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Uneven Interhemispheric Connections Between Left and Right Primary Sensori-Motor Areas

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Abstract: To clarify the characteristics of interhemispheric connections, we investigated cortico-cortical evoked potentials (CCEP) in human. Fourteen patients with temporal lobe epilepsy who underwent invasive EEG monitoring with bilaterally implanted subdural electrodes were studied. Electric pulse stimuli were given in a bipolar fashion at two adjacent electrodes on and around the motor area (MA) or sensory area (SA), and CCEP responses were recorded by averaging electrocorticograms from the contralateral hemisphere. Seventy-two pairs of electrodes were stimulated, and 468 recordings were analyzed. Fifty-one of 468 recordings demonstrated CCEP responses. Of 51 responses, 16 consisted of an initial positive triphasic wave (Type 1), 27 had an initial negative biphasic wave (Type 2), and 8 showed an initial positive biphasic wave (type 3). The mean latencies of the earliest peaks were 13.1, 28.9, and 29.4 ms in Types 1, 2, and 3 responses, respectively. The responses were more frequently evoked by stimulating facial MA (f-MA) and nonfacial MA (nf-MA) than by stimulating SA or nonelocquent area. In both f-MA and nf-MA stimulation, the responses were more frequently recorded at the contralateral f-MA than at the contralateral nf-MA or other areas. SA stimulation never evoked CCEP responses at the contralateral MA or SA. The amplitudes were maximal when f-MA was stimulated and responses recorded at the contralateral f-MA. These findings suggest that the interhemispheric connections are uneven. Both f-MA and nf-MA send dense interhemispheric connections to the contralateral f-MA. SA may have no or only rare direct connection with the contralateral MA or SA. *Hum Brain Mapp 33:14–26, 2012.* © 2011 Wiley Periodicals, Inc.

Key words: neural networks; corpus callosum; human brain; primary motor cortex; primary sensory cortex; intracranial recording; subdural electrode; functional mapping; evoked potentials; epilepsy

INTRODUCTION

Neural connections in the human brain have attracted interest recently, and human neural pathways have been demonstrated by MRI studies [Mori et al., 2000]. Electrophysiologically, these connections may also be examined by cortico-cortical evoked potential (CCEP) studies [Brugge et al., 2003; Greenlee et al., 2004; Matsumoto et al., 2004, 2005, 2007; Rutecki et al., 1989; Terada et al., 2008; Umeoka et al., 2009; Wilson et al., 1990, 1991].

Previously, we recorded CCEP responses from the contralateral hemisphere by stimulating facial motor area

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TABLE I. Number of electrodes identifying eloquent areas by standard cortical stimulations, and number of electrodes recording CCEP responses for each area stimulated

		Standard cortical stimulation			Cortico-cortical evoked potential study															
					Stimulated area															
		Number of electrodes identifying eloquent areas			f-MA				nf-MA				SA				NEA			
	Sex/				Number of electrodes recording CCEP in each area															
Pt.	age	f-MA	nf-MA	SA	f-MA	nf-MA	SA	NEA	f-MA	nf-MA	SA	NEA	f-MA	nf-MA	SA	NEA	f-MA	nf-MA	SA	NEA
1	F/36			2											2	6				
2	F/32	2	2		1	1		4	1	1		4					8	8		44
3	M/29			2												4				8
4	M/36	3			4			8												
5	F/21	3			4			8									2			2
6	F/21	1		1				4								4	1		1	17
7	M/21	4	2		4	2		6	2	1		3					4	2		6
8	F/22																			5
9	F/43	6		2	8		4	18					8			12	14		6	30
10	M/35		2	3					2	3	5			2	3	5		1	2	1
11	F/34	4		2			4	12					4			4	8		8	32
12	F/29	1		4									2		4	8	2		8	20
13	F/16	4	2		6	4		8	2			4					4	2		6
14	M/23																			10

Pt, patient number; M, male; F, female; f-MA, facial motor area; nf-MA, nonfacial motor area; SA, somatosensory area; NEA, noneloquent area.

(f-MA) in three epilepsy patients [Terada et al., 2008]. Our result demonstrated that most of these interhemispheric CCEP responses showed initial positive triphasic waveforms (P1-N1-P2). P1 had 1 or 2 notches, although P1 was absent in two of eight responses. The latency of P1 ranged 9.2 to 23.8 ms. The response was not evoked when non-motor area (non-MA) was stimulated, while stimulation of the motor area (MA) evoked CCEP responses at both MA and non-MA electrodes in the contralateral hemisphere. Therefore, we speculate that the stimulation produces one-way volley, and that orthodromic impulses may play an important role for this CCEP response. Regarding the location relationship between stimulation and response, stimulation of upper areas evoked responses recorded from the upper areas, while stimulation of lower areas produced responses recorded from the lower areas. These findings suggest that the neural connections may project to contralateral homonymous areas. However, our previous study examined only a small number of patients and evaluated only the f-MA. Therefore, we were not able to characterize the interhemispheric connections between bilateral MA more precisely.

In this study, we evaluated 468 CCEP recordings from 14 epilepsy patients to clarify the characteristics of interhemispheric neural connections arising from the MA. Furthermore, we also succeeded to stimulate the sensory area (SA) and evaluated interhemispheric connections originating from the SA.

SUBJECTS AND METHODS

Subjects, Electrodes Implantation, and Functional Mapping

The data were obtained from 14 patients with medically intractable temporal lobe epilepsy (5 men and 9 women, aged 16–43 years) (Table I). The Institutional Review Board approved this study, and informed consent was obtained from all patients. Interictal neurological examinations detected no focal neurological abnormalities in all patients. Routine noninvasive evaluations including MRI, SPECT, and scalp EEG/video monitoring failed to determine the epileptogenic zone. Therefore, these patients underwent long-term invasive EEG/video monitoring with chronically implanted subdural and depth electrodes as a part of presurgical evaluation [Mihara and Baba, 2001].

Each subdural electrode was 2.3 mm in diameter and made of platinum-iridium alloy. The center-to-center interelectrode distance was 10 mm. The locations and the numbers of subdural and depth electrodes implanted were standardized (see Fig. 1) [Mihara and Baba, 2001]. Briefly, two bundles of depth electrodes were inserted targeting

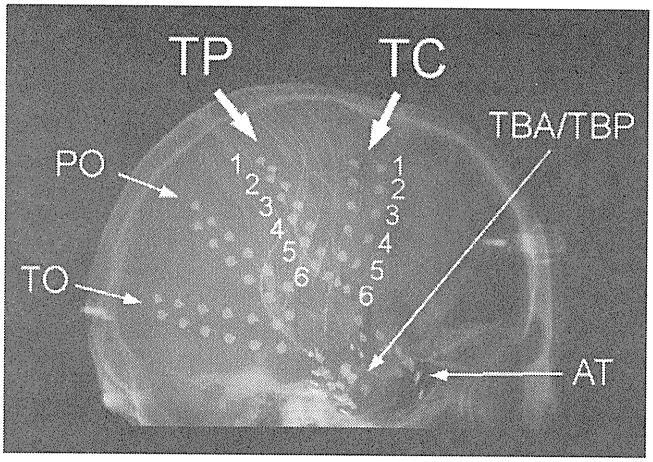

Figure 1.
X-ray image showing the standardized locations of subdural electrodes. Subdural plates (2 × 6; TBA and TBP) cover basal temporal regions, and 5 subdural strips (1 × 6) cover extratemporal areas on each side (AT, anterior temporal; TC, temporo-central; TP, temporo-parietal; PO, parieto-occipital; and TO, temporo-occipital). Plates and strips were placed almost symmetrically on both sides. The tip electrode of each bundle was designated "1," and the number is increased in order up to "6" for the most proximal electrode.

the amygdala and hippocampus on each side. A subdural plate (2 × 6) was slipped under the basal temporal lobe on each side. To detect epileptiform activities of extra-temporal areas, a subdural strip (1 × 6) was placed to cover the anterior temporal region (AT), and four strips were slipped radially from the burr hole to cover the temporo-central (TC), temporo-parietal (TP), parieto-occipital (PO), and temporo-occipital regions (TO). All bundles, plates, and strips were placed almost symmetrically on both sides. The tip electrode of each bundle was designated "1," and the number was increased in order up to "6" for the most proximal electrodes.

Standard cortical stimulation was performed [Lesser and Gordon, 2000] to determine the MA, SA, and other eloquent areas. A constant-current biphasic square electric pulse with a duration of 0.3 ms and frequency of 50 Hz was delivered for 1 to 5 sec (SEN-3301/SSI04J, Nihon Koden Corp., Tokyo). When pure motor or sensory response was evoked upon stimulation of an electrode, the electrode was defined as MA or SA. If both motor and sensory responses were observed at a single electrode, such electrode was excluded from further CCEP analysis in this study. The f-MA (MA of mouth, tongue, or face) and nonfacial MA (nf-MA; MA of finger or hand) were analyzed separately because CCEP responses of these areas have different characteristics.

The locations of electrodes were also anatomically confirmed by using 3D reconstruction MRI imaging (MRI-Cro: "http://www.cabiatl.com/mricro/") in each patient. Electrodes locating on the precentral gyrus were defined as MA-MRI, and electrodes on the postcentral gyrus were defined as SA-MRI. When electrodes were not on the precentral or postcentral gyri, they were named NEA-MRI.

Stimulation and Data Acquisition for CCEP

CCEP recordings were performed after clinical evaluations were completed, and therefore did not interfere with clinical evaluations. All CCEP recordings were performed while the patients were awake and sitting in bed.

For CCEP recording, we conducted stimulation by applying the same parameters as in the previous reports [Terada et al., 2008; Umeoka et al., 2009]. Briefly, the electrical stimulation consisted of a constant-current square pulse at a duration of 0.3 ms with a frequency of 1 Hz in alternating polarity (SEN-3301/SSI04J, Nihon Koden Corp., Tokyo). Two adjacent electrodes were stimulated in bipolar fashion. As we analyzed f-MA, nf-MA, and SA stimulations separately, we did not use the responses evoked by simultaneous stimulation of different eloquent areas; e.g., stimulation of an electrode pair covering f-MA and nf-MA. For the same reason, we did not use the responses evoked by stimulation of an electrode pair covering MA-MRI and SA-MRI. For comparison, not only eloquent areas, but also noneloquent areas (NEA) were stimulated for CCEP recording. The current intensity was set at 80% of the intensity that produced clinical signs or after-discharges during standard cortical stimulation for eloquent areas. For NEA, 80% of the maximal intensity employed in cortical stimulation was used. Even using lower stimulus intensity, patients sometimes demonstrated clinical responses during CCEP recording. In such cases, we decreased the intensity until no clinical response was observed. No clinical seizure occurred during CCEP recordings.

For CCEP recording, an evoked potential machine was used (Neuropack sigma, Nihon Koden Corp., Tokyo). Sampling rate was set at 5,000–10,000 Hz. The low frequency filter was set at 10 Hz, and the high frequency filter at 2,000–5,000 Hz depending on the sampling rate. Electrocorticograms were recorded with reference to a subdural electrode placed on a noneloquent indifferent area. For CCEP recording, 20 to 50 electrocorticographic responses were averaged and time-locked to the stimulus.

For statistical analyses, chi-square test and *t*-test were used (StatMate III, Advanced Technology for Medicine & Science, Tokyo).

RESULTS

Cortical stimulation identified the f-MA (28 electrodes), nf-MA (8 electrodes), and SA (16 electrodes including 8 electrodes for facial SA and 8 electrodes for nonfacial SA) in 14 patients (Table I). All these eloquent areas were detected by stimulating electrodes of the TC or TP strips (see Fig. 1). Therefore, CCEP were evaluated by

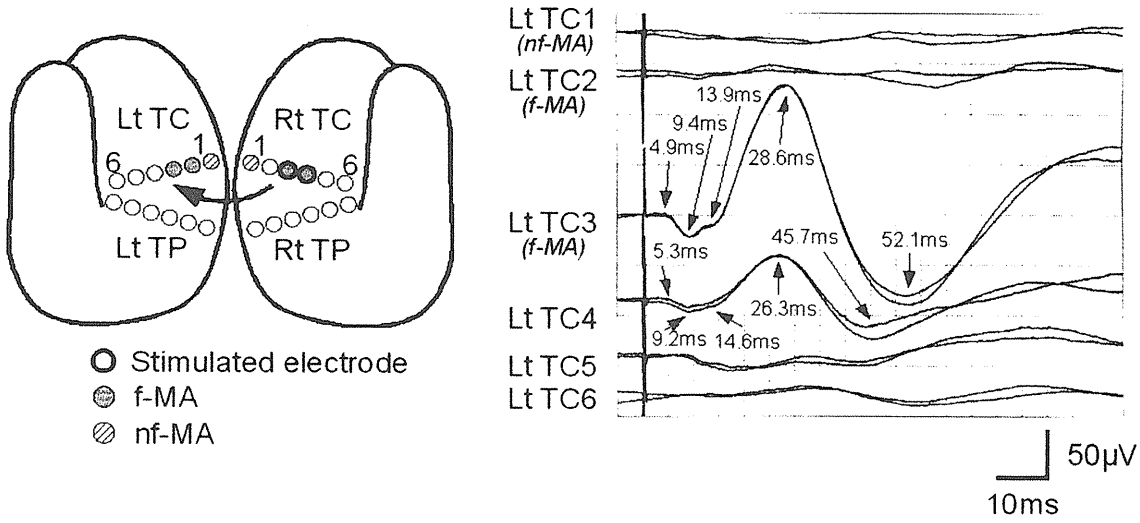

Figure 2.

Typical Type I response observed in Patient 7. The schematic figure shows the location of eloquent area and the stimulated electrodes. Bold circles signify the stimulated electrodes. Gray circles indicate electrodes located over facial motor area (f-MA), and hatched circles over nonfacial motor area (nf-MA). Two waveforms are displayed in each channel to confirm their reproducibility. CCEP responses were evoked by stimulating f-MA (Rt TC3/4), and were recorded from contralateral electrodes. The third and fourth channels (Lt TC3 on f-MA and Lt TC4 on non-eloquent area) demonstrate initial positive triphasic waveforms. Although there may be responses at the fifth and sixth channels, they are not analyzed in this study because they are too small.

stimulating TC or TP electrodes and recording from the contralateral TC or TP electrodes. As transcallosal CCEP responses were well recognized at the contralateral homologous area in the previous study [Terada et al., 2008], the homonymous electrodes and their contiguous electrodes were mainly selected as recording sites. Because of time pressure, not all pairs could be examined. Finally, we stimulated a total of 72 pairs of electrodes, and 468 recordings were evaluated (Table I). Of 468 recordings, 51 demonstrated definitive CCEP responses and were used in subsequent analyses.

Waveforms

As reported previously, initial positive triphasic waves (P1-N1-P2) were recorded from the contralateral hemisphere (Figs. 2–4; Type 1 response). Type 1 responses were found in 16 recordings; 12 by f-MA stimulation, 2 by SA stimulation, and 2 by NEA stimulation. The recorded sites were the f-MA (seven responses), SA (one response), and NEA (eight responses). The mean onset latency was 5.2 ms [standard deviation (SD): 1.0], and the mean latencies of P1, N1, and P2 were 13.1 ms (SD: 3.3), 30.1 ms (SD: 2.9), and 56.9 ms (SD: 7.9), respectively. The mean amplitude was 16.0 μV (SD: 8.7) from onset to P1, 77.3 μV (SD: 59.4) from P1 to N1, and 107.9 μV (SD: 72.2) from N1 to P2. A notch was seen superimposing on P1 in all Type 1 responses except one, in which 2 notches were detected (see Fig. 3).

In 27 recordings, initial negative biphasic waves (N1-P2) were observed (Fig. 5; Type 2 responses) were obtained by f-MA stimulation (16 responses), nf-MA stimulation (6 responses), and NEA stimulation (5 responses). The recorded sites were the f-MA (9 responses), nf-MA (1 response), SA (1 response), and NEA (16 responses). The mean onset latency was 11.1 ms (SD: 3.7), and latencies of N1 and P1 were 28.9 ms (SD: 5.0) and 52.5 ms (SD: 8.9), respectively. The mean amplitude was 27.5 μV (SD: 17.2) from onset to N1, and 49.1 μV (SD: 27.4) from N1 to P2. In 7 of 27 responses, a notch was seen superimposing on N1 (see Fig. 5). This notch was observed when stimulating f-MA (4 responses), nf-MA (1 response), or NEA (2 responses), and recorded at f-MA (3 responses) or NEA (4 responses).

In addition, initial positive biphasic waveforms (P1′-N1′) were identified in 8 recordings (Fig. 6; Type 3 response). Type 3 responses were obtained by f-MA stimulation (four responses), nf-MA stimulation (one responses), or NEA stimulation (three responses), and recorded at f-MA (five responses), nf-MA (two responses), or NEA (one response). The mean latencies of onset, P1′ and N1′ were 17.0 ms (SD: 6.0), 29.4 ms (SD: 4.5), and 49.4 ms (SD: 5.7), respectively. The mean amplitude was 20.9 μV (SD: 10.9) from onset to P1′, and 34.6 μV (SD: 16.5) from P1′ to N1′.

Statistical Analysis

Comparison among stimulation and recording sites

Chi-square test was used to analyze the effect of the stimulation site. The analysis demonstrated that the

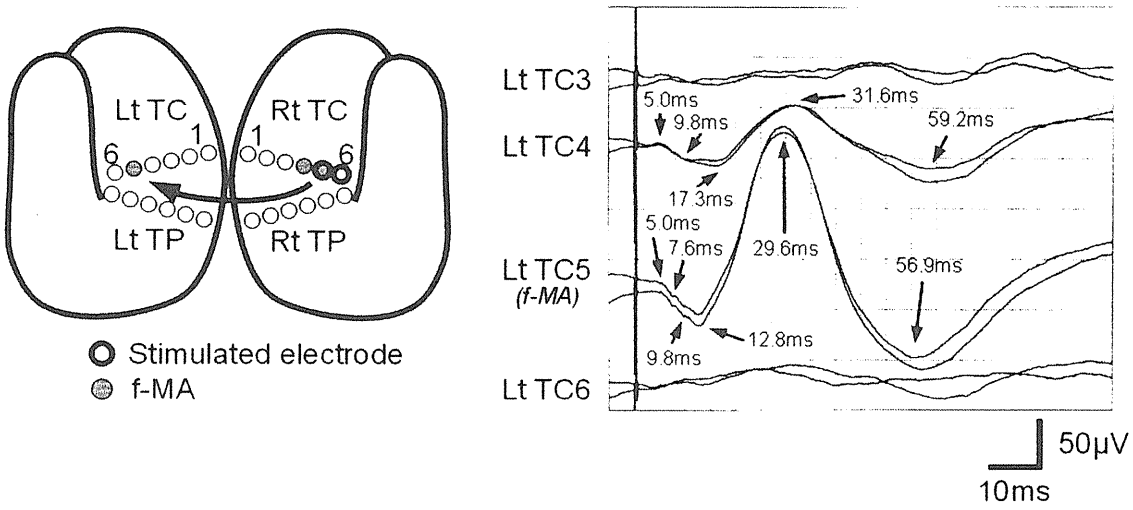

Figure 3.

Type I response observed in Patient 5. The schematic figure shows the location of eloquent area and the stimulated electrodes. Bold circles signify the stimulated electrodes. Gray circles indicate electrodes located over facial motor area (f-MA). Two waveforms are displayed in each channel to confirm their reproducibility. CCEP responses were evoked by stimulating an electrodes pair including f-MA (Rt TC5), and were recorded from contralateral electrodes. The second and third channels (Lt TC4 on noneloquent area and Lt TC5 on f-MA) demonstrate initial positive triphasic waveforms.

stimulating site affected the positive CCEP response rate ($P < 0.001$). In each comparison between eloquent sites, a significant difference was observed between f-MA and SA ($P < 0.001$), between f-MA and NEA ($P < 0.001$), between nf-MA and SA ($P < 0.001$), and between nf-MA and NEA ($P < 0.001$) (Table II). These findings thus suggested that f-MA stimulation and nf-MA stimulation evoked contralateral hemispheric CCEP responses more frequently than SA stimulation or NEA stimulation.

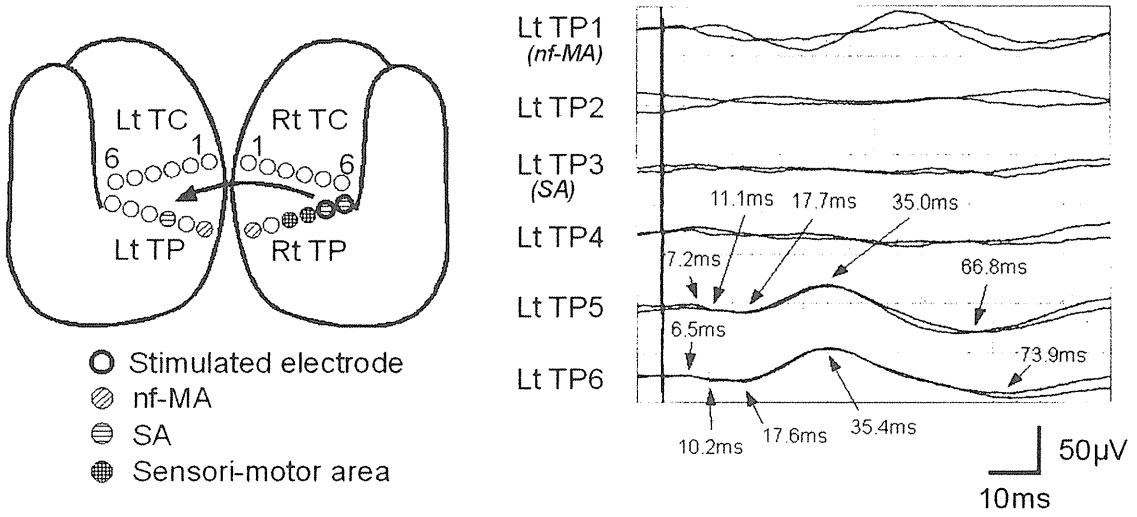

Figure 4.

Type I response observed in Patient 10. The schematic figure shows the location of eloquent area and the stimulated electrodes. In addition to the symbols described in Figure 2, sensory area (SA; circle with horizontal lines) and sensori-motor area (circle with crossed lines) are demonstrated. CCEP responses were evoked by stimulating SA (Rt TP5/6), and were recorded from contralateral electrodes. The fifth and sixth channels (Lt TP5/6 on noneloquent area) demonstrate initial positive triphasic waveforms. Although the first channel may show some response, it is not used in subsequent analysis because it is not reproducible.

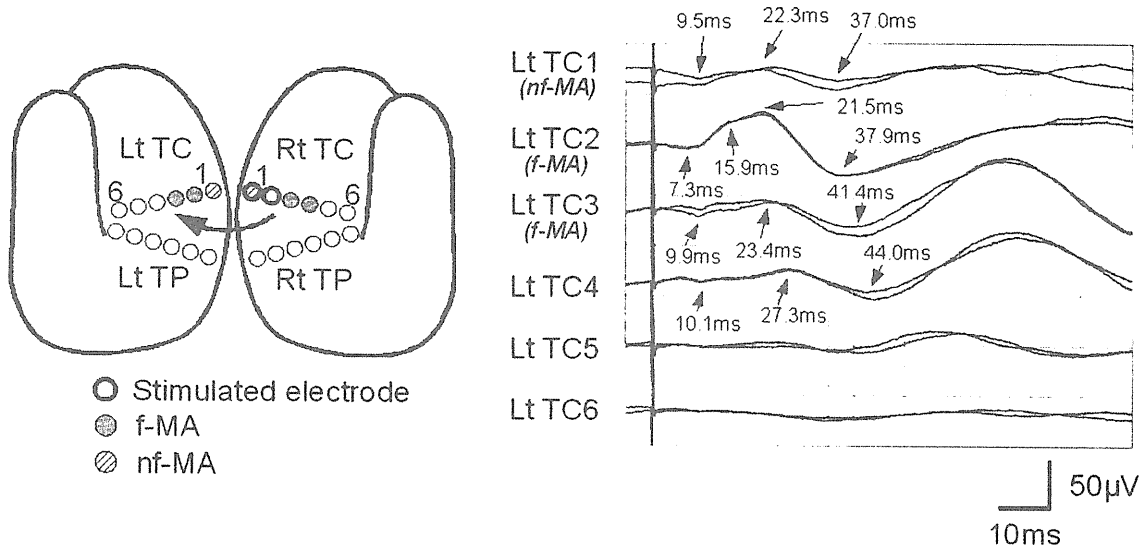

Figure 5.

Typical Type 2 responses observed in Patient 7. The schematic figure shows the location of eloquent area and the stimulated electrodes (see Fig. 2 for explanation). CCEP responses are evoked by stimulating nonfacial motor area (nf-MA; Rt TC1) and noneloquent area (NEA; Rt TC2), and were recorded from contralateral electrodes. The first, second, third, and fourth channels (Lt TC1 on nf-MA, Lt TC2/3 on facial motor area [f-MA] and Lt TC4 on NEA) demonstrate initial negative biphasic waveforms. At Lt TC2, the initial negative peak (N1) has a notch at 15.9 ms.

Chi-square analysis on the effect of the recording site demonstrated that the recording site was important for a positive contralateral CCEP response for f-MA and nf-MA stimulations ($P < 0.01$ and $P < 0.05$, respectively), but had no significant effect for SA and NEA stimulations (Table II). For f-MA stimulation, a significant difference in positive CCEP response was found between f-MA and SA recordings ($P < 0.05$) and between f-MA and NEA recordings ($P < 0.005$). For nf-MA stimulation, a significant difference was also observed between f-MA and SA recordings

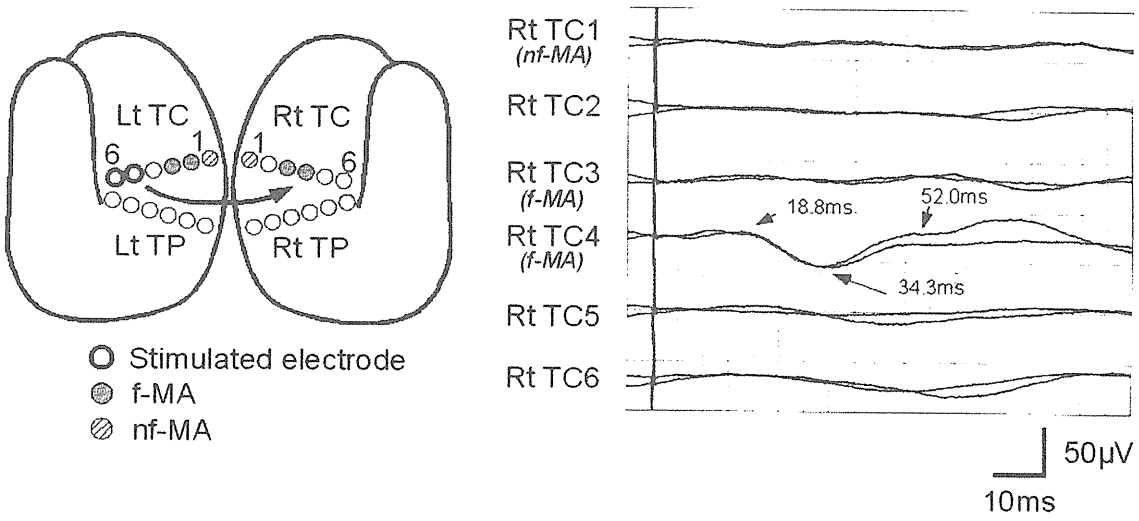

Figure 6.

Typical Type 3 responses observed in Patient 7. The schematic figure shows the location of eloquent area and the stimulated electrodes (see Fig. 2 for explanation). CCEP responses are evoked by stimulating noneloquent area (NEA; Lt TC5/6), and were recorded from contralateral electrodes. The fourth channel (Rt TC4 on facial motor area [f-MA]) demonstrates an initial positive biphasic waveform.

TABLE II. Number of trials and responses recorded from stimulation of pairs of electrodes (for cortical stimulation-defined eloquent areas)

Stimulation	Recording	Number of trials	CCEP response		Mean response rate per stimulation area	Response type		
			Number	%		Type 1	Type 2	Type 3
f-MA	f-MA	27	15	55.6[a]	29.1[b]	7	5	3
	nf-MA	7	1	14.3				1
	SA	8	1	12.5			1	
	NEA	68	15	22.1		5	10	
nf-MA	f-MA	5	4	80.0[a]	25.0[b]		3	1
	nf-MA	4	1	25.0			1	
	SA	3	0	0				
	NEA	16	2	12.5			2	
SA	f-MA	14	0	0	2.9			
	nf-MA	2	0	0				
	SA	9	0	0				
	NEA	43	2	4.7		2		
NEA	f-MA	43	2	4.7	3.8		1	1
	nf-MA	13	1	7.7				1
	SA	25	1	4.0		1		
	NEA	181	6	3.3		1	4	1

f-MA, facial motor area; nf-MA, nonfacial motor area; SA, somatosensory area; NEA, noneloquent area.
[a]Significantly higher rate compared with SA ($P < 0.05$), and NEA recording ($P < 0.005$).
[b]Significantly higher rate compared with SA stimulation ($P < 0.001$) and NEA stimulation ($P < 0.001$).

($P < 0.05$) and between f-MA and NEA recordings ($P < 0.005$). These data suggested that both f-MA and nf-MA stimulations tended to evoke contralateral CCEP responses at the f-MA.

The same statistical analysis was performed among MA-MRI, SA-MRI, and NEA-MRI (Table III). The statistical analysis demonstrated that the stimulating site affected the positive CCEP response rate ($P < 0.001$). In each comparison between eloquent sites, a significant difference was observed between MA-MRI and SA-MRI ($P < 0.001$), between MA-MRI and NEA-MRI ($P < 0.001$), and between SA-MRI and NEA-MRI ($P < 0.01$) (Table III). These findings indicated that both MA-MRI stimulation and SA-MRI stimulation evoked contralateral hemispheric CCEP responses more frequently than NEA-MRI stimulation, and that MA-MRI stimulation evoked the responses much more frequently than SA-MRI stimulation.

TABLE III. Number of trials and responses recorded from stimulation of pairs of electrodes (for MRI-defined eloquent areas)

Stimulation	Recording	Number of trials	CCEP response		Mean response rate per stimulation area	Response type		
			Number	%		Type 1	Type 2	Type 3
MA-MRI	MA-MRI	53	19	35.8[a]	25.4[b]	5	10	4
	SA-MRI	29	8	27.6		3	5	
	NEA-MRI	56	8	14.3		4	4	
SA-MRI	MA-MRI	45	7	15.6	8.8[c]	3	2	2
	SA-MRI	38	3	7.9		1	2	
	NEA-MRI	64	3	4.7			2	1
NEA-MRI	MA-MRI	47	1	2.1	1.8			1
	SA-MRI	34	1	2.9			1	
	NEA-MRI	83	1	1.2			1	

MA-MRI, motor area defined by MRI imaging; SA-MRI, somatosensory area defined by MRI imaging; NEA-MRI, noneloquent area defined by MRI imaging.
[a]Significantly higher rate compared with NEA-MRI recording ($P < 0.01$).
[b]Significantly higher rate compared with SA-MRI stimulation ($P < 0.001$) and NEA-MRI stimulation ($P < 0.001$).
[c]Significantly higher rate compared with NEA-MRI stimulation ($P < 0.01$).

TABLE IV. Amplitudes and latencies of major wave components in Type I responses

Stimulation	Recording	Latency ± SD (ms)				Amplitude ± SD (μV)		
		Onset	P1	N1	P2	P1	N1	P2
f-MA	f-MA	4.8 ± 0.7	11.9 ± 2.8	29.4 ± 2.0	56.0 ± 4.7	22.3 ± 7.5[a]	119.7 ± 61.8[b]	162.0 ± 73.9[b]
	nf-MA							
	SA							
	NEA	4.9 ± 0.8	13.7 ± 3.6	29.9 ± 2.9	53.5 ± 9.3	14.6 ± 6.4	61.4 ± 31.6	83.2 ± 37.0
nf-MA	f-MA							
	nf-MA							
	SA							
	NEA							
SA	f-MA							
	nf-MA							
	SA							
	NEA	6.9 ± 0.5	17.7 ± 0.1	35.2 ± 0.3	70.4 ± 5.0	7.0 ± 1.4	30.5 ± 3.5	48.5 ± 0.7
NEA	f-MA							
	nf-MA							
	SA	6.2	10.1	27.1	55.4	5.0	15.0	40.0
	NEA	5.5	13.1	28.7	55.7	8.0	15.0	39.0

SD, standard deviation; f-MA, facial motor area; nf-MA, nonfacial motor area; SA, somatosensory area; NEA, noneloquent area.
[a]Significantly greater compared with other stimulation/recording patterns ($P < 0.01$).
[b]Significantly greater compared with other stimulation/recording patterns ($P < 0.05$).

The statistical analysis on the effect of the recording site demonstrated that the recording site was important for a positive contralateral CCEP response only for MA-MRI ($P < 0.05$) (Table III). For MA-MRI stimulation, a significant difference in positive CCEP response was found between MA-MRI and NEA-MRI recordings ($P < 0.01$). These data also suggested that MA stimulation tended to evoke contralateral CCEP responses at the MA.

Comparisons of latencies and amplitudes

The latencies and the amplitudes were analyzed statistically using t-test, for each waveform type (Tables IV–VI). Because of the limited data available, not all comparisons were possible. Therefore, comparisons of waveform parameters were performed only between f-MA recording with contralateral f-MA stimulation (the most frequently

TABLE V. Amplitudes and latencies of major wave components in Type 2 responses

Stimulation	Recording	Latency ± SD (ms)			Amplitude ± SD (μV)	
		Onset	N1	P2	N1	P2
f-MA	f-MA	7.8 ± 0.6[a]	24.3 ± 1.9[a]	47.6 ± 11.4	30.2 ± 23.0	56.0 ± 29.6
	nf-MA					
	SA	9.0	33.2	29.0	14.0	29.0
	NEA	12.1 ± 4.2	33.1 ± 2.9	58.7 ± 4.8	34.3 ± 19.9	54.6 ± 35.7
nf-MA	f-MA	11.3 ± 4.9	23.7 ± 2.4	44.4 ± 8.4	19.3 ± 16.2	55.0 ± 25.5
	nf-MA	9.5	22.3	37.0	16.0	18.0
	SA					
	NEA	13.5 ± 4.7	31.5 ± 5.9	49.3 ± 7.5	15.0 ± 1.4	40.0 ± 19.8
SA	f-MA					
	nf-MA					
	SA					
	NEA					
NEA	f-MA	9.6	26.6	50.6	18.0	36.0
	nf-MA					
	SA					
	NEA	11.8 ± 3.5	28.2 ± 5.0	52.9 ± 5.6	28.5 ± 4.9	42.8 ± 10.5

SD, standard deviation; f-MA, facial motor area; nf-MA, nonfacial motor area; SA, somatosensory area; NEA, noneloquent area.
[a]Significantly shorter compared with other stimulation/recording patterns ($P < 0.001$).

TABLE VI. Amplitudes and latencies of major wave components in Type 3 responses

Stimulation	Recording	Latency ± SD (ms)			Amplitude ± SD (μV)	
		Onset	P1′	N1′	P1′	N1′
f-MA	f-MA	20.0 ± 4.5	31.6 ± 4.1	52.0 ± 5.6	20.0 ± 15.6	38.3 ± 27.5
	nf-MA	15.1	22.2	43.7	11.0	29.0
	SA					
	NEA					
nf-MA	f-MA	10.0	28.9	53.1	25.0	48.0
	nf-MA					
	SA					
	NEA					
SA	f-MA					
	nf-MA					
	SA					
	NEA					
NEA	f-MA	18.8	34.3	52.0	35.0	30.0
	nf-MA	21.7	29.4	50.9	16.0	30.0
	SA					
	NEA	7.6	25.7	39.8	20.0	25.0

SD, standard deviation; f-MA, facial motor area; nf-MA, nonfacial motor area; SA, somatosensory area; NEA, noneloquent area.

recorded and the most prominent waveforms obtained in this study) versus all other stimulation/recording patterns.

For Type 1 response, no significant differences in latencies such as latencies of onset, P1, N1, and P2 were observed in all comparisons. On the other hand, all amplitudes were significantly greater in the waveforms of f-MA recording with contralateral f-MA stimulation than other waveforms: from onset to P1 ($P < 0.01$), from P1 to N1 ($P < 0.05$), and from N1 to P2 ($P < 0.05$) (Table IV). For Type 2 response, the latencies of onset ($P < 0.001$) and N1 ($P < 0.001$) were shorter in the waveforms of f-MA recording with contralateral f-MA stimulation than other waveforms. However, no significant differences were detected in the comparisons of the latency of P2 and of all amplitudes (Table V). For Type 3, no significant differences were observed in all comparisons (Table VI).

DISCUSSION

Consistent with our previous report [Terada et al., 2008], CCEP responses were recorded from the contralateral hemisphere in the current study. Compared with the previous study, this study investigated a larger number of patients, and furthermore succeeded to stimulate not only f-MA but also nf-MA and SA. The data obtained allowed us to clarify the characteristics of these interhemispheric connections more precisely. All patients in the current study had temporal lobe epilepsy. Therefore, we presume that all the CCEP responses observed in the present study may reflect normal physiological phenomena.

Effect of Stimulation and Recording Sites

Facial motor area stimulation

CCEP responses were recorded from the contralateral hemisphere more frequently by stimulating f-MA (29.1%) than by stimulating SA (2.9%) or NEA (3.8%). And, f-MA stimulation evoked CCEP responses more frequently at the contralateral f-MA (55.6%) than at nf-MA (14.3%), SA (12.5%), or NEA (22.1%), although the differences were only significant when compared with SA or NEA recordings, probably because the number of data was too small. Furthermore, the amplitudes of all components in Type 1 response were significantly greater when stimulating f-MA and recording from contralateral f-MA. These data suggest that compared to other areas, the f-MA has denser interhemispheric connections with the contralateral f-MA. From the physiological point of view, these connections are supposed to play an important role to control facial movements, which are usually symmetric or not independent between both sides.

Nonfacial motor area stimulation

CCEP responses were recorded from the contralateral hemisphere more frequently by stimulating nf-MA (25.0%) than by stimulating SA (2.9%) or NEA (3.8%). Furthermore, nf-MA stimulation evoked CCEP responses more frequently at the contralateral f-MA (80.0%) than at nf-MA (25.0%), SA (0%), or NEA (12.5%), although the differences were only significant when compared with SA or NEA recordings. There were no apparent differences in amplitudes when compared with SA or NEA stimulation,

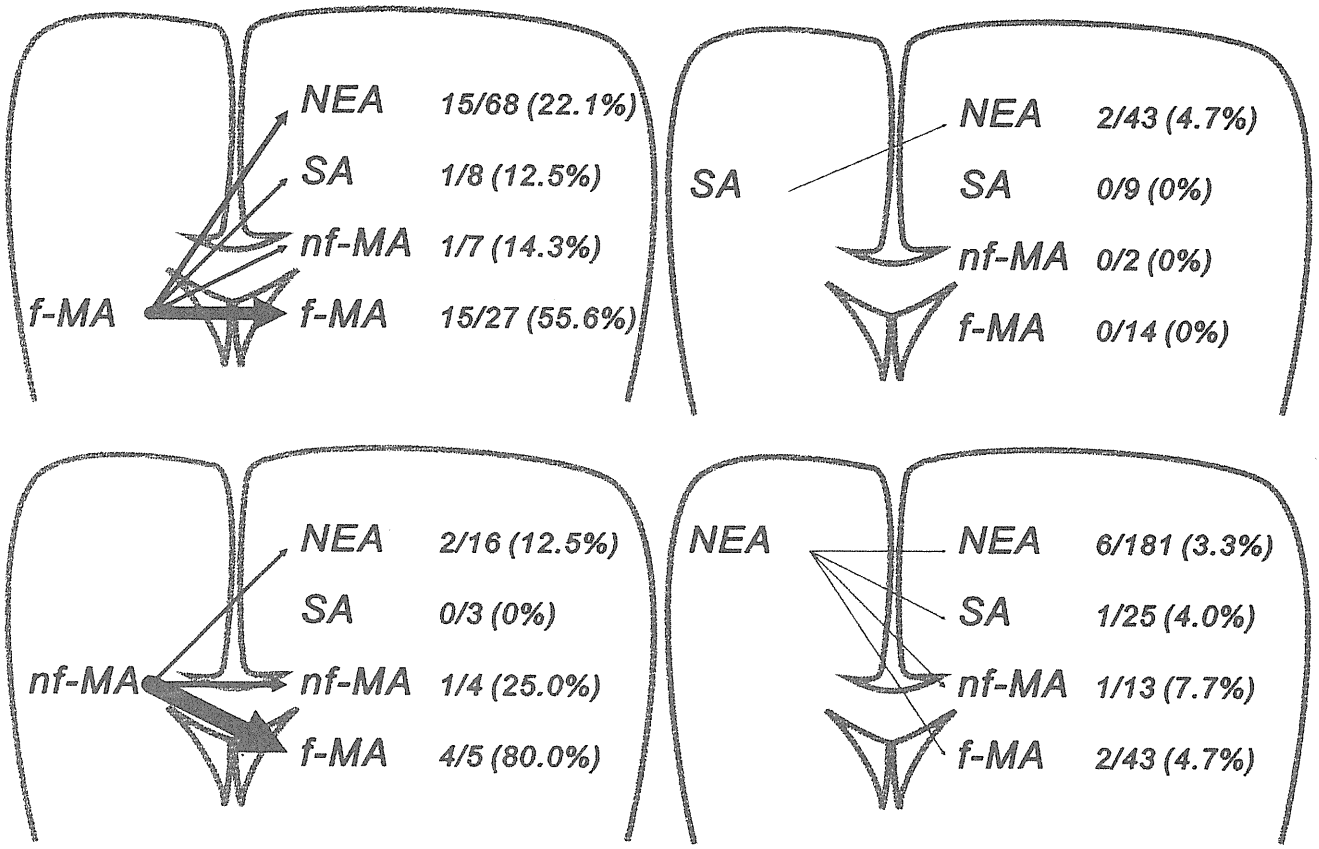

Figure 7.

Schematic presentation of the results. Arrows indicate the interhemispheric connections. The line thicknesses correspond to the positive rate of CCEP responses; i.e., the thicker the line is, the more frequently the interhemispheric responses can be recorded. It is demonstrated that both facial motor area (f-MA) and nonfacial motor area (nf-MA) send their neural connections to the contralateral f-MA rather than nf-MA or other areas. Furthermore, it is also seen that both somatosensory area (SA) and noneloquent area (NEA) send sparse connections to the contralateral hemisphere.

although statistical analysis could not be performed. These findings suggest that interhemispheric connections originating from the nf-MA extend to the contralateral f-MA more frequently than to other areas including the contralateral homologous nf-MA. From the physiological viewpoint, the relatively sparse connections between bilateral nf-MA may correspond to the fact that left and right hands are controlled separately and may move independently in humans.

In a previous electrophysiological study, Ugawa et al. [1993] demonstrated interhemispheric connections between strictly homotopic areas in left and right MA using transcranial magnetic stimulation. In an anatomical study conducted in humans, Aboitiz et al. [1992] also noticed that most fibers in the corpus callosum connect the corresponding areas of the left and right hemispheres. Furthermore, our previous report suggests that the interhemispheric connections are between bilateral homologous areas, although the data were limited only to f-MA stimulation [Terada et al., 2008]. In contrast, the current study demonstrated that the neural connections between left and right MA were uneven. Both f-MA and nf-MA send interhemispheric fibers to the contralateral f-MA more frequently than to the contralateral nf-MA (see Fig. 7). On the other hand, compared with nf-MA, f-MA tends to receive more interhemispheric connections from the contralateral MA, both f-MA and nf-MA. Anatomical analysis in animals demonstrated uneven transcallosal connections between left and right MA [Gould et al., 1986; Pandya and Vignolo, 1971). They reported that motor representation of the distal forelimb has no or greatly reduced callosal connections, as was also observed in the present human study.

Sensory area and noneloquent area stimulation

Stimulation of SA or NEA evoked only rare CCEP responses that could be recorded from the contralateral hemisphere. Especially, SA stimulation never evoked any response at the contralateral MA or SA, even though both facial and nonfacial SA were examined. For both SA and

NEA stimulation, there were no significant differences in positive response rate among the recording sites. These findings indicate that there is no or only very sparse neural connection from the SA or NEA to the contralateral hemisphere in humans. There was no previous report on the interhemispheric connection between left and right SA in humans by any method. However, animal studies have demonstrated transcallosal connection between bilateral SA by anatomical investigations [Cusick et al., 1985; Jones and Powell, 1969; Pandya and Vignolo, 1968] and also by electrophysiological studies [Chang, 1953; Curtis, 1940a]. The discrepancy between this study and the previous reports may represent the difference in functional organization between humans and animals or the difference in methodology.

Analysis of MRI-defined eloquent areas

Recently, 3D reconstruction MRI imaging is used to identify "motor area," "somatosensory area," or other eloquent areas. In this study, we also used the same method, although we could not differentiate between f-MA and nf-MA by MRI imaging. In the results, it was also demonstrated that MA-MRI (25.4%) more frequently sent the interhemispheric neural connections than SA-MRI (8.8%) or NEA-MRI (1.8%). It was also demonstrated that MA-MRI stimulation more frequently demonstrated the CCEP responses in the contralateral MA-MRI (35.8%) than SA-MRI (27.8%) or NEA-MRI (14.3%). These findings are concordant with the analysis mentioned above.

In this analysis, however, the statistically significant difference was also observed in comparison between SA-MRI stimulation (8.8%) and NEA-MRI stimulation (1.8%). In the analysis discussed above, there was no statistically significant difference between SA stimulation (2.9%) and NEA stimulation (3.8%). By stimulating SA-MRI, 13 of 147 trials demonstrated CCEP responses in the contralateral hemisphere. Of 13, six stimulations resulted in motor response in cortical stimulation, even the electrical stimuli were given on SA-MRI. It was most likely that these six stimulations might activate the adjacent MA, and, therefore, resulted in activation of the interhemispheric neural connections arising from the MA. This kind of phenomenon was called "distant response" by Penfield and Jasper [1954].

Waveform types

In this study, three types of waveforms were recorded, which we designated Type 1, Type 2, and Type 3. Judged from the waveforms and peak latencies, the generators of N1 and P2 in Type 1 and Type 2 are most likely to be identical, while an additional generator may give rise to P1 in Type 1.

Type 1 responses were mainly recorded while stimulating f-MA (12 of 16 Type 1 responses) and while recording at f-MA (seven responses). Interestingly, this response was never recorded when nf-MA was stimulated. Therefore, we speculate that P1 in Type 1 response may be a relatively specific component generated by the contralateral f-MA.

In Type 1 response, one or two notches always superimpose on P1. As discussed in our previous report [Terada et al., 2008], this notch may represent the high frequency oscillation seen in somatosensory evoked potential [Hashimoto et al., 1996; Maegaki et al., 2000], or the d-wave and i-wave observed in transcranial magnetic stimulation [Hanajima et al., 2001], or the different latencies between anodal and cathodal stimuli. Further study is needed to specify the significance of the notches.

Judged from the peak latencies, P1′ and N1′ of Type 3 may correspond to the opposite tail of dipoles of N1 and P2. However, because of technical limitation (spatial sampling problem in subdural recording), we could not analyze their distributions and fields. Therefore, we could not confirm the presence of this dipole. Further study, including EEG or MEG studies, is necessary to clarify the relationship between N1-P2 in Type 1/2 response and P1′-N1′ in Type 3 responses.

Latencies

In this study, the onset of P1 in Type 1 response was 3.6–7.2 ms, and the peak latency of P1 in Type 1 was 7.6–13.6 ms. The onset of N1 in Type 2 was 7.1–20.6 ms, the peak latency of N1 15.9–38.6 ms, the onset of P1′ in Type 3 7.6–24.2 ms, and the latency of P1′ 22.2–36.2 ms.

Shibasaki et al. [1978] demonstrated the latency difference of C reflexes in bilateral limbs in patients with cortical myoclonus, and suggested that the transit time between bilateral hemispheres is 9–11 ms. Brown et al. [1991] also demonstrated similar side-to-side difference of C reflexes in patients with cortical myoclonus. Their data suggested that the interhemispheric transit time is 10.1–15.6 ms. Transcranial magnetic stimulation also demonstrated transcallosal connections between bilateral MA. When the ipsilateral MA was stimulated as the conditioning stimulation, EMG responses evoked by contralateral MA stimulation was reduced significantly. This interhemispheric inhibition was maximal when the stimulus interval was approximately 8–9 ms [Ferbert et al., 1992]. Ugawa et al. [1993] reported that stimulation of the ipsilateral MA facilitated the response for the contralateral MA stimulation, and demonstrated that this effect was prominent when the conditioning stimulation was given 8 ms before the contralateral stimulation. Cracco et al. [1989] and Amassian and Cracco [1987] reported cortical responses similar to our results by transcranial electrical or magnetic stimulations. Their peak latencies of the initial positive peak were 8.8–12.2 and 9–14 ms, respectively. These studies suggest that the transcallosal transit time is approximately 8–14 ms for left and right MA, and are almost concordant with our result (the peak latency of P1 in Type 1, the onset of N1 in Type 2, or the onset of P1′ in Type 3).

Hanajima et al. [2001] showed the occurrence of interhemispheric facilitation 4–5 ms after contralateral MA stimulation, followed by late inhibition maximal at 11 ms. This facilitation occurred much earlier than our initial peak, but occurred with the similar timing with the onset of P1 in Type 1. Then, it is possible that the very early portion of our CCEP components (P1 in Type 1 response) corresponds to this facilitation.

In animal studies, the initial positive wave lasted approximately 15 ms and the second negative wave lasted approximately 75 ms in cat [Curtis, 1940b]. Cukiert and Timo-Iaria [1989] reported that the initial response started at 2–10 ms and the second peak at 10–25 ms. Single neuron recording in animals demonstrated that the initial unit arrived at 6–8 ms by stimulating the opposite pyramidal tract in cat [Asanuma and Okuda, 1962]. The latencies obtained in the present study are consistent with those of previous works.

Anatomically, Aboitiz [1992] reported the presence of fast-conducting, large-caliber fibers between bilateral MA and SA in human. Hofer and Frahm [2006] reported connecting fibers of larger diameters (>3 μm) between bilateral MA located posterior to the midbody of corpus callosum. The estimated conduction velocity of these fibers is 40 mm/ms, corresponding to a transcallosal transit time of 2.5–3.2 ms [Aboitiz et al., 1992]. This time lag is much shorter than the latency of our initial positive peak, and even shorter than the onset of the positive wave. This discrepancy may be explained by the time lag between the stimulation and volley generation at the stimulated site, as well as the time lag between the arrival time of the volley and the EPSP generation at the recording site. It is also possible that we might have missed the earliest potential of CCEP in the present study.

Generators

As discussed above, we speculate that there are at least two independent generators for the current CCEP, corresponding to the initial (P1 in Type 1) and the following peaks. Curtis [1940b] reported that the initial positive and the second negative peaks responded differently to chemical agents. He, therefore, concluded that ascending fibers in the upper layers of the cortex give rise to the initial positive peak, and descending fibers, which reach the deeper cortical layers from interneuron in the upper layer, generate the next negative peak. Chang [1953] analyzed the effects of Novocaine and strychnine to these components, and compared the potentials between stimulation of contralateral hemisphere and direct stimulation on corpus callosum. He speculated that the initial positive wave is caused by the antidromic volley and the presynaptic orthodromic volley, and the second peak is the activity of the superficially placed callosal afferent and their postsynaptic neurons. The feline study of Cukiert and Timo-Iaria [1989] suggested that the early and late components reflect most probably the involvement of mono- and polysynaptic pathways, respectively, on account of the differences in latency, response to stimulus frequency, and the stability.

CONCLUSION

As previously reported, we demonstrated interhemispheric connections between left and right MA in humans in this study. In addition, we also demonstrated that the interhemispheric connections were uneven. The f-MA has dense connections with the contralateral f-MA, and the nf-MA also has dense connections with the contralateral f-MA but less dense connections with the contralateral homologous nf-MA. The SA has no or only sparse connection with the contralateral MA or SA.

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診　断

Wadaテストによる言語・記憶機能検査
―てんかん外科の手術前検査における役割―

The role of the Wada test in the surgical treatment of epilepsy

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はじめに

Wadaテストは内頚動脈アモバルビタール法とも呼ばれるものであり，言語優位半球の同定を可能にする有力な検査法として，1948年にJuhn Wada(和田淳)博士により開発された．この翌年，雑誌『医学生物学』に発表された論文[1]はすぐ英訳され，Wadaテストが世界中で実施されるようになった．その後，言語機能のみならず記憶機能検査においても使用されるようになり，今日に至っている[2,3]．てんかん外科における手術前検査としては，言語，記憶機能の評価だけではなく，てんかん原性領域の側方性の同定[4]や，術後発作転帰の予測[5]など，多様な脳機能検査に威力を発揮してきた．

Wadaテストは，現在，言語優位半球の同定法として最も信頼度の高い検査である．しかし，21世紀に入って，アモバルビタールが入手困難になったこと，ならびに磁気共鳴イメージング(magnetic resonance imaging；MRI)，脳磁図(magnetoencephalography；MEG)をはじめとする非侵襲的検査手法の技術向上による脳機能評価法の拡大によって，Wadaテストの位置付けあるいは意義に変化が生じ始めている．

本稿では，Wadaテストを主としててんかん外科治療の観点から，その実際の内容をやや詳細に概観するとともに，世界での使用状況と趨勢を展望する．さらにWadaテストの代替検査として行われている非侵襲的手法についても言及する．

一般的なテスト内容と主要な特長

概略としては，脳血管造影検査用に挿入されたカテーテル(通常，大腿動脈から挿入)を頭頚部まで進め，左または右内頚動脈から麻酔薬を注入して同側大脳半球を一過性に不活化することにより，脳機能局在の確

認を行う方法である．50年以上にわたって世界中で広く実施されている検査法であることから，共通の統一された実施手順が存在するものと思われがちであるが，実際には多くのバリエーションが存在する．言語優位半球の同定のみならず，記憶機能検査，さらにはてんかん外科手術前検査など多様な用途に使用されていることから，詳細な部分に関しては施設ごとに異なっている場合が多い．

紙面の制約を勘案し，ここではこれらの多様なバリエーションには言及せず，多くの施設で実施されている，言語と記憶機能検査としてのWadaテストの基本と共通的な技術について述べることにする．

1. Wadaテストの手順(表1)

(1) ベースラインの確認

言語機能に関する検査であることから明らかなように，被験者の理解と協力が必須である．このため，精神症状や著しい知能障害など，検査遂行の妨げとなるような問題がないかを検査前に確認することがまず第1である．検査前日，または検査数時間前に手順の説明と，言語・記憶機能のベースライン確認のための言語・記憶検査課題項目の練習を実施しておく．

(2) 麻酔薬注入による対側の一過性半身麻痺の確認

麻酔の効果は，注入直後に対側半身に一過性麻痺が生じることで確認される．検査は，両上肢を挙上した状態や，両手の指の反復運動を継続した状態で開始し，カテーテルから麻酔薬を3～5秒かけて注入し，注入後に対側上肢が落下する，または，対側の指の反復運動が停止することで対側半身の麻痺を確認する．麻酔効果の持続時間は3～5分程度とかなり短いため，この間に効率的に言語検査，記憶検査を実施する必要がある．

ただし，施術としては次項で述べる言語課題は麻酔薬注入前から開始することになる．

(3) 言語機能検査における課題および評価

言語機能は，麻酔薬注入後の失語症状の有無により評価する．そのため，実際には麻酔薬注入前に，被験者に言語課題(数唱，1週間の曜日名を順番に言う，など)を開始するように指示する．そのうえで，課題継続中にカテーテルから麻酔薬を注入し，意識レベル，麻痺の状況を確認しつつ，言語機能検査を行う．このために使用される検査課題は，物品呼称，読字，音声提示言語の復唱，言語理解を評価するための簡単な口頭指示(開閉眼，挺舌など)などである．

麻酔薬注入により，なんらかの言語機能の阻害が出

表1　Wadaテストの手順

検査前日または数時間前	
0	被験者への検査課題・手順説明およびベースライン確認
検査当日	
1	内頸動脈へのカテーテル挿入を確認
2	言語課題(数唱など)開始
3	麻酔薬注入
4	対側半身麻痺の確認・意識状態の確認
5	言語課題(物品呼称，読字，聴覚言語理解など)継続
6	記憶課題も同時進行
7	半身麻痺の回復確認
8	言語機能回復確認
9	記憶課題再認検査
10	30分程度の間隔を空けて対側の検査(手順1～9反復)

言語・記憶課題はベースライン検査用と初回側用，対側用に異なるものを3セット用意する．

現する．言語優位側では全失語がみられる．麻酔薬注入前から継続していた数唱などの正常な言語表出が停止し，言語理解も不能となる．言語機能は数分で緩やかに回復するが，回復過程で，保続や錯語などの失語症状がみられることが多い．一方，非言語優位側では，一時的な言語停止が生じるが，全失語ではない．また，回復も早く(使用する麻酔薬や被験者の個人差はあるが，通常数十秒程度)，言語停止を認めない場合もある．回復過程で構音障害を認めることがあっても，物品呼称，読字，復唱，口頭命令遂行などは可能で，失語症状は認めない．

言語優位側の判定には，通常，言語停止持続時間の左右差を用い，麻酔薬注入後の言語停止の時間が長い側を言語優位側と判定する．錯語などの失語症状の有無も参考になる．ただし，言語停止の左右での時間差が30秒以内の場合，両側言語支配を疑う必要がある．言語優位側の判定について側性指数(laterality index)を使う施設も存在する[6]．

(4) 記憶機能検査における課題および評価

記憶機能の検査のみを目的とする課題を設定することはなく，通常は麻酔薬注入後の麻痺作用が持続している状態で実施される言語課題の項目が，記憶課題をかねる場合が多い．被験者に対して，あらかじめ検査中の特定の課題項目を覚えておくように指示しておく．記憶機能検査をかねる課題項目を提示するタイミングは施設により異なっており，実際には麻酔による半身麻痺出現直後に課題を開始する施設や，麻酔薬注入後に最初の言語反応が認められてから記憶課題を実施する施設などがある．

記憶課題項目の提示に関しては，視覚的に提示する場合と聴覚的に提示する場合がある．視覚提示項目としては，日常的に使用する物品(時計，ペンなど)またはその線画，動植物の線画，文字言語(単語)，無意味図形，写真(人物，物品，動植物)などがある．聴覚提示項目としては，音声言語(単語，語句，簡単な文章など)が用いられる．提示項目数は施設ごとに異なるが，麻酔効果の持続する数分間に提示可能な項目数は最大十数個程度である．

(5) 麻酔からの回復確認

一過性の半身麻痺と言語機能が回復したのを確認してから(通常，麻酔薬注入10～15分後)，記憶課題の再生，再認検査を実施する．既出の課題の自発的な再生とともに，新規項目を含む課題もあわせて実施し，正しく再認できたものも正解として結果を評価する．

2. 主要な特長

Wadaテストの当初からの目的であり，今日においても最も重要な役割のひとつは，言語優位半球の同定である．具体的な内容および手順を概観した前項においてみたように，言語機能は，麻酔薬注入後の失語の状態により判断されるため信頼性が高い．すなわち，言語優位側では全失語が観察されるのに対し，非言語優位側では，一時的な言語停止が生じても回復は早く，言語停止を認めない場合もある．この明確な相異により言語優位側を特定できる．

一方，てんかん外科治療における記憶機能の検査としての重要な目的は，一側の側頭葉切除による術後障害として記憶障害を生じる危険がないかどうかを評価することである．多くの施設において，患側の麻酔薬注入で記憶機能検査成績が67％(全記憶項目の3分の2)以上であれば，患側切除後に記憶障害の危険がなく，67％未満であれば術後記憶障害の危険がある，との判定がなされている[2]．Wadaテストのみにより術後の記憶障害のリスクを完全に特定できるわけではないが，術前評価法の第一選択としての重要性を有するものである．

テストの実施および評価における留意点

1. 実施上の注意点

(1) リスク，合併症

Wadaテストは動脈穿刺，カテーテル挿入を伴う侵襲的検査である．脳血管造影検査と同等のリスクお

よび不快感を患者に与えることに留意しなくてはならない．生じうる危険としては，動脈壁損傷，血栓による末梢または脳血管の塞栓，動脈スパズム，薬剤アレルギーなどがある．若年の被験者に比べて比較的高齢(平均51.3歳)の被験者で，頚動脈解離の合併症がみられたとの報告もある[7]．多施設調査による合併症の発生率は，約1％である[8,9]．危険性については，十分に説明のうえ，文書による同意を得て実施する必要がある．

(2) 脳血管造影検査

脳血管造影検査は，血管の走行，異常の有無を確認すると同時に，Wadaテストの結果に影響を与える可能性のある血管走行の個人差，特に同側の後大脳動脈や対側の前大脳動脈への流入がないかを確認するためにも必要である．脳血管撮影検査とWadaテストの実施順序は施設によって異なっており，脳血管撮影実施後にWadaテストを実施する場合や，一側のWadaテスト実施後に脳血管撮影検査を実施し，最後に対側のWadaテストを実施する場合がある．

(3) 麻酔薬の種類

使用される麻酔薬は，前述のようにアモバルビタールが入手困難になったために，複数の代替薬が存在し，施設により使用薬は異なる．アモバルビタール以外に使用されている麻酔薬は，プロポフォール，ペントバルビタール，セコバルビタール，メトヘキシタールなどがある(メトヘキシタールはわが国では未承認)．使用する麻酔薬によって，使用量，麻酔からの回復時間が異なる．使用量は，注入半球の対側半身に一過性の麻痺を生じるのに十分な量で，施設ごとに使用量が定められている．当院は，プロポフォール(成人量で7 mg)を使用している．

(4) 脳波の同時記録

施設によっては，麻酔状態の評価のため脳波を測定しながらWadaテストを実施する．麻酔により同側半球に徐波が出現するのを確認して言語課題，記憶課題を実施し，徐波が消失してから記憶再生，再認検査を実施する．

(5) 検査側の順序

ほとんどの施設で両側の検査を実施している．左右どちら側から検査を開始するかは，施設ごと，また症例ごとに異なる．患側から検査を開始する施設，想定される言語非優位側から検査を開始する施設がある．通常，同日に両側の検査を実施するが，一側の検査を実施したあとに残存麻酔薬の影響を除外したうえで対側の検査を実施する必要がある．アモバルビタールを使用する場合，多くの施設では30分が麻酔薬の排出および効果消失に十分な時間と想定して検査を実施している．

2. 評価における注意点

言語優位半球同定に関して，信頼性，妥当性の高い検査であることは論を俟たないであろう．しかし，いかなる方法も万能ではなく，目的に応じて適切に使い分けることが肝要である．侵襲的検査であるために，複数回の検査で再現性を検討することは困難であるが，医療上の必要から再検査を実施した症例で，再現性をもって言語優位側が確認されたとの報告がある[10]．Wadaテストに代わる検査法について評価した研究も，言語優位側同定についてはWadaテストとの整合性をその検出感度の基準としている[11]．留意すべき点は，侵襲性の高い検査であることと，言語優位半球を同定する検査であり，個々の言語野の局在を同定するものではないということである．Broca野，Wernicke野などの言語野の同定には，皮質電気刺激検査，機能的MRI(functional MRI；fMRI)検査などを用いる必要がある．

記憶機能検査としてのWadaテストについては，その信頼性が十分であるとはいえない点を理解しておくことが必要である[12]．まず，海馬の血管支配は前部が内頚動脈系，後部が後大脳動脈であることから，内頚動脈に注入した麻酔薬で海馬全体を不活化することはできず，したがって，海馬を中心とした記憶機能の

正確な評価は不可能である．海馬へのより選択的な流入を工夫したり，後大脳動脈に特化してWadaテストで記憶機能を評価した報告もあるが[13,14]，合併症などの問題もあり普及していない．さらに，麻酔効果は個々の症例での変動が大きく，また，軽度の意識低下，症例によっては脱抑制的行動変化が生じることもあり，麻酔の副次的効果も記憶機能に影響していることを考慮する必要がある．

多くの施設において，患側の麻酔薬注入で記憶機能検査成績が67％(全記憶項目の3分の2)以上であれば，患側切除後に記憶障害の危険がなく，67％未満であれば術後記憶障害の危険がある，との判断であることを前述したが，カットオフを50％にしている施設もある．左右での差，およびてんかん焦点側との関係を考慮することも大切である．素材特異性記憶，すなわち，言語性記憶と非言語性記憶の術後記憶障害の危険性評価のためにWadaテストの記憶検査を用いる施設もあるが，結果にばらつきがあり，定説は得られていない．

世界におけるWadaテストの実施状況と趨勢

1990年代初頭，Wadaテストはてんかん外科手術の術前検査としてほぼ全例で実施されていた[8]．しかしながら，2000～2005年まで欧州のてんかんセンター26施設で実施された大規模調査では，てんかん外科手術前検査として実施されるWadaテストの割合は2000年の56％から，2005年の35％に減少している[9]．側頭葉てんかん外科治療に限定した国際調査では，地域差が大きく，欧州と比較して，北米の施設でWadaテストが実施される割合が多かった[15]．現在，欧米においてはWadaテストを全く行わず，次項で述べる非侵襲的術前検査のみでてんかん外科手術を行う施設もある．

てんかん外科手術の術前検査としてのWadaテストの減少の理由には，冒頭で述べた麻酔薬入手困難，侵襲的検査であり合併症の危険があること，ほかの低侵襲または非侵襲的検査の精度向上などが挙げられる．側頭葉てんかん，特に，内側側頭葉てんかんの外科治療については，手術法の開発，すなわち，選択的扁桃体海馬切除術の導入により，切除範囲に言語野が含まれる可能性がきわめて低くなったことも一因と考えられる．

Wadaテストに代わる検査法

表2に，わが国で使用可能な言語優位半球同定検査法とそれぞれの特徴を示す．

現在，Wadaテストに代わる非侵襲的検査法として世界で最も使用されているのはfMRIであろう．臨床的に普及している機器であり，また，高解像度の脳画像検査が可能である．しかしながら，以下のような制限がある．

① 機器はfMRI撮像可能な機種，性能を備えている必要がある
② 動きのアーチファクトに弱く，一定時間静止できない被験者は検査不能
③ ペースメーカーや，頭頸部に金属装置のある被験者は検査不能
④ 大きな脳内病変や血管奇形は，脳機能局在の評価が不正確になる可能性がある
⑤ 撮影用コイル，検査台の大きさの関係で，頭が大きい被験者や極度の肥満者は検査できない
⑥ 表出言語を伴う検査課題は頭顎部の動きでアーチファクトが生じて使用できない
⑦ 課題はすべて被験者の沈黙下で行うため被験者が十分に検査に協力し課題遂行を行うことを前提とする

反復性経頭蓋磁気刺激法(repetitive transcranial magnetic stimulation；rTMS)は，コイルに強力な電流を流して電磁誘導による垂直方向の磁場を発生させ，その磁場の周囲に生じる二次電流により脳神経細胞を刺激する．rTMSは，特定の脳部位に一過性の機能障害を生じさせることによって機能評価をすると

表2　わが国で実施可能な言語優位半球検査法

検査法	測定原理	測定法(直接/間接)	Wada テスト結果との一致(%)	利　点	問題点
Wada テスト	麻酔による不活化	直　接	N/A	結果が明確 信頼性高	侵襲大 合併症の危険性
PET	視覚/聴覚刺激に対する神経細胞の活動に伴う血液動態反応	間　接	96 %[16]	低侵襲 信頼性高	核種による被曝 限られた施設のみ 結果解析がやや複雑
fMRI	視覚/聴覚刺激に対する神経細胞の活動に伴う BOLD 効果	間　接	研究でばらつきあり 79 %[17]～91 %[18]	非侵襲 空間解像度高	施設による設備差大 機器の騒音大 結果解析がやや複雑
MEG	視覚/聴覚刺激に対する神経細胞の電気活動で生じる磁場	直　接	87 %[19]	非侵襲 時間解像度高	限られた施設のみ 機種による測定差 結果解析が複雑
NIRS	視覚/聴覚刺激に対する神経細胞の活動に伴う血液動態反応	間　接	85 %[20]	非侵襲 被験者の体動の影響を比較的受けにくい	限られた施設のみ 表層皮質の評価のみ
SPECT	視覚/聴覚刺激に対する神経細胞の活動に伴う血液動態反応	間　接	直接比較研究なし	低侵襲 多数施設で検査可	核種による被曝 ベースラインと比較必要 解像度やや低
rTMS	頭皮上からの電気刺激による不活化	直　接	報告少なく評価困難	非侵襲 操作比較的容易	刺激による痛み 発作誘発の危険性

いう点で Wada テストと共通点があるが，刺激による痛みや頭痛が生じることがあり，また，てんかん症例の場合には，発作誘発の危険性があるため，Wada テストの代替法としての研究報告は少ない．

MEG は，神経細胞の活動によって生じる微弱な磁場を計測する方法で，非侵襲的な検査であるが，臨床的に普及した検査機器ではなく，また，複雑な検査結果解析を要する．

近赤外線分光法(near-infrared spectroscopy；NIRS)を用いた光トポグラフィは，神経細胞の活動に伴う血液動態を検出する間接的検査法である．安全に実施でき，また，被験者の体動の影響を比較的受けにくい検査法ではあるが，観察できるのは，頭皮から 20 mm までの脳表層の活動のみである．

単一光子放射断層撮影(single photon emission computed tomography；SPECT)とポジトロン断層法(positron emission tomography；PET)も神経細胞の活動に伴う血液動態を検出する間接的検査法である．放射性同位元素を用いるため，被曝の影響を考慮する必要がある．

おわりに

Wada テストは，言語優位半球同定にはきわめて有効な検査であるが，侵襲度の高い検査である．適用については，対象となる症例ごとに，慎重に危険性と有益性を検討して判断する必要がある．Wada テストに代わる非侵襲的検査法は複数あるが，それぞれに利点，留意点がある．fMRI は最も有望な検査法であ

るが，臨床的な普及のためには，使用する言語・記憶検査課題を含め，検査技術の向上と標準化が望まれる．

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