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Disturbance of semantic processing in temporal lobe epilepsy demonstrated with scalp ERPs

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We investigated event-related potentials (N400, LPC and CNV) elicited in temporal lobe epilepsy (TLE) patients and control subjects from scalp electrodes, using a word-pair category matching paradigm. Each prime consisted of a Japanese noun (constructed from 2–4 characters of the *Hiragana*) followed by a Chinese character (*Kanji*) as the target, the latter representing one of five semantic categories. There were two equally probable target conditions: match or mismatch. Each target was preceded by a prime, either belonging to, or not belonging to, the same semantic category. The subjects were required to respond with a specified button press to the given target, according to the condition. We found RTs to be longer under the mismatch condition in both subject groups. The N400 amplitude was reduced in TLE subjects under both conditions, although LPC and CNV amplitudes showed no significant differences. These results suggest that scalp N400 is capable of demonstrating disturbance of semantic processing in TLE non-invasively.

Key words: ERP; N400; CNV; LPC; TLE; semantic processing.

INTRODUCTION

A number of studies have been devoted to impairment of cognitive function in temporal lobe epilepsy (TLE); with language and memory dysfunction, in particular, being widely researched. Troster and his colleagues[1] reported that impaired verbal fluency in TLE was due to disruption of semantic networks in semantic memory. The purpose of this paper is to clarify cognitive disturbances in TLE using the N400, which is an event-related potential (ERP) component involved in semantic processing.

Originally, Kutas and Hillyard[2] found this negative component to be evoked at around 400 ms after sentence endings featuring a semantically incongruent word; or a word that was semantically acceptable but unpredictable in the context of the sentence[3], and coined 'N400' for its name. These studies suggested that the N400 was involved in semantic priming or activation. It can also be elicited with a word-series paradigm[4], a paired-word paradigm[5], a pseudo-oddball word paradigm[6] or a categorization paradigm[7]. Recently, it has also been used in applicational studies, such as into age-related cognitive change[8], cognitive dysfunction in schizophrenia[9], Alzheimer's disease[10] and aphasia[11].

While cognitive disturbance in TLE has long been an object of study, with much emphasis on the role of the P300 in particular[12], there have recently been a number of studies on the role played by N400. Beck *et al.*[13] revealed that the N400 amplitude correlated with pyramidal cell density in the hippocampus (CA2) in TLE patients. Elger *et al.*[14] reported that there were at least two generators of word-specific N400: one in the middle temporal gyrus of the left (dominant) hemisphere, and one in the left anterior medial temporal lobe (AMTL), the former correlating with immediate, and the latter correlating with delayed, verbal recall. In previous studies on N400 in TLE patients, ERPs have been recorded with depth and subdural electrodes. Al-

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though these can record EEGs more clearly than scalp electrodes, they are invasive. Because of this invasive element, recording with such electrodes is limited to candidates for temporal lobectomy, and, therefore, such ERPs are never available from healthy control subjects. As it is important to assess cognitive dysfunction in TLE patients non-invasively, we investigated ERPs using scalp electrodes.

In this study, we employed the same paradigm used in our previous study on the effect of age on N400[8]. In that study, the N400 amplitude was found to be reduced in elderly subjects. We will discuss the differences between those results and those of the present study later.

The paradigm used in this study was simple, therefore even enabling subjects with cognitive disturbances to perform the required task easily. The ease of such a paradigm is important for its clinical application.

In this study, the reaction time (RT), the CNV and the late positive component (LPC) were also investigated to obtain information on dysfunction in semantic processing in TLE patients.

METHOD

Subjects

We examined ten TLE patients, all outpatients being treated at the Epilepsy Clinic of the Department of Psychiatry and Neurology, Hokkaido University Hospital. All of them had experienced complex partial seizures. Their clinical features and interictal EEG findings indicated a left temporal lobe origin. Tables 1 and 2 show the medical and neuropsychological profiles of each patient. Informed consent was obtained from all of them. In addition, ten male students from Hokkaido University were engaged as control subjects (mean age = 24.3 years). All subjects, in both groups, were right-handed and had normal, or corrected to normal, vision.

Experimental procedure

A category matching paradigm was employed to elicit ERPs. Each trial consisted of a warning, a prime and a target stimulus. The target was a Chinese character, or '*Kanji*', indicating one of five semantic categories (color, tree, fish, bird and insect). The prime was a word made up of two to four characters from the Japanese syllabary, the *Hiragana*, and consisted of one of 35 nouns (seven nouns per semantic category)[†]. The following two target conditions were presented according to the semantic relationship between a target and its preceding prime: (1) a match condition, in which the target was preceded by a prime that belonged to the same semantic category, or (2) a mismatch condition, in which the target was preceded by a prime that did not belong to the same semantic category (Fig. 1). Each condition was presented in random order, with the same probability. The warning sign lasted for 1000 ms, and the onset-to-onset interval of each warning sign and prime was 1040 ms; prime and target stimuli lasted for 400 ms, and the onset-to-onset interval of each prime and target stimulus was 1040 ms. Stimuli subtended a vertical length of 5 mm and a horizontal length ranging from 5 to 20 mm. Stimulus presentation was controlled by a personal computer.

Exemplar of stimulus

Stimulus Condition	Exemplar prime - target
Match	すずめ - 鳥 (sparrow - bird)
Mismatch	とんぼ - 魚 (dragonfly - fish)

Fig. 1: Exemplar of the prime and target stimuli under each condition. Prime stimuli were written in the Japanese syllabary, *Hiragana,* and target stimuli in Chinese characters, or *Kanji*. An English translation of the stimuli is given in parentheses.

Subjects sat about 80 cm away from the CRT display. They were instructed to press a key switch to match-condition targets with one thumb and to mismatch-condition targets with the other thumb, as quickly as possible. The assignment of response hands was counterbalanced across the subjects. The subjects were also requested to refrain from blinking, except when the warning sign was on.

Recording and analysis

We analyzed EEGs recorded from the F_z, C_z, and P_z electrode sites. All the electrodes were referred to linked ear lobes. Impedances were kept below 5 kΩ.

[†] The Japanese writing system consists of three sets of symbols: the *Kanji* and two types of syllabary—the *Hiragana* and the *Katakana*. In general, the *Kanji* are used to represent words or their semantic components, while syllabaries are used to represent the sounds of the language.

Table 1: Background and neuropsychological profile of patients.

No./Gender	Age(Y.)	WAIS-R TIQ	VIQ	PIQ	WMS MQ
1/F	31.5	84	86	85	70
2/F	25.1	103	89	122	96
3/F	26.1	77	64	100	61
4/F	23.8	116	122	101	121
5/F	39.3	98	111	81	102
6/F	25.8	69	58	90	72
7/F	34.2	89	88	92	95
8/F	21.3	125	112	137	115
9/F	32.8	78	77	85	100
10/F	24.2	83	77	95	80
Average (SD)	28.4(5.7)	92.2(18.0)	88.4(21.0)	98.8(17.8)	91.2(19.8)

WAIS-R: Wechsler Adult Intelligence Scale-Revised; TIQ: total intelligence quotient; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; WMS: Wechsler Memory Scale; MQ: memory quotient.

Table 2: History of epilepsy.

No.	Age at onset (y. o.)	Epilepsy duration (y.)	Seizure frequency	IID focus	AED	Neuroimaging
1	8	23	yearly	Lt-aT	CZP	W. N. L
2	21	3	yearly	Lt-aT	CBZ	W. N. L
3	9	17	monthly	Lt-aT	CBZ	W. N. L
4	22	1	yearly	Lt-aT	PHT	W. N. L
5	37	2	yearly	Lt-aT-mT	CBZ	Rt-frontal Aracnoid cys
6	13	12	monthly	Lt-aT	CBZ	W. N. L
7	4	30	yearly	Lt-aT	CBZ + PRM	Lt-temporal sclerosis
8	14	7	monthly	Lt-aT-mT	CBZ + PHT + VPA	W. N. L
9	16	17	free	Lt-aT-mT	PHT	W. N. L
10	15	10	free	Lt-mT-pT	CBZ	W. N. L

CBZ: carbamazepine; CZP: clonazepam; PHT: phenytoin; PRM: primidone; VPA: sodium valproate; aT: antero-temporal; mT: mid-temporal; pT: postero-temporal.

EOG was monitored to exclude epochs contaminated with blinks from the analysis. The bandpass was set at 0.04–30 Hz. EEGs and EOG were digitized off-line with a personal computer. ERPs for the prime and target stimuli were averaged off-line for 2400 ms, with a 200 ms baseline before the prime stimulus onset (sampling rate = 250 Hz). Those for the target stimuli were averaged off-line for 1000 ms, with a 200 ms baseline before the target stimulus onset (sampling rate = 500 Hz). Trials with an error response or response omission were excluded from the ERP averaging. All subjects had at least 50 good trials for the prime and target stimuli, and at least 25 good trials for the target stimuli under each condition.

The N400 amplitude was measured as the mean voltage between 226 and 276 ms under the match condition, and between 276 and 326 ms under the mismatch condition, relative to a 200 ms baseline before the target stimulus onset. LPC amplitude was measured as the mean voltage between 326 and 376 ms under the match condition, and between 476 and 526 ms under the mismatch condition, relative to a 200 ms baseline before the target stimulus onset. The CNV amplitude was measured as the mean voltage between 1200 to 1400 ms after the prime stimulus onset, with respect to a 200 ms baseline before the prime stimulus onset.

We used analysis of variance (ANOVA) for statistical analysis, and vector analysis to assess scalp distribution differences between the two groups and between conditions[15]. Greenhouse and Geisser correction was employed where appropriate. The Tukey method was employed for *post hoc* comparison, with a significance level of $P < 0.05$.

RESULTS

Behavioral data

Table 3 shows the mean RTs and error rates for each condition in both subject groups. The RTs and error data were analyzed with a two-factor (two subjects (control vs. TLE) × 2 stimulus conditions (match vs. mismatch)) ANOVA. RTs were longer under the mismatch condition than under the match condition

($F(1, 18) = 28.72$, $P < 0.001$). The RTs in the TLE patients were longer than in the control subjects, although the difference did not reach a significant level ($P = 0.11$). The interaction was not significant. The error rates showed no significant effects.

ERP data

Figure 2 shows the grand average ERPs for the prime and target, and Fig. 3 shows the grand average ERPs for the target.

In the grand average ERPs for the prime and target (Fig. 2), ERPs in the TLE subjects were more positive than in the control subjects, with a latency of 300–600 ms after presentation of the prime stimulus. After 600 ms, a prominent CNV was elicited in both subject groups. No difference was found, however, after a latency of 1000 ms.

In the control subjects' grand average ERPs for the target (Fig. 3), the prominent negative-going component peaked at around 250 ms under the match condition and around at 350 ms under the mismatch condition, corresponding to that for N400. N400 had a larger amplitude and a longer duration under the mismatch condition than under the match condition. The LPC followed the N400 under each condition with an almost identical amplitude. The N400 amplitude was smaller in the TLE subjects than in the control subjects. In addition, the difference between stimulus conditions was unclear in the TLE subjects. The LPC amplitude was larger under the mismatch condition than under the match condition in the TLE subjects.

The mean amplitudes of N400, LPC and CNV are given in Table 4.

N400 amplitude

The N400 data were analyzed with a three-factor (two subjects × two conditions × three electrode sites (F_z, C_z, and P_z)) ANOVA. The N400 amplitudes were larger in the control subjects than in the TLE patients ($F(1, 18) = 4.605$, $P < 0.05$). The interaction between condition × site ($F(2, 36) = 38.77$, $P < 0.001$, $e = 0.769$) was also significant. Subsequent tests indicated that this significant interaction arose from the fact that the effect for site was significant under the match condition ($F_z < C_z$ and P_z), with the effects of condition being significant at F_z (mismatch > match) and at P_z (mismatch < match).

Vector analysis was employed to assess scalp distribution differences between subject groups and between conditions. The N400 amplitudes were reanalyzed after the data had been normalized by vector length, using a two subjects × two conditions × three electrode sites ANOVA[15]. The analysis confirmed that the interactions between condition × site ($F(2, 36) = 32.82$, $P < 0.001$, $e = 0.778$), subject × site ($F(2, 36) = 5.042$, $P < 0.02$, $e = 0.93$), and subject × condition × site ($F(2, 36) = 11.77$, $P < 0.001$, $e = 0.778$) were significant. Subsequent tests indicated that the significant interaction between subject × condition × site arose from the fact that the effect for site was significant in the control subjects under both conditions (match; C_z and $P_z > F_z$, mismatch; $C_z > P_z$), while it was not significant in the TLE subjects under either condition.

Table 3: Reaction times and error rates.

Stimulus condition	Control	TLE
	Reaction times (ms)	
Match	480.7 (92.51)	558.7 (108.0)
Mismatch	536.8 (93.12)	621.8 (139.6)
	Error rates (%)	
Match	0.50 (0.58)	0.80 (0.59)
Mismatch	0.60 (0.81)	1.30 (1.16)

Note: Standard deviations are given in parentheses.

Table 4: Mean amplitudes of N400, LPC and CNV.

Stimulus condition		Control	TLE
		Mean N400 amplitudes (μV)	
Match	F_z	3.95 (2.90)	5.15 (5.88)
	C_z	1.09 (1.93)	4.83 (5.87)
	P_z	0.46 (1.72)	3.10 (3.92)
Mismatch	F_z	0.63 (2.59)	4.21 (5.51)
	C_z	−0.30 (2.80)	5.47 (6.85)
	P_z	2.11 (2.32)	6.60 (5.53)
		Mean LPC amplitudes (μV)	
Match	F_z	7.29 (5.24)	9.76 (6.42)
	C_z	10.77 (7.61)	12.11 (8.08)
	P_z	12.25 (7.19)	12.19 (6.96)
Mismatch	F_z	5.89 (3.36)	11.48 (5.91)
	C_z	8.64 (5.04)	13.74 (8.67)
	P_z	11.89 (5.69)	14.99 (7.43)
		Mean CNV amplitudes (μV)	
	F_z	−1.03 (6.59)	1.11 (4.13)
	C_z	4.53 (4.66)	3.37 (3.96)
	P_z	3.79 (3.17)	4.11 (3.62)

Note: Standard deviations are given in parentheses.

LPC amplitude

The LPC data were analyzed with a three-factor (two subjects × two conditions × three sites) ANOVA, which revealed a significant effect for site ($F(2, 36) = 18.38$, $P < 0.001$, $e = 1.00$), and an interaction between condition × site ($F(2, 36) = 4.218$, $P = 0.023$, $e = 0.985$). Analysis of the LPC amplitude vectors confirmed an interaction between condition × site ($F(2, 36) = 4.589$, $P < 0.02$, $e = 0.973$). This

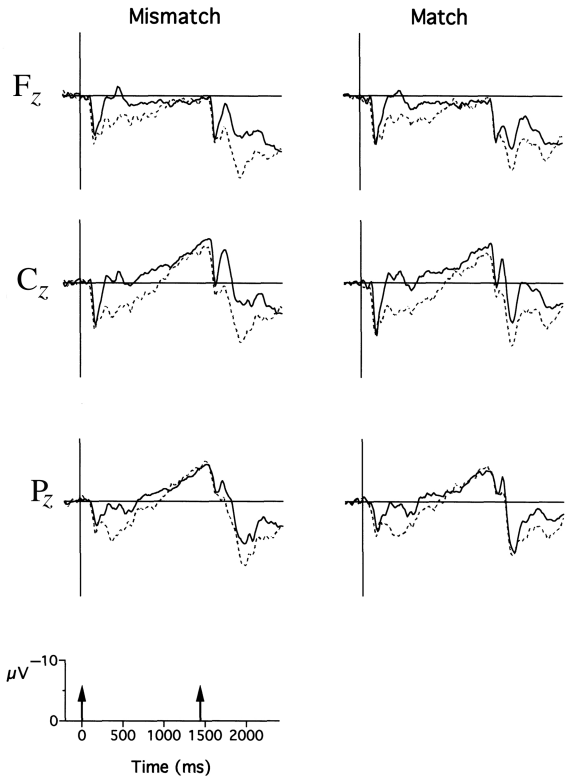

Fig. 2: Grand averaged ERPs for the prime and target stimuli. Solid curves show ERPs in the control subjects, and broken curves show those in the TLE subjects. On the scale, the left arrow indicates the time of the prime stimulus presentation, and the right arrow indicates the time of the target stimulus presentation.

interaction arose from the fact that the scalp distribution of LPC amplitudes was different between stimulus conditions: that is to say, the difference in amplitude between C_z and P_z was larger under the mismatch condition than under the match condition, while that between F_z and C_z was almost identical under both conditions.

CNV amplitude

The CNV data were analyzed with a two subjects × three sites ANOVA. The CNV amplitudes at C_z and P_z were larger than at F_z ($F(2, 36) = 34.59$, $P < 0.001$, $e = 0.58$). Analysis of the CNV amplitude vectors showed that interaction was not significant.

DISCUSSION

The RTs in the TLE patients were longer than in the control subjects, although the difference did not reach a significant level. Several researchers have reported that antiepileptic drugs (AEDs) prolonged RTs in therapeutic plasma concentration[16] and interfered with cognitive function, including motor and mental speed[17]. Here, a semantic priming effect was observed in both subject groups (control subjects: 56.1 ms; TLE patients: 63.1 ms).

The amplitudes of N400 were reduced in the TLE patients, with this reduction being observed under both stimulus conditions. The scalp distribution of N400 was different between the two subject groups. Vector analysis of the N400 amplitude revealed that the effect of the site was significant only in the control subjects, and that it was larger at C_z than at P_z under the mismatch condition. On the other hand, it showed no such difference in scalp distribution under the mismatch condition in the TLE subjects. This points to a large reduction in N400 under the mismatch condition at C_z in the TLE patients. This, therefore, clarified a disturbance of semantic processing in TLE patients using N400. In our previous study, we reported that a reduction in N400 under the mismatch condition along with age-related functional change in semantic processing. There is a difference in the pattern of N400 reduction between the two studies. This N400 reduction in the TLE patients under both stimulus conditions in the present study suggests the presence of a disturbance in its generators. McCarthy *et al.*[18] reported the presence of N400 generators in the AMTL. Beck *et al.*[13] revealed that the N400 amplitude correlated with pyramidal cell density in the hippocampus (CA2) in TLE patients. Elger *et al.*[14] reported that there were at least two generators of word-specific N400: in the middle temporal gyrus of the left (dominant) hemi-

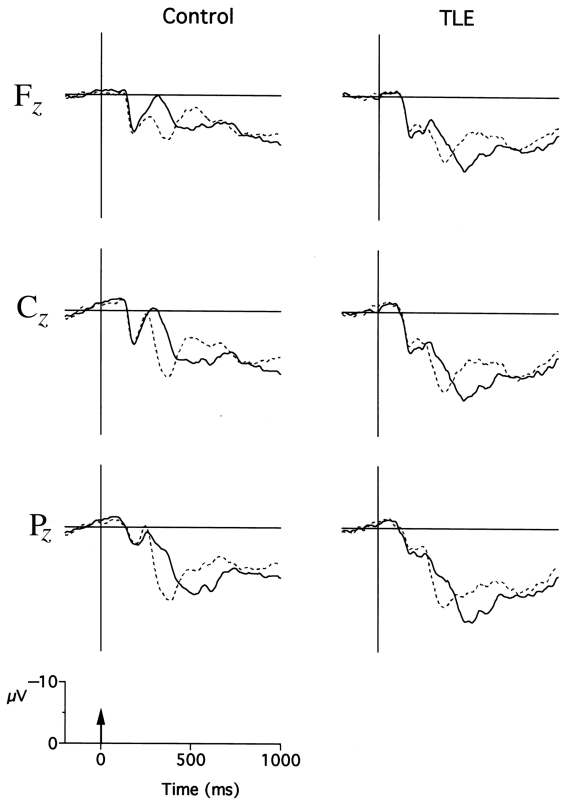

Fig. 3: Grand averaged ERPs for the target stimulus. Solid curves show ERPs under the mismatch condition, and broken curves show those under the match condition. On the scale, the arrow indicates the time of the target stimulus presentation.

sphere and in the left anterior medial temporal lobe. Although there is no agreement on this point, that the AMTL or the middle temporal gyrus are damaged in all TLE patients, it is still possible that N400 reduction arises from a dysfunction of its generators. In our TLE patients, neuro-imaging study demonstrated left temporal sclerosis in only one patient. This suggests that electrophysiological study could demonstrate cognitive dysfunction when there were no visible findings from imaging studies available.

Let us consider these results from the point of view of how the N400 is related to cognitive function. Semantic priming consists of two processes: an automatic process, which has a facilitating effect, and a conscious process, which has an inhibitory effect[19]. Several researchers have reported that N400 was modulated by attention-mediated processes and was related to an inhibitory effect[20, 21]. On the other hand, Revensuo and Laine[22] have reported that the N400 was observed in the absence of conscious understanding in a global aphasic patient. In our previous study[8], we suggested that N400 reduction in elderly subjects was not due to an attention disturbance, because the CNV was larger in these elderly subjects than in young subjects. Returning to the present study, however, while the N400 was smaller in TLE patients, the CNV showed no significant difference. These results suggest, therefore, that this reduction in N400 in TLE patients cannot be attributed to an attentional disturbance either.

The LPC in the TLE patients was larger than in the control subjects under the mismatch condition, although it did not reach a significant level. Although the precise nature of the LPC is still unclear, Juottonen *et al.*[23] have reported that LPC elicited by a semantic paradigm is possibly an indication of attention-demanding processes rather than automatic processes. In the present study, while the N400 was reduced in the TLE subjects, the LPC was somewhat larger. This means that the semantic process and neural structure related to N400 are different from those related to the LPC, and that attention-demanding processes are not impaired in TLE patients.

Because we intended to compare changes of ERPs in TLE subjects in this study with those in elderly subjects in our previous study[8], we employed almost the same control subjects in both studies. The control subjects are 4 years younger than the TLE subjects, and the former are all male and the latter are nine female patients and a male patient.

Since the difference in age between the two groups is 4 years, we consider that there were few age-related

effects on ERPs. Although N400 asymmetries between men and women were reported[24], there is no clear evidence to suggest that amplitudes of N400 and LPC elicited with a word paradigm at midline electrodes are smaller in women than in men. We believe that there were few, if any, effects due to gender on our ERPs data at midline electrodes.

All the TLE subjects in this study were under medication. Munte *et al.*[25] reported that benzodiazepines caused a reduction in the N400. One of our patients had taken clonazepam, and it is possible that it was this that resulted in the N400 reduction in this patient. We lack precise information on the effects of other AEDs on N400 as little research has been done so far on the pharmacological effects on this component. There is a wealth of evidence, however, showing that AEDs induce cognitive dysfunction[16] and affect ERP components[26]. Although the possibility that AEDs affected the N400 here cannot be denied, it seems reasonable to assume that the N400 reduction in these TLE subjects was not due to this, as they did not affect the other ERP components: the CNV and LPC.

These results suggest that this reduction of N400 in the TLE subjects arose from a disturbance in the automatic process. It is, as yet, unclear as to how such a disturbance in the automatic process would affect language in daily life, thought, or personality. This is something that needs to be clarified in further research on TLE patients.

In this study, we clarified a dysfunction in semantic processing in TLE using scalp N400. Scalp N400 was able to demonstrate cognitive dysfunction in TLE patients non-invasively.

To summarize, this study aimed at clarifying dysfunction in semantic processing using scalp ERPs. N400 amplitudes were found to be reduced in TLE patients. It was also found that attentional disturbance was not the main factor in this N400 reduction. From these results, it is clear that scalp N400 is capable of demonstrating cognitive dysfunction in TLE patients non-invasively.

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