TABLE 1. Patient Characteristics and Results of Trial Stimulation[a]

Patient	Age, y/Sex	Pain Duration, mo	Underlying Disease	Painful Region Treated	Motor Weakness	Sensory Disturbance		Baseline VAS Score	VAS Score After Trial	% Change in VAS Score	Trial Stimulation Result	IPG Implantation
						Allod	Hyperp					
1	59/M	48	L sc inf	R LL	Mild	+	–	7	7	0	Poor	–
2	54/F	12	L thal hem	R UL	Mild	+	+	10	7.5	25	Poor	+
3	59/F	97	R put hem	L LL	Mild	–	+	8	4	50	Good	+
4	65/M	30	R thal hem	L LL	—	–	–	9	4	56	Good	+
5	71/M	19	L thal hem	R UL	Moderate	+	–	10	10	0	Poor	–
6	64/F	68	L put hem	R LL	Mild	+	–	10	7	30	Fair	+
7	74/F	156	L put hem	R LL	Mild	–	–	8	8	0	Poor	–
8	75/F	24	L thal hem	R LL	Mild	–	–	7	3	57	Good	+
9	75/M	24	R put hem	L LL	—	–	–	10	7	30	Fair	–
10	58/M	60	L pontine inf	R LL	Mild	+	–	6	3	50	Good	–
11	66/F	32	R put hem	L LL	Mild	+	–	7	3	57	Good	+
12	67/M	52	L thal inf	R UL	Mild	+	+	8.5	8.5	0	Poor	–
13	57/M	80	R put hem	L LL	—	+	+	6	6	0	Poor	–
14	72/M	83	L thal hem	R LL	Moderate	–	–	8.5	7.5	12	Poor	–
15	65/M	33	L thal inf	R UL	Mild	–	–	9	6	33	Fair	+
16	48/M	11	R put hem	L LL	Mild	+	–	8.6	3	65	Good	+
17	69/M	6	L thal hem	R LL	Mild	+	+	8	8	0	Poor	–
18	66/M	81	R put hem	L LL	—	–	+	8.5	7	18	Poor	–
19	67/M	14	L medullary inf	R LL	—	+	–	5	5	0	Poor	–
20	61/M	29	L pontine inf	R UL	Mild	+	–	9	6	33	Fair	–
21	72/M	16	L put hem	R LL	Mild	+	+	9	9	0	Poor	–
22	76/M	41	L thal hem	R UL	Moderate	–	–	8.5	2.5	71	Good	–
23	62/F	6	R sc hem	L LL	Mild	+	+	8	5.6	30	Fair	–
24	51/F	46	R put hem	L LL & UL	Mild	+	–	7	3	57	Good	+
25	65/F	20	R medullary inf	L LL	—	+	+	9.5	8.5	10	Poor	–
26	64/M	56	R put hem	L LL	Mild	+	+	8	8	0	Poor	–
27	56/M	6	R thal hem	L LL	—	–	–	7.8	5	25	Poor	–
28	74/M	93	L thal inf	R LL	Mild	–	–	8	5	38	Fair	–
29	62/M	19	L put hem	R LL	Mild	–	–	7	7	0	Poor	–
30	71/M	82	R thal hem	L LL & UL	Mild	+	+	6.5	1.5	77	Good	+

[a] Allod, allodynia; Hyperp, hyperpathia, VAS, visual analogue scale; IPG, implantable pulse generator; L, left; R, right; LL, lower limb; UL, upper limb; thal, thalamic; hem, hemorrhage; put, putaminal; inf, infarction; sc, subcortical; +, presence; –, absence. Median VAS score in target regions decreased significantly from 8.5 to 6 after trial ($P < .001$).

Clinical Factors Related to the Outcome of Trial Stimulation

Based on the degree of pain relief during trial stimulation, patients were classified into 2 groups: good and fair in one group and poor in the other. Clinical factors such as age, sex, painful region treated (upper vs lower limb), duration of pain, cause of stroke (putaminal vs thalamic hemorrhage), presence or absence of hyperpathia or allodynia, and degree of motor weakness (absent or mild vs moderate) were compared between the 2 groups using the Mann-Whitney *U* test for age and duration of pain and the Fisher exact test for the remaining factors.

Statistical Analysis

VAS scores before the trial, during trial stimulation, and at latest follow-up were compared using the Wilcoxon signed-rank test for nonparametric data. For the 2 patients with 2 implanted electrodes, VAS score reduction for the thoracic electrode was used for statisti-

TABLE 2. Patient Characteristics and Long-Term Follow-up of 10 Patients With Permanent Implants[a]

Patient	Age, y/Sex	Pain Duration, mo	Underlying Disease	Painful Region Treated	Motor Weakness	Sensory Disturbance		% VAS Score Reduction During Trial	Latest Follow-up		Follow-up, mo
						Allod	Hyperp		%VAS Score Reduction	PGIC Rating	
2	54/F	12	L thal hem	R UL	Mild	+	+	25	20	5	16
3	59,/F	97	R put hem	L LL	Mild	–	+	50	50	2	62
4	65/M	30	R thal hem	L LL	—	–	–	56	50	2	60
6	64/F	68	L put hem	R LL	Mild	+	–	30	30	3	6
8	75/F	24	L thal hem	R LL	Mild	–	–	57	57	2	41
11	66/F	32	R put hem	L LL	Mild	+	–	57	57	2	24
15	65/M	33	L thal inf	R UL	Mild	–	–	33	33	2	25
16	48/M	11	R put hem	L LL	Mild	+	–	65	19	4	12
24	51/F	46	R put hem	L LL and UL[b]	Mild	+	–	57	57	2	12
30	71/M	82	R thal hem	L LL and UL[b]	Mild	+	+	77	ND[c]	ND[c]	ND[c]

[a] Allod, allodynia; Hyperp, hyperpathia; VAS, visual analogue scale; PGIC, Patient Global Impression of Change (scale) (2, much improved; 4, no change; 5, minimally worse); L, left; thal, thalamic; hem, hemorrhage; R, right; UL, upper limb; LL, lower limb; put, putaminal; inf, infarction; ND, not determined.
[b] These patients had 2 electrodes implanted, but in the statistical analysis, only results for the thoracic electrode are included.
[c] This patient had less than 6 months of follow-up at the time of latest follow-up and was therefore excluded from long-term-follow-up analysis.

cal analysis. In all comparisons, findings with $P < .05$ were considered significant.

Ethical Issues

Informed consent was given by each patient, and an approval was obtained from the local Ethical Review Board of Osaka University Hospital.

RESULTS

Trial Stimulation

For trial stimulation, 30 patients had a single lead implanted (24 at the thoracic level for lower limb pain and 6 at the cervical level for upper limb pain). Pain relief was good in 9 patients (30%), fair in 6 patients (20%), and poor in 15 patients (50%). The median VAS score in target areas decreased significantly from 8.0 (range, 5.0-10.0) to 6.0 (range, 1.5-10.0) after the trial ($P < .001$).

Permanent Implantation

Of the 30 patients receiving the trial SCS, only 10 patients decided in favor of a permanent SCS system implantation. Two patients had 2 leads implanted, 1 at the thoracic level for lower limb pain and 1 at the cervical level for upper limb pain (patients 24 and 30; Table 1). The clinical characteristics of the 10 patients who underwent implantation are presented in Table 2.

Of the 10 patients with permanent implants, the degree of pain relief during SCS trial was good in 7 patients, fair in 2 patients, and poor in 1 patient. Only 1 patient with a poor response to trial stimulation decided to have a permanent implant (patient 2; Table 2). That patient was satisfied with a modest degree of pain relief (25% VAS score reduction) and elected to have the implant despite a detailed explanation of the low potential for a favorable long-term outcome.

Results at Latest Follow-up

At the time of the latest check, 1 patient (patient 30) had less than 6 months of follow-up and was therefore excluded from the long-term follow-up analysis. The remaining 9 patients had a mean duration of 28 months of follow-up (range, 6-62 months). At the latest follow-up, 7 patients reported significant pain relief on the VAS scale (5 good and 2 fair). On the PGIC scale, 6 patients reported a rating of 2 (much improved) and 1 patient reported a rating of 3 (minimally improved). All 7 patients used the stimulator regularly (2-10 times daily; Table 2). The remaining 2 patients reported poor pain relief; 1 reported a rating of 4 (no change) and 1 a rating of 5 (minimally worse) on the PGIC scale. The median VAS score in the 9 patients decreased significantly from 8.6 (range, 7.0-10.0) to 4.5 (range, 3.0-8.0; $P = .008$; Figure 2). The mean VAS score reduction in all 9 patients was 41.5% (range, 19%-57%). In the 7 patients with good long-term outcome, the mean VAS score reduction was 46.5% (range, 30%-57%).

Analysis of data from the 2 patients who showed poor long-term results revealed that patient 2 had an initially modest response to trial stimulation. Thereafter, she experienced decreased analgesic efficacy of SCS along with uncomfortable paresthesia in response to stimulation. The other patient (patient 16) had a good response to trial and initial stimulation, but subsequently experienced progressive loss of efficacy of SCS.

The most common stimulation parameters were an amplitude of 1.5 to 3 V (range, 1.5-6 V), a pulse width of 210 μs (range,

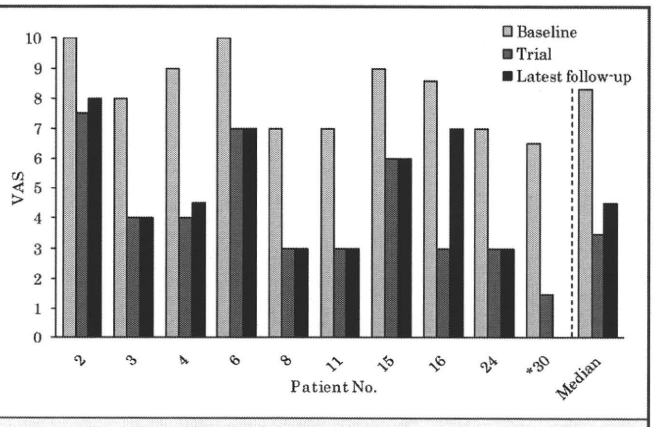

FIGURE 2. *Bar graph showing changes in visual analogue scale (VAS) scores for 10 permanently implanted patients during trial stimulation and latest follow-up The median VAS score in target areas decreased significantly from 8.3 (range, 6.5-10.0) to 3.5 (range, 1.5-10.0) after the trial (P < .001) and to 4.5 at latest follow-up (range, 3.0-8.0; P = .008). *Patient 30 had less than 6 months of follow-up and was therefore excluded from long-term follow-up analysis.*

210-350 μs), and a frequency of 31 Hz (range, 10-50 Hz) with a bipolar configuration.

Complications

The complications observed included only minor displacement of the electrode tip in 2 patients. This displacement was not associated with a change of efficacy of stimulation, and thus no repositioning was attempted. During the follow-up period, 1 patient (patient 4) died 3 years after implantation of a cause unrelated to SCS.

Clinical Factors Related to the Outcome of Trial Stimulation

There was no significant difference between the 2 groups in any of the factors examined. The incidence of hyperpathia was higher in the poor group than in the good and fair groups, but this result was below the threshold for significance ($P = .074$; data not shown).

DISCUSSION

SCS has previously been considered ineffective for CPSP despite the paucity of data in the literature to support this idea.[6,7] This study is the first to find that SCS may provide improved pain control in a group of patients with medically refractory CPSP. We found that half of the patients exhibited significant pain relief during trial stimulation (Table 1). Moreover, 7 of 9 patients continued to exhibit significant pain relief over a mean follow-up period of 28 months (range, 6-62 months; Table 2). Among these 7 patients, 6 patients reported a rating of 2 (much improved), whereas 1 reported a rating of 3 (minimally improved) on the PGIC scale, and the mean VAS score reduction was 46.5%.

A previous report indicated that 80% of failed back surgery syndrome patients achieve more than 50% pain reduction during trial stimulation.[9] We obtained a lower rate of success during trial stimulation, with 50% of our patients reporting more than 30% pain reduction, and 30% reporting more than 50% pain reduction. However, this modest degree of efficacy is important considering the severity of pain in these patients, the refractory nature of their pain, and the paucity of alterative therapeutic options.

To our knowledge, only 2 previous retrospective studies investigated the use of SCS in CPSP.[6,7,10,11] In agreement with our findings, the first study reported long-term efficacy in 3 of 10 patients,[10] whereas the second study reported long-term pain reduction (≥60%) in only 3 of 45 patients.[11] Using 30% or greater pain reduction as a threshold for success, 6 of our 30 patients (with a mean VAS score reduction of 51.5%) were considered to have a satisfactory outcome, as supported by their choice of much improved on the PGIC scale. The discrepancy between our findings and those of the Katayama et al[11] study may be because of differences in the threshold indicator of a good outcome. Although no consensus exists regarding the definition of a good outcome in chronic pain studies, the criterion of 50% pain relief is increasingly challenged because pain reduction as low as 30% corresponds to a clinically important improvement in many patients.[7,15] We therefore suspect that the clinical efficacy of SCS may have been previously underestimated as a result of the use of an unsuitably high threshold for success.

Therapeutic options for medically refractory CPSP are limited.[16] MCS is reported to provide pain relief in 50% of patients with CPSP.[8] However, because MCS requires a craniotomy, its use is limited to specialized neurosurgical centers.[6] In contrast, the SCS technique is relatively simple, less invasive, and can be mastered not only by neurosurgeons but by many anesthesiologists and pain clinicians as well.[17] Compared with other neurostimulation procedures, percutaneous trial SCS is better tolerated by patients and the electrodes can be removed easily if a trial fails. In our series, the minimal invasiveness and high degree of safety of SCS were demonstrated by the absence of significant complications.

The distribution of CPSP throughout the body may be quite variable. CPSP most often occurs in a hemibody fashion, but may be restricted to distal parts of the body such as the hand or foot.[6] Because coverage of the entire targeted region of pain by stimulation paresthesia is essential for the success of SCS,[18] we selected the most painful region, which is somewhat restricted, as a target for SCS. In this context, a majority of our patients had leg pain most frequently caused by putaminal hemorrhage. Putaminal hemorrhage that affects the posterior part of the internal capsule has the propensity to cause pain that is most severe in, or confined to, the leg.[19] We considered patients with leg-dominant CPSP suitable candidates for SCS because thoracic electrodes are less susceptible to displacement than cervical electrodes.[20] In addition, lower limb pain is not considered a good indication for MCS, given the technical difficulties associated with implanting electrodes on the medial surface of the brain.[8]

In our analysis of clinical factors that may be predictive of response to trial stimulation, we found that patients with hyperpathia tended to respond less well to trial stimulation than those without. This observation is consistent with a previous report in which SCS was less effective for control of evoked pain than spontaneous pain.[21] We also found that the effects of trial stimulation were sustained after permanent implantation in the majority of patients. SCS trial stimulation is thus advantageous for predicting efficacy in a minimally invasive manner before permanent implantation.

The mechanism behind the pain-relieving effects of SCS is still not fully understood. Inhibition at the spinal segmental level and activation of supraspinal mechanisms have been suggested as possible neurophysiological mechanisms.[22] Positron emission tomography and functional magnetic resonance imaging studies have detected brain activation during SCS.[23] Using H(2) 15O positron emission tomography, we recently observed activation not only in somatosensory areas but also in those areas concerned with emotional aspects of pain such as the anterior cingulate cortex and prefrontal areas.[22] CPSP is thought to be caused by abnormal processing of nociceptive information rostral to the level of deafferentation.[11] Therefore, we speculate that the pain-relieving effect of SCS in CPSP may be interpreted in light of its supraspinal mechanisms.

Study Limitations

Two limitations of our study are its retrospective design and small sample size. Unfortunately, it is difficult to recruit a large number of CPSP patients in 1 center owing to the low prevalence and underdiagnosis of this condition.[6] A third limitation is that our study lacked a control arm. Because SCS induces perceptible sensation, it is difficult to conduct prospective, crossover, placebo-controlled studies or blinded evaluations.[24] Therefore, the role of the placebo effect remains an unresolved problem in SCS literature.[24] However, the sustained pain relief in our patients and its correlation to certain stimulation parameters argue against a placebo effect. In the face of unblinded assessment, it may be claimed that placebo effects themselves can run as high as our relatively low threshold of success (30% pain reduction). However, using double-blind testing in MCS patients, Rasche et al[16] found all placebo responders to have less than 30% pain reduction. Therefore, the author concluded that setting the bar at 30% was helpful to discriminate between true and placebo responders. We could not recruit case-matched controls, as our surgical practice allowed us to provide long-term follow-up care only for surgically treated patients. In view of the lack of a control group, one may argue that the long-term pain-relieving effect of SCS may be attributed to spontaneous regression of symptoms; however, in our experience, as in that of others, medically refractory CPSP usually persists over a long time and rarely regresses spontaneously.[4]

Despite these limitations, our data support the idea that SCS may provide improved pain control in a group of patients with severe CPSP that is refractory to other treatments. A prospective, controlled study with a larger population of patients is needed to provide stronger evidence of the efficacy of SCS in CPSP.

CONCLUSION

This study is the first to find that SCS may provide improved pain control in a group of patients with medically intractable CPSP. The efficacy of SCS in CPSP is generally modest, both in terms of the success rate and degree of pain relief. However, this modest degree of efficacy is important considering the severity of pain in these patients, the refractory nature of their pain, and the paucity of alterative therapeutic options. A further prospective, controlled study with a larger population of patients is needed to provide stronger evidence of the efficacy of SCS in CPSP and define the patient population who are most likely to benefit from SCS treatment.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

This article reports the authors' experience using spinal cord stimulation to treat central poststroke pain. This pain syndrome is quite difficult to treat using typical pain management techniques such as physiotherapy and pharmacologic measures. The few reports in existence describe fairly unimpressive results for the efficacy of spinal cord stimulation in poststroke pain. I applaud the authors' persistence in providing additional evidence of the use of this technique. Apparently there may be hope yet for this technique in poststroke pain.

Of the 30 patients who underwent a trial of spinal cord stimulation, 10 underwent permanent placement, and 9 were available for follow-up. Good or fair pain relief was seen in 7 of 9 patients (78%) with just over a mean 2-year follow-up. Outcome measures were change in visual analogue scale scores and a patient satisfaction rating (Patient Global Impression of Change). Minor, clinically insignificant migrations were seen in 2 patients.

These results are not all that different from results of spinal cord stimulation used to treat other neuropathic pain syndromes. Given that poststroke patients who do not respond to less invasive pain management strategies have few remaining treatment options, an overall 30% (9/30) success rate, as seen in this study, is better than nothing. At least most of the treatment failures can be screened by the trial process, thus reducing the overall cost of the therapy. Patients with permanent implants had nearly an 80% success rate at 2 years.

Additionally, regarding the authors' belief that a 50% response rate as a definition of a "successful" implant, I agree that this is arbitrary and restrictive. It is a reasonable number, however, for research purposes and allows a degree of standardization of outcomes between studies. As noted by these authors, in clinical practice, patients will often be satisfied with less than 50% pain relief. I routinely see this in my practice, and this issue should be kept in mind when interpreting the outcomes of any pain study.

I completely agree with the authors' belief that spinal cord stimulation should be one of many neurostimulation techniques available to treat the medically-refractory post-stroke pain patient. Depending upon the distribution of pain, motor cortex stimulation, spinal cord stimulation, spinal nerve root stimulation, peripheral nerve stimulation, and subcutaneous peripheral nerve stimulation should all be considered as reasonable options. Generally, I favor the least invasive, safest, and most effective technique that covers the pain most completely. This study provides evidence that spinal cord stimulation, like these other forms of neurostimulation, should not be excluded a priori as a treatment option, but should be used when appropriate when less invasive measures fail.

Christopher J. Winfree
New York, New York

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Language dominance and mapping based on neuromagnetic oscillatory changes: comparison with invasive procedures

Clinical article

Masayuki Hirata, M.D., Ph.D.,[1,2] Tetsu Goto, M.D.,[1] Gareth Barnes, Ph.D.,[3] Yuka Umekawa, M.S.,[2] Takufumi Yanagisawa, M.D.,[1] Amami Kato, M.D., Ph.D.,[4] Satoru Oshino, M.D., Ph.D.,[1] Haruhiko Kishima, M.D., Ph.D.,[1] Naoya Hashimoto, M.D., Ph.D.,[1] Youichi Saitoh, M.D., Ph.D.,[1] Naoki Tani, M.D.,[1] Shiro Yorifuji, M.D., Ph.D.,[2] and Toshiki Yoshimine, M.D., Ph.D.[1]

[1]Department of Neurosurgery, Osaka University Medical School; [2]Division of Functional Diagnostic Science, Osaka University Graduate School of Medicine, Suita; [4]Department of Neurosurgery, Kinki University School of Medicine, Sayama, Osaka, Japan; and [3]Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, United Kingdom

Object. Event-related cerebral oscillatory changes reflect regional brain activation. In a previous study, the authors proposed a new method to determine language dominance: examine frontal oscillatory changes during silent reading by using synthetic aperture magnetometry (SAM). The authors' aims in the present study were to establish a normal template for this method, to confirm the results of their previous study with a larger patient population, and to evaluate their method with respect to language localization.

Methods. A statistical group analysis of 14 healthy volunteers was conducted to establish a normal control. Language dominance and localization were then evaluated in a larger population of 123 consecutive patients. Study participants were instructed to silently read 100 visually presented words. Using SAM, the spatial distribution of the oscillatory changes was obtained as the Student t statistic by comparing the current density for each voxel between 1 second before and 1 second after each word presentation. Group analyses of the healthy volunteers were performed using statistical nonparametric mapping. Language dominance in the patients was determined according to the laterality index (LI) calculated using peak t values of the left and right frontal desynchronizations. Language dominance was prospectively assessed, and the results were compared with those of the Wada test (63 patients). Language localization results were quantitatively compared with those of stimulation mapping (17 patients).

Results. Group analysis of the healthy volunteers indicated β to low γ band desynchronization in the left frontal area and α to β desynchronization in the left parietotemporal areas. In patients, the frontal language areas were detected in 118 persons (95.9%). Lateralization of β or low γ desynchronization in the inferior or middle frontal gyri corresponded well with language dominance. The introduction of the LI resulted in a quantitative evaluation of language dominance, whose results were concordant with those of the Wada test in 51 (85.0%) of 60 cases. The distance between the estimated frontal language areas and stimulation-positive sites was 6.0 ± 7.1 mm (mean ± SD).

Conclusions. This study is the first in which magnetoencephalography (MEG) was used to determine language dominance in a large population, and the results were compared with those of the Wada test. Moreover, language localization results obtained using MEG were compared with those obtained by invasive mapping. The authors' method, which is based on neuromagnetic oscillatory changes, is a new approach for noninvasively evaluating the frontal language areas, a procedure that has been problematic using MEG dipole methods. Synthetic aperture magnetometry is a noninvasive alternative to Wada testing for language dominance and helps to determine stimulation sites for invasive mapping. *(DOI: 10.3171/2009.7.JNS09239)*

Key Words • **functional brain mapping** • **language area** • **oscillation** • **language dominance** • **magnetoencephalography** • **synthetic aperture magnetometry**

The Wada test,[46] or intracarotid anesthetic agent injection procedure, is most often used to determine language dominance. However, it is an invasive test that involves the risks associated with cerebral angiography. Total complication rates of 1.2–17.0% have been reported, as have 0.3–6.9% rates of neurological complications, including transient ischemic attack (0.3–2.1%), cerebral infarction (0–1.0%), hematoma at the puncture site (0.4–4.2%), arterial dissection (0.07–0.4%), and aller-

Abbreviations used in this paper: BA = Brodmann area; ECD = equivalent current dipole; ECoG = electrocorticography; ERD = event-related desynchronization; ERS = event-related synchronization; fMR = functional MR; LI = laterality index; MEG = magnetoencephalography; MNI = Montreal Neurological Institute; SAM = synthetic aperture magnetometry.

gic reaction (0.03–0.1%).[9,12,14,21,23,47] The Wada test does not always indicate the correct language dominance because of crossed circulation from the contralateral hemisphere. Neither can it provide information about language localization. Furthermore, amobarbital has recently become difficult to obtain.[13] Thus, there has been great interest in replacing the Wada test with a noninvasive procedure.[1]

Electrical cortical stimulation, the gold standard for language localization, is performed with either chronic subdural electrodes or a bipolar electrical stimulator during awake surgery. The use of chronic subdural electrodes requires an additional surgical procedure and a test period and presents increased risks of infection, seizure, and CSF leakage, among other complications.[25] Moreover, cortical stimulation during awake surgery tends to prolong the operative time, inducing patient anxiety and an increased risk of seizure.[20]

Functional neuroimaging provides functional information less invasively or altogether noninvasively. Several PET and many fMR imaging studies have demonstrated the estimation of language dominance and localization.[2–4,10,18,40] However, standard noninvasive methods of determining language dominance have yet to be established. Authors of a recent fMR imaging study have reported that the accuracy of this imaging modality is insufficient as an alternative to invasive mapping.[33] Indeed, cerebral blood flow does not necessarily correlate with brain function itself, especially in pathological states.[45]

Magnetoencephalography directly measures neurophysiological processes with as high a temporal resolution as, and a higher spatial resolution than, electroencephalography and may be the most appropriate tool to directly evaluate brain function, including language function. With respect to language dominance, Papanicolaou et al.[27] have shown excellent results using the ECD model; however, this method has some difficulty in consistently detecting the frontal language areas. In a later study, these same authors[28] reported that in using the ECD method, they detected frontal language areas in only 45% of cases. Therefore, one could say that MEG has had difficulty competing with both PET and fMR imaging in localizing language areas, especially the frontal language areas.

Basic brain rhythms change their signal power due to brain activation. Event-related synchronization (ERS) is an increase in the oscillation amplitude of a specific frequency band that occurs in relation to specific neural activity.[30] The opposite phenomenon, a decrease in oscillation amplitude, is known as event-related desynchronization (ERD).[31] Many MEG studies[16,39,43] as well as ECoG studies[7,8,37] have shown that these oscillatory changes reflect cerebral functional activation well.

In a previous study, we proposed a new method of determining language dominance based on the local oscillatory changes related to silent reading, and we demonstrated that the lateralization of β or low γ band desynchronization in the inferior or middle frontal gyrus is a good indicator of the side of language dominance.[17] In the present study, based on local oscillatory changes (ERD and ERS) related to silent reading, language dominance was prospectively evaluated in a much larger population, and language localization was noninvasively analyzed using SAM. Group analysis of healthy volunteers was also performed to establish normal controls.

Methods

Study Population

In accordance with the Helsinki Declaration, informed consent was obtained from all study participants. The ethics committee of Osaka University Hospital approved the protocol.

Fourteen healthy volunteers (5 male and 9 female, with a mean age [± SD] of 25.4 ± 5.3 years) and 123 consecutive preoperative neurosurgical patients (75 male and 48 female, with a mean age of 36.3 ± 16.7 years) with intractable epilepsy (44 patients) or lesions around the language areas (brain tumor, 57 patients; vascular lesion, 17 patients; other, 5 patients) participated in this study. Handedness was determined using the handedness quotient according to the Edinburgh Handedness Inventory.[26] All healthy volunteers were strongly right-handed. Among the patients, 109 were right-handed, 8 were left-handed, and 6 were ambidextrous. In 106 of the 123 patients, language dominance was prospectively determined using MEG, and the findings were compared with results of the Wada test in 63 cases. The results of language localization were compared with those of stimulation mapping in 17 cases—with subdural electrodes in 13 and intraoperative cortical stimulation in 4 (Table 1).

Magnetoencephalography Task

A silent reading task was performed during MEG in each participant, who sat with eyes open in a comfortable chair in a magnetically shielded room. After the presentation of an eye fixation point for 3 seconds, a 3-character Japanese hiragana semantic word was shown for 3 seconds on an 80-inch rear projection screen (RUX87, Kimoto Co., Ltd.) located 1.5 m away from the participant. Visual stimuli were generated using a ViSaGe visual presentation system (Cambridge Research Systems, Ltd.) and were projected by a DLP projector (Depth Q, MacNaughton, Inc.) located outside the shielded room. Participants were instructed to read each word only once and without phonation immediately after presentation of the word. One session consisted of 100 different word presentations. Words were selected from an elementary school dictionary for quick and easy understanding by all participants. The word stimuli subtended a horizontal visual angle of 3° and a vertical angle of 1°; thus, no eye movements were necessary to scan the presented word.

Magnetoencephalography Measurements

A whole-head, 64-channel MEG system (model 100, NeuroSQUID, CTF Systems, Inc.) was used for recordings. Magnetoencephalography signals were digitized at a sampling rate of 625 Hz and filtered with a 200-Hz online, low pass filter. Notch filters were used at 60 and 120 Hz to eliminate alternating current line noise. Data of 5000-msec duration with a 2500-msec prestimulus interval were collected for each of the 100 trials. At the beginning and end of each measurement, the participant's head

TABLE 1: Summary of characteristics in patients who underwent stimulation mapping*

Case No.	Sex, Age (yrs)	Side of Lesion	Lesion Site	Diagnosis	Edinburgh Inventory: Handedness	Edinburgh Inventory: Quotient	Results of Wada Test	Results of SAM	Type of Invasive Mapping
1	M, 18	lt	parietal lobe	epilepsy	lt	−92	rt	lt	subdural
2	F, 35	lt	frontotemporal	cavernoma	rt	83	lt	lt	awake
3	M, 24	lt	temporal lobe	epilepsy	rt	100	lt	lt	subdural
4	M, 14	lt	temporal lobe	epilepsy	rt	100	lt	lt	subdural
5	M, 43	lt	temporal lobe	epilepsy	rt	60	lt	lt	subdural
6	M, 34	lt	Broca area	anaplastic oligoastrocytoma	amb	6	lt	lt	awake
7	M, 62	lt	Broca area	glioma	rt	100	lt	lt	subdural
8	M, 25	lt	temporal lobe	epilepsy	rt	100	bilat†	bilat	subdural
9	M, 47	lt	temporal lobe	epilepsy	rt	100	lt	lt	subdural
10	F, 42	lt	Broca area	astrocytoma GIII	rt	100	lt	lt	awake
11	F, 28	lt	temporal lobe	epilepsy	rt	90	bilat‡	lt	subdural
12	M, 31	lt	parietal lobe	epilepsy	rt	78	I§	rt	subdural
13	F, 25	lt	parietotemporal lobe	epilepsy	rt	—	lt	lt	subdural
14	F, 58	lt	temporal lobe	epilepsy	rt	—	bilat†	lt	subdural
15	M, 37	lt	Broca area	oligodendroglioma	rt	—	lt	lt	awake
16	M, 34	lt	temporal lobe	cavernoma	rt	—	I¶	rt	subdural
17	F, 18	lt	temporal lobe	epilepsy	rt	—	lt	lt	subdural

* amb = ambidextrous; GIII = Grade III; I = inconclusive; — = not performed.
† Aphasic symptoms were induced bilaterally but were more severe in the left side than the right.
‡ Aphasic symptoms were induced bilaterally but were more severe in the right side than the left.
§ Patient had occlusion of the left internal carotid artery. Only the right side test was performed, showing aphasic symptoms.
¶ Patient showed no aphasic symptoms during the Wada test.

position was registered with localization coils placed at the nasion and bilateral preauricular points. For each participant, MR images were obtained using either of two 1.5-T units (1.5T Signa EXCITE HD, GE Medical Systems; or MAGNETOM Vision Plus, Siemens) or a 3-T (3T Signa EXCITE HD, GE Medical Systems) MR imaging system in a T1-weighted sequence of 130 sagittal slices (gapless 1.4-mm thickness) with fiducial skin markers at the nasion and bilateral preauricular points. Registering the head position at these 3 points allowed the MEG data to be superimposed on the individual MR images with an anatomical accuracy of a few millimeters.

Magnetoencephalographic Analyses

Cerebral oscillatory changes related to silent reading were estimated with SAM, whose detailed algorithm is described elsewhere.[32,43] Synthetic aperture magnetometry estimates the source power with high spatial resolution by forming a linear combination of sensors that can suppress the signals from environmental noise or other brain areas without attenuating the power from the target voxel. The MEG data were divided into 5 frequency bands as follows: θ (3–8 Hz), α (8–13 Hz), β (13–25 Hz), low γ (25–50 Hz), and high γ (50–100 Hz) bands. Current density for each voxel was calculated using the multisphere head model based on the individual MR image. Changes in the current density for each voxel between the active state (0–1000 msec after stimulus) and the control state (1000–0 msec before stimulus) were statistically analyzed with the Student t-test. Synthetic aperture magnetometry images were constructed on a 5 × 5 × 5–mm grid throughout the entire brain. Negative and positive t values indicate ERD and ERS, respectively. Voxels with current density differences at $p < 0.001$ were considered statistically significant. In the patients, t values were calculated using the jackknife method, and the distribution of t values was displayed on the individual MR images for each frequency band.

In the healthy volunteers, pseudo–t values were calculated. Group analyses were then performed using a nonparametric permutation toolbox for SPM2 known as statistical nonparametric mapping (http://www.fil.ion.ucl.ac.uk/spm/snpm/).[38] The functional images were normalized to template brain images created by the MNI.[11] Permutation tests (256 permutations) were performed using a pseudo–t statistic incorporating variance smoothing with a Gaussian kernel (full width at half maximum) of 20 mm. Voxels with differences at $p < 0.05$ (corrected) were considered statistically significant.

Three-dimensional images were made using MRI3DX (http://www.jiscmail.ac.uk//lists/mri3dX.html) on a template brain for healthy group data and individual brains for each patient's data.

Language dominance was determined according to the LI, which was calculated using peak t values of the left and right frontal desynchronizations. Details of the definition of the LI and the protocol to determine lan-

guage dominance have been described in our previous study.[17] Briefly, the LI is defined as follows: 2(TR − TL)/(|TR| + |TL|), where the t values of the most prominent ERD in the specified frequency band within the related region and its contralateral homologous region were selected, and of these 2 selected values, the t value on the right side is TR and on the left side is TL. The priority of the regions used for calculating the LI was as follows: inferior frontal area > middle frontal area. The priority of the frequency bands used to calculate the LI was as follows: low γ band > β band > α band. Finally, the criteria for language dominance were as follows: when LI < −0.1, language dominance was right sided; when −0.1 ≤ LI ≤ 0.1, language dominance was bilateral; and when 0.1 < LI, dominance was left sided. Language dominance was prospectively evaluated in all but the initial 17 patients (including 14 patients who underwent the Wada test) who had been retrospectively studied to establish the criteria for language dominance.

With respect to language localization, voxels with statistically significant differences in each frequency band were superimposed on individual 3D MR images using MRI3DX. The oscillatory changes within the brain were displayed with partial transparency so that the deeper the oscillatory changes were, the more attenuated they appeared. Anatomical localizations of significant oscillatory changes were determined by reference to a standard stereotactic atlas.[42] The Talairach atlas also provided associations between the BAs and stereotactic coordinates. Because the MNI template used in SPM2 is different from the Talairach brain, MNI coordinates were transformed into Talairach coordinates.[22]

The Wada Test

Language dominance was determined using the Wada test[46] in 77 patients. After a catheter was placed in 1 extracranial internal carotid artery, thiamylal sodium dissolved in saline was slowly injected until complete paralysis of the contralateral hand was obvious. Approximately 15 mg of thiamylal sodium was needed for hemispheric anesthesia. Patients were subjected to language tasks: object naming, picture naming, repetition, and word reading. In those who recovered from hemispheric anesthesia before the neurological evaluation was completed, additional thiamylal sodium was injected and the residual evaluation was performed. More than 30 minutes after the injection of thiamylal sodium and after confirming that paralysis was no longer present, the other side was tested. Neuropsychologists blinded to the MEG results judged the Wada test results. Anomia, hesitation, paraphasia, and anarthria were considered aphasic symptoms. Dysarthria was excluded from aphasic symptoms. Investigators who analyzed the MEG data were blinded to the Wada test results.

Cortical Stimulation

Electrical cortical stimulation using bipolar, biphasic square-wave pulses was applied according to standard procedures.[20,25] After-discharge was monitored to prevent the occurrence of a seizure. The pulse duration was 0.2 msec and the stimulus frequency was 50 Hz. Stimulus intensity began at 2 mA and was progressively increased by 2-mA steps until a neurological change was elicited, the stimulus intensity reached a maximum of 15 mA, or after-discharges were provoked. As a rule, stimulation lasted for up to 5 seconds, although sometimes longer-duration stimulation was required if the participant showed no neurological changes. Picture naming and repetition tasks were used for the neurological evaluation performed by the neuropsychologists. Anomia, hesitation, paraphasia, and anarthria were considered aphasic symptoms. Dysarthria was excluded from the aphasic symptoms.

Chronic subdural electrodes consisted of 20 pole grid electrodes and/or 4 pole strip electrodes (Unique Medical) with interelectrode intervals of 10 mm and electrode diameters of 3 mm.

Propofol and dexmedetomidine were used to induce general anesthesia during the awake surgeries. The laryngeal mask was removed just before intraoperative cortical stimulation was applied, and a bipolar cortical stimulator with a 3-mm interelectrode interval (Unique Medical) was used.

Comparison of Localizations Determined With MEG and Cortical Stimulation Methods

The locations of subdural electrodes were determined from a fusion image of the CT scan (electrodes) and MR image (brain surface). The locations of stimulated sites during awake surgery were recorded by a neuronavigation system. In the case of bipolar stimulation, the location of the cathode electrodes was defined as the stimulation site. The voxels with significant ERDs in the θ, α, β, low γ, and high γ bands were superimposed on MR images. The distance between these voxels and stimulation-positive sites was calculated and defined as the difference in language localization between MEG and stimulation mapping.

Results

Healthy Volunteers

The Edinburgh Inventory indicated a mean handedness quotient of 92.0 ± 10.6% in healthy volunteers. Group analysis for the healthy volunteers indicated that statistically significant β and low γ ERDs were observed in the frontal areas with the highest t value (Table 2 and Fig. 1C and D). These ERDs were strongly lateralized to the left. The β ERD was located in the left precentral sulcus (BA6 and 44), and the low γ ERD, which was located in the left inferior and middle frontal gyri (BA10, 46, 45, and 44), was more anterior than the β ERD. High γ ERD was well localized in the left inferior and middle frontal gyri anteriorly, although it was not statistically significant (Fig. 1E). Both α and β ERDs were found in the left temporoparietooccipital junction (BA7, 19, 22, 39, 40, and 42) with statistical significance (Fig. 1B and C). These ERDs in the posterior language areas were also lateralized to the left, except for the α ERD in the occipital areas (BA19), but not as strongly as the frontal ERDs. High γ ERS was found in the bilateral occipital areas (Fig. 1E), and θ ERS appeared in the bilateral medial prefrontal areas (Fig. 1A), although these synchronizations were not statistically significant.

TABLE 2: Statistical nonparametric mapping group SAM results corrected for 14 healthy volunteers

Frequency Band	Anatomical Area	Side of Significant ERD/ERS	Broadman Area	MNI Coordinates (mm)			Cluster Size	p Value	Pseudo-T Value
				X	Y	Z			
α ERS	superior frontal gyrus	lt	10	14	64	32	74	0.0156	4.52
	middle frontal gyrus	rt	8	−32	42	50	89	0.0195	4.46
	middle frontal gyrus	rt	10	−38	58	20	14	0.0352	4.04
α ERD	lat occipital sulcus	rt	19	−36	−68	12	1667	0.0039	5.14
	middle occipital gyrus	rt	19	−38	−90	22		0.043	4.22
	superior occipital gyrus	rt	19	−28	−78	40		0.043	4.2
	angular gyrus	lt	39	34	−64	18	1448	0.0078	4.69
	superior temporal sulcus	lt	22	48	−54	16		0.0156	4.49
	superior temporal sulcus	lt	22	56	−46	12		0.0156	4.42
	intraparietal sulcus	lt	7	20	−64	50	32	0.0156	4.4
	parietooccipital sulcus	lt	7	12	−70	30	11	0.0312	4.27
β ERD	precentral sulcus	lt	6, 44	50	−2	8	729	0.0078	4.77
	precentral sulcus	lt	6, 44	48	−6	26		0.0156	4.31
	intraparietal sulcus	lt	40	32	−48	42	1590	0.0078	4.74
	intraparietal sulcus	lt	7	26	−54	42		0.0078	4.72
	intraparietal sulcus	lt	7	12	−60	34		0.0117	4.5
	transverse temporal gyrus	lt	42	44	−36	20	73	0.0195	4.23
	angular gyrus	rt	39	−38	−66	14	177	0.0195	4.22
	lat occipital sulcus	rt	19	−34	−64	6		0.0234	4.17
	intraparietal sulcus	rt	7	−22	−56	46	139	0.0234	4.2
	intraparietal sulcus	rt	7	−26	−62	32	—	0.0234	4.19
low γ ERD	inferior & middle frontal gyri	lt	10, 46, 45, 44	30	54	−10	16,248	0.0078	5.19
	posterior cingulate gyrus	lt	31	10	−48	36	1158	0.0156	4.31
	middle frontal gyrus	rt	46	−50	48	6	49	0.0195	4.23
	middle frontal gyrus	lt	46	44	48	28	1	0.0469	3.79

These results were concordant with our findings in previous studies in healthy volunteers[15] and patients.[17]

Patient Population

The Wada Test. The Wada test was performed in 77 patients, showing left language dominance in 61 (79.2%), right dominance in 6 (7.8%), bilateral dominance in 7 (9.1%), and inconclusive results in 3 (3.9%). Nine of 14 left-handed and ambidextrous patients underwent the Wada test (Table 3). The patient in 1 of the inconclusive cases (Case 12 in Table 1) had an occlusion of the left internal carotid artery; therefore, only a right side injection was performed, which led to aphasic symptoms. The patient in the second inconclusive case (Case 16 in Table 1) did not present any aphasic symptoms during the procedure. In the third inconclusive case—invasive mapping was not performed in this case—the Wada test failed due to the deterioration of consciousness induced by barbiturate injection.

Cortical Stimulation

Chronic subdural stimulation was performed in 13 patients, and intraoperative cortical stimulation during awake surgery was conducted in 4 patients. Cortical stimulation was performed in the left hemisphere in all cases. In 12 patients, aphasic symptoms were induced in 65 stimulated sites. In the patients in Cases 1, 2, 4, 12, and 17, electrical cortical stimulation did not reveal any stimulation-positive sites. Procedures were incompletely performed in 2 patients (both chronic subdural stimulation: Cases 5 and 17) because of seizure evoked by electrical stimulation.

Magnetoencephalography and its Comparison With the Wada Test and Cortical Stimulation

The frontal language areas were detected in 118 patients (95.9%), which was high enough to determine language dominance. Lateralization of the β and low γ ERDs in the inferior or middle frontal gyrus corresponded well with language dominance as determined by the Wada test, as we previously reported.[17] The introduction of the LI enabled quantitative evaluation of language dominance. In 63 patients, language dominance results of MEG were prospectively compared with results of the Wada test (Table 3). In 3 patients, the Wada test was inconclusive. Magnetoencephalography results were concordant with those of the Wada test in 51 (85.0%; left 45, right 4, bilateral 2) of the 60 patients. Sensitivity was 86.7% and specificity

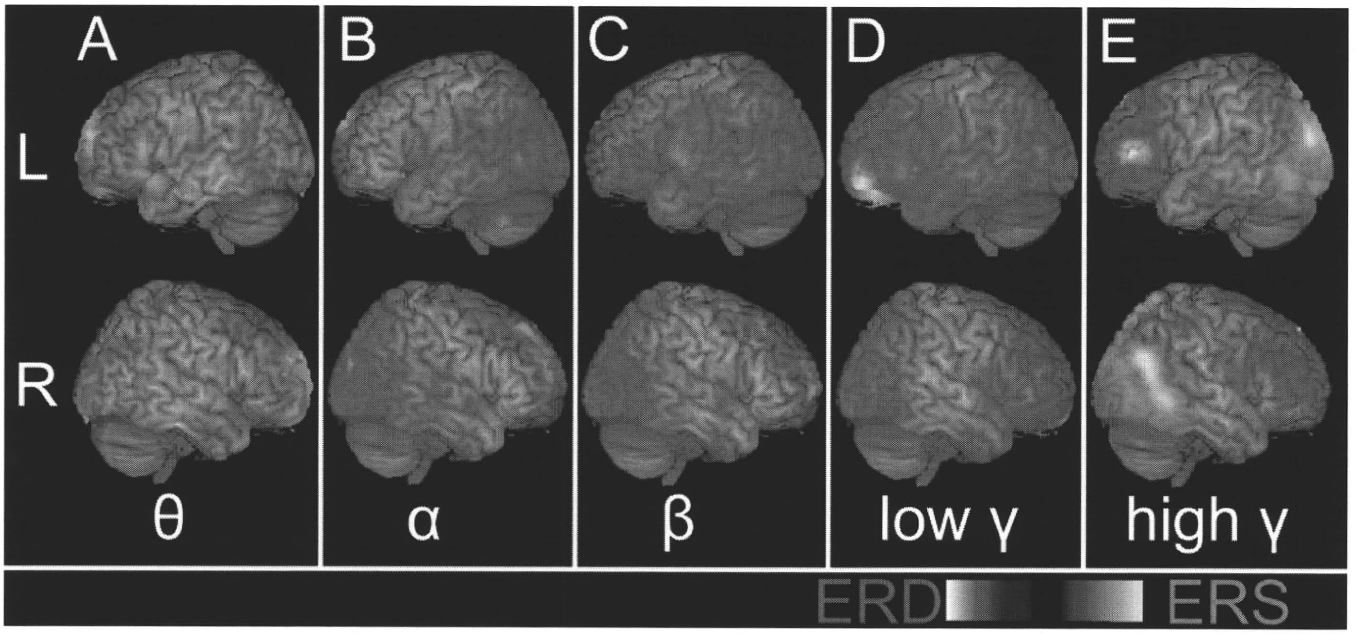

Fig. 1. Group-analyzed images obtained in healthy volunteers, showing the cerebral oscillatory changes induced by silent word reading. **A:** The θ band (3–8 Hz). **B:** The α band (8–13 Hz). **C:** The β band (13–25 Hz). **D:** Low γ band (25–50 Hz). **E:** High γ band (50–100 Hz). *Magenta areas* indicate ERD; *yellow areas,* ERS. Spatial distribution of the t values were superimposed on the MNI template brain.

was 96.7%. In the left-handed and ambidextrous patients, concordance with the Wada test was 77.8%, sensitivity was 77.8%, and specificity was 100%.

Localization of the frontal language areas based on SAM was compared with localization based on stimulation mapping in 12 cases, excluding Cases 1, 2, 4, 12, and 17 in which there were no stimulation-positive sites (Table 1). Estimated frontal language areas were generally concordant with the stimulation mapping results. The difference in localization between ERD voxels and stimulation-positive sites was 6.0 ± 7.1 mm (range 0–23.0 mm). However, in the patient in Case 7, who presented with motor dysphasia preoperatively, there was a considerable difference (maximum 23.0 mm) between the β ERD voxels and stimulation-positive sites, although the β ERDs were detected diffusely in the left frontal area (Fig. 3 *right*). In stimulation mapping, advance information about language localization provided by the MEG analysis helped us to decide where to place the subdural electrodes as well as where to stimulate during both awake surgery and electrical stimulation of subdural electrodes. Because the time for mapping is limited, especially during awake surgery, advance information from MEG studies enabled us to perform effective functional mapping.

Illustrative Cases

Case 6. This 34-year-old man initially reported numbness around his mouth and in his left hand. He also suffered a motor aphasic attack. Magnetic resonance images revealed a heterogeneously enhanced large mass lesion in the left inferior frontal gyrus (Fig. 2A and B). Magnetoencephalography detected α and β ERDs in the left inferior frontal gyrus just posterior to the lesion (Fig. 2C). The Wada test indicated that language dominance was left sided, findings consistent with the MEG results. Awake surgery was performed. Electrical cortical stimulation applied, as described in *Methods*, at sites almost identical with the ERDs detected with MEG induced anarthria. Moreover, cortical stimulation just anterior to the main ERD, detected partially as a low γ ERD according to MEG, induced anomia or paraphasia symptoms. The MEG results allowed for more efficient, time-saving invasive mapping. Stimulation-positive sites were recorded using a neuronavigation system (Fig. 2E), which was also useful for safe and maximal tumor removal (Fig. 2F). Postoperative MR imaging showed no residual enhanced lesion (Fig. 2G). The patient experienced only transient, mild word-finding difficulty.

Case 7. This 62-year-old man presented with mild motor dysphasia. Magnetic resonance images revealed an enhanced mass lesion in the left inferior frontal gyrus. Magnetoencephalography showed a β ERD in the left precentral gyrus. The Wada test indicated that his language dominance was left sided. Subdural electrodes were placed over the left frontal area, and electrical stimulation applied to those overlapping the β ERD–induced anarthria. Note, however, that anomia was also induced by electrical stimulation to broad areas more anterolateral to the β ERD (Fig. 3 *right*).

Case 9. This 47-year-old man suffered from intractable epilepsy. Electroencephalography, MEG, and SPECT suggested left temporal lobe epilepsy. Language MEG indicated prominent and diffuse α to β ERDs in the left frontal area (Fig. 3 *left*). Chronic subdural electrodes were placed over the frontotemporal areas, and electrical stimulation applied to the electrodes overlapping the low γ ERD induced anomia and hesitation symptoms.

Case 10. This 42-year-old woman suffered from

TABLE 3: Comparison of estimated language dominance using SAM and results of the Wada test

SAM	Wada Test			
	Lt	Bilat	Rt	Inconclusive
all 63 cases				
lt	45	3	0	1
bilat	1	2	0	0
rt	1	1	4	2
inconclusive	3	0	0	0
9 lt-handed or amb patients				
lt	4	0	0	0
bilat	0	0	0	0
rt	0	0	3	0
inconclusive	2	0	0	0

chronic headache, although she did not present with any aphasic symptoms. A T2-weighted MR image demonstrated a high-intensity lesion in the left precentral gyrus (Fig. 4A). A low-grade glioma was suspected. Magnetoencephalography showed a low γ ERD in the left inferior frontal sulcus just anterior to the lesion (Fig. 4B). The Wada test showed that her language dominance was left sided, results concordant with the MEG findings. Awake surgery was performed. Frontal language areas were identified using cortical stimulation with a bipolar stimulator. Electrical stimulation at the same site as the low γ ERD induced a hesitation symptom. In addition to this MEG-positive site, electrical stimulation just superior to the lesion induced anarthria and anomia. Although MEG did not detect these additional positive sites, it did help to effectively perform stimulation mapping within a limited time. The patient did not experience any aphasic symptoms postoperatively. A postoperative MR image showed no residual T2-weighted high-intensity lesion (Fig. 4C).

Discussion

This trial represents the first MEG study in a large clinical population in which language dominance and localization were noninvasively assessed and the results prospectively compared with those of the Wada test and cortical stimulation, respectively, and a normal group was included.

Group Analysis of Healthy Volunteers

Our previous clinical study showed that β and low γ ERDs are induced in the inferior and middle frontal areas lateralized to the dominant hemisphere.[17] Group analysis of healthy volunteers in the present study further delineated this left lateralized frontal ERD. It was more anteriorly localized (BA10) in the high γ band and more posteriorly distributed (BA44 and 13) in the β band, and the low γ band ERD was distributed with the highest t value in the left inferior and middle frontal cortex (BA46 and 44) and the insular cortex (BA13). These results confirmed the validity of our criteria for language dominance based on the frontal ERD.

The bilateral frontal pole (BA10) showed θ and α

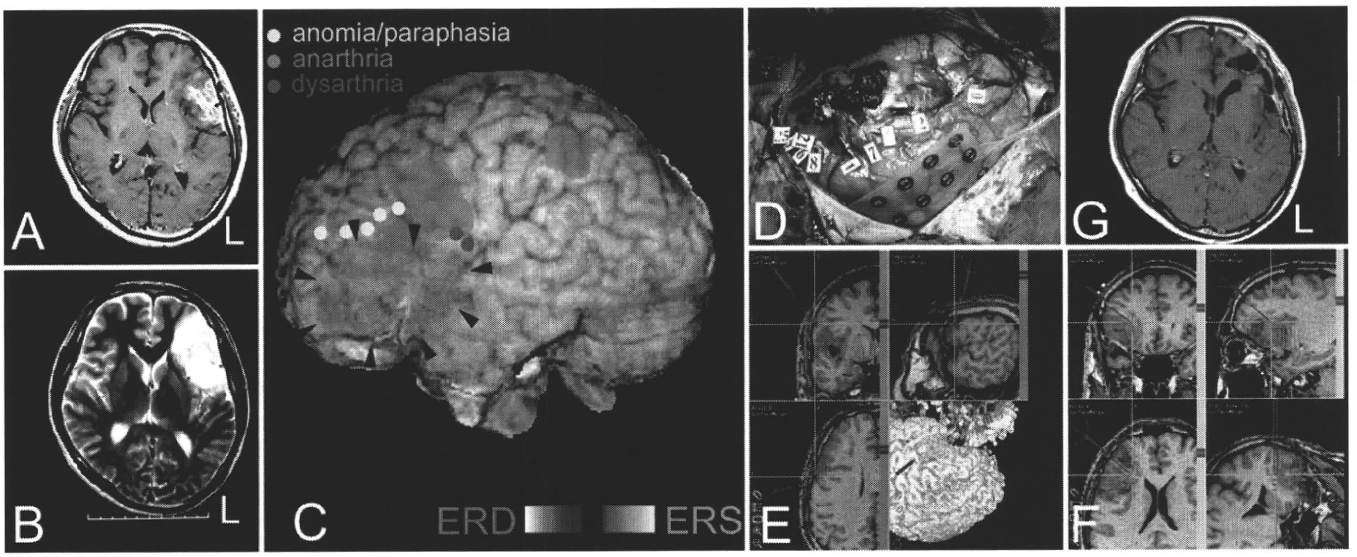

Fig. 2. Case 6. Images obtained in a patient with anaplastic oligoastrocytoma in the Broca area. **A:** Preoperative Gd-enhanced T1-weighted MR image revealing a heterogeneously enhanced large tumor in the left inferior frontal gyrus. **B:** Preoperative T2-weighted MR image showing most of the inferior frontal gyrus occupied by the tumor. **C:** An MEG image showing language localization superimposed on the patient's MR image. *Black arrowheads* indicate the tumor boundary. Stimulation-positive sites, indicated by the *colored dots*, were also superimposed on the MR image. *Magenta areas* indicate statistically significant ERD detected on MEG; *yellow areas* indicate statistically significant ERS detected on MEG. A p value < 0.001 was considered statistically significant. **D:** Photograph showing electrical cortical stimulation during awake surgery. Subdural electrodes were placed to monitor after-discharge. *Numbered papers* indicate stimulation-positive sites. **E:** Navigation display during stimulation mapping demonstrating a navigation probe pointing to a stimulation-positive site. **F:** Navigation display during tumor removal showing a navigation probe pointing to the deepest tumor boundary portion. **G:** Postoperative MR image showing no apparent enhanced mass lesion.

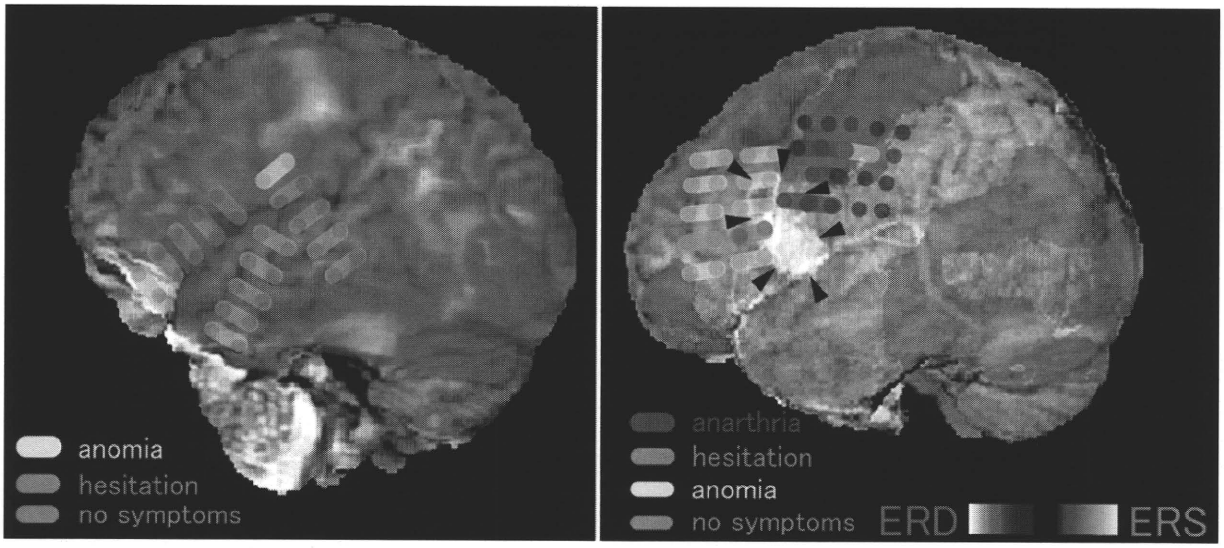

Fig. 3. Illustrative MEG images superimposed on the individual MR images. Stimulation sites, indicated as *colored dots*, were also superimposed on the same MR images. ***Left:*** Images obtained in the patient in Case 9 with temporal lobe epilepsy. ***Right:*** Images obtained in the patient in Case 7 with a glioma in the Broca area. *Black arrowheads* indicate the tumor boundary. *Magenta areas* indicate statistically significant ERD detected by MEG; *yellow areas*, statistically significant ERS detected by MEG. A p value < 0.001 was considered as statistically significant.

ERS. This ERS is most probably attributable to the frontal midline θ rhythm, which is generated in relation to mental concentration or focused attention.[35] Ishii et al.,[19] using SAM, have concluded that this rhythm is located in the medial prefrontal cortex.

In the posterior language regions, the left angular gyrus (BA39), left posterior superior temporal sulcus (BA22), and right occipital cortex (BA19) showed significant α ERDs. The left intraparietal sulcus (BA40, 7) showed a significant β ERD. These oscillatory changes are most probably attributable to receptive language processing and visual information processing. These oscillatory changes, except for the occipital cortex (BA19), generally exhibited left lateralization, but not so strongly as the frontal language areas. In our earlier clinical study,[17] oscillatory changes in the posterior regions did not show left lateralization with statistical significance. One of the possible reasons is that the posterior language area is not as lateralized as the frontal language area.[1,24] Another reason is that the control stimulus (a simple eye fixation marker: +) in our silent reading task is not sufficiently balanced with respect to visual response, resulting in a contamination of visual information processing as well as pure language processing. The introduction of a visually balanced control stimulus may improve lateralization of the posterior language area.

Language Dominance

In our previous study,[17] we proposed a noninvasive method for the quantitative determination of language dominance using SAM. The present prospective study in a larger population confirmed the validity of our method. Language dominance in left-handed or ambidextrous patients was also validated in a larger population (9 patients); this is clinically significant because language dominance in left-handed or ambidextrous patients has considerable interindividual variation, and handedness does not serve as an indicator of language dominance. Consistencies with the Wada test in the present study were as high as those in an ECD-based study and other fMR imaging and PET studies.[18,28,34,48] Thus, our method, which is based on event-related cerebral oscillatory changes detected via spatially filtered MEG, is competitive with ECD, fMR imaging, and PET studies with respect to the evaluation of language dominance.

It should be noted that even the Wada test does not always correctly indicate dominance, because the induced aphasic symptoms are sometimes influenced by crossed flow from the contralateral carotid artery via the anterior communicating artery, the test sometimes results in an incomplete evaluation, or the test is not executable because of severe stenosis or occlusion of the carotid artery (Case 12). In the present study, the Wada test was inconclusive in 3 cases (3.9%). Note also that the time for evaluation is limited because the procedure is basically invasive, requiring intraarterial catheterization. Furthermore, the Wada test does not provide any information about language localization. In this sense, our noninvasive method is a promising means of evaluating language dominance as well as language localization.

Even when language dominance determined by the Wada test is presumed to be perfectly correct, the sensitivity and specificity of our method were 85.0% and 96.5%, respectively. Sensitivity was rather low, compared with the specificity—contrary to the findings of an ECD study.[28] One of the reasons is attributable to the narrow range of our LI criteria for assigning bilateral representation (−0.1 to 0.1). If we were to choose a broader range, sensitivity would improve, although specificity would decrease.

We introduced a hierarchy of frequency bands into the criteria for determining language dominance: the first priority is the low γ band, the second the β band, and the third the α band. A slowing down of the basic oscillation is the most commonly observed phenomenon in pathological states. We took into account this slowing down

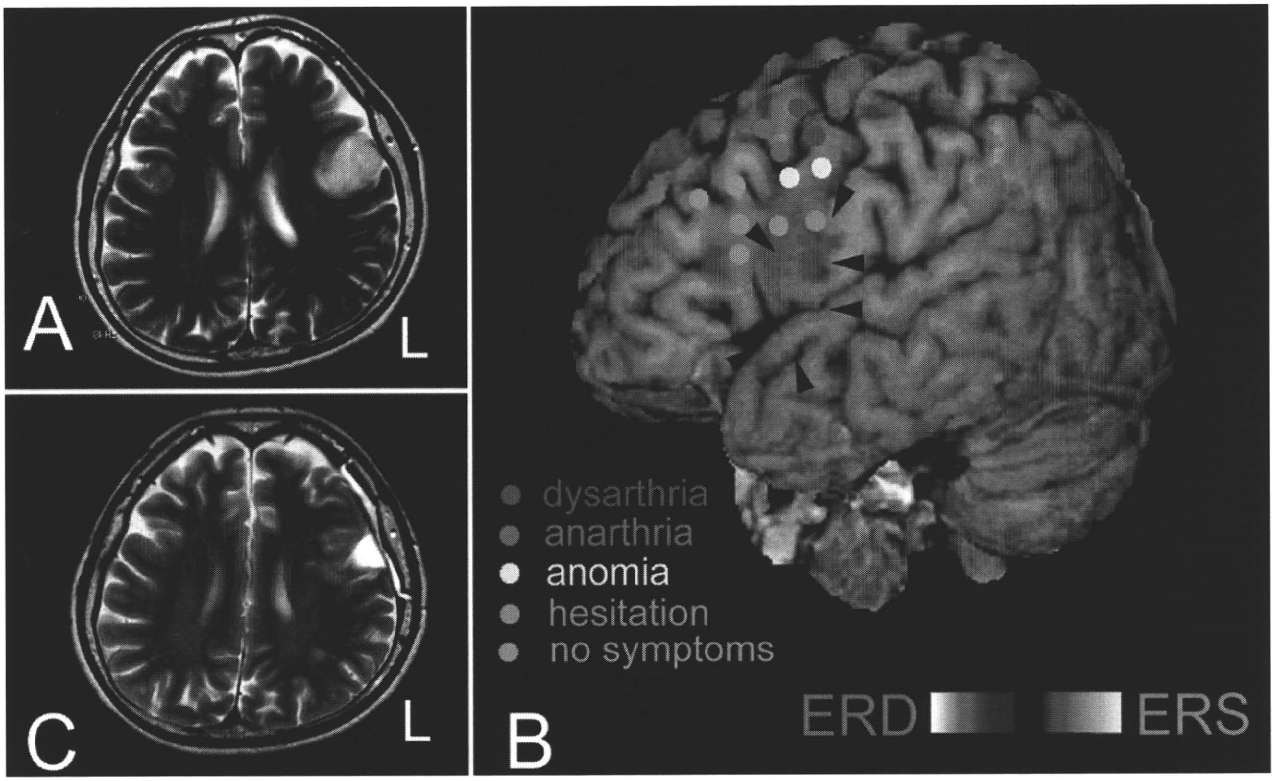

Fig. 4. Case 10. Images obtained in a patient with an astrocytoma in the Broca area. **A:** Preoperative T1-weighted MR image demonstrating an astrocytoma. **B:** An MEG image showing language localization superimposed on an MR image. *Black arrowheads* indicate the tumor boundary. Stimulation sites, indicated as *colored dots*, were also superimposed on the MR image. *Magenta areas* indicate statistically significant ERD detected by MEG; *yellow areas*, statistically significant ERS detected by MEG. A p value < 0.001 was considered statistically significant. **C:** Postoperative T2-weighted MR image demonstrating no apparent mass lesion.

to make the criteria as robust as possible; having done so may have contributed to the high consistency with the Wada test.

Time frequency analysis showed that the β to low γ ERD was most prominent in the window from 150–600 msec (unpublished data). Therefore, the optimal time window for analysis is not 0–1000 msec but 150–600 msec. Refinement of the time window for analysis may improve the sensitivity to detect the language-specific responses.

In epilepsy surgery, the evaluation of memory dominance is also indispensable as a preoperative examination, because the medial temporal structures, including the hippocampus, are often resected in cases of temporal lobe epilepsy. Another important role for the Wada test is to evaluate memory dominancy including verbal memory. At present, our method evaluates language function only, not verbal memory. The evaluation of verbal memory using MEG clearly needs further investigation if the Wada test is to be completely replaced by MEG.

Language Localization

As far as language localization is concerned, the average distance between ERD voxels and stimulation-positive sites was 6.0 ± 7.1 mm. This result is comparable to the findings of fMR imaging[33,36] and PET,[4] although the evaluation methods in these studies are different from ours. Our method seems to be sufficiently precise as a screening test but insufficient as a definitive diagnostic evaluation. In the present study, MEG results helped to determine the stimulation sites during invasive mapping and possibly to shorten the time required for stimulation mapping.

To date, MEG had been considered suitable for detecting the posterior language areas but not the frontal ones.[29] The ECD method based on averaged evoked responses also appears to have limitations in the frontal language area. For example, authors of the most representative ECD study have reported that the frontal language areas were detected in only 45% of cases.[28] This limitation was probably due to the fact that late responses are canceled out through the averaging process of ECD calculations, especially in the higher-frequency bands in which the phase was perhaps more variable. The ECD method also has some difficulty in detecting individual posterior language areas such as the posterior superior temporal gyrus, posterior temporal base, and angular gyrus—which may explain why most ECD studies describe desynchronizations concentrated around the posterior superior temporal area, that is, the intermediate areas between the angular cortex and basal temporooccipital cortex.[27,28,41] In contrast, spatially filtered MEG analyses based on event-related cerebral oscillatory changes have enabled us to consistently detect both the frontal and individual posterior language areas. Data in the present study show that spatially filtered MEG is competitive with fMR imaging and PET techniques even in the frontal language areas.

Once again, for the reasons described above, the introduction of a control stimulus visually balanced with active stimuli would improve specific detection of the proper posterior language areas as well as the evaluation of language dominance in the posterior language areas independent of that in the frontal language areas.

There were also some differences in the localization of frontal language areas between MEG and stimulation mapping. Our method failed to detect some stimulation-positive sites. The silent word-reading test used in our study may not have been an optimal task for complete detection of the frontal language area. Additional tasks, such as the verb-generation, picture-naming, or sentence-reading task, might improve detectability.

Cases in which patients present with aphasic symptoms, such as Case 7, require careful consideration. In such cases, the most prominent oscillatory changes might not necessarily indicate the proper indispensable language area, but rather the compensatory responses in neighboring or contralateral areas. These compensatory responses might be prominent but functionally minor.

Neurophysiological Aspects

Magnetoencephalography and ECoG directly measure neurophysiological responses. This means that we can obtain more information about functional localization from a comparison with the subdural electrodes based on not only the electrical cortical stimulation but also the ECoG oscillatory changes during the same language task. Such comparisons will contribute to further improving the potential of MEG. Recently, several ECoG studies have documented cerebral oscillatory changes related to language processing.[5,6,37,44] These studies have revealed that in addition to α and β ERDs, language processing induces a γ ERS, which better reflects the spatial distribution of the functional areas.[6,37]

Compared with fMR imaging and PET, MEG has extremely high temporal resolution. Time-locked tasks, such as those adopted in the present study, will contribute to our understanding of the dynamic process of language function as well as elucidate neurophysiological mechanisms of pathological states.

Conclusions

Functional imaging with spatially filtered MEG based on cortical oscillatory changes is competitive with ECD, fMR imaging, and PET studies with respect to estimating language dominance. However, to replace the Wada test with MEG, one must also establish the method for evaluating verbal memory dominance. With regard to language localization, our method consistently detects the frontal language areas, which has been difficult with ECD. Our method is a promising means of preoperative evaluation and helps in choosing stimulation sites during invasive mapping.

Disclosure

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Address correspondence to: Masayuki Hirata, M.D., Ph.D., Department of Neurosurgery, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka, 565-0871 Japan. email: mhirata@nsurg.med.osaka-u.ac.jp.

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Real-time control of a prosthetic hand using human electrocorticography signals

Technical note

TAKUFUMI YANAGISAWA, M.D., PH.D.,[1,2] MASAYUKI HIRATA, M.D., PH.D.,[1] YOUICHI SAITOH, M.D., PH.D.,[1] TETSU GOTO, M.D., PH.D.,[1] HARUHIKO KISHIMA, M.D., PH.D.,[1] RYOHEI FUKUMA, M.S.,[2,3] HIROSHI YOKOI, PH.D.,[4] YUKIYASU KAMITANI, PH.D.,[2,3] AND TOSHIKI YOSHIMINE, M.D., PH.D.[1]

[1]Department of Neurosurgery, Osaka University Medical School, Osaka; [2]ATR Computational Neuroscience Laboratories, Kyoto; [3]Nara Institute of Science and Technology; and [4]Department of Precision Engineering, University of Tokyo, Japan

Object. A brain-machine interface (BMI) offers patients with severe motor disabilities greater independence by controlling external devices such as prosthetic arms. Among the available signal sources for the BMI, electrocorticography (ECoG) provides a clinically feasible signal with long-term stability and low clinical risk. Although ECoG signals have been used to infer arm movements, no study has examined its use to control a prosthetic arm in real time. The authors present an integrated BMI system for the control of a prosthetic hand using ECoG signals in a patient who had suffered a stroke. This system used the power modulations of the ECoG signal that are characteristic during movements of the patient's hand and enabled control of the prosthetic hand with movements that mimicked the patient's hand movements.

Methods. A poststroke patient with subdural electrodes placed over his sensorimotor cortex performed 3 types of simple hand movements following a sound cue (calibration period). Time-frequency analysis was performed with the ECoG signals to select 3 frequency bands (1–8, 25–40, and 80–150 Hz) that revealed characteristic power modulation during the movements. Using these selected features, 2 classifiers (decoders) were trained to predict the movement state—that is, whether the patient was moving his hand or not—and the movement type based on a linear support vector machine. The decoding accuracy was compared among the 3 frequency bands to identify the most informative features. With the trained decoders, novel ECoG signals were decoded online while the patient performed the same task without cues (free-run period). According to the results of the real-time decoding, the prosthetic hand mimicked the patient's hand movements.

Results. Offline cross-validation analysis of the ECoG data measured during the calibration period revealed that the state and movement type of the patient's hand were predicted with an accuracy of 79.6% (chance 50%) and 68.3% (chance 33.3%), respectively. Using the trained decoders, the onset of the hand movement was detected within 0.37 ± 0.29 seconds of the actual movement. At the detected onset timing, the type of movement was inferred with an accuracy of 69.2%. In the free-run period, the patient's hand movements were faithfully mimicked by the prosthetic hand in real time.

Conclusions. The present integrated BMI system successfully decoded the hand movements of a poststroke patient and controlled a prosthetic hand in real time. This success paves the way for the restoration of the patient's motor function using a prosthetic arm controlled by a BMI using ECoG signals. *(DOI: 10.3171/2011.1.JNS101421)*

KEY WORDS • brain-machine interface • prosthetic hand • electrocorticography signal • real time • support vector machine

THERE are several diseases and conditions that lead to a loss of muscle control without disruption of the patients' cognitive abilities. These include amyotrophic lateral sclerosis, brainstem stroke, spinal cord injury, muscular dystrophy, and cerebral palsy. Brain-machine interface technology can offer these patients greater independence and a higher quality of life, providing the individual with control of external devices with which to communicate with others and manipulate their environment according to their will.[29]

Several signal platforms could be used as input signals for BMIs in a clinical setting: EEG,[30] MEG,[27] neuronal ensemble activity recorded intracortically (single units)[8,9,28] and/or local field potentials,[1,15] and ECoG.[14,18,21] Each type of signal has proven to be useful for BMIs, although each has advantages and disadvantages regarding utility in an applied setting. Although EEG and MEG

Abbreviations used in this paper: BMI = brain-machine interface; ECoG = electrocorticography; EEG = electroencephalography; EMG = electromyography; FFT = fast Fourier transform; MEG = magnetoencephalography; SVM = support vector machine.

signals can be measured noninvasively,[30] they have low spatial resolution compared with the other signals and are susceptible to artifacts from other sources.[7] Single-unit recordings have been shown to convey large amounts of information for the successful control of a prosthetic arm in a self-feeding task of monkeys.[26] This type of BMI system has already been applied to paralyzed patients,[9] but the clinical implementation of intracortical BMIs is currently impeded by difficulty in maintaining stable long-term recordings and the substantial technical requirements of the recordings.[6,22] Electrocorticography has a higher spatial resolution and better signal-to-noise ratio than EEG or MEG. Its signals have been used to control the movement of a cursor on a computer screen,[21] to reconstruct the trajectory of a 2D arm movement,[18] and to decode a single finger movement.[16] Moreover, ECoG recordings have superior long-term stability than intracortical single-unit recordings, as well as lower technical difficulty and clinical risk.[4] Even though ECoG signals have been shown to be useful for BMI systems, they have not been used to control the movement of a prosthetic hand. Here, we propose an integrated BMI system to control the movement of a prosthetic hand using ECoG signals generated while the patient moved his hand.

Previously, we developed a system in which a patient's EMG signals were used to control the movement of a prosthetic hand.[12,17] This system records the EMG signals and converts them into a power spectrum to classify some simple movements. The user can control the prosthetic hand by performing or attempting to perform simple hand movements, such as hand grasping, hand opening, and making a scissor shape. By combining such simple movements, an amputee was able to use the prosthetic hand for writing by holding a pen, cooking by grasping a kitchen knife, and other activities of daily living.[32] In the present study, we removed the EMG sensors and control unit from this system and attached a new unit that records and classifies ECoG signals to control the prosthetic hand. The new integrated system was designed to classify some simple movements using only 3 frequency power bands of the ECoG signals.

With the new integrated system, the ECoG signals of a stroke patient were recorded when he performed 3 types of hand movements. Time-frequency analysis of the signals demonstrated that 3 frequency power bands contained the characteristic features relating to the movements. With these features, the state and the type of movement were inferred by 2 decoders. The decoding accuracy was compared among the 3 frequency bands to identify the most informative band. With the 2 decoders, the freely performed movements were inferred so that the prosthetic hand faithfully mimicked the individual's hand in real time.

Methods

Patient

This 64-year-old man with thalamic pain on the left side of his body participated in this study. He had incomplete left hemiparesis due to a right thalamic hemorrhage 7 years earlier. He was barely able to perform simple hand movements (grasping, opening, and making a scissor shape). Subdural electrodes had been implanted on the right sensorimotor cortex to reduce intractable pain by delivering electrical stimulation.[10] First, 2 sheets of a 30-electrode array were temporarily implanted on a broad cortical area around his hand motor strip to determine an optimal stimulation site where the maximum reduction of his pain was achieved. The number and location of the electrodes were chosen to stimulate the cortical area corresponding to the body parts with pain. These electrodes were implanted for 2 weeks. Then, after the optimal site was determined, an array of 4 electrodes was implanted at the optimal site for chronic stimulation to reduce the pain. The patient participated in our study during the 2 weeks of temporary electrode placement. He was informed of the purpose and possible consequences of this study, and written informed consent was obtained. The ethics committee of Osaka University Hospital approved the present study.

Prosthetic Hand

The prosthetic hand was an experimental anthropomorphic hand developed by Dr. Yokoi.[12] The general movement mechanisms and degrees of freedom of the hand mimicked those of a human hand. The hand was equipped with 8 DC motors to independently actuate 8 individual tendons of the hand. The 8 tendons work in a coordinated manner to accomplish flexion or extension of each individual finger. The commands to the hand were updated by the host computer system every 200 msec.

Recording Methods

Sixty planar-surface platinum grid electrodes (2 sheets of a 5 × 6 array, Unique Medical Co.) were placed over the patient's right sensorimotor cortex (see Fig. 2A). The electrodes had a diameter of 3 mm and a center-to-center interelectrode distance of 7 mm. Video recording was performed during experiments. Electromyography recordings of the contralateral flexor digitorum superficialis muscle were collected at the same time. The video and EMG recordings were not used for the decoding but were used to identify the onset of the actual movement during offline analysis.

The location of the implanted electrodes was identified by standard neurosurgical techniques, both anatomically and electrophysiologically. After induction of general anesthesia, we performed a frontoparietal craniotomy over the sensorimotor cortex. The location of the central sulcus was estimated using preoperative MR imaging and confirmed by the phase reversal of the N20 component of the intraoperative somatosensory evoked potentials.

Movement Tasks

Experiments were performed in an electromagnetically shielded room approximately 1 week after electrode placement. The patient was instructed to perform 3 types of movements with his left hand: a grasping motion, a hand-opening motion, and a scissor-shape motion (extension of the second and third fingers). He selected and

performed 1 of the 3 hand movements immediately after the presentation of a sound cue that recurred every 5.5 seconds (calibration period [Fig. 1A]). The sound cue was delivered from a loudspeaker controlled by Matlab 2007b (Mathworks), consisting of 3 beeps presented every 1 second. The patient was instructed to move his hand just after the third sound and to return his hand to a resting position immediately after the movement. For the resting position, the patient was instructed to relax his hand while slightly flexing his fingers. The 3 types of movement were performed approximately 40 times each. This calibration period took approximately 20 minutes with some breaks in between. During this period, there was no training of the patient.

After the calibration period with the external cues, the patient performed the same task at self-paced intervals without any external cues (free-run session [Fig. 1B]). The free-run session lasted for approximately 20 minutes with some breaks. Therefore, all of the experiments in this study took only approximately 1 hour. Notably, the patient performed the free-run task without training to control the prosthetic hand; indeed, it was only necessary to train the decoder to the ECoG signals obtained in the calibration period (see the *Decoding Algorithms* section for details).

Data Collection and Preprocessing

Electrocorticography signals were measured using a 128-channel digital EEG system (EEG 2000, Nihon Koden Corp.) and digitized at a sampling rate of 1000 Hz. All subdural electrodes were referenced to a scalp electrode placed on the nasion. The bandpass filter for the data analysis was set to 0.16–300 Hz.

At first, during the calibration period, the ECoG signals of all implanted electrodes were examined for 4000 msec in each session (–2000 to 2000 msec from the cue onset of each movement). A time-frequency analysis of the ECoG signals was performed using EEGLAB v5.03.[5] The power spectrum of the ECoG signals was analyzed for each electrode and each type of movement. From the results of the power spectrum, we identified 3 frequency power bands with characteristic modulation during the movement tasks: 1–8, 25–40, and 80–150 Hz

For the decoding analysis, the ECoG signals of all implanted electrodes were obtained by reference to the 3 beeps. Figure 1A shows the duration of the ECoG signals used for the decoding analysis: "N," ECoG signals of 1 second after the first sound; "R," ECoG signals of 1 second after the second sound; and "M," ECoG signals of 1 second after the third sound. An FFT algorithm was performed for each 1-second signal to obtain the 3 frequency power bands (1–8, 25–40, and 80–150 Hz). The FFT was performed using EEGLAB v5.03. For each trial and electrode, the R and M frequency power bands were normalized by dividing them with the corresponding power of N. The normalized M and R power bands were used as the input features for the following decoding analysis (Fig. 1A).

In the free-run session, the 1-second ECoG signals were recorded online every 200 msec. The FFT algorithm was performed for each 1-second signal to obtain the 3 frequency power bands for each electrode. The frequency power bands of each electrode were divided by the corresponding power bands of the baseline features (baseline features were defined as the mean frequency power bands of N that were obtained by averaging the features of N for all trials in the calibration period).

Decoding Algorithms

With the features obtained in the calibration period, we constructed 2 decoders, or linear classifiers, to infer the patient's movements on a trial-by-trial basis. The decoders were trained or calculated using mathematical algorithms to infer the patient's movements using only a novel ECoG signal. The normalized powers of the 3 frequency bands (features) were used to train the 2 decoders based on the linear SVM.[31] Decoder 1 was trained to classify the movement state R or M, with the features of R and M (Fig. 1A). Decoder 2 was trained to predict the types of performed movement with the features of M (Fig. 1A). The mathematical details of these decoders are described in the supplementary section and the following references (http://www.cns.atr.jp/dni/en/downloads/brain-decoder-toolbox).[11,31]

The decoding accuracy was compared among the decoding of each of the 3 frequency bands to identify the most informative frequency band. The decoding accuracy was estimated by using a 5-fold cross-validation method *(Appendix)*.

Real-Time Decoding and Prosthetic Hand Control

The 2 decoders trained by the ECoG signals with the external cues were applied to the novel ECoG signals in real time. Decoder 1 classified the ECoG signals as either R or M to infer the onset of movement. When the inferred state changed from R to the two successive M decoder results, movement onset was inferred (or defined) as the time between R and M. Then, Decoder 2 classified the type of movement using the feature of the second M (Fig. 1B).

According to the decoding results, the prosthetic hand was controlled to mimic the patient's movements. When the decoding result from Decoder 1 was R, the prosthetic hand was moved to the predefined resting position. When movement onset was inferred by Decoder 1, then Decoder 2 inferred the type of movement using the current ECoG signals. Then, the prosthetic hand was moved to the predefined posture of the inferred movement. The posture was maintained for 1 second, regardless of the decoding results from Decoder 1. After 1 second, the prosthetic hand was moved back to the resting position.

Results

Offline Time-Frequency Analysis

During the movements in the calibration period, the power spectrum of the ECoG signals on the sensorimotor cortex varied consistently. Figure 2B illustrates an example of the power spectrum time locked to the external sound cue during the grasping movement. The signal was recorded from an electrode on the primary motor cortex

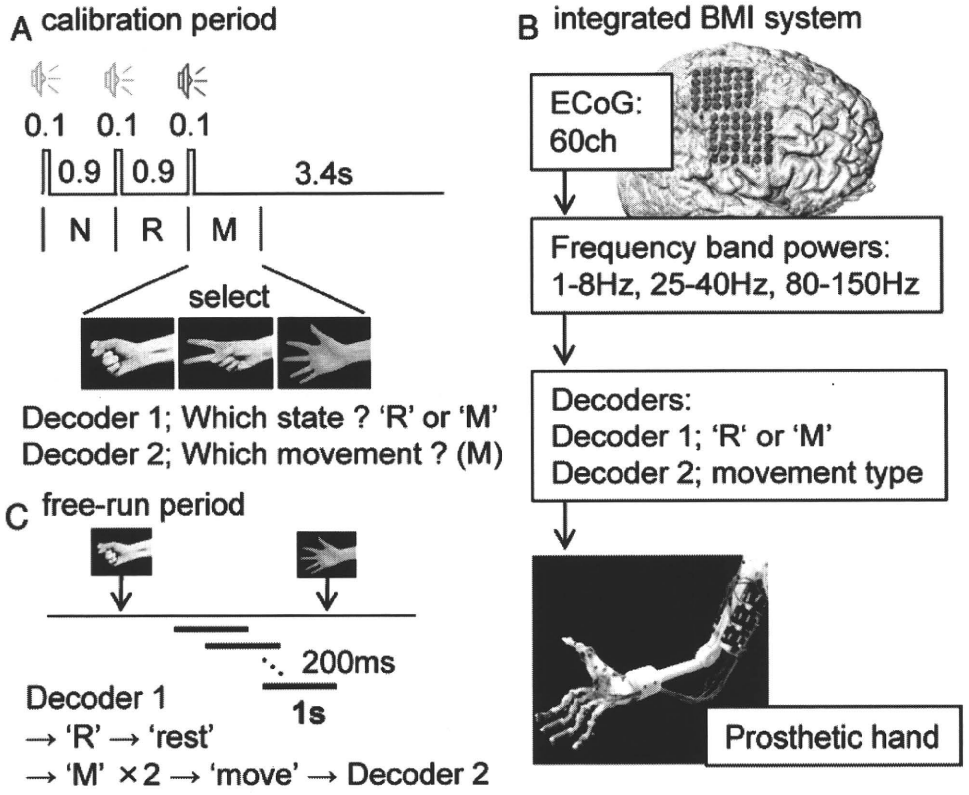

Fig. 1. Illustrations of the task and the integrated real-time decoding system. **A:** The task in the calibration period. The 1-second ECoG signals after each sound were defined as: 1st, "N" for normalization; 2nd, "R" for resting state; and 3rd, "M" for moving state. Decoders 1 and 2 were trained with the R + M and M ECoG signals, respectively. The representative photographs of hands show the task movements performed by a healthy individual. **B:** The task in the free-run period. The 1-second ECoG signals obtained every 200 msec were classified by Decoders 1 and 2 when the patient performed 1 of the 3 hand movements with arbitrary timing. **C:** Illustration of the integrated BMI system.

indicated by a blue arrow in Fig. 2A. As shown in Fig. 2B, the power reduction of the beta band (25–40 Hz) (event-related desynchronization) and the power increase of the theta (1–8 Hz) and gamma (80–150 Hz) bands (event-related synchronization) were observed around the movement onset. These frequency features, event-related desynchronization and event-related synchronization, were observed consistently on the sensorimotor cortex during the movement task.

The spatial distribution of these features on the electrodes differed depending on the movement (Fig. 2C). The increase in the power of the gamma and theta bands was observed at the localized area of the primary motor cortex. However, the decrease in the power of the beta band was observed diffusely around the primary motor cortex (Fig. 2C). The spatial distribution of each frequency power band differed among the 3 types of movement, especially for the gamma and theta bands. We selected these 3 frequency power bands as the input features for decoding.

Offline Analysis of Decoding

The patient's hand movement was inferred by the decoders using the frequency features of the ECoG signals on a trial-by-trial basis. Offline cross-validation analysis of the ECoG data measured during the calibration period revealed that the patient's state and the movement type were predicted with an accuracy of 79.6% (chance 50%) and 68.3% (chance 33.3%), respectively (Fig. 3). Among the 3 frequency bands, the gamma band power exhibited the best performance for the decoding of both the states and types of movement (Fig. 3).

Next, the trained Decoder 1 was tested to determine whether it could detect the onset of movement on a trial-by-trial basis. For the calibration period, the 1-second ECoG signals were classified using Decoder 1 for every 200 msec from –2 to 2 seconds relative to the onset cue. As shown in Fig. 4 left, the inferred rate of M was low before the onset cue and high after the cue. When we defined the onset as the time Decoder 1 inferred 2 successive M results after R, the movement onset was frequently inferred just after the actual onset cue (Fig. 4 right). Notably, 88% of the inferred onsets of movement were distributed between –0.5 to 0.5 seconds from the actual onset of the cue. For the calibration period, the movement onset was accurately inferred by the trained Decoder 1.

Real-Time Prosthetic Hand Control

Using the trained decoders, the ECoG signals were decoded in real time when the patient performed the 3 types of hand movement at an arbitrary timing (free-run period). Decoder 1 detected 61.0% of the movement onsets within 1 second from the actual onset of movement detected by the EMG signals. The mean difference be-