Extraoperative functional mapping of motor areas in epileptic patients by high-frequency cortical stimulation

Clinical article

NAOTAKA USUI, M.D., KIYOHITO TERADA, M.D., KOICHI BABA, M.D., KAZUMI MATSUDA, M.D., TAKAYASU TOTTORI, M.D., SHUICHI UMEOKA, M.D., TADAKIHI HARA, M.D., FUMIHITO NAKAMURA, M.D., KIICHI USUI, M.D., AND YUSHI INOUE, M.D.

National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

Object. The aim of this study was to investigate the usefulness of a short train of high-frequency (500 Hz) cortical stimulation to delineate the primary motor cortex (MI), supplementary motor area (SMA), primary somatosensory cortex (SI), supplementary sensory area (SSA), negative motor area (NMA), and supplementary negative motor area (SNMA) in patients with epilepsy who were undergoing functional mapping.

Methods. Seventeen patients were studied, all of whom underwent functional mapping using 50-Hz electrical stimulation. After these clinical evaluations, cortical stimulations with a short train of electrical pulses at 500 Hz were performed through subdural electrodes placed at the MI, SMA, SI, SSA, NMA, and SNMA, which had been identified by 50-Hz stimulation, and surrounding cortical areas, while surface electromyography readings were recorded.

Results. Stimulation of the MI elicited motor evoked potentials (MEPs) in contralateral muscles. Stimulation of the SMA also induced MEPs in contralateral muscles but with longer latencies compared with the MI stimulation. Stimulation of the SMA did not elicit MEPs in ipsilateral muscles. Stimulation of the SI, SSA, NMA, and SNMA did not induce MEPs in any muscle. In one patient, MEPs were elicited without seizure induction by 500-Hz stimulation of the electrodes, whereas a 50-Hz stimulation of the same electrodes induced his habitual seizures.

Conclusions. Extraoperative high-frequency stimulation with MEP monitoring is a useful complementary method for cortical mapping without inducing seizure. Stimulation of SMA induces MEPs in contralateral muscles, with longer latencies compared with the stimulation of MI. This finding may be useful for the differentiation between MI and SMA, especially in the foot motor areas. (DOI: 10.3171/JNS/2008/109/10/0605)

KEY WORDS • cortical stimulation • motor evoked potential • primary motor area • supplementary motor area

Abbreviations used in this paper: ADM = abductor digiti minimi; APB = abductor pollicis brevis; BIC = biceps brachii; DIO = dorsal interossei; DLT = deltoid; ECR = extensor carpi radialis longus; EEG = electroencephalography; EMG = electromyography; FCR = flexor carpi radialis; FCU = flexor carpi ulnaris; GC = gastrocnemius; HAM = hamstring; MEP = motor evoked potential; MI = primary motor cortex; NMA = negative motor area; ORB = orbicularis oris; QF = quadriceps femoris; SCM = sternocleidomastoid; SI = primary somatosensory cortex; SMA = supplementary motor area; SNMA = supplementary negative motor area; SSA = supplementary sensory area; TA = tibialis anterior; TRI = triceps brachialis.

from forearm and hand muscles. Compared with the traditional method of applying a train of pulses at lower frequency (50–60 Hz), muscle responses could be obtained at an intensity of much lower charge. Furthermore, the distributions and the latencies of the MEPs could be analyzed more precisely than the traditional technique. This new technique has been widely used for motor pathway monitoring during neurosurgery. However, there is no report of the use of this technique for extraoperative cortical mapping.

In this study, high-frequency electrical stimulation was applied in patients with epilepsy who were undergoing functional cortical mapping for presurgical evaluation. The effects of high-frequency electrical stimulation on MI, SMA, SI, SSA, NMA, and SNMA were investigated. Using a lower stimulation intensity combined with EMG, more precise mapping of somatotopic representation without obvious movements is possible, and the onset
Patient Population

We studied 17 patients (5 female and 12 male patients; age range 11–43 years) with intractable localization-related epilepsy who were undergoing evaluation before epilepsy surgery. All patients had long-term implantation of subdural grid or strip electrodes. Informed consent was obtained from all patients or their parents after the purpose and possible consequences of this study were explained. In 4 patients (Cases 3, 11, 14, and 16), depth electrodes were also used for EEG recording but were not used for the stimulation. Clinical features of the patients are shown in Table 1.

Methods

Cortical Mapping

Cortical mapping by 50-Hz electric cortical stimulation at individual electrodes was conducted for clinical purposes. Repetitive square-wave electrical currents of alternating polarity with a pulse width of 0.3 msec and a frequency of 50 Hz were delivered to each subdural electrode. Throughout the stimulation, electrocorticographs were monitored continuously to detect induced afterdischarges or EEG seizure patterns. Stimulus current was increased gradually until either a maximum of 15 mA was reached or afterdischarges were elicited. Positive motor and sensory areas were defined by positive responses occurring at contralateral or bilateral body parts consistent with somatotopy. The MI and SMA type responses were differentiated by the distribution and the characteristics of the movements.

It is known that SMA is not a pure motor area, but rather a mixed sensorimotor area with predominantly motor representation. However, if pure sensory responses were elicited by the stimulation of interhemispheric electrodes and these responses were not consistent with SI somatotopy, we defined these electrode locations as the SSA. A negative motor response was defined as the cessation of voluntary tonic muscle contraction or of rapid alternating movements without loss of awareness, or any other positive responses during the stimulation. This response has been described in an area anterior to the primary face motor area, mainly in the inferior frontal gyrus. If this response was obtained by the stimulation of an interhemispheric electrode, the electrical latency of MEP can be measured. Initially, we performed cortical mapping with standard 50-Hz stimulation. Then, we applied 500-Hz cortical stimulation with MEP monitoring on the motor areas identified by 50-Hz mapping, and attempted to examine the usefulness of 500-Hz stimulation to complement 50-Hz stimulation.

Other advantages of this method over the conventional 50-Hz stimulation include a lower possibility of seizure induction. Sometimes a 50-Hz stimulation of the cortical area in the vicinity of the epileptogenic area induces seizures and makes precise mapping of cortical function difficult. The total charge of the stimulation is much lower in this method compared with that of a 50-Hz stimulation.

One specific aim of this study was to differentiate between MI and SMA, especially in the foot motor areas. Animal studies have shown that there is no precise boundary between the hindlimb representation of SMA and that of MI. Usually these 2 areas are differentiated by observation of the location and the type of movements elicited by 50-Hz stimulation; however, visual differentiation is sometimes very difficult. Analysis of the onset latency of MEPs elicited by 500-Hz stimulation is expected to allow differentiation of MI and SMA.

TABLE 1

Clinical characteristics in 17 patients undergoing surgery for intractable epilepsy*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Epilepsy Type</th>
<th>Stimulated Area</th>
<th>EMG Height (cm)</th>
<th>Op Type</th>
<th>Deficit</th>
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<tr>
<td>1</td>
<td>13, M</td>
<td>perirolandic</td>
<td>MI, SMA, SNMA</td>
<td>unilat</td>
<td>150</td>
<td>corticectomy</td>
</tr>
<tr>
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<td>31, M</td>
<td>frontal</td>
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<td>181</td>
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<tr>
<td>3</td>
<td>35, M</td>
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<td>MI</td>
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</tr>
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<tr>
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<td>MI, SI, SSA</td>
<td>bilat</td>
<td>176</td>
<td>corticectomy</td>
</tr>
<tr>
<td>6</td>
<td>29, F</td>
<td>partial</td>
<td>MI, MI/SI</td>
<td>bilat</td>
<td>152</td>
<td>not done</td>
</tr>
<tr>
<td>7</td>
<td>31, M</td>
<td>frontal</td>
<td>MI, SI</td>
<td>unilat</td>
<td>168</td>
<td>FL</td>
</tr>
<tr>
<td>8</td>
<td>36, M</td>
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<td>MI, SMA, SI, SNMA</td>
<td>bilat</td>
<td>170</td>
<td>FL</td>
</tr>
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<td>9</td>
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<td>MI, SI, MI/SI, NMA</td>
<td>bilat</td>
<td>170</td>
<td>TL</td>
</tr>
<tr>
<td>10</td>
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<td>temporal</td>
<td>MI, SMA, SNMA</td>
<td>bilat</td>
<td>170</td>
<td>TL</td>
</tr>
<tr>
<td>11</td>
<td>36, F</td>
<td>temporal</td>
<td>SI</td>
<td>bilat</td>
<td>160</td>
<td>SA</td>
</tr>
<tr>
<td>12</td>
<td>11, F</td>
<td>occipital</td>
<td>MI, MI/SI</td>
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<td>160.7</td>
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<tr>
<td>14</td>
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<td>bilat</td>
<td>152</td>
<td>TL</td>
</tr>
<tr>
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<td>SI, SI/NMA, SII</td>
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<td>not done</td>
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<td>bilat</td>
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<td>not done</td>
</tr>
<tr>
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<td>SSA, SSA, MI/SI, SI</td>
<td>bilat</td>
<td>155</td>
<td>not done</td>
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</table>

* FL = frontal lobectomy; NA = not applicable; OL = occipital lobectomy; SA = selective amygdalohippocampectomy; TL = temporal lobectomy; trans = transient.
Electrical Cortical 500-Hz Stimulation

After completing the cortical mapping described above, a short train of electrical pulses at 500 Hz was delivered through subdural electrodes located at the MI (13 patients), SMA (7), SI (11), SSA (2), NMA (1), SNMA (3), and surrounding cortical areas, while surface EMG findings were recorded from the muscles of the contralateral extremities in 5 patients, and from the bilateral extremities in 12 patients. Pairs of cup electrodes were placed 3 cm apart on the skin overlying each muscle. The muscles for monitoring were selected in each patient by considering the locations of intracranial electrodes and the results of the standard cortical stimulation. Because of the limitation of our evoked potential machine (Neuropack Sigma, Nihon-Kohden), only 8 EMG studies could be monitored simultaneously. One train of stimuli consisted of 5 pulses. The duration of each pulse was 0.3 msec. The current was given at 80% of the intensity that produced clinical signs by 50-Hz cortical stimulation. Monopolar cathodal stimulation was delivered through the cortical electrodes. The anode was set at a subdural electrode far away from the cathode, which showed no response when stimulated. In a preliminary study, we used both anodal and cathodal stimulations, and found that MEPs were more readily elicited by cathodal than by anodal stimulation. Consequently, cathodal stimulation was used in the present study.

The MEPs were analyzed using the surface EMG findings displayed on the cathode-ray tube monitor of the evoked potential machine. For EMG recording, the analysis window was set at 45–95 msec. The bandpass filter was set at 50–10 kHz. To confirm the reproducibility, at least 2 trials were done for each electrode pair. Onset latencies of MEPs were measured on the cathode-ray tube monitor by visual inspection.

Statistical Analysis

Statistical analysis was performed using the Fisher exact probability test. An error probability of < 0.05 was considered to be indicative of significance.

Surgery and Postoperative Deficits

Eleven of 17 patients underwent epilepsy surgery including lesionectomy, cortectomy, or large lobectomy according to the epileptogenic zones. In 6 patients, resection in the vicinity of the sensorimotor areas was performed. Except for the patient in Case 1, whose epileptogenic zone overlapped with the primary motor area, sensorimotor cortex was spared as much as possible according to the results of cortical mapping by 50- and 500-Hz stimulation with MEP monitoring. In 4 of the 6 patients in whom frontal or perirolandic epilepsy was diagnosed, the precentral gyrus was spared, and 2 of them manifested transient hemiparesis immediately after surgery but recovered almost completely. One patient with parietal lobe epilepsy who underwent resection of the precuneus close to the sensorimotor area had mild sensory disturbance in the distal right foot (Case 4). Another patient (Case 1) who underwent resection of primary motor area for cortical dysplasia (Fig. 1A) had permanent hemiparesis postoperatively.

Results

The numbers of electrodes that responded to 50-Hz stimulation, the stimulus intensities, muscles, and latencies of MEP by 500-Hz stimulation are shown in Table 2. In a total of 17 patients, MI was identified at 53 electrodes by 50-Hz stimulation. A 500-Hz stimulation of these MI electrodes yielded MEPs from 29 (55%) of 53 electrodes. The SMA was identified at 20 electrodes by 50-Hz stimulation, and MEP was obtained from 7 (35%) of the 20 electrodes.

Stimulation of SI (11 patients), SSA (2 patients), NMA (1 patient), and SNMA (3 patients) did not induce MEPs. In 4 patients (Cases 2, 9, 10, and 17), an MEP was obtained by 500-Hz stimulation of the electrode in which 50-Hz stimulation had elicited no response. Each patient had 1 electrode activated only by 500-Hz stimulation, and this electrode was adjacent to one that was activated by 50-Hz stimulation. The electrodes activated only by 500-Hz stimulation are not shown in Table 2.

A 50-Hz stimulation induced seizures in 2 patients with perirolandic epilepsy (Cases 1 and 5); however, no adverse effects, including seizure induction, were observed after 500-Hz cortical stimulation in all patients, including 4 with perirolandic epilepsy. In 1 patient (Case 1), 50-Hz stimulation of HS2 and HS3 electrodes induced habitual seizures. The MEPs were elicited by 500-Hz stimulation of the same electrodes without seizure induction (Fig. 1).

We have never noted any problems macroscopically when we exposed the cortex while removing the electrodes. We did not observe any problems related to 500-Hz compared with 50-Hz stimulation.

Stimulation of the MI

When the MI was stimulated, MEPs were elicited in contralateral muscles in 12 of 13 patients. In 1 patient (Case 12), stimulation of MI did not induce MEPs, but stimulation of MI/SI elicited MEPs in contralateral muscles. By MI stimulation, MEPs were induced in ORB muscle in 4 patients, SCM in 1, BIC in 3, TR1 in 1, DLT in 1, ECR in 9, FCR in 1, FCU in 1, APB in 7, DIO in 4, ADM in 2, HAM in 1, QF in 2, TA in 1, and GC in 1 patient. The stimulation intensity ranged from 1 to 9 mA. In 5 electrodes in 4 patients, hand muscles were activated without activation of
other muscles. The distribution of MEPs is shown in Table 3. The muscles were defined as distal or proximal relative to the elbow or knee joint. In 3 electrodes in 3 patients, only proximal muscles were activated. In 2 electrodes in 2 patients, the same stimulation activated both proximal and distal muscles in the same limb. However, stimulation of MI never induced MEPs in both upper and lower extremities by the same stimulation. In 1 of 12 patients, stimulation of the face motor area identified by 50-Hz stimulation elicited MEPs in both contralateral and ipsilateral ORB and contralateral SCM (Case 6). The onset latency of MEP in the ipsilateral muscle was 4.4 msec longer than that in the contralateral muscle.

The onset latencies of MEPs are summarized in Table 4. The onset latencies of MEPs of each muscle varied widely among patients. When the stimulation elicited MEPs in multiple muscles within 1 limb, the onset latency was usually longer for distal muscles, except in 1 patient (Case 2). In this patient, by stimulation of the electrode at which a 50-Hz stimulation induced elbow flexion, the onset latency of BIC (22.3 msec) was 2.7 msec longer than that of FCR (19.6 msec). In 5 patients, the onset latency of the same muscle differed depending on the electrode stimulated. In the patient in Case 5, for example, stimulation of the F3 electrode, at which 50-Hz stimulation induced shoulder and elbow flexion, elicited MEPs in the left ECR, with a latency of 18.6 msec. Stimulation of the F2 electrode, at which 50-Hz stimulation elicited shoulder abduction, elicited MEP in the same muscle, with a latency of 21.6 msec (3 msec longer) (Fig. 2).

Stimulation of the SMA

When the SMA was stimulated, MEPs were elicited in contralateral muscles (distal and/or proximal) in 5 of 7 patients. The MEPs were induced in DLT in 3 patients, TRI in 2, ECR in 1, DIO in 1, QF in 2, TA in 3, and GC in 1 patient. The stimulation intensity ranged from 3 to 10.4 mA. As shown in Table 3, although there was no statistically significant difference in the distribution of MEPs between MI and SMA stimulations, the MEPs of DLT and TRI were more readily elicited by SMA than by MI stimulation. The same stimulus induced MEPs in both upper and lower extremities at 2 electrodes in 2 patients. In 2 patients (Cases 8 and 17) in whom facial muscles were monitored during SMA stimulation, MEPs in facial
Muscles were never elicited. In 5 patients with bilateral EMG monitoring, MEPs were elicited in contralateral muscles in 3 patients, whereas an ipsilateral MEP was not elicited, although the stimulated electrodes demonstrated bilateral motor representation by 50-Hz stimulation in 2 of 3 patients.

The latencies of MEPs in each muscle are summarized in Table 4. The onset latency was longer or almost the same for more distal muscles within the same patient. The onset latencies of MEPs were longer by SMA stimulation compared with MI stimulation. For upper-limb muscles, the MEP latencies induced by SMA stimulation were apparently longer than those by MI stimulation. For lower-limb muscles, differences in the onset latencies were not remarkable as a whole. In 3 patients (Cases 1, 4, and 10), MEPs were obtained at the same muscles by both MI and SMA stimulation. In these 3 patients, the onset latencies of MEPs were compared directly between MI and SMA stimulations (Table 5). In the patient in Case 4, stimulation of electrode HS5 (foot MI) elicited MEPs in the right leg muscles (QF, TA, and GC) at 25.1 msec. Stimulation of electrode HI3 (SMA) elicited MEPs in the right TA and GC at 30.4 msec (5.3 msec longer) (Fig. 3). Stimulation of electrode HS4 (SMA) also induced MEPs in the right QF, TA, and GC at 26.1 msec. We suspected that the HS4 electrode was probably located at the border of MI and SMA, and consequently excluded this electrode from the data in Tables 3–5.

Discussion

For intraoperative functional motor mapping by means of MEP recording in response to cortical stimulation, double or 5–10 trains of pulses with high frequency (400–500 Hz) have been used. The excitatory postsynaptic potential elicited at motoneurons by a single activation on the corticomotoneuronal tract is known to last between 7 and 10 msec. When the total charge intensity is constant, high-

### Table 2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. of Electrodes†</th>
<th>Electrode Location</th>
<th>Stimulus Intensity (mA)</th>
<th>MEPs (onset latency, in msec)</th>
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<td>1</td>
<td>4</td>
<td>MI/finger</td>
<td>5</td>
<td>ECR, APB (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MI/forearm</td>
<td>5</td>
<td>ECR (16), APB (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MI/shoulder</td>
<td>1.5</td>
<td>DLT (10), BIC (12), TRI (12)</td>
</tr>
<tr>
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<td></td>
<td>SMA/arm</td>
<td>5</td>
<td>DLT (27), TRI (27)</td>
</tr>
<tr>
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<td>6</td>
<td>MI/finger</td>
<td>2</td>
<td>APB (17.9)</td>
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<td>ECR (19.9), FCR (19.9), APB (25.8), ADM (25.8)</td>
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<td>1.5</td>
<td>BIC (22.3), FCR (19.6), ADM (27.3)</td>
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<td>MI/leg</td>
<td>2</td>
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<td>3–5</td>
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<td>MI/leg (proximal)</td>
<td>3</td>
<td>TA (26.5), GC (26.5)</td>
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<td>3</td>
<td>TA (26.2), GC (26.2)</td>
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<td>3</td>
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<td>8</td>
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<td>MI/shoulder</td>
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<td>ORB (17.8)</td>
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<td>lt ORB (16.4)</td>
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<td>0</td>
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<td>TA (30)</td>
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* LE = lower extremity; UE = upper extremity.
† Number of electrodes identified by 50-Hz stimulation.
‡ This electrode was excluded from Tables 3–5 because we suspected it was located at the border of the MI and SMA.
er stimulation frequency is more effective as long as the frequency is \(< 500\) Hz, which is compatible with the monosynaptic character of the corticomotoneuronal tract.

Safety of the Procedure

It was uncertain whether this stimulus paradigm is applicable for extraoperative cortical stimulation of chronically implanted subdural electrodes in terms of stimulus strength. In this study, we investigated the safety and the usefulness of this method for functional mapping of motor areas. The total charge of stimulation is much lower compared with the standard 50-Hz stimulation. Accordingly, the risk of seizure induction should be much lower in 500-Hz stimulation. Actually, no seizure was induced in this study, although epileptogenicity was demonstrated in the vicinity of the motor area in at least 4 patients. On the contrary, seizures were induced in 2 patients with periorbital electrographic epilepsy by 50-Hz stimulation. In 1 patient (Case 1, Fig. 1), 50-Hz stimulation of electrodes HS3 and HS4 induced the habitual seizure, whereas 500-Hz stimulation of the same electrodes elicited MEPs in leg muscles without inducing seizures. When an epileptogenic area exists in the vicinity of the motor area and seizure induction by 50-Hz stimulation is anticipated, a train of 500-Hz stimulation may be a useful method for eliciting MEPs with less risk of seizure induction.

Stimulus Parameters

Some authors have suggested that anodal stimulation is more effective. Cathodal monopolar stimulation was used in the present study, because cathodal stimulation was more effective in our preliminary study, although anodal stimulation was also effective. Hern et al. suggested that surface anodal stimulation excites pyramidal neurons directly, whereas surface cathodal stimulation activates interneurons and indirectly activates pyramidal neurons. The relationship between the electrodes and cortical surface can be very variable in the setting of long-term subdural EEG monitoring. Therefore, it is not surprising that surface cathodal stimulation induces MEPs as effectively as surface anodal stimulation.

For the 500-Hz stimulation, we used 80% of the intensity used in 50-Hz stimulation. It is possible that responses could have been missed at 500 Hz as a result of the relatively low stimulation intensity. Further studies are necessary to clarify the optimal stimulus intensity that will elicit MEPs without afterdischarge or seizure induction.

### Stimulation of the MI

**Representation.** Stimulation of the MI elicited MEPs in both distal and proximal contralateral muscles. The MEPs in ECR and APB were more frequently induced than in other muscles. This may suggest that the representation for these muscles is wider than other muscles in MI, or that the threshold is lower for these muscles. Hand muscles such as APB and DIO were activated without activation of other muscles. In 1 patient (Case 6), MEPs from the ipsilateral ORB had longer latencies (4.4 msec longer) compared with the contralateral muscle. This may be due to the ipsilateral efferent of the face MI. Another possibility is transcallosal connection of bilateral face motor areas.

**Latency.** The MEP latency of the same muscle differed considerably in different patients. This may be due to the difference in the length of the extremities. Therefore, the onset latencies of MEPs should be compared within patients.

Stimulation of MI elicited MEPs from multiple muscles in the contralateral limb, and the onset latency was usually longer for more distal muscles. The patient in Case 2 was an exception; the onset latency of BIC was 2.7 msec longer than that of FCR. The stimulated electrode was probably located closer to the area for FCR than that for BIC, and thus, BIC might be activated indirectly.

In the same patient, the onset latency of MEPs in the same muscle differed depending on the electrode stimulated. The difference in onset latency may be due to the existence of an interneuron at the cortical or spinal level. The electrode with the shorter latency may be closer to the representative motor area. Electrical cortical stimulation at a frequency of 50 Hz potentially causes current spread to produce a positive response in remote areas. Therefore, responses obtained by 50-Hz stimulation may represent the function of a cortical domain wider than the stimulated area. Use of MEPs and high-frequency stimulation is expected to allow more precise mapping of the representative motor areas. High-frequency cortical stimulation combined with EMG recording is less sensitive than the
standard 50-Hz stimulation, but may be more specific for cortical function. Also, it can be used as a confirmation of the finding obtained from 50-Hz stimulation.

**Sensitivity.** In a total of 17 patients, the MI was identified at 53 electrodes by 50-Hz stimulation. A 500-Hz stimulation of these MI electrodes induced MEPs in 29 (55%) of the 53. Therefore, the sensitivity of 500-Hz stimulation was lower than that of the standard 50-Hz stimulation. The responses induced by 500-Hz stimulation are specific for the muscles monitored, but only a limited number of muscles can be monitored. The low sensitivity of 500-Hz stimulation may be due to this limitation. In addition, the low stimulus intensity may also account for the relatively low sensitivity, and more responses may be obtained by increasing the stimulus intensity. In 4 patients, an MEP was elicited by 500-Hz stimulation of electrodes that showed no response to 50-Hz stimulation. These electrodes were located adjacent to electrodes that were activated by 50-Hz stimulation. Therefore, high-frequency stimulation may be used to complement the standard 50-Hz stimulation. Because the usefulness of this method in reducing surgical morbidity was not confirmed in this study, further research is needed to examine this issue.

**Stimulation of the SMA**

Stimulation of SMA induced MEPs in contralateral muscles (both distal and proximal) with longer latencies compared with MI stimulation. In a preliminary study, we applied single-pulse stimulation on the SMA extraoperatively, but were not able to elicit MEPs. Rubboli et al. delvered single-pulse stimulation on motor areas, and reported that SMA stimulation induced only pure silent period. Although it is known that single-pulse electric cortical stimulation on the precentral gyrus elicits MEPs without inducing seizures under a condition of muscle contraction, we demonstrated that a train of pulses at 500 Hz also elicited MEPs without inducing seizures even in resting condition. Trains of pulses may have advantages over a single pulse because this method can induce MEPs not only by MI but also by SMA stimulation. One important purpose of this study was to map the SMA; therefore, we used a train of pulses rather than a single pulse. Although it has been established that intracortical microstimulation of the SMA in monkeys elicits both forelimb and hindlimb movements, this is the first report that SMA stimulation induces MEPs in humans.

Stimulation of the SMA is capable of eliciting MEPs directly through projections to the spinal interneurons and alpha motoneurons or by engaging the primary motor area through corticocortical connections. As shown by a study in which the antidromic stimulus technique was used in monkeys, the conduction velocity in the corticospinal tract arising from the caudal part of the SMA (corresponding to SMA proper) was much slower (~ 10 m/second) than that arising from the MI (~ 40–50 m/second). Studies in monkeys and in humans also showed that the SMA has a rich connection with the MI.

**Representation.** It is generally believed that the SMA primarily controls proximal or axial muscles. In our study, however, there was no significant difference in proximal and distal distribution of MEPs elicited by MI and SMA stimulation. Actually, there is some evidence of distal limb representation in the SMA. In the present study, stimulation of MI never induced MEPs in both upper and lower extremities by the same stimulation. In contrast, the same stimulus of SMA sometimes elicited MEPs in both upper and lower extremities. This finding is concordant with previous studies in which standard 50-Hz stimulation was used in humans.

**Figure 2.** Case 5. Cortical stimulation studies. *Left:* Functional mapping by 50-Hz stimulation. The stimulation of electrode F2 elicited left shoulder abduction. Stimulation of F3 elicited left shoulder/elbow flexion. *Right:* High-frequency (500-Hz) stimulation of F2 and F3 electrodes elicited MEPs in the left ECR, with different onset latencies; the difference was 3.0 msec.
includes ipsilateral descending pathways such as the ventral corticospinal tract. The threshold for activation may be higher for these ipsilateral descending fibers than for contralateral fibers. Bilateral limb movements elicited by the standard 50-Hz stimulation may be due to activation of the ipsilateral descending pathway, or to activation of contralateral SMA via the transcallosal connection.

In 2 patients with facial muscle monitoring, no MEPs in these muscles were recorded by 500-Hz stimulation of the SMA, and no facial movements were induced by 50-Hz stimulation. This is in agreement with the results of Macpherson et al., who observed no facial muscle movements by intracortical microstimulation of the SMA in awake monkeys. On the contrary, Fried et al. elicited...
Motor mapping with 500-Hz stimulation

TABLE 5
Onset latencies of MEPs obtained at the same muscles by both MI and SMA stimulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Muscle</th>
<th>MI Latency (msec)</th>
<th>MI Intensity (mA)</th>
<th>SMA Latency (msec)</th>
<th>SMA Intensity (mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DLT</td>
<td>10</td>
<td>1.5</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>TA</td>
<td>25.1–26.5</td>
<td>2</td>
<td>30.4</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>ECR</td>
<td>20.3</td>
<td>9</td>
<td>26</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Latency. If one assumes that the conduction velocity of the corticospinal tract from the SMA is ~ 10 m/second, the MEP latencies of lower- and upper-extremity muscles in the patient in Case 10 are too short. Therefore, SMA stimulation may elicit MEPs via the corticocortical connection of the SMA to MI. This will be discussed later, in the Comparison With MI Stimulation section.

Sensitivity. The SMA was identified at 20 electrodes of 7 patients by 50-Hz stimulation, and MEPs were recorded in 7 (35%) of the 20 electrodes. The sensitivity of this method for MI was 29 (55%) of 53. This difference may be due to the difference in the MEP threshold for SMA and MI.

Comparison With MI Stimulation

The stimulus intensity tended to be higher for SMA than for MI stimulation. Because the current was delivered at 80% of the intensity that produced clinical signs by 50-Hz cortical stimulation, this tendency only reflects the fact that the 50-Hz stimulus intensity that induces a clinical response for the SMA is higher than that for the MI.

The differences in onset latency of MEPs induced by MI and SMA stimulation may be clinically useful. Distinct differences in onset latency were observed in upper-limb muscles. Differentiation of SMA from lower-extremity MI can be very difficult if using visual inspection of motor responses elicited by standard 50-Hz stimulation alone. Although the absolute value of onset latency cannot be used for differentiation purposes, differentiation may be possible by comparing the onset latencies in each patient. In the patient in Case 1, the differences in onset latency for upper-limb muscles were 15–17 msec. In the patient in Case 4, the differences in latency for lower-limb muscles were much shorter (3.9–5.3 msec). Even considering the interpatient variability, the fact that latency differences were shorter for the lower limb cannot be explained by the difference in conduction velocity via the corticospinal tract. If one assumes that the conduction velocity of the corticospinal tract from the SMA is ~ 10 m/second, the latency of the MEP by SMA stimulation is too short in Cases 4 and 10. Therefore the difference between the latency by SMA stimulation and that by MI stimulation may be attributed to the corticocortical connection of the SMA and MI. In Case 1, it is possible that the MEP obtained by SMA stimulation was induced directly via the corticospinal tract from the SMA. By comparing the latencies of MEPs in each patient, the lower-extremity MI and SMA may be differentiated more precisely.

Another important difference between SMA and MI stimulation is the distribution of the muscles that are activated. The same stimulus of the SMA may activate the muscles of both upper and lower extremities, whereas MI stimulation does not. This fact may be also useful for differentiation.

From the surgical standpoint, the differentiation between the SMA and lower-extremity MI is very important because the resection of MI produces permanent postoperative motor impairment, whereas resection of the SMA does not. Further studies are needed to clarify the usefulness of this method for differentiation between the SMA and MI.

Stimulation of the SI

Stimulation of the SI never elicited MEPs. This result is consistent with experimental data in monkeys, which demonstrate inhibitory or extremely weak effects of electrical microstimulation of SI neurons on muscle activity compared with MI neurons, even at high stimulus intensities. Wannier and colleagues concluded that SI neurons have a significantly lower motor output capacity with respect to MI neurons.

Stimulation of the SSA, NMA, and SNMA

Stimulation of the SSA, NMA, and SNMA elicited no MEPs. The presence of a well-defined SSA has not been confirmed. The so-called SMA is considered to be actually a mixed sensorimotor area with predominantly motor representation. Because SMA stimulation elicited MEPs, whereas SSA stimulation did not, the 2 areas can thus be differentiated. However, the number of electrodes used in our method is still small, and the presence of the SSA cannot be confirmed.

Ikeda et al. performed single-pulse electrical stimulation on the sensorimotor areas including the NMA. Under resting condition, no MEPs were elicited when the NMA was stimulated. Although the NMA may have a neuronal connection with the MI, the threshold for obtaining MEPs by NMA stimulation may be very high. Another possibility is that the connection of the NMA may be mainly inhibitory.

It has been suggested that the NMA corresponds to area F5, and that the SNMA corresponds to area F6. Area F6 has no direct connections with the spinal cord or MI. Therefore, it is conceivable that a train of high-frequency stimulation of the SNMA does not induce MEPs.

Conclusions

Extraoperative high-frequency stimulation with MEP monitoring is a method to complement cortical mapping. No adverse effects, including seizure induction, were observed by 500-Hz cortical stimulation in all patients, in-
cluding 4 patients with perirolandic epilepsy. When an epileptogenic area is known to exist in the vicinity of the motor area and seizure induction is anticipated by stimulation with 50 Hz, then cortical stimulation with a train of 500-Hz pulses may be a useful method for eliciting MEPs with less risk of seizure induction. Although the sensitivity of 500-Hz stimulation was not high, the sensitivity of this method may be improved by identifying the optimal stimulus intensity. Stimulation of the SMA induces MEPs with less risk of seizure induction. Although the sensitivity of 500-Hz pulses may be a useful method for eliciting MEPs in epilepsy patients: information from subdural electrodes in the baboon’s motor cortex. J Physiol 161:3656–3666, 1991

Disclosure

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Disclaimer

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References