and those with epilepsy [34]. Their results showed longer MMN duration and increased amplitude in the frontal region for patients with epilepsy. These results suggest that patients with epilepsy have abnormal processing of auditory stimuli. MMN is thus useful for differential diagnosis of epilepsy.

In terms of epilepsy subtype, a few researchers have addressed MMN for patients with TLE [33,35]. There is evidence that the source of MMN is largely in the superior temporal cortex [36]. In particular, one of the cortical generators of MMN probably originates from the primary auditory cortex or in that vicinity [37]. MMN abnormality may therefore be present in patients with TLE. Lin reported that TLE patients showed longer latencies in magnetically measured MMN (MMNm) in response to tone changes [37]. Miyajima also found delayed latencies of MMN to tone stimuli in TLE patients [38]. Interestingly, they reported

that MMN at fronto-central sites was enhanced, but no differences were apparent at mastoid sites. They concluded that enhanced frontocentral MMN may reflect hyperexcitability of frontal lobes in compensation for dysfunction of the temporal lobes. In contrast, Hara recorded MMN in TLE patients during the presentation of speech sounds, comprising alternation of the vowels ‘a’ and ‘o’ [33]. They found that MMN response at bilateral mastoid sites was reduced, whereas MMN response at fronto-central sites did not change significantly. MMN is generated by separable sources in the frontal and temporal lobes, with sources differentially affected for tone and speech sounds in TLE patients.

On the other hand, Boatmen et al. evaluated speech recognition in children with BCECTS [39]. They showed that MMN was absent or prolonged in speech, but not in tones. Furthermore, Honbolygo found MMN was obtained for phoneme differences, but absent for stress pattern differences in Landau-Kleffner syndrome (LKS) [40]. These results suggest that children with BCECTS and LKS show impaired selective cognition of speech sounds.

For the effect of treatment, Borghetti investigated changes to MMN in epilepsy patients implanted with a vagus nerve stimulator (VNS) [41]. After one year of follow-up, MMN latencies and amplitudes showed no significant changes following VNS implantation. However, in two cases with abnormal MMN before VNS implantation, MMN showed reduced latency and increased amplitude after implantation. Pre-attentive processes were thus improved by VNS implantation.

### Go/NoGo Task

The Go/NoGo task is one of the useful paradigms for recording ERPs to investigate the neural mechanisms underlying response execution and inhibition. In NoGo trials, the N2 component (NoGoN2) around 140-300 ms and the P3 component (NoGoP3) around 300-500 ms are prominently elicited at the frontocentral electrodes, compared with go trials [42]. These components have been called ‘NoGo potentials’, and have been interpreted as indices of response inhibitory process in the frontal lobe [43]. In general, the Go/NoGo task is used with auditory or visual stimulation in continuous performance task (CPT).

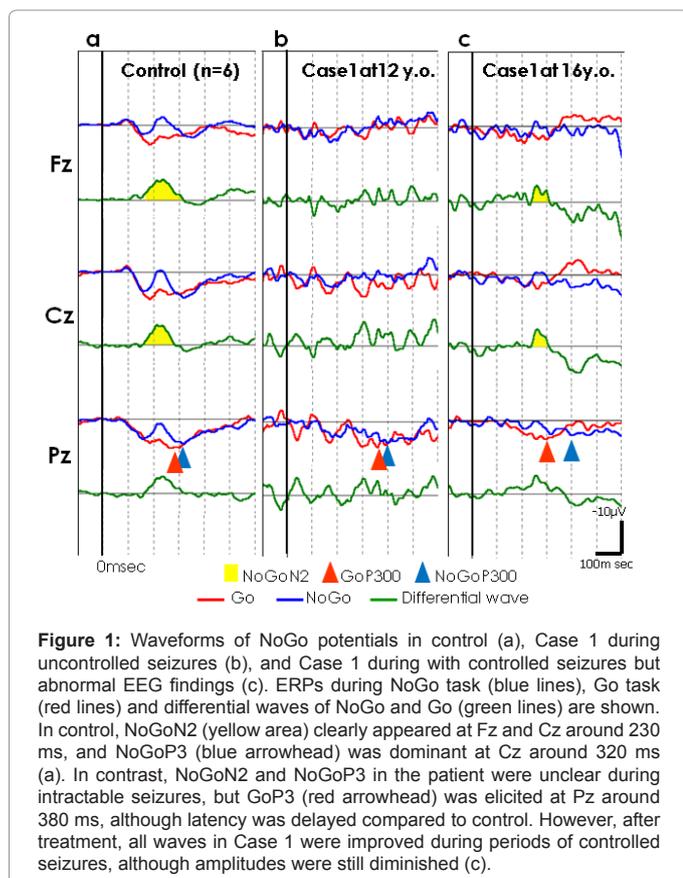
The Go/NoGo task is also a useful method to assess frontal inhibition function in patients with epilepsy, although very few studies have examined NoGo potentials in patients with epilepsy. Pachalska evaluated a child with BCECTS presenting with symptoms of attention deficit/hyperactivity disorder using the Go/NoGo task [44]. The NoGoP3 amplitude of the patient was decreased before treatment, but improved after treatment.

We examined NoGo potentials of patients with frontal lobe epilepsy (FLE) to assess frontal inhibition function. Clinical characteristics of patients with FLE are shown in Table 2. The patient in Case 1 experienced absence seizures originating from a frontal origin. She had intractable absence seizures and cognitive impairments. At 10 years old, she was examined using the Wisconsin card sorting test, a test applied clinically

Case No	Sex	Age, years	Age at Seizure Onset, years	Seizure Type	Ictal EEG	Interictal EEG	Treatment	Seizure Outcome
		1 <sup>st</sup> /2 <sup>nd</sup>						
1	F	10/16	9	Atypical absence	3-4 Hz S&W	Spikes at lt. F	VPA, AZA, LOF	None
2	M	11/14	9	CPS, sGTC	N.D.	Spikes at rt. Fp	CBZ	None
3	M	14/17	3	sGTC	N.D.	Spike & waves at bil. F	VPA	None

CPS: complex partial seizures, sGTC: secondary generalized epilepsy, N.D.: not done, VPA: sodium valproate, AZA: acetazolamide, LOF: ethyl loflazepate, CBZ: carbamazepine

Table 2: Clinical characteristics of the patients.



the coming target 'red'. In the corresponding NoGo trial, the response was to be withheld when a color other than 'red' (blue, green, yellow) appeared after the white color. In the control group, NoGoN2 clearly appeared at Fz and Cz, and NoGoP3 was dominant at Cz (Figure 1a). In Case 1, during the phase in which she experienced frequent seizures and continuous spikes and waves on EEG at 12 years old, the NoGo potentials were unclear with NoGoN2 and diminished with NoGoP3 (Figure 1b). However, in the phase where she became seizure-free but EEG findings were abnormal at 16 years old, small NoGoN2 appeared and the latency of NoGo P300 was still prolonged (Figure 1c). The results of other cases are shown in Table 3. In Cases 2 and 3, although NoGo potentials had been abnormal during treatment with abnormal EEG findings, findings of NoGo potentials became near-normal with improvements in EEG. These results suggest that patients with FLE have response inhibition deficits, and that impairments may be reversible with recovery from epilepsy. ERP studies are thus also useful for the evaluation of treatment for FLE.

### Others

Cognitive negative variation (CNV) is a long-latency ERP related to the association or contingency between two stimuli. CNV originates from the frontal lobe for at least some CNV components. Only one study has examined CNV for epilepsy patients. Drake et al. recorded CNV in patients with CPS and secondarily generalized seizures (SGS) [45]. Patients with CPS presenting with and without SGS showed lower areas under the CNV curve than controls, and CNV amplitude was significantly reduced. They concluded that CNV may differ between PE and controls. Patients with CPS may be impaired in terms of continuous attention.

Abnormal cognitive and memory functions are common complications of epilepsy. Although memory dysfunction in TLE is generally considered an abnormality of long-term memory, evidence is increasing that short-term memory (STM) is also involved. Assessing the function of STM for epilepsy patients, Grippo recorded ERPs with a working memory paradigm, a digit-probe identification-and-matching task, in TLE patients [46]. They found slow reaction time, reduced amplitude of the N170 wave and a broad late negative shift in patients. These abnormalities of ERP provide further objective evidence that abnormalities of STM processes contribute to the memory deficits in TLE. Myatchin also examined ERPs with another working memory paradigm (1-back matching task) in children with epilepsy [47,48]. Even if the patient was well-controlled or had idiopathic benign epilepsy, different cortical activation patterns were seen during a visual working memory task. This paradigm is very useful for clarifying frontal function in epilepsy. Further studies with other types of epilepsy are warranted.

Studies of face perception with ERPs have recently undergone various developments. The face is a source of extremely important social signals for humans. The origins of face perception for traditional models are generally considered to involve the fusiform gyrus, lateral occipital cortex, and superior temporal sulcus. ERPs on face perception have been focused on the N170 (N1). This component shows greater amplitudes in response to faces than to stimuli from other categories. In a study on epilepsy, Sun investigated the effects of AEDs using the ERPs of face perception [49]. N170 was lower in patient groups, and becomes lower after topiramate (TPM) treatment compared to VPA. They concluded that the imperative effects of TPM on visual perception function reflected by N170 were more obvious than those of VPA.

	Case 1	Case 2	Case 3
<b>1<sup>st</sup></b>	Seizures increased, abnormal EEG	Seizure free, abnormal EEG	Seizure free, abnormal EEG
<b>NoGoN2</b>	Not clear	Latency: slightly prolonged	Latency: normal
		Amplitude: decreased	Amplitude: slightly decreased
		Distribution: Cz-Pz	Distribution: Pz
<b>NoGoP3</b>	Latency: prolonged	Latency: prolonged	Latency: normal
	Amplitude: decreased	Amplitude: decreased	Amplitude: decreased
	Distribution: Pz	Distribution: Fz-Cz	Distribution: Cz
<b>2<sup>nd</sup></b>	Seizure free, abnormal EEG	Seizure free, normal EEG	Seizure free, normal EEG
<b>NoGoN2</b>	Latency: prolonged	Latency: normal	Latency: normal
	Amplitude: decreased	Amplitude: normal	Amplitude: decreased
	Distribution: Fz-Pz	Distribution: Cz-Pz	Distribution: Fz
<b>NoGoP3</b>	Latency: prolonged	Latency: normal	Latency: normal
	Amplitude: decreased	Amplitude: normal	Amplitude: normal
	Distribution: Cz-Pz	Distribution: Cz	Distribution: Cz

ERPs: event-related potentials, EEG: electroencepharogram

**Table 3:** Results of ERPs during NoGo tasks.

to assess executive abilities. She had only one category completed (CA) and 13 perseverative errors (PEN). Patients in Cases 2 and 3 had complex partial seizures and secondary generalized convulsions originating from the frontal lobe. The visual NoGo paradigm was used with five different colors in CPT. Colors were presented in random order on a monitor. In the Go trial, subjects were asked to respond to the red color after the white color. Thus, the white color was a cue for

## Conclusion

ERPs are a useful method for evaluating cognitive function, diagnosis, and effects of treatment in patients not only with psychogenic disorders, but also with epilepsy. The paradigms are very variable, including the oddball paradigm for P300 or MMN, NoGo paradigms, working memory paradigm, and face perceptual paradigms. Researchers should properly select the paradigms for each purpose. For assessing frontal functions, NoGo or working memory tasks are recommended. The oddball paradigm of P300 is beneficial for selective attention or cognition using several modes of perception.

Many researchers have addressed the impairment of cognitive functions in patients with epilepsy. Impairments may originate in the individual process of epileptogenesis, spreading from epileptic foci and the effects of AEDs. Under treatment, cognitive function was frequently impaired. Researchers should always consider the repercussions of AEDs in terms of cognitive function. Determination of ERPs offers an objective measure to examine the cognitive functions affected in patients.

Many reports have examined the origin of ERPs. In particular, depth EEG for preoperative patients presents a wealth of information. However, studies of depth EEG cannot provide results for comparison with normal controls. On the other hand, neuroradiological studies such as functional magnetic resonance imaging with ERPs or magnetoencephalography are also useful as methods for assessing the mechanisms of ERPs. Further studies will clarify the neuropsychogenic and neuropathological mechanisms in epilepsy using ERP analyses combined with other methods.

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