There is no current consensus on the ideal surgical approach. Most neurosurgeons implant an electrode in the epidural space, but some implant it subdurally or in the interhemispheric or within the central sulci. The direction of the implanted paddle also remains controversial. This chapter summarizes and compares these various procedures.

ANATOMICAL LOCALIZATION

As detailed in chapter 1, there are several landmarks for detecting the location of central sulcus on the scalp and cortical surface. The central sulcus can be expected to lie approximately 4 - 5.4 cm posterior to the coronal suture on the scalp midline, and can be localized with the aid of Taylor-Haughton lines (Figure 1). The central sulcus is easily located with preoperative magnetic resonance imaging (MRI): it is characterized by the lack of sulcal branches, and lies just anterior to the pars marginalis of the cingulate sulcus on the interhemispheric surface (Naidich et al 1995, 2001). Oblique MRI views easily show the central sulcus (Figure 2). Penfield's Homunclus is commonly used for identification of the corresponding body parts on the precentral or postcentral gyrus. As discussed in chapter 1, the precentral knob sign corresponding to the hand is easily identified on surface MRI anatomic scans. From these findings, the position for the craniotomy can be decided.

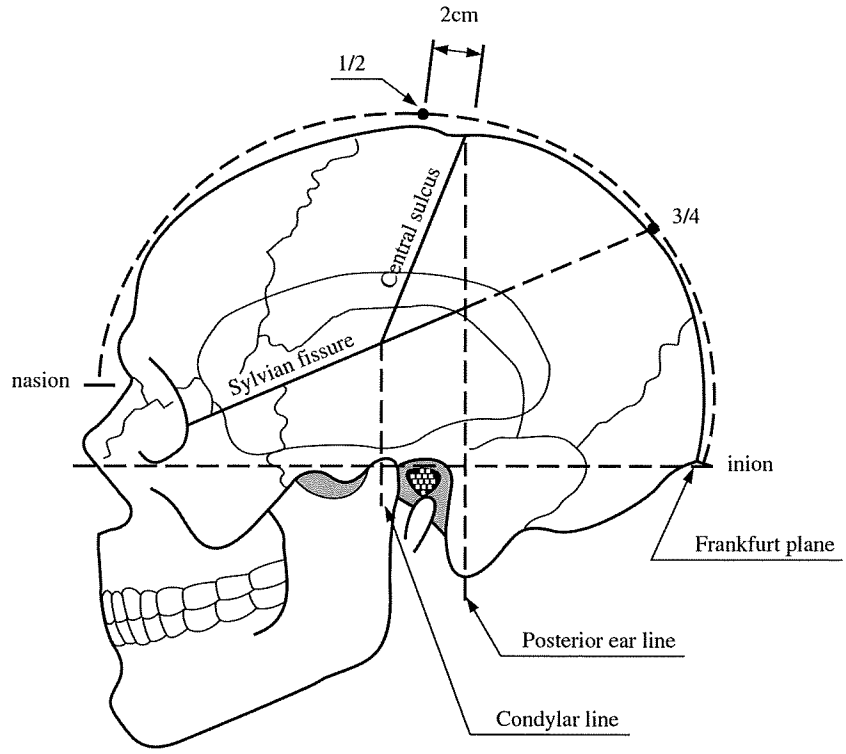

Figure 1. Taylor-Haughton line indicates the position of the central sulcus from the scalp. Taylor-Haughton (T-H) lines can be constructed on an angiogram, CT scout film, or skull x-ray, and can then be reconstructed on the patient based on visible external landmarks. The Frankfurt plane (a.k.a. baseline) is the line from the inferior margin of the orbit through the upper margin of the external auditory meatus (EAM) (as distinguished from Reid's base line, running from the inferior orbital margin through the center of the EAM). The distance from the nasion to the inion is measured across the top of the calvaria and is divided into quarters (this can be done simply with a measuring tape). The

posterior ear line runs perpendicular to the baseline through the mastoid process (intersecting the skull sagittal midline about 1 cm behind the vertex and 3-4 cm behind the coronal suture). The condylar line runs perpendicular to the baseline through the mandibular condyle (intersecting the line representing the sylvian fissure). The Sylvian fissure (a.k.a. lateral fissure) is approximated by a line connecting the lateral canthus to the point 3/4 of the way posterior along the arc running over convexity from nasion to inion (or by a line drawn 45° to Reid's line starting at the pterion). A point 5 cm straight up from the external auditory meatus intercepts MI. The angular gyrus (which includes Wernicke's area) is located just above the pinna, with significant individual variability in its location.

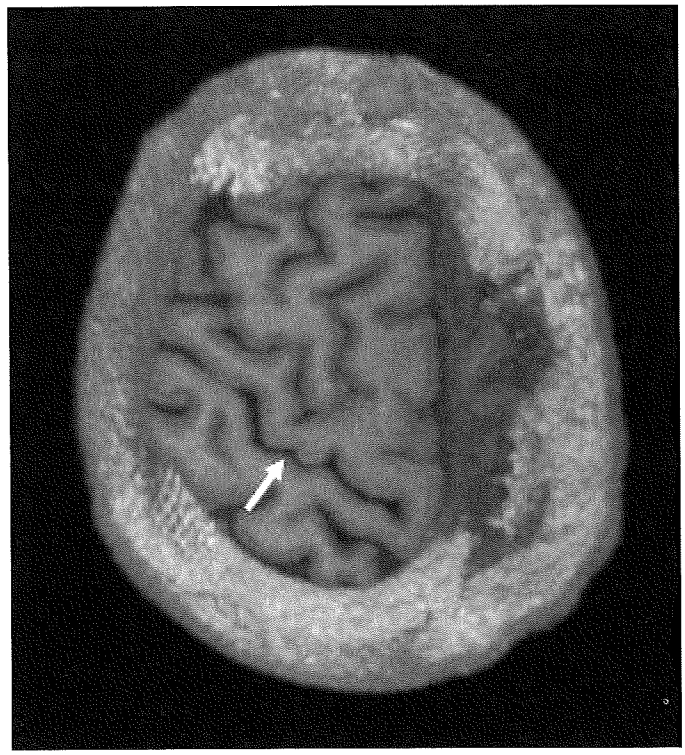

Figure 2. Reconstructed oblique MRI view of the central sulcus (arrow: central sulcus).

A simple way to locate the motor strip is to use a Callosal Grid system (Lehman and Kim 1995). Establishing a horizontal plane (HP) through the inferior border of the genu and the splenium of the corpus callosum creates such a proportional grid system. Three vertical planes perpendicular to HP are constructed: the anterior callosal plane (AC), the posterior callosal plane (PC), and the midcallosal plane (MC) in the midpoint between the AC and MC. If the grid is overlapped over the cortical surface, the junctional point between the HP and the MC corresponds with the inferior point of the central sulcus, where a central artery enters the central sulcus. The superior central sulcus lies 4mm anterior to PC. Imaginary lines connect the inferior and superior points that constitute the central sulcus.

ELECTROPHYSIOLOGICAL LOCALIZATION

SSEPs can be measured by stimulating the contralateral median nerve at the wrist; stimuli consist of single shocks (0.5 ms, 4.7 Hz, 20 mA) to produce a small, but consistent contraction of the thumb. SSEPs are recorded from each cortical electrode referenced to the

ipsilateral ear lobe. Individual SSEP signals are differentially amplified and filtered: 200 are averaged through a digital signal analyzer with sample interval of 40 mcsec. The phase reversal of the N20 (sensory cortex) /P20 (motor cortex) waves is used to confirm the location of the central sulcus (Wood et al 1988, Velasco et al 2002), using a 20/32-contact grid and the central scalp EEG leads or directly using the definitive 4-contact strip overlying the dura (Figure 3). Polarity inversion of potentials across the sulcus is less reliable and technically more difficult for trigeminal SEPs (McCarthy et al 1993) and only occasionally a phase reversal has been described for tibial nerve SEPs (Maegaki et al 2000). Other later components (P25-N25; P30-N30) also present phase reversals, but may not be observed. Phase reversal seems to be a rather constant feature of SSEPs, provided that the orientation of the electrode is perpendicular to the Rolandic fissure, otherwise it may not be present. The Rolandic fissure being tortuous and oblique along the convexity of the brain, it is difficult to believe that phase reversal may be obtained in all cases without the assistance of visual inspection of the sulci, as in the case of epidural recordings (Velasco et al 2002). Although N20 is generally recordable, the P20 component may be missing, even in awake or mildly sedated patients, in part due to the dipole generator of the early component at each side of the fissure which, having an oblique depth posterior trajectory with respect to the cortical surface, orients the N20 component toward the surface and the P20 component toward the depth. Moreover, the N20/P20 reversal is only useful for hand representation targeting. The rolandic tortuosity that in some parts becomes parallel to the midsagittal line complicates the placement of the 4-contact strip on MI by determining reversal only in a single point. Even worse, maximal N20 amplitude can be reached on either motor or sensory cortex in several patients (Wood et al 1988, Velasco et al 2002). Both components can be severely attenuated by nervous system lesions: patients with phantom-limb pain, brachial plexus avulsion, severe stroke or other similar conditions may thus show no SSEPs.

Most importantly, inferring the position of the motor hand area from the position of the maximum amplitude median nerve SEP is impossible. Indeed, Woolsey et al (1979) demonstrated that the face-arm boundary is situated more laterally on the postcentral gyrus than on the precentral gyrus, by 1–2 cm. It is therefore necessary to map the motor cortex. Penfield and Boldrey (1937) first systematically stimulated the sensory-motor cortex and described the sensory and motor "homunculus". They utilized a bipolar direct stimulation of the cortex, applying 50–60 Hz stimuli up to 20 mA for 1–4 s, and looked for movements or sensations in the awake patient. This technique required awake surgery, often induced complex movements involving more than one muscle and provoked epileptic seizures in a high percentage of cases (20–25%). As regards the leg representation, Woolsey et al (1979) found that in only one third of the cases the lower extremity is on the medial surface of the hemisphere, in two thirds of the cases it extends on the lateral surface and, in 27% of the cases, the whole lower extremity is on the lateral surface. Recently, an enlarged and displaced motor map for the hand area was described in Parkinson's disease patients. Map shifts were found in the majority of the patients (12/15), both in untreated early cases and treated cases of long duration, with a correlation between the inter-side difference in the severity of PD symptoms (UPDRS) and interhemispheric map displacement (Thickbroom et al 2006). In sum, guidance of epidural electrode placement is often inadequate or impossible by SSEPs.

According to Velasco et al (2002), recording corticocortical evoked responses (CCER) is simple and reliable and superior to SSEPs. MI stimulation elicits negative CCER over the frontal scalp, whereas SI stimulation elicits positive responses over parietal and occipital scalp regions.

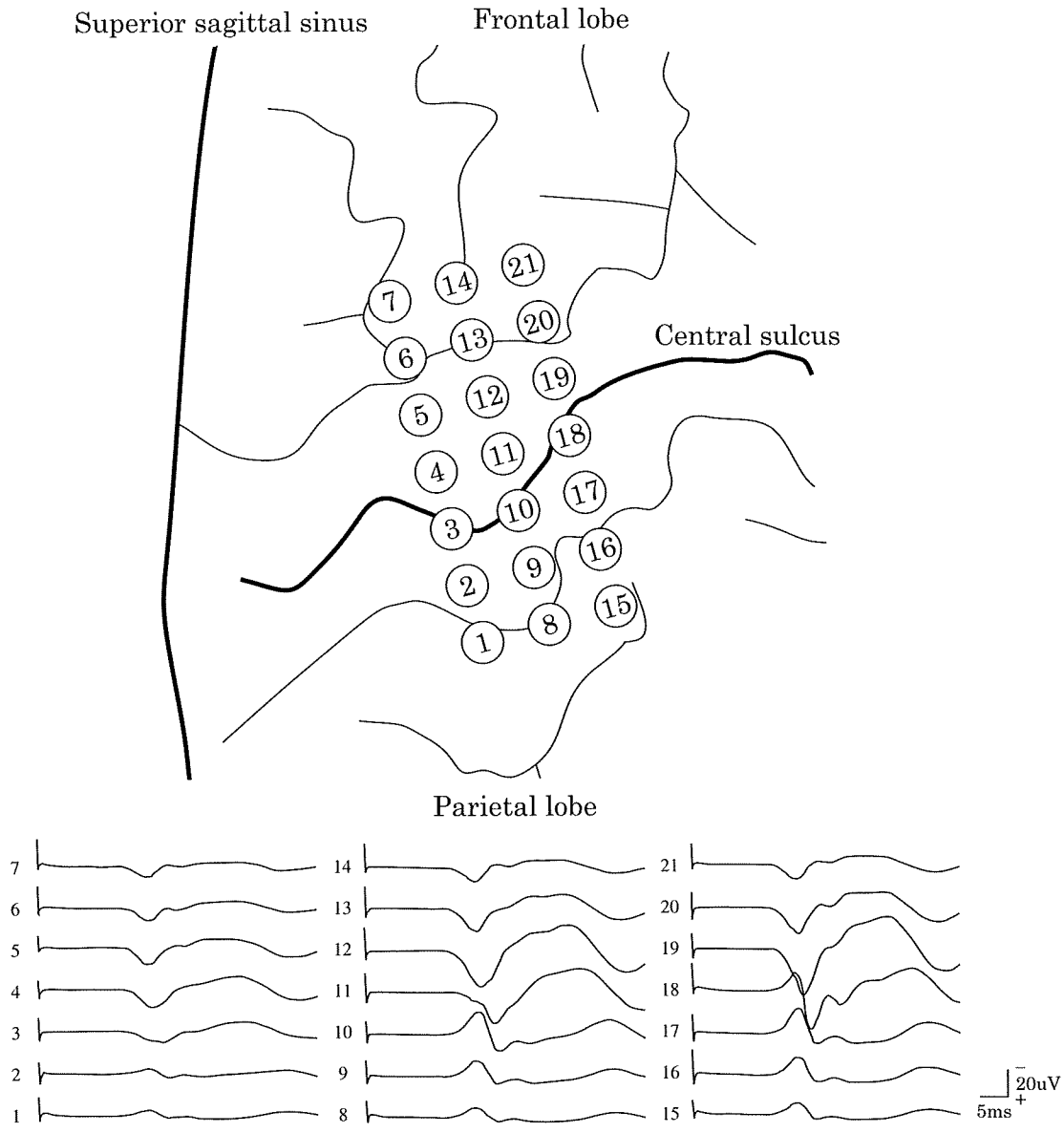

Figure 3. SSEPs show phase reversal of the N20 wave, when the median nerve is stimulated. The black wide line indicates the estimated location of the central sulcus.

Most neurosurgeons attempt intraoperative test stimulation by using the quadripolar or the grid electrodes. Test bipolar stimulation (210-1000 μs –generally 400-500-μs, 1-5 Hz up to 100Hz, at increasing voltage or intensity –up to 50 mA, anodally, but also cathodally) is applied by means of the contacts situated over the motor or sensory cortex. In general, the amplitude needed to produce motor responses is higher using epidural rather than subdural stimulation. Motor contraction can be elicited at relatively lower amplitudes when general anesthesia is not employed. 1Hz stimulation is preferred to higher frequencies, since the former does not habituate and has less potential to trigger seizures. Muscle responses are

recorded from muscle bellies of the contralateral hemibody, with EMG needle electrodes or visually. The supposed advantage of a grid electrode is nixed by the observation that over 75% of the cortical surface is not covered by its contacts, not to mention the imperfect superposition with the definitive strip electrode.

Under local anesthesia, the patients may describe pain reduction, paresthesias in the painful body part, muscle twitching or contraction or nothing at all (Canavero and Bonicalzi 2002, Velasco et al 2002). Interestingly, stimulation of both MI and SI can elicit similar motor or sensory responses and both motor and sensory responses can be obtained from the same contacts (Schmid et al 1980, Wood et al 1988, Canavero and Bonicalzi 2002, 2007), making it difficult to rely on motor and sensory responses to differentiate MI from SI.

In some institutions, motor evoked potentials (MEPs) are measured under general anesthesia. Holsheimer et al (2007) stressed the importance of intra-operative MEP measurement obtained by monopolar and bipolar stimulation for determining the location of the electrodes bringing most pain relief during chronic ECS. Monopolar stimulation appeared superior at determining the optimal point for chronic motor cortex stimulation. They concluded that the anode yielding the largest intra-operative MEP should be selected as the cathode for chronic stimulation. Intraoperative D-wave recording of corticospinal MEPs have been utilized to optimize electrode placement; the D-wave has been recorded with a flexible wire electrode placed epidurally in the cervical (C3-4) spinal cord during high intensity anodal monopolar stimulation of each plate electrode under general anesthesia. The aim was to evoke the D-wave of highest amplitude. Pain reductions significantly correlated with the recorded amplitude of the D wave employing the same stimulation electrode. The result was analgesia with lower voltages than generally required (Yamamoto et al 2007).

LOCALIZATION BY FUNCTIONAL MRI (FMRI)

fMRI has been explored extensively in terms of functional localization. In particular, sequential tapping of fingers in a predetermined fixed order or repetitive opposition of the thumb and each of the remaining fingers activates MI contralaterally (but also the ipsilateral MI, supplementary motor and premotor areas and the primary somatosensory areas bilaterally). This method appears to be superior to the competing methods described above. Pirotte et al (2005) utilized fMRI to identify the hand and tongue motor area. fMRI data were coregistered on 3D T1-weighted MRI anatomical scans and matched with data from intraoperative neurophysiology. The operation was performed under TIVA (see ahead); they utilized median-nerve SEP phase reversal to identify the central sulcus and mapped the motor cortex using the 60 Hz Penfield's technique. In 61% of cases, they found a good correlation between fMRI and intraoperative neurophysiological data, with a mean distance of 3.8 ± 1.3 mm between the two hot spots, which is sufficiently accurate, considering that the activation area of an electrode measures 5 mm; in 33% of the cases, intraoperative neurophysiology provided ambiguous results because of electrical artifacts, influence of anesthesia, SEP attenuation, diffuse motor responses, or sensorimotor disconnection. Some of these problems were due to an inadequate mapping technique; in 6% of the cases they reported poorly localization with both fMRI and intraoperative neurophysiology.

Blood oxygenation level depending (BOLD) fMRI data of motor functions of the tongue, arm or leg are obtained by using standardized paradigms, such as repetitive contraction of the lips, cyclic finger tapping of the contralateral hand, or flexion-and-extension of the toes of the contralateral foot at a rate of 1 Hz after a training session before imaging is performed. Post-stroke motor deficits may hamper examination, but fMRI is particularly useful for amputees or plexus avulsion patients, since virtual movements of the phantom or paralytic limb easily induce contralateral precentral and postcentral gyri activations. Blocks of 30 seconds of alternating activation and rest are repeated a few times (Canavero and Bonicalzi 2007). Generally, a focal cortical activation area (diameter 5-10 mm) after hand motor tasks is localized to the contralateral precentral gyrus, but differences between the two sides in the surface and minor displacements of the precentral activation area are frequently observed (also due to cortical remapping). It remains a matter of debate which area is more suitable as a stimulation target, the mirror image of the activation site on the healthy side or the displaced activation site on the affected side. Stippich et al (2004) developed a fully automated super-fast fMRI method for SI localization.

Diffusion tensor imaging (DTI) tractography has been suggested as a means to identify the motor cortex (Kamada et al 2005), but it should be taken in mind that TDI is a mathematical probability function, not an anatomical image.

Central sulcus veins have been used as landmarks during subdural approaches, but, being sometimes located deep in the sulcus, cannot be identified by examining only the cortical surface (Saitoh and Yoshimine 2007).

NEURONAVIGATION

Several kinds of navigation systems for neurosurgical assistance can be used to estimate the position of the central sulcus or other structures, both on the dura mater and scalp (Tirakotai et al 2007). Neuronavigation combined with fMRI data help to decide the best position for craniotomy and for placement of the stimulating paddle (Rasche et al 2006). While in most cases fMRI data can be satisfactory matched with navigation data, in some cases, motion artifacts and low signal levels interfere with fMRI data analysis. A drawback of neuronavigation is the requirement that the patient's head be fixed in a 3-point pin holder or vacuum headrest (Tirakotai et al 2007), which several patients may not tolerate under local anesthesia. For this reason, other surgeons prefer not to fix the patient's head and operate without navigation.

TECHNIQUES OF IMPLANTATION

Implanted electrodes used in reported studies have generally been Resume (Medtronic) or Lamitrode (ANS) stimulating quadripolar strips; eight-contact paddles have been used in one failed trial (NCT00122915). Most neurosurgeons (including Tsubokawa) implant the strip in the epidural space, but a few insert the strip subdurally (Saitoh et al 2000, 2007, Kleiner-

Fisman et al 2003, Strafella et al 2007). In patients with extensive painful areas, two strips are positioned.

Anethesia is induced with a loading dose of Remifentanil 3–4 ng/ml in continuous infusion followed after 5–8 min by Propofol 5.5 μg/ml as induction dose (Total intravenous anesthesia, TIVA). Endotracheal intubation is facilitated by vecuronium bromide 0.1 mg/kg; no further doses of muscle relaxants are administered throughout surgery. The lungs are mechanically ventilated with a 50% O2 in air mixture, in order to maintain end tidal concentrations of CO2 (ETCO2) at 30–35 mmHg. Anesthesia is maintained with Remifentanil (5–6 ng/ml, up to 7-8 ng/ml if necessary) and Propofol (2.5-3.0 μg/ml). At the end of the surgical procedure, all patients are awakened within 15–30 min from cessation of TIVA.

A small craniotomy or burr-hole is made around the central sulcus. The four-contact electrode array (each contact 5 mm in diameter; inter-contact distance center-to-center 1 cm) is usually placed in the epidural space. The best location and orientation of the electrode array are generally determined in such a way that bipolar stimulation with an appropriate pair of electrodes can be attained. Some surgeons place the electrode perpendicular to the central sulcus above the precentral (cathode) and postcentral (anode) gyri for the supposed improved selectivity (e.g. Nguyen et al 1999), others in a parallel fashion, i.e. with all contacts on MI or SI (e.g. Canavero and Bonicalzi 2002, Rasche et al 2006), but there appears to be no difference between the results of these two approaches (Tsubokawa et al 1991, 1993). Moreover, no polarity-related difference in pain relief is seen for most patients with epidural electrodes (Katayama et al 1998).

Saitoh et al (2000; Hosomi et al 2008) implanted the paddle subdurally on the cerebral or interhemispheric surface) or within the central sulcus. The latter makes it possible to stimulate the primary motor cortex more directly (Takahashi et al 2002, White et al 1997). Nuti et al (2005) implanted the strip electrode on the interhemispheric surface to treat leg pain. In some patients with brain atrophy, the cortical surface and the dura mater are wide apart, in which case patients may fail to respond to extradural stimulation: a subdural approach may be considered in a few, highly select cases.

After the implantation of the electrodes, a test period of a few days to 2-4 weeks follows. If the stimulation proves effective, under general anesthesia, a pulse generator is then implanted subcutaneously below the clavicle and connected to the paddle via a subcutaneous extension. For movement disorders patients, a single surgical procedure may be used (Canavero and Bonicalzi 2007b).

Stimulating paddles have been implanted through several approaches:

1-Epidural Single Burr-Hole (Figure 4)

Both Tsubokawa et al (1991) and Meyerson et al (1993) performed MI ECS using a single burr-hole made on the central sulcus under local anesthesia. For leg pain, a paddle is placed on the medial edge of the hemisphere, but involves some risk of developing an epidural hematoma. This technique may require relocations before an optimal position is

found, and thus increase the risk of epidural bleeding due to dural detachment. However, this was not a problem in recent navigated series (Rasche et al 2006).

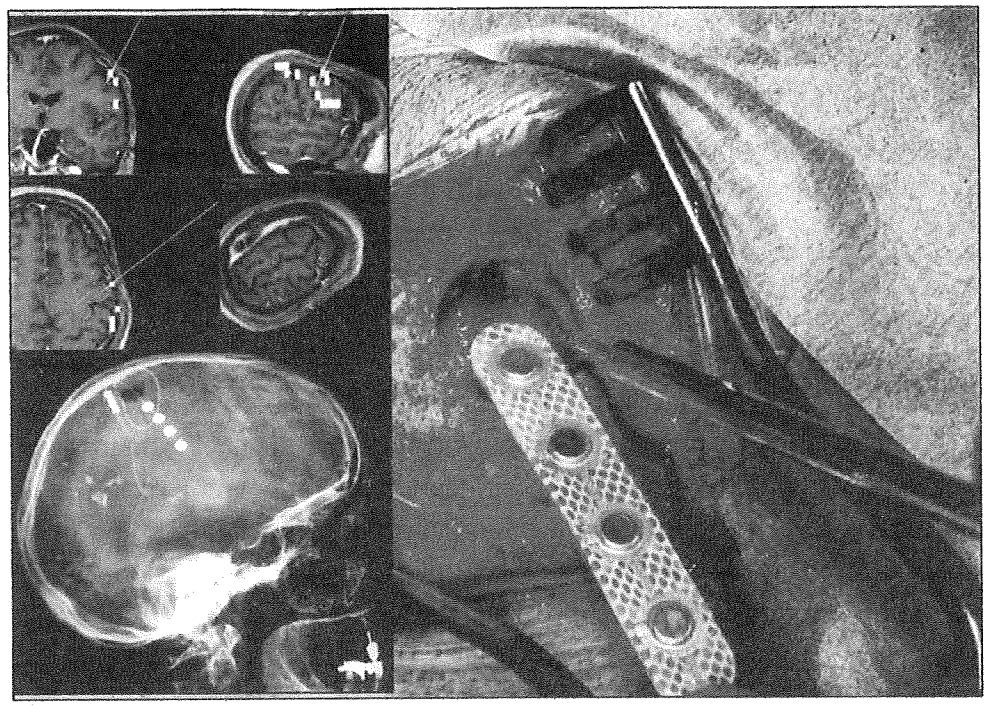

Figure 4. Single burr-hole surgery with the assistance of neuronavigation system and fMRI (courtesy of Dr. Rasche). Insertion of the stimulating paddle (which is shown reversed for clarity) is performed via a single burr hole.

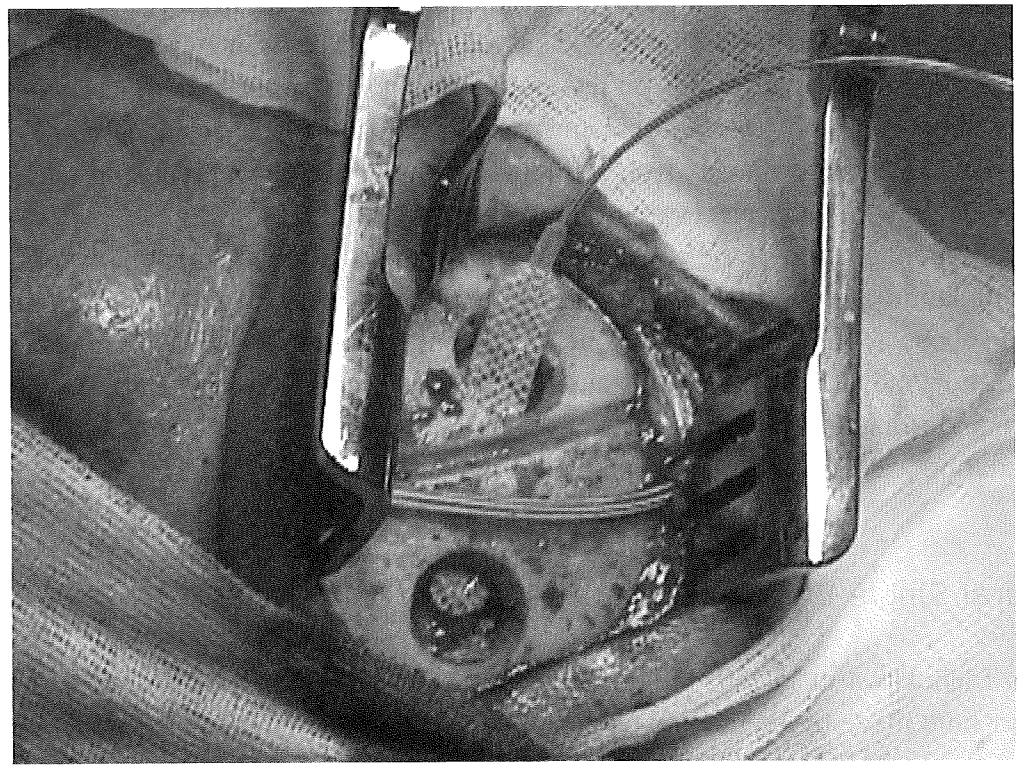

Figure 5. Two burr-hole surgery is shown. The locations of burr holes are marked on the scalp depending on the anatomical landmarks (courtesy of Prof. Canavero).

2-Two Epidural Burr-Holes (Figure 5)

Canavero (Canavero and Bonicalzi 2002) makes an oblique linear skin incision (6-10cm) parallel to and 1 cm ahead of or behind the projection of the central sulcus and then drills two burr holes at a distance of 2-4 cm (plus a bony groove parallel to the paddle to accommodate the connector between the looping lead and the extension). A stimulating paddle is inserted from the edge of one burr hole into the epidural space overlying the precentral gyrus or post central gyrus contralateral to the painful area or most disabled side for movement disorders. The bony bridge between the two holes will then hold the plate in place and simultaneously reduce the durocortical gap. For facial or leg targets, the paddle can be gently advanced caudally or rostrally by up to 2 cm. This technique entails no risk of epidural hematoma, and accidental displacement of the electrode has never been observed (S Canavero, personal communication).

3-Epidural Bone flap

Because of greater availability of the epidural area for electrophysiological exploration and mapping, the procedure has been proposed to result in improved outcome (Nguyen et al 1999), but this has not been confirmed. A small craniotomy (4-5 cm) is made on the central sulcus. The center of the craniotomy should correspond to the target as determined by imaging. This technique allows SSEP recordings from electrodes placed on the dura mater. The paddle is fixed to the dura mater with two stitches (making accidental displacement impossible), which may theoretically catch on a vessel and cause intracerebral bleeding. The risk of inadvertent opening of the dura during bone detachment must be borne in mind.

4-Subdural Method

In patients with advanced cortical atrophy, epidural stimulation may fail due to the duro-cortical separation. The cortical surface and interhemispheric surfaces subdurally may be elected as targets for stimulation. However, large bridging veins sometimes interfere with implantation on the interhemispheric surface and adhesion may occur due to subarachnoid hemorrhage. Moreover, dissection of the central sulcus involves the risk of developing new neurological deficits due to brain damage or vein obstruction. For upper limb and/or face pain, the arachnoid membrane of the central sulcus must be carefully dissected and the vessels within the central sulcus must be freed with a microsurgical procedure to expose the hidden lateral walls of the precentral and postcentral gyri (Saitoh et al 2006). Since the paddle is too stiff to be placed within the central sulcus, it must be trimmed off (Figure 6). Saitoh et al (2000) limited most of the implantations within the central sulcus to patients with severe motor weakness or lack of function. In their series, test stimulation of MI within the central sulcus was more effective in most cases than was subdural stimulation on the cerebral surface, but long-term clinical results were not on a par with ECS (Saitoh and Yoshimine 2007) and

patients who received the implantation within the central sulcus gained only temporary pain reduction (maximum: 6 months) (Hosomi et al 2008). At the end of surgery, the lead extension is fixed to the dura or the border of the burr hole with a silk suture to prevent dislocation. However, migration of the electrodes seems to be more of a problem with a subdural than an extradural approach. A meticulous, watertight dural closure is mandatory to minimize the risk of cerebrospinal fluid leakage.

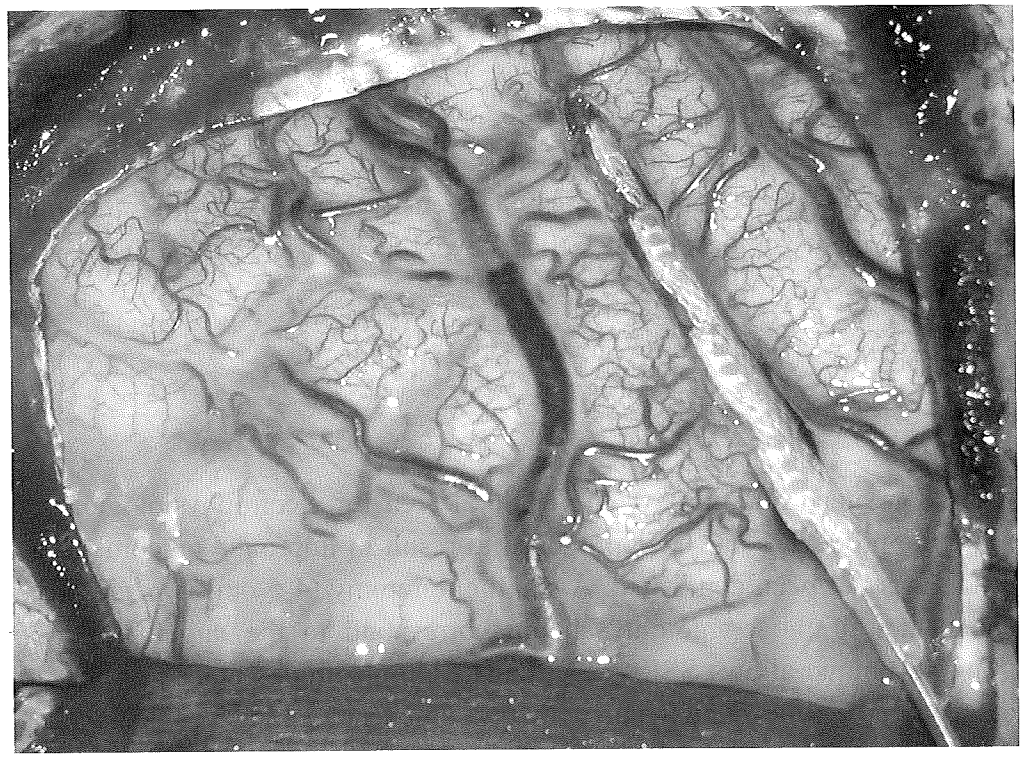

Figure 6. After trimming to reduce stiffness, a Resume paddle is implanted within the central sulcus.

COMPLICATIONS

Of all published cases of invasive cortical stimulation, 11.4% were associated with one or more adverse effects. Speech disorders (aphasia/dysarthria), although rare and generally temporary, have been observed (Ebel et al 1996, Canavero and Bonicalzi 2002). Some cases of headache reportedly associated with stimulation of the face area may actually be due to contraction of the temporalis muscle (Canavero and Bonicalzi 2002). However, local pain may be relieved by incision and resuturing of the dura around the electrode or, more simply, by bipolar coagulation. Other reported side effects include fatigue, paresthesia and dysesthesia (2.2% of cases), but also, exceptionally, impairment in motor imagery tasks (Tomasino et al 2005) and supernumerary phantom arms (Canavero and Bonicalzi 2002, 2007).

Montes et al (2002) analyzed event-related potentials (ERPs) and behavioral performance during an auditory target-detection task in 11 consecutive patients obtained during MI ECS and 10 minutes after switching off stimulation. While sensory responses remained unaffected by MCS, there was a significant delay of brain potentials reflecting target detection in the

older patients (N2 and P3), rapidly reversible after MI ECS discontinuation. No effect was observed in patients younger than 50 years. Individually, the effect was highly variable from no effect to a delay of tens of milliseconds. Cognitive effects of MCS appeared as mild and non-specific, directly related to the stimulation period (i.e. with no post-effect), in a manner reminding of cognitive effects reported during MI rTMS. Thus, MCS may interfere with relatively simple cognitive processes such as those underlying target detection, notably in the elderly and in the presence of preexistent cerebral lesions.

Occurrence of epileptic seizures, probably due to differences in testing conditions, has been reported during test stimulation in a minority of patients. The low rate of epileptic seizures during chronic stimulation (0.2%) means that stimulation of MI within an appropriate range of parameters is reasonably safe. The most serious reported complications are epidural or subdural hematomas. These are definitely exceptional with an extradural approach, and some surgeons never observed one, making the risk of peri-operative hemorrhage much lower compared to deep brain stimulation. However, in our series using a subdural approach, two patients developed cerebral hemorrhage: one died and the other remained in a vegetative state (Hosomi et al 2008). This is especially true for patients with post-stroke pain, who are likely to develop a new stroke in the years following the first one.

Some wound infections have been reported by most surgeons. If the infection occurs, all devices including the paddle, extension leads, and pulse generators must be removed temporally. Patients with post-stroke pain frequently have diabetes mellitus and thus are at greater risk.

The implanted pulse generator (IPG) can accidentally turn off due to electromagnetic interference from household devices in close (<10 cm) proximity, such as electric appliances of any kind, but also anti-theft devices and metal detectors or magnets in loudspeakers.

At impedances >2000 Ω, a connection problem, such as a broken cable or a lead fracture, must be suspected. The operator should thus measure impedance in a unipolar configuration in order to assign a value to the single contact. The so-called radio test may be useful: IPGs emit a signal at 500-550 kHz which can be received as a continuous hum on a small battery operated AM radio receiver.

SAFETY OF STIMULATORS

The output of commercial stimulators are either of the "controlled current" (CC) or "controlled voltage" (CV) type. CC output circuits are somewhat more complex and less power-efficient than the CV type, but may provide a more stable level of stimulation, especially where the electrode impedance may fluctuate as a result of e.g. changing contact with tissue, formation of scar tissue, polarization potentials on the metal/electrolyte interface. Most of the stimulus voltage of macro-electrodes is dissipated in the impedance of the tissue. If the impedance changes in a CC circuit, the output voltage automatically rises to keep the current flow constant. If the impedance changes in a CV circuit, the voltage stays the same and the current changes.

Stimulators use pulsatile rather than sinusoidal current waveforms. The stimulus waveform may be monophasic or biphasic. In biphasic stimulation, the negative voltage

applied is balanced by an equal amount of positive voltage. This is generally considered to be far safer than monophasic stimulation as it allows for a balance of ionic exchange at the electrode-cortex interface. If the charge is not balanced, it is possible that metal ion deposition will occur at the interface, which may cause deleterious effects for both the tissue and the electrode (Polikov et al 2005). A fast-rising rectangular pulse of negative current is the most efficient stimulating waveform.

Each pulse delivers a charge (Q) of current per phase (CPP):

(1) $Q = A \times PW$

Charge density (CD) of the different cathodal pulses is given by:

(2) $QD = A \times PW$ / *cathodal area.*

These formulae indicate that:

1) maximal safety (i.e. minimal tissue damage) is obtained by applying short pulse durations (Crago et al 1974), i.e. slightly greater than chronaxie, which are also ideal to evoke neuronal responses (Tehovnik 1996).
2) QD for a given current is limited by the size of the electrode: more current is required to stimulate the cortex using large electrode than using small electrodes, but decreasing the surface area of the electrode may increase the extent of histological damage. Consequently, paddle or strip electrodes containing multiple contacts are ideal to recruit more neurons in the stimulation field. The QD threshold is lower when using surface electrodes (ECS) versus depth electrodes (DBS). Luckily, functional alteration can be achieved by charge densities much lower than those required for histological damage.

The least damaging pulse waveform is that with no net direct current (DC), which can lead to tissue damage even at very low intensity. The current density and charge per phase (CPP)- but not frequency, waveform or periods between pulses- are likely the most important factors in determining safety of a particular stimulation protocol (McCreery et al 1990). Ideally, the CPP and current density ought to be minimized. According to Pudenz et al (1975, 1977), CPP must not exceed 0.3 μC(oulombs) in each half of the stimulating pulse. In a human study, subdural stimulation with 0.3 ms square wave pulses at 50 Hz and 12.5-15 mA delivered for 24 hours achieved a maximum CPP of 4-4.4 μC, with a maximum charge density of 52-57 μC/cm2, which suggests a greater ability of the human brain to accommodate higher currents and current densities (Gordon et al 1990). Choice of stimulation features must aim to prevent electrode dissolution and generation of electrochemical toxic products at the electrode interface (by electrode polarization and hydrolysis: Bartlett et al 1977). Electrodes should be made of corrosion-resistant noble metals or alloys, such as platinum-iridium (actually, there is a small corrosion rate, which may in principle lead to toxic cumulative effects over many years). *A charge-balanced symmetrical biphasic waveform with two closely spaced pulses of equal charge, cathodal followed by anodal, is the stimulus waveform recommended for avoiding tissue damage and electrode corrosion.* In fact, the electrochemical reactions occurring during the first pulse (phase) are reversed by the following pulse of opposite polarity. However, biphasic symmetrical stimulus waveforms result in less selectivity than monophasic waveforms.

Prolonged stimulation at an intensity well below threshold for histologically detectable neural damage may nonetheless induce pronounced and prolonged elevation of the electrical threshold of stimulated neurons.

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High-frequency rTMS over the supplementary motor area improves bradykinesia in Parkinson's disease: Subanalysis of double-blind sham-controlled study

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ABSTRACT

A double-blind sham-controlled study demonstrated that high-frequency repetitive transcranial magnetic stimulation (rTMS) over the supplementary motor area (SMA) provided relief of motor symptoms in patients with Parkinson's disease (PD). However, it remains to be determined which parkinsonian symptoms were improved by this treatment. Subanalysis of Unified Parkinson Disease Rating Scale revealed that rTMS over SMA significantly improved bradykinesia in PD. Results support the hypothesis that neuronal activity of SMA was profoundly associated with hypokinetic symptoms in PD.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method used for human brain stimulation, offering potential for Parkinson's disease (PD) treatment [1]. High-frequency rTMS induces facilitation of some cortical neuronal excitability [1]. The supplementary motor area (SMA) executes complex function in motor regulation [2]; PD patients have shown SMA impairment [3–7]. In a double-blind sham-controlled study, the effect of high-frequency rTMS over SMA was compared with that of a realistic sham stimulation [8]. The SMA-stimulation group exhibited modest but significant improvements in motor symptoms: mean improvements in motor scores were 4.5 points in the SMA-stimulation group (i.e. 20% reduction from baseline) and −0.1 points in the sham-stimulation group (i.e. 0% reduction from baseline). The results implied to us that SMA is an appropriate stimulation site for PD treatment, but which symptoms were improved by SMA stimulation remains unknown. We therefore analyzed the subscores of UPDRS to clarify the nature of improvements provided by SMA stimulation.

2. Patients and methods

2.1. Study design and patients

This study, performed at 15 centers throughout Japan, was a double-blind trial with a parallel design comparing SMA stimulation with sham stimulation. The study design — inclusion and exclusion criteria, clinical evaluations, evaluation time points, and procedures for interventions — has been described in detail [8].

In brief, all patients provided written informed consent before intervention. The protocol was approved by the ethics committee at each participating center. The inclusion criteria were idiopathic PD patients according to the British Parkinson's Disease Society Brain Bank criteria [9]. The exclusion criteria were dementia, major psychiatric illness, contraindications to TMS [10] and patients who had undergone TMS treatment prior to the study. Patients were assigned randomly to the SMA-stimulation group and sham-stimulation group at each center.

Clinical evaluations were conducted by another doctor who was completely blind to the type of intervention. All assessments were performed at the same time during the daily treatment cycle in each subject in all interventions to exclude some effects of time in daily life. The evaluation time points were selected when anti-parkinsonian drugs had some effect (neither the off state nor the best on state) to evaluate an add-on effect of rTMS to the usual treatment. Although a definite off and best on condition seem more appropriate for the treatment study, we were unable to set this level because our studied

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patients were all outpatients. This possible heterogeneity might limit the validity of this study's results.

The Unified Parkinson's Disease Rating Scale (UPDRS) [11] was assessed before intervention (week 1) and immediately before the stimulation sessions at weeks 2, 4, 6, and 8. They were also assessed at weeks 10 and 12. The primary outcome measure was score changes in UPDRS part 3 (UPDRS-III). It was analyzed according to the intention-to-treat (ITT) principle using the last observation carried forward (LOCF) analysis.

One session of intervention was performed once a week for the first 8 weeks. For SMA stimulation, focal rTMS was applied using a hand-held figure-of-eight coil (9 cm external diameter at each wing) connected to a magnetic stimulator, which gives a biphasic pulse; 1000 magnetic stimuli were given in one session. One train consisted of 50 pulses at 5 Hz with inter-train interval of 50 s. The stimulus intensity was fixed at the 110% active motor threshold (AMT) for the right TA muscle. The coil was centered at points 3 cm anterior to the leg motor area in the sagittal midline. For sham stimulation, we employed a realistic sham-stimulation method [8,12].

2.2. Data analysis

We performed a subanalysis of subscores of UPDRS-III on the SMA and sham-stimulation groups. The tremor score was the sum of items 20 and 21. The rigidity score was the sum of item 22 for the neck and upper/lower limbs. Other scores were speech (item 18), facial expression (item 19), rising from chair (item 27), posture (item 28), gait (item 29), postural stability (item 30), and body bradykinesia (item 31). The "bradykinesia" score was the sum of items 23–26. Item 31 was not included because it might not reflect bradykinesia directly: it was rated by the examiner's global impression after observing spontaneous gestures while sitting, and the nature of rising and walking. The above scores at baseline (week 1) and those at week 12 were compared using two-way repeated measures analysis of variance (ANOVA) (between-subject factor, INTERVENTION (SMA/sham); within-subject factor, TIME (week)). The Greenhouse–Geisser correction was used if necessary to correct for nonsphericity. Post hoc paired t tests (2 tailed) were used for additional analyses: p values less than 0.05 were considered significant. These statistical analyses were conducted on actual values of the scores.

To evaluate possible effects of our SMA stimulus on the primary leg motor area adjacent to the SMA, we analyzed the bradykinesia score in SMA group in the following ways. First, the patients in SMA group were divided into two groups based on gait improvements (item 29). The improvement group comprised patients who showed −1 point or greater improvement in the gait score. The non-improvement group comprised patients who showed 0 points or worsening of item 29. Subsequently, we compared changes in bradykinesia scores (items 23–26) in these groups using Wilcoxon's rank sum test. We also performed Fisher's exact test to determine whether item 29 and the bradykinesia score are independent. Second, the patients in the SMA group were divided into two groups based on improvements of the lower extremity function (item 26). Here again, the improvement group comprised patients who showed −1 point or greater improvement, whereas the non-improvement group comprised patients who showed 0 points or worsening for item 26. We then compared the changes in upper extremity functions (items 23–25) in these groups using Wilcoxon's rank sum test. We also performed Fisher's exact test to determine whether score changes of items 23–25 and item 26 were independent. Finally, for general interest, we performed additional correlation analyses to explore a possible relation between the baseline UPDRS-III score and the degree of bradykinesia score response to SMA stimulus. Statistical analyses were performed using software (SPSS Statistical Package, ver. 13.0; SPSS Inc.).

3. Results

We have already shown that background clinical features such as gender, Hoehn and Yahr stage, age, age of onset, duration of illness, and initial values of UPDRS-III were not different between the two intervention groups (Table 1) [8]. The means (SD) of the modified Hoehn and Yahr stage were 2.8 (0.6) for the SMA-stimulation group, and 2.9 (0.7) for the sham-stimulation group. Of the 99 patients, one was excluded from analysis because the medical treatment was changed during intervention.

Among the subscores of UPDRS-III, a significant interaction between INTERVENTION and TIME was found only in the bradykinesia score (Table 2) (two-way repeated measures ANOVA: effect of INTERVENTION, $F_{1,96}=4.207$, $p=0.043$; effect of TIME, $F_{1,96}=9.012$, $p=0.003$; TIME × INTERVENTION interaction, $F_{1,96}=5.976$, $p=0.016$). Post hoc analysis revealed a significant improvement in the bradykinesia score at week 12. No significant interaction was found in the other subscores (Table 2).

Comparison of the bradykinesia scores (items 23–26) between gait improvement and non-improvement groups based on item 29 shows that the median of score changes in the improvement group was −3 (range, −11 to 1); that in the non-improvement group was −2 (range, −6 to 6). We found no significant difference between the two groups ($p=0.075$). Table 3 presents a 2 × 2 cross table of changes in item 29 and bradykinesia scores. Fisher's exact test also revealed these factors as independent ($p=0.304$). We next compared changes in upper extremity functions (items 23–25) between the lower limb function improvement and non-improvement groups. We argue that if the current over the SMA spreads to the primary motor cortex for leg muscles and if it might contribute to bradykinesia score improvement, then it would present some dissociation between the changes in these scores. The median of score changes in the improvement group was −2 (range, −9 to 2); that in the non-improvement group was −1 (range, −4 to 5). We found a significant difference between the two groups ($p=0.024$), indicating that the changes in items 23–25 were associated with those in item 26. Table 4 shows a 2 × 2 cross table of changes in items 23–25 (upper extremity functions) and item 26 (lower extremity function). Fisher's exact test revealed that these factors are dependent ($p=0.039$). Finally, no significant correlation was found between baseline UPDRS-III scores and changes in the sum of items 23–26 (bradykinesia score) (correlation coefficient, −0.222, $p=0.103$).

Table 1
Baseline Characteristics of Patients.

	SMA group ($N=55$)	Sham group ($N=43$)
Age (year)		
Mean (SD)	65.3 (8.9)	67.4 (8.5)
Median (range)	66 (39–82)	69 (43–82)
Interquartile range	59.0–71.5	63.5–72.5
Male sex — no. (%)	29 (53)	25 (58)
Age of onset (year)		
Mean (SD)	57.2 (9.9)	59.5 (10.2)
Median (range)	58 (28–78)	61 (34–79)
Interquartile range	50.0–65.0	56.0–66.5
Duration of illness (year)		
Mean (SD)	8.1 (4.2)	7.8 (6.7)
Median (range)	8.0 (1–16)	5.0 (1–32)
Interquartile range	5.0–11.0	3.0–10.5
Hoehn–Yahr stage — no. (%)		
1	0 (0)	0 (0)
2	19 (34.5)	13 (30.2)
3	33 (60.0)	23 (53.5)
4	3 (5.5)	7 (16.3)
5	0 (0)	0 (0)

No significant difference was found between two groups for any parameter.
SMA, Supplementary motor area.

Table 2
ANOVA results.

Subscores of UPDRS-III	Item	SMA		Sham			*df*	*F*	*p*
		Baseline mean (SD)	Week 12 mean (SD)	Baseline mean (SD)	Week 12 mean (SD)				
Speech	18	0.87 (0.64)	0.92 (0.53)	1.05 (0.82)	1.16 (0.84)	TIME	1	2.907	0.091
						INTERVENTION	1	2.311	0.132
						TIME × INTERVENTION	1	0.380	0.539
Facial expression	19	1.12 (0.69)	1.10 (0.55)	1.40 (0.82)	1.35 (0.87)	TIME	1	0.470	0.495
						INTERVENTION	1	3.339	0.056
						TIME × INTERVENTION	1	0.007	0.933
Tremor	20,21	4.84 (3.65)	4.20 (3.01)	5.20 (4.10)	5.23 (4.38)	TIME	1	1.566	0.214
						INTERVENTION	1	2.099	0.151
						TIME × INTERVENTION	1	2.099	0.151
Rigidity	22	4.85 (3.18)	3.72 (2.77)	5.53 (3.63)	4.90 (3.72)	TIME	1	11.435	0.001
						INTERVENTION	1	2.239	0.138
						TIME × INTERVENTION	1	0.926	0.338
Bradykinesia	23–26	7.82 (3.68)	6.00 (4.07)	8.77 (4.90)	8.58 (5.59)	TIME	1	9.012	0.003
						INTERVENTION	1	4.207	0.043
						TIME × INTERVENTION	1	5.976	0.016
Arising from chair	27	0.60 (0.65)	0.53 (0.76)	0.86 (0.94)	0.98 (0.96)	TIME	1	0.104	0.747
						INTERVENTION	1	5.308	0.023
						TIME × INTERVENTION	1	1.965	0.164
Posture	28	1.20 (0.80)	0.98 (0.69)	1.51 (0.98)	1.44 (0.93)	TIME	1	6.818	0.010
						INTERVENTION	1	5.185	0.025
						TIME × INTERVENTION	1	1.811	0.182
Gait	29	1.15 (0.79)	1.04 (0.69)	1.30 (0.74)	1.30 (0.77)	TIME	1	0.996	0.321
						INTERVENTION	1	2.161	0.145
						TIME × INTERVENTION	1	0.996	0.321
Postural stability	30	1.12 (0.85)	0.93 (0.89)	1.21 (0.99)	1.21 (0.91)	TIME	1	1.816	0.181
						INTERVENTION	1	1.225	0.271
						TIME × INTERVENTION	1	1.816	0.181
Body bradykinesia	31	1.52 (0.79)	1.13 (0.77)	1.69 (0.99)	1.53 (0.93)	TIME	1	19.800	<0.001
						INTERVENTION	1	3.095	0.082
						TIME × INTERVENTION	1	3.517	0.064

4. Discussion

The present results showed that, in comparison to the sham stimulation, significant improvements in bradykinesia were induced by the SMA stimulation.

The pathophysiology of parkinsonian motor symptoms remains a matter of controversy [13]. Hypokinetic symptoms are apparently implicated in impaired activity of the SMA, presumably ascribed to decreased positive efferent feedback arising from the basal ganglia–thalamocortical motor loop [3–7]. The fact that only the bradykinesia scores were significantly decreased by the SMA stimulation concurs with the view that hypokinetic symptoms are associated with the SMA dysfunction in PD patients [2–7]. Furthermore, these improvements were observed two weeks after the end of the rTMS protocol. Although the mechanism of this delay remains to be determined, possible cumulative effects of rTMS and a long-lasting effect of rTMS, which lasted up to 8 days in the primate brain [14], might partly explain this delay.

We noted at least four limitations of this study. First, the SMA might not be stimulated or other parts might be affected, although the effects should be derived mainly from modulation of neuronal activity of SMA, according to several precedent reports [15]. Moreover, the evaluation of possible effects of our SMA stimulus on the primary leg motor area showed that our SMA stimulus produced substantial effects on motor functions of the upper extremities as well as on the lower extremities. Based on these observations, improvement in bradykinesia is ascribed to modulation of motor functions of upper and lower extremities. Second, more data related to UPDRS scores (in the off and best on) should be provided. Consequently, the improvement might well be attributable simply to the medication and not to rTMS of the SMA. However, it was impossible to assess an off state in our patients because all outpatients had difficulty in making hospital visits during off states. Furthermore, the baseline scores of assessments did not differ between SMA and sham groups. Importantly, we found no significant effect of the stage of the disease on the UPDRS score changes [8]. No significant correlation was found between the baseline state and the response of bradykinesia to our SMA stimulus. Third, the structure of the UPDRS motor part might be inappropriate to assess (possible) improvements of other motor symptoms (e.g. gait, postural stability,) which contain a single score item. The assessment might therefore lack sufficient sensitivity to detect small changes. Finally, recent studies of rTMS over SMA with small numbers of PD patients revealed worsening of complex movements [16]. That discrepancy might be ascribed to methodological differences such as the coil orientation (handle pointing laterally in this study versus no description in the previous study [16]), stimulus intensity (110% AMT for foot muscles in this study versus various stimulus intensities of 58–110% resting motor threshold for hand muscles in the earlier study [16]), stimulus frequency (5 Hz in

Table 3
2 × 2 cross table of changes in item 29 and bradykinesia score.

		Item 29 (gait)		Sum
		Improvement	Non-improvement	
Bradykinesia score (items 23–26)	Improvement	10	28	38
	Non-improvement	2	15	17
Sum		12	43	55

Table 4
2 × 2 cross table of changes in items 23–25 (upper extremity functions) and item 26 (lower extremity function).

		Item 26 (L/E)		Sum
		Improvement	Non-improvement	
Items 23–25 (U/E)	Improvement	24	5	29
	Non-improvement	14	12	26
Sum		38	17	55

this study versus 10 Hz [16]), session numbers (multiple sessions versus single session [16]), timing of evaluation (two weeks after rTMS versus immediately after rTMS session [16]), and the number of subjects (99 patients in this study, but only 10 subjects in the previous study [16]).

Although some shortcomings limit the scientific validity of this study, the SMA stimulation might exert modest improvement of hypokinetic symptoms in PD. These results support the hypothesis that neuronal activity of SMA is associated with hypokinetic symptoms in PD.

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Appendix A

The following doctors and institutions participated in the Group to Study Effectiveness of rTMS on Parkinson's Disease, Japan.

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Primary motor cortical metaplasticity induced by priming over the supplementary motor area

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Motor cortical plasticity induced by repetitive transcranial magnetic stimulation (rTMS) sometimes depends on the prior history of neuronal activity. These effects of preceding stimulation on subsequent rTMS-induced plasticity have been suggested to share a similar mechanism to that of metaplasticity, a homeostatic regulation of synaptic plasticity. To explore metaplasticity in humans, many investigations have used designs in which both priming and conditioning are applied over the primary motor cortex (M1), but the effects of priming stimulation over other motor-related cortical areas have not been well documented. Since the supplementary motor area (SMA) has anatomical and functional cortico-cortical connections with M1, here we studied the homeostatic effects of priming stimulation over the SMA on subsequent rTMS-induced plasticity of M1. For priming and subsequent conditioning, we employed a new rTMS protocol, quadripulse stimulation (QPS), which produces a broad range of motor cortical plasticity depending on the interval of the pulses within a burst. The plastic changes induced by QPS at various intervals were altered by priming stimulation over the SMA, which did not change motor-evoked potential sizes on its own but specifically modulated the excitatory I-wave circuits. The data support the view that the homeostatic changes are mediated via mechanisms of metaplasticity and highlight an important interplay between M1 and SMA regarding homeostatic plasticity in humans.

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Abbreviations CS, conditioning stimulus; FDI, first dorsal interosseous muscle; ICF, intracortical facilitation; ISI, inter-stimulus intervals; ITT, inter-train interval; LICI, long-interval intracortical inhibition; LTD, long-term depression; LTP, long-term potentiation; M1, primary motor cortex; MEP, motor-evoked potential; PMd and PMv, dorsal and ventral premotor cortex; QPS, quadripulse stimulation; rTMS, repetitive transcranial magnetic stimulation; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; SMA, supplementary motor area; TA, right tibialis anterior muscle; TS, test stimulus.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a promising method to induce plastic changes in humans (Hallett, 2007). In some cases, the rTMS-induced plasticity is *N*-methyl-D-aspartate (NMDA) dependent, supporting the idea that changes in synaptic efficacy, such as long-term potentiation (LTP) and long-term depression (LTD), are implicated in rTMS-induced plasticity (Stefan *et al.* 2002; Huang *et al.* 2007). Several human studies have also shown effects of a prior history of neuronal activity on subsequent rTMS-induced plasticity (e.g. Siebner *et al.* 2004; Hamada *et al.* 2008*a*). These findings have been compared with metaplasticity, homeostatic regulation of synaptic plasticity in which the capacity of synapses to exhibit plasticity depends on prior levels of neuronal activity (Abraham & Bear, 1996; Ziemann & Siebner, 2008). This form of plasticity regulation might relate directly to the Bienenstock–Cooper–Munro (BCM) theory, a prevailing model for homeostatic mechanisms of synaptic plasticity (Bienenstock *et al.* 1982; Abraham, 2008).

The protocol for studying metaplasticity in an experimental context is to apply a period of priming

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