BFMDR Scale handwriting score was 4 preoperatively. His physical and mental conditions were completely normal. A brain MR imaging study revealed no abnormal findings, and other laboratory investigations demonstrated normal results. His personal and family histories were unremarkable.

Surgery. Two quadripolar electrodes for DBS were implanted: one into the left VO/VIM and the other into the GPI, after injection of a local anesthetic (Fig. 2). The coordinates of the tentative target points in the VO/VIM and the GPI were defined on a digitized version of a human brain atlas. Also, microrecordings were performed to monitor the extracellular activities in the vicinity of both tentative target points. The target for the VO/VIM was localized 6.5 mm anterior to the PC, 0.5 mm inferior to the AC–PC line, and 13.5 mm distant from the midline of the brain. The target for the GPI was localized at a point in the midcommissural point, 5 mm inferior to the AC–PC line, and 18 mm distant from the midline of the brain. We performed intraoperative neurological evaluations at the different DBS lead sites while the patient was writing. An immediate effect was clearly noted during VO/VIM stimulation, which appeared to be better than GPI stimulation. The gradual effects of GPI DBS, however, were observed, and this could not be denied because of the intraoperative neurological findings. We decided therefore to implant a DBS lead into each of the VO/VIM and the GPI in this, the first case. After the surgery, we performed a stimulation test for 1 week and carefully compared the effectiveness of VO/VIM and GPI stimulation.

Postoperative Examination and Course. Over the next week, various stimulation patterns were attempted to confirm the clinical effects and to compare the effects obtained with the two targets. Figure 3 shows the letters written presurgically, during VO/VIM stimulation, and during GPI stimulation. Based on the improvement rate on the handwriting scale, the patient's subjective feelings, and the entirety of letters written by the patient, we decided to connect the VO/VIM–DBS lead with an implantable pulse generator after the 1-week test stimulation. Considering the decrease in the thalamic stimulation effect, a lead for pallidal stimulation was implanted in the subgaleal space around the bur hole without connection to the pulse generator. The patient exhibited no surgery-related complications or stimulation-induced adverse effects due to the effective stimulation parameters.

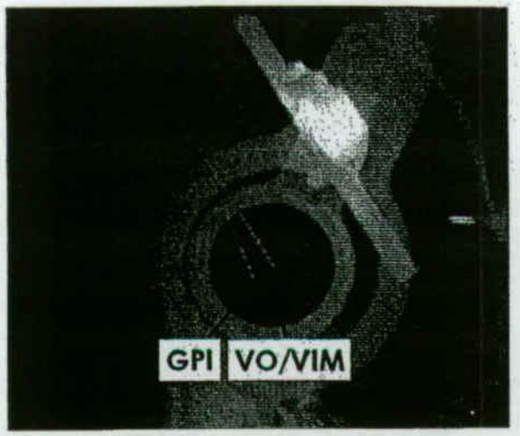

FIG. 2. Radiograph demonstrating the two DBS leads implanted at the VO/VIM and GPI in the same patient.

Discussion

Writer's cramp has been regarded as a type of primary focal hand dystonia. Clinically, it involves severe difficulty in the continuation of writing, which is produced by spasm of the fingers that hold the writing instrument or by spasm of the entire hand. In general, the symptoms of writer's cramp are refractory to medical treatment. Attempting to achieve temporary improvement, intramuscular injections of botulinus toxin have been performed, but symptom recurrence is the rule, and the response to repetitive injection is sometimes reduced effectiveness. The authors of several reports have suggested the usefulness of stereotactic thalamotomy against dystonic hand cramping. Stereotactic thalamotomy was first introduced as a treatment for writer's cramp by Siegfreid et al.[17] Its successful therapeutic effect in patients with writer's cramp was thereafter reported in two studies.[1,14] Recently, Goto et al.[6] indicated that writer's cramp could be markedly relieved after stereotactic thalamotomy of the anterior VO and the posterior VO of the thalamus. Also, Taira and Hori[18] obtained satisfactory results in 12 patients with writer's cramp using this procedure, and emphasized the validity of stereotactic VO thalamotomy for writer's cramp. More recently, Shibata et al.[16] have described a case of medication-refractory writer's cramp in which the patient was successfully treated by stereotactic VO thalamotomy. However, there has been concern that such a destructive procedure might cause irreversible adverse effects. Chronic DBS therapy, in contrast, is currently considered an effective alternative to thalamotomy and/or pallidotomy, offering the advantages of reversibility, adaptability to changing clinical situations, and being probably associated with a lower incidence of postsurgical neurological deficits.[2,19]

There is cause to assert the superiority of thalamic DBS over thalamotomy as a treatment for writer's cramp. The stereotactic targeting strategies differ between thalamic DBS and thalamotomy.[9] In thalamotomy, a minimal radiofrequency lesion is created within the most appropriate site, providing maximal benefits without any side effects. This strategy depends on the assumption that there is a concentrated cluster of neural elements that are responsible for the pathological condition. However, this assumption is not necessarily true—such neural elements may sometimes spread out across wide areas. Thalamic DBS is not based on such an assumption. The thalamic electrode can be arranged in such a way that a wide area can be stimulated, if necessary.

In the present study the results obtained for the selection of active contacts suggest that bipolar stimulation, which covered a wide area of the VO/VIM, appeared to be the most appropriate pattern of therapeutic stimulation. In contrast, radiofrequency-induced lesions for thalamotomy cannot be arranged in such a way that a wide area is covered because of the inevitable occurrence of adverse effects. For

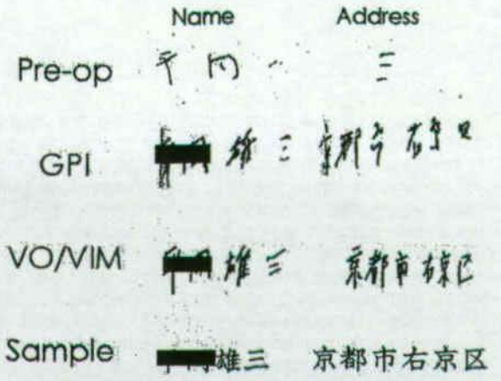

FIG. 3. Letters written by the patient presurgically, during VO/VIM stimulation, and during GPI stimulation, along with sample printed Japanese letters for comparison.

these reasons, we consider thalamic DBS to offer a more suitable therapy for writer's cramp than thalamotomy.

In addition, the concept of DBS of the GPI has frequently been introduced as a treatment for dystonic movement disorders over the past several years.[5,8,20,21] A prospective controlled multicenter study of this treatment modality in patients with primary generalized dystonia has already been published, and its usefulness for such treatment has been confirmed.[22] The authors of other papers have described the usefulness of GPI DBS as a treatment for dystonia—not only generalized dystonia but also other types, including focal or segmental dystonia.[10–13] Based on these data, GPI DBS appears to be an attractive treatment for writer's cramp, which is considered to be a form of focal hand dystonia. Choosing, as a target, between the GPI or the VO/VIM was thus not easy in our first case, and we therefore implanted two electrodes, one into the VO/VIM and one into the GPI.

Comparison of the results obtained with each of these two electrodes showed that thalamic stimulation was more effective than GPI DBS in treating writer's cramp. Since the successful outcome we observed after thalamic stimulation in our initial case, we have used this procedure to treat writer's cramp in four other patients, and the outcomes in all five cases were most gratifying. There was no surgery-related death or morbidity, and no stimulation-induced adverse effects. In view of these results, thalamic stimulation is thought to represent a useful treatment for writer's cramp.

Despite the various attempts at treatment, the pathophysiology of writer's cramp remains unclear. Several speculations concerning its background mechanisms have been made. Kaji et al.[7] suggested that a disorder of a motor subroutine might exist in the motor cortex–basal ganglia–thalamus-cortex loop in patients with dystonia. Moreover, a disorder of sensorimotor functional integration during motor tasks induces dystonic involuntary movements.[7,23] Writer's cramp could involve a functional abnormality of such a motor loop, as well as other dystonias during the writing task specifically. Improvement following stimulation of the motor thalamus is considered to be a result of normalization of abnormal activities in the pallidothalamocortical motor circuit. According to the description offered by Taira and Hori,[18] it is reasonable to infer that VO stimulation interrupts a functional abnormality of the cortex motor loop in an individual's writer's cramp, because the VO receives significant input from the GPI. However, we observed that stimulation that included the VIM, which receives input mainly from the cerebellum, more effectively improved writer's cramp. We cannot provide any evidence to explain this outcome, but the result itself indicates that both the basal ganglia–thalamus loop and the cerebellum are associated with writer's cramp. Greater experience with this treatment is needed to confirm this result. Also, additional studies are needed to determine the detailed pathophysiology of writer's cramp and the mechanisms of the DBS effects on such a pathological condition.

Conclusions

We have described five cases of writer's cramp in patients in whom thalamic DBS successfully resolved symptoms. Insofar as we are aware, this is the first series in which writer's cramp was treated using DBS therapy. In one case that provided an opportunity for us to compare the respective effects of VO/VIM and GPI stimulation, VO/VIM stimulation yielded the better effect. Also, the maximum effect was obtained when the stimulation widely covered the area from the VO to the VIM. Thalamic stimulation appears to represent a valuable therapeutic option, and the success achieved with this surgical treatment leads us to view writer's cramp from a new perspective.

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Recording of Corticospinal Evoked Potential for Optimum Placement of Motor Cortex Stimulation Electrodes in the Treatment of Post-stroke Pain

—Two Case Reports—

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Abstract

The corticospinal motor evoked potential (MEP) evoked by motor cortex stimulation was investigated as an intraoperative index for the placement of stimulation electrodes in the epidural space over the motor cortex for the treatment of post-stroke pain. A grid of plate electrodes was placed in the epidural space to cover the motor cortex, sensory cortex, and premotor cortex employing a magnetic resonance imaging-guided neuronavigation system in two patients with severe post-stroke pain in the right extremities, a 66-year-old man with dysesthesia manifesting as burning and aching sensation, and a 67-year-old woman with dysesthesia manifesting as pricking sensation. The D-wave of the corticospinal MEP was recorded with a flexible wire electrode placed in the epidural space of the spinal cord during anodal monopolar stimulation of each plate electrode under general anesthesia. The grid electrode was fixed in position with dural sutures and the craniotomy closed. The effect of pain reduction induced by anodal monopolar stimulation of the same plate electrodes was examined using the visual analogue scale (VAS) on a separate day in the awake state without anesthesia. Comparison of the percentage VAS reduction and the recorded amplitude of the D-wave employing the same stimulation electrode revealed significant correlations in Case 1 ($r = 0.828$, $p < 0.01$) and Case 2 ($r = 0.807$, $p < 0.01$). The grid electrode was then replaced with two RESUME electrodes over the hand and foot areas, and the optimum positions were identified by D-wave recording before electrode fixation. Both patients reported satisfactory pain alleviation with lower stimulation voltages than usually required for patients with similar symptoms. These results indicate the potential of D-wave recording as an intraoperative indicator for the placement of stimulating electrodes over the motor cortex for pain relief.

Key words: motor evoked potential, post-stroke pain, motor cortex stimulation, corticospinal motor evoked potential, D-wave

Introduction

Motor cortex stimulation therapy was first proposed for the treatment of post-stroke pain,[19–21] and subsequently numerous studies have examined the effectiveness for neuropathic pain and central pain.[2–4,7,8,11–13,16,17,22] In the large series, the long-term success rate for pain alleviation was about 50%. The pain control provided by motor cortex depends on stimulation of neuronal circuits mediated by corticospinal tract neurons originating from the motor cortex.[9] Activation of the thalamic nuclei directly connected with the motor and premotor cortices causes a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the medial thalamus, anterior cingulate, and upper brainstem, and motor cortex stimulation attenuates the nociceptive spinal reflexes.[5] Motor cortex stimulation also produces significant transient inhibition of the responses of the spinal cord dorsal horn neu-

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rons to higher intensity mechanical stimuli without affecting the response to innocuous stimuli.[18] Therefore, at least part of the antinociceptive effect induced by motor cortex stimulation involves the corticospinal tract neurons originating from the motor cortex.

Correct placement of the cortical electrode, which induces the muscle twitches or muscle contractions, is most important to achieve effective pain relief in post-stroke pain.[9,21] The recommended position of the cortical stimulation electrode is over the painful area.[14,17,21] Various surgical techniques are available for the accurate placement of epidural or subdural electrodes over the motor cortex.[14,17,21] However, a standard method has not yet been established. Anatomical identification of the central sulcus by phase reversal of N20 with monitoring of the somatosensory evoked potential or magnetic resonance (MR) imaging-guided neuronavigation may allow exact positioning of the stimulation electrode on the precentral gyrus directly or epidurally. However, the activation of the corticospinal tract neurons originating from the motor cortex cannot be predicted. Moreover, anodal monopolar cortical stimulation activates vertically oriented pyramidal neurons,[1] whereas only cathodal bipolar cortical stimulation, which tends to excite the superficial horizontal fibers and cortical interneurons, is available from the implantable pulse generator approved for clinical use.

The corticospinal motor evoked potential (MEP) evoked by direct stimulation of the motor cortex can be recorded from the epidural space of the spinal cord, and has been used for the intraoperative monitoring of motor function.[6,23] The corticospinal MEP response consists of an initial D-wave and a later sequence of volleys termed I-waves.[1,15] The D-wave reflects impulses arising from direct activation of the axons of corticospinal tract neurons, whereas the I-waves reflect neurons via synaptic activity.

The present study examined the relationship between pain reduction on the visual analogue scale (VAS) and the recorded amplitude of the D-wave during stimulation of various points of the motor cortex to evaluate the D-wave as an index for the placement of the epidural electrode in the treatment of post-stroke pain.

Patients and Methods

This study included two patients, a 66-year-old man with post-stroke pain in the right extremities caused by left pons bleeding manifesting as dysesthesia with burning and aching sensation for 25 months (Case 1), and a 67-year-old woman with post-stroke pain in the right extremities caused by thalamic bleeding manifesting as dysesthesia with pricking sensation for 24 months (Case 2). Both patients felt most severe pain in the upper extremity. Both patients could walk unaided, and had grade 4 motor function of the right extremity by the muscle maneuver test (MMT).[23] Both patients gave informed consent for intraoperative monitoring of the corticospinal MEP and test stimulation employing a grid electrode implanted in the epidural space just over the motor cortex. The present study was approved by the Committee for Clinical Trials and Research in Humans of our university and by the Japanese Ministry of Health and Welfare as part of an advanced medical care program.

A flexible four-channel, platinum wire electrode (3487A PISCES-Quad; Medtronic, Inc., Minneapolis, Minn., U.S.A.) was inserted into the epidural space of the cervical vertebrae, at the C2 to C4 levels, on the day before the operation. The patient was placed in the abdominal prone position, and an 18-gauge Touhy needle included in the electrode package was inserted into the midline epidural space at the cervical and thoracic junction under radiographic control. The spinal epidural space was confirmed from the change of resistance observed during saline injection through the Touhy needle. The electrode was inserted into the epidural space with a stylet via the Touhy needle and advanced to the appropriate position under radiographic control. The stylet and Touhy needle were then removed, and the electrode was fixed with adhesive tape and a drape placed on the skin (Fig. 1).

On the next day, a craniotomy sufficient to expose the postcentral gyrus, precentral gyrus, and posterior parts of the superior, middle, and inferior frontal gyri was performed under general anesthesia with muscle relaxant and completely controlled ventilation. The grid electrode, comprising 20 plate electrodes of 5 mm diameter and each separated by 5 mm, with each of the plate electrodes embedded in thin and soft silicone material (Unique Medical Co., Ltd., Komae, Tokyo), was placed in the epidural space over the motor, sensory, and premotor cortices employing an MR imaging-guided neuronavigator (Fig. 2). The ground electrode was placed on the forehead. The cerebral cortex was stimulated utilizing each contact point of the grid electrode. The stimulation was applied as a monophasic square wave pulse of 0.2 msec duration delivered at 2 Hz, and anodal monopolar stimulation with an intensity of 30 mA was selected for monitoring of the D-wave. A recording electrode with four contact points was used for bipolar recording between adjacent contact

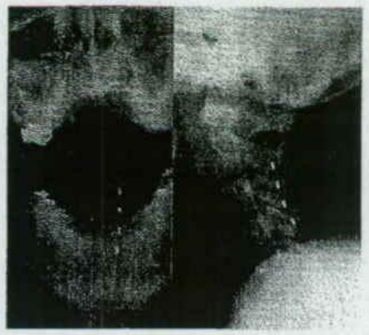

Fig. 1 Radiographs showing a four-channel wire electrode placed within the epidural space of the cervical spinal cord at the C2 to C4 levels.

Fig. 2 Radiograph showing an epidural grid electrode implanted in the epidural space for direct cortical stimulation, and the electrode in the epidural space of the cervical spinal cord (arrow). Same orientation as Fig. 4.

points, and the signals were fed into an amplifier with a band pass range of 5 Hz to 5 kHz and averaged for 32 sweeps using Synax 2100 (NEC Co., Tokyo).

After recording the corticospinal MEP, the epidural grid electrode was fixed to the dura with sutures at several points to maintain the grid electrode location, and the wound was closed. The effect on pain induced by monopolar anodal cortical stimulation employing the contact points of the grid electrode was examined using the VAS on another day in the awake state without anesthesia. This test stimulation used a frequency of 25 Hz with a

Fig. 3 Radiograph showing the two RESUME motor cortex stimulation electrodes placed on the hand and foot areas.

duration of 0.2 msec, and the best stimulation intensity was selected between 10 to 20 mA. The change of the VAS was expressed as percentage VAS reduction, calculated as (1 − VAS with stimulation/VAS without stimulation) × 100%. The percentage VAS reduction and the recorded amplitude of the D-wave using the same stimulating electrode were then compared by simple regression analysis.

After confirming that pain alleviation was obtained with cortical stimulation, chronic implantation of the electrode for motor cortex stimulation was performed under general anesthesia with muscle relaxant. Until this second operation, the recording electrode was left in the cervical epidural space. The epidural grid electrode was replaced with a four-channel plate electrode (3587A RESUME · II; Medtronic, Inc.), which has four contact points consisting of plate electrodes of 5 mm diameter and spaced 5 mm apart. The optimum location of the two RESUME electrodes for stimulation of the hand and foot areas was identified by monitoring the D-wave with bipolar stimulation of the most distant two contact points of the four (Fig. 3). After confirming the best location for the RESUME electrodes, which evoked the D-wave at the highest amplitude by bipolar stimulation, the edge of the RESUME electrode was sutured to the dura, to prevent movement of the electrode. This procedure was essential to ensure steady attachment between the dura and contact points. An implantable pulse generator was implanted under the anterior chest wall at the same time, and connected to the RESUME electrode with an extension cable.

Results

D-waves were detected after stimulation of 14 of the

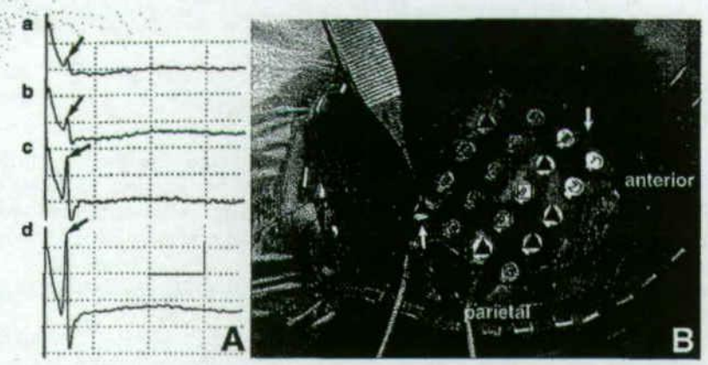

Fig. 4 **A: Representative D-waves (arrows) classified into amplitudes of under 2 μV (a), 2 to 5 μV (b), 5 to 10 μV (c), and over 10 μV (d). Time scale, 5 msec; amplitude, 5 μV. B: Photograph of the intraoperative epidural grid electrode placed over the sensory, primary motor, and premotor cortices in Case 1. The amplitude of the D-wave evoked by the stimulation of each plate electrode was classified as over 10 μV (*open circles*), 5 to 10 μV (*open squares*), 2 to 5 μV (*open triangles*), and under 2 μV (*closed triangles*). *Thick line*: Central sulcus estimated by magnetic resonance imaging-guided navigation.**

20 contact points of the grid electrode in Case 1, and 11 contact points in Case 2. The recorded amplitudes of the D-waves were classified into over 10 μV, 5 to 10 μV, 2 to 5 μV, and less than 2 μV (Fig. 4A). The evoked amplitudes of the D-waves were plotted on an intraoperative view of the grid electrode (Fig. 4B). The contact points which evoked D-wave amplitudes of over 10 μV were located just anterior to the central sulcus as estimated by MR imaging-guided neuronavigation.

Figure 5 illustrates the relationships between the recorded amplitude of the D-wave and the percentage VAS reduction in Cases 1 and 2. Simple regression analysis showed significant correlations in Case 1 ($r = 0.828$, $p < 0.01$) and Case 2 ($r = 0.807$, $p < 0.01$).

Discussion

The present study used high intensity anodal monopolar stimulation so that both the electrode contact areas and the surrounding cortical areas were stimulated together, thus stimulating a wider area of the cerebral cortex than previously,[23] so we could compare the amplitude of the D-wave with the percentage VAS reduction. The percentage VAS reduction was significantly correlated with the D-wave amplitude, indicating that D-wave recording provides an intraoperative guide for placing the stimulating electrode at the optimum position on the motor cortex.

Chronic implantation of the RESUME electrodes was performed in the epidural space exposed by the craniotomy. The electrodes were placed parallel to the sagittal sinus over the central sulcus in the foot area, and parallel to the central sulcus over the motor strip in the hand area. The optimum positions were identified by searching for the D-wave with the highest amplitude evoked by bipolar stimulation. Both patients complained of most severe pain in the upper extremity, but also of dysesthesia of the lower extremity. Therefore, both hand and foot areas were stimulated together, since it is important to induce muscle contraction or muscle twitch in the painful area for the motor cortex stimulation therapy.[10,19-22]

Our previous experience with patients with MMT of 4 suggested that the threshold intensity to induce muscle contraction under stimulation conditions of 25 Hz with 0.2 msec duration is 5.8 ± 0.9 V ($n = 10$). In the present patients, muscle contraction was induced at 2.9 V in Case 1 and 3.3 V in Case 2. Both patients were satisfied by the results of chronic motor cortex stimulation. These findings confirm the importance of identifying the optimum point for motor cortex stimulation therapy in the treatment of post-stroke pain.

Corticospinal MEP monitoring requires insertion of the recording electrode into the cervical epidural space. The recording electrode can be easily and safely placed in the epidural space by the same technique as used for transcutaneous spinal cord stimulation for the treatment of pain, and we have already

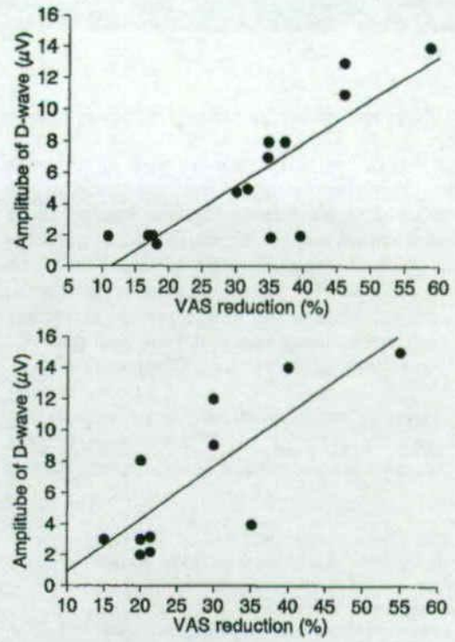

Fig. 5 **Correlations of the recorded amplitude of the D-wave and the percentage visual analogue scale (VAS) reduction in Case 1 (upper) and Case 2 (lower). Simple regression analysis showed significant correlations in Case 1 ($Y = -3.033 + 0.274X$, $r = 0.828$, $p < 0.01$) and Case 2 ($Y = -2.575 + 0.339X$, $r = 0.807$, $p < 0.01$). Percentage VAS reduction = (1 − VAS with stimulation/VAS without stimulation) × 100%.**

experienced over 250 cases without irreversible complications arising from such electrode insertion. Monitoring of the muscle responses to direct motor cortex stimulation is also useful for the monitoring of cerebral ischemia.[6] Another advantage is that, unlike muscle responses to motor cortex stimulation, the D-wave of the corticospinal MEP is resistant to surgical doses of anesthetics and is unaffected by muscle relaxants, apart from changes to the excitability of the spinal motor neurons, and so the amplitude can be easily correlated with the site of cortical stimulation.

The present study indicates that monitoring of the D-wave provides a good indicator of the optimum placement of the chronic electrode for the treatment of post-stroke pain, and thus allows implantation of the motor cortex stimulation electrode in a one-stage operation under general anesthesia.

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Direct Effect of Subthalamic Nucleus Stimulation on Levodopa-Induced Peak-Dose Dyskinesia in Patients with Parkinson's Disease[1]

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Key Words
Levodopa-induced dyskinesia · Subthalamic nucleus · Deep brain stimulation · Parkinson's disease

Abstract
We examined the direct effect of deep brain stimulation of the subthalamic nucleus (STN-DBS) on levodopa-induced peak-dose dyskinesia in 45 patients with Parkinson's disease (PD) without reducing the levodopa dosage during the early period after surgery. In 8 patients (18%), the dyskinesia was quickly attenuated by bipolar stimulation in an experimental trial (5 min) with the contacts placed within the area above the STN. In contrast, bipolar stimulation using contacts placed within the STN itself tended to provoke or exacerbate the dyskinesia, indicating that dyskinesia could be inhibited by stimulation of the areas above the STN rather than the STN itself. In an attempt to control the cardinal symptoms of PD and dyskinesia at the same time, we employed bipolar stimulation with a longer interpolar distance as a therapeutic procedure (2 weeks), using contacts within the STN as a cathode and contacts within the area above the STN as an anode. Bilateral STN-DBS significantly attenuated the dyskinesia as evaluated by the dyskinesia severity rating scale ($p < 0.05$). In 24 patients (53%), almost complete control of the dyskinesia was observed. The contacts used as an anode in these patients were located more dorsally compared to those of the remaining patients, suggesting again that the dyskinesia was inhibited by stimulation of the areas above the STN rather than the STN itself. In the area above the STN, pallidothalamic, pallidosubthalamic and subthalamopallidal fibers are densely distributed. It appears that stimulation of these fibers may cause effects similar to thalamic or pallidal DBS and therefore inhibit peak-dose dyskinesia. Bipolar STN-DBS with contacts placed within the area above the STN as an anode appears to represent a useful option for controlling both the cardinal symptoms of PD and peak-dose dyskinesia at the same time.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) greatly attenuates the cardinal symptoms of Parkinson's disease (PD) during the off period [1–3]. Levodopa-induced dyskinesia (LID), especially peak-dose dyskinesia, can also be controlled by an indirect effect of

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DBS of the STN (STN-DBS) through a reduced requirement in the levodopa dosage [4, 5]. In addition some authors have reported that LID can be directly attenuated by STN-DBS [6–8]. We examined the direct effect of STN-DBS on peak-dose dyskinesia during the early period after surgery without reducing the levodopa dosage.

Patients and Methods

We analyzed the effect of STN-DBS in 79 patients with PD who presented with severe LID before surgery. Among them, peak-dose dyskinesia was predominant in 49, diphasic dyskinesia in 26 and off-period dystonia in 49 patients. In the present study we focused on the direct effect of STN-DBS on peak-dose dyskinesia, which was evaluated during a 2-week period after surgery without reducing the levodopa dosage.

Implantation of the DBS leads was performed bilaterally at the same time in all patients, employing a Leksell microstereotactic system (Elekta Instrument AB, Sweden) and magnetic-resonance-imaging (MRI)-guided targeting. The levodopa dosage was unchanged perioperatively. The DBS leads (Medtronic 3387; Minneapolis, Minn., USA) with 4 contact points, sequentially numbered 0–3 from the most distal (0) to the most proximal contact (3), were placed in such a way that the tip of contact 0 was located on the ventral boundary of the STN, which was identified by neuronal recording with tungsten semimicroelectrodes (impedance 0.2–0.5 MΩ at 1,000 Hz), passing through the center of the STN. Each contact of the DBS leads was 1.5 mm long, and the contacts were 1.5 mm apart from each other. Postoperative MRI was performed to confirm the localization of the DBS leads. The tip of contact 0 was located 4.0–4.5 mm posterior and 5.0–5.5 mm inferior to the midcommissural point and 11.0–12.0 mm from the midline. The location of each contact was determined in relation to the anterodorsal boundary of the STN, which was identified by intraoperative neuronal recording with semimicroelectrodes.

In the 49 patients examined, 98 leads were implanted. Among them, contact 2 was placed on the anterodorsal boundary of the STN in 51 and within the area just above the STN in 47 leads. This indicates that contacts 0 and 1 were located within the STN. The location of contact 3 varied depending on the frontal angle of the DBS lead in reference to the intercommissural line. In 24 leads which were placed with angles of <47°, contact 3 appeared to be situated in the internal capsule just anterior to the zona incerta, since we never encountered thalamic neuronal activities during intraoperative neuronal recording with semimicroelectrodes. In the remaining leads, contact 3 appeared to be located within the zona incerta or the anterior thalamic region.

Among the 49 patients, the peak-dose dyskinesia was attenuated spontaneously without stimulation in 4 patients for at least a week after surgery. The direct effect of STN-DBS on the observable peak-dose dyskinesia was therefore evaluated in 45 patients without reducing the levodopa dosage. The dyskinesia severity rating scale was employed to evaluate the severity of LID, scoring the dyskinesia in 6 body parts (neck, trunk and each of the 4 extremities) on a 5-point scale (ranging from 0 to 4; e.g. 0 = absent, 4 = severe). We first examined the immediate change in dyskinesia severity in response to bipolar stimulation as an experimental trial (duration of stimulation 5 min) using various combinations of contacts with short interpolar distance. Subsequently we analyzed the changes in dyskinesia severity by bilateral STN-DBS as a therapeutic procedure (duration of stimulation 2 weeks) in comparison with the preoperative dyskinesia severity.

Results

In 8 (18%) of the 45 patients, the peak-dose dyskinesia was quickly attenuated by bipolar stimulation in the experimental trial. In all cases bipolar stimulation of the area above the STN, using contact 2 as the cathode and contact 3 as the anode, attenuated the dyskinesia most effectively. This effect was observed in limb dyskinesia contralateral to unilateral stimulation. Axial dyskinesia was attenuated by bilateral stimulation. Complete control was achieved in 6 patients. The stimulation intensities required for complete control ranged from 1.5 to 3.0 V. These effects were usually induced within 3–5 min after the initiation of stimulation and reappeared within 1–3 min after the termination of stimulation. Dyskinesia was never attenuated by stimulation of the area above the STN in any of the patients.

In contrast, bipolar stimulation with a short interpolar distance, using contacts 0 and 1, tended to provoke or exacerbate the dyskinesia. In the 8 patients who demonstrated attenuation of dyskinesia by bipolar stimulation using contacts 2 and 3, the dyskinesia was attenuated by bipolar stimulation within the STN with contacts 0 and 1, indicating that dyskinesia could be inhibited by stimulation of the areas above the STN rather than the STN itself.

In an attempt to control both the cardinal symptoms of PD and peak-dose dyskinesia at the same time, we employed bipolar stimulation with a long interpolar distance as a therapeutic procedure, using contact 0 or 1 within the STN as a cathode and contact 3 within the area above the STN as an anode. Bilateral STN-DBS significantly attenuated the dyskinesia in patients with peak-dose dyskinesia ($p < 0.05$) and off-period dystonia ($p < 0.02$; fig. 1).

Almost complete control of the peak-dose dyskinesia was observed in 24 (53%) of the 45 patients. The contact 3 used as an anode in these patients was located more dorsally than the contact 3 in the remaining patients, suggesting again that the dyskinesia was inhibited by anodal stimulation of the areas above the STN rather than the STN itself (fig. 2).

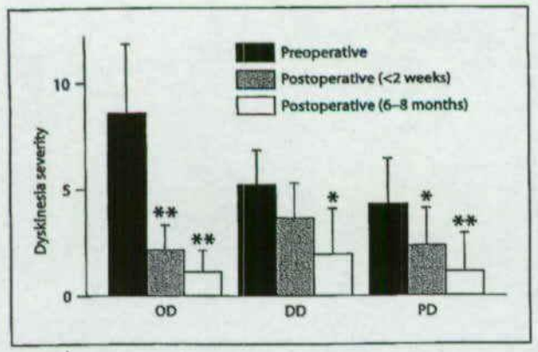

Fig. 1. Changes in score on the dyskinesia severity rating scale at 2 weeks and 6–8 months after initiation of therapeutic STN-DBS without reducing the levodopa dosage. OD = Off-period dystonia (n = 49); DD = diphasic dyskinesia (n = 26); PD = peak-dose dyskinesia (n = 49). * $p < 0.05$; ** $p < 0.02$.

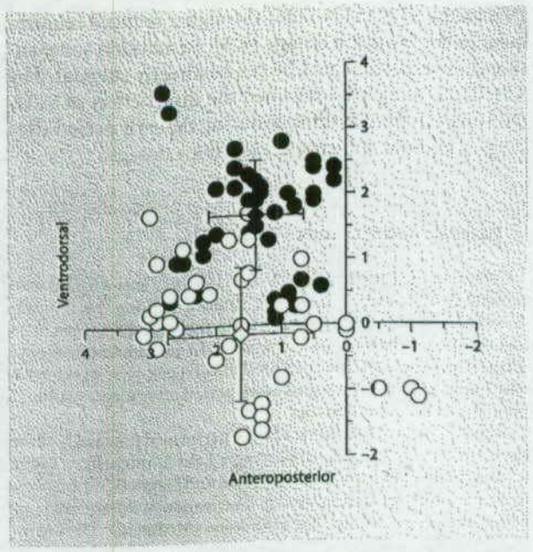

Fig. 2. Location of the contacts used as an anode. ● = location of the contacts (n = 48) in patients (n = 24) in whom almost complete control of peak-dose dyskinesia was observed; ○ = location of the contacts (n = 42) in the remaining patients (n = 21). Some symbols overlap.

At 6–8 months after surgery, the dyskinesia severity further decreased in patients with peak-dose dyskinesia and off-period dystonia. The dyskinesia severity also fell significantly in patients with diphasic dyskinesia, compared to the preoperative dyskinesia severity (fig. 1). These additional effects at 6–8 months were apparently attributable to a reduced requirement in the levodopa dosage.

Discussion

The present investigation demonstrated that direct inhibition of peak-dose dyskinesia by STN-DBS is not an uncommon phenomenon. Such an effect is induced by stimulation of the area above the STN rather than the STN itself. This observation is in agreement with a previous case report [6]. Furthermore, the present study confirmed that therapeutic STN-DBS sometimes attenuates peak-dose dyskinesia even before reducing the levodopa dosage. This finding is consistent with the previous observation that dyskinesia could sometimes no longer be induced by the preoperative levodopa dosage when STN-DBS was continued [4, 5].

For the purpose of controlling the cardinal symptoms of PD, monopolar stimulation has commonly been employed using certain contacts as a cathode [e.g. 9–11]. In contrast, the present study indicated that peak-dose dyskinesia could be effectively inhibited by bipolar stimulation using a contact located within the areas above the STN as an anode. It remains uncertain whether anodal stimulation is more appropriate than cathodal stimulation for controlling peak-dose dyskinesia. It appears, however, that bipolar stimulation with contacts placed within the STN as a cathode and contacts placed within the area above the STN as an anode represents a useful option for controlling both the cardinal symptoms of PD and peak-dose dyskinesias at the same time.

Thalamic DBS with contacts placed within the thalamic nucleus ventralis oralis, or within the thalamic nucleus ventralis intermedius at the proximity of the thalamic nuclei centromedianus et parafascicularis, inhibits LID [12–14]. It is also well known that pallidal DBS directly inhibits LID. These findings suggest that these thalamic nuclei and the globus pallidus are involved in the pathophysiology of LID.

It is possible that direct inhibition by stimulation with contacts placed within the area above the STN might be induced by current spread into these thalamic nuclei and/or the globus pallidus. This possibility seems unlikely, however, since the locations of the contacts used for stimulation were considerably distant from these structures. It is more reasonable to assume that contacts placed within the area above the STN stimulated fibers running through this area and connecting these structures.

In the area above the STN, pallidothalamic, pallidosubthalamic and subthalamopallidal fibers are densely distributed. Stimulation of these fibers may cause similar effects to thalamic and pallidal DBS and therefore directly inhibit peak-dose dyskinesia. We believe that in order to maximize the benefits provided by STN-DBS, the DBS leads should be implanted such that the contacts cover the STN itself as well as the areas above the STN.

Acknowledgment

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Thalamic Sensory Relay Nucleus Stimulation for the Treatment of Peripheral Deafferentation Pain[1]

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Key Words
Deep brain stimulation · Deafferentation pain · Phantom limb pain · Root injury pain · Microrecording · Thalamic sensory relay nucleus

Abstract
We applied chronic deep brain stimulation (DBS) of the thalamic nucleus ventralis caudalis (Vc) for the treatment of peripheral deafferentation pain. The subjects included 11 cases of phantom limb pain and 7 of root or nerve injury pain without phantom sensation. In the phantom limb pain patients, the spike density markedly increased in the same area of the Vc where microstimulation induced paresthesia in the part with phantom sensation. Reorganization of the receptive field representation within the Vc was also demonstrated by microrecording and microstimulation. In the root or nerve injury pain patients with severe allodynia and without phantom sensation, oscillating neural hyperactivity appeared when the allodynia was induced during single-cell recording in the Vc. In both groups stimulation of these areas with the DBS electrode was useful for achieving pain reduction. Inhibition of spinothalamic tract neurons, restoration of the original receptive field representation and modulation of thalamocortical rhythmic oscillations are proposed to play important roles in a possible mechanism of Vc-DBS for the treatment of deafferentation pain.

Introduction

It has been reported that hyperactive neurons, which are implicated in the mechanisms of deafferentation pain, are present within the sensory pathway above the level of the deafferentation site. We therefore selected our therapeutic method depending on the site of deafferentation. Based on its site, we classified deafferentation pain as peripheral or central. Peripheral deafferentation pain includes phantom limb pain and root and nerve injury pain, while central deafferentation pain includes thalamic pain, Wallenberg's syndrome and spinal cord injury pain. We clinically applied chronic stimulation of the thalamic nucleus ventralis caudalis (Vc) for the treatment of peripheral deafferentation pain [1, 2] and motor cortex stimulation for central deafferentation pain [3, 4]. In this paper we examine the long-term effects of Vc deep brain

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Table 1. Chronic stimulation of the Vc-DBS

Cause of pain	>60% pain reduction in VAS	Mean reduction in VAS, %
Group I (n = 11)	8/11 (73%)	69.1
Group II (n = 7)	6/7 (86%)	62.1
Total	14/18 (78%)	66.4

The pain reduction rate was evaluated 1 year after the start of Vc-DBS employing a VAS.

stimulation (DBS) for the treatment of peripheral deafferentation pain and discuss the mechanism of pain reduction induced by Vc-DBS in peripheral deafferentation pain patients.

Patients and Methods

The subjects included 18 cases of peripheral deafferentation pain and were divided into 2 groups. Of the 18 patients, 11 (group I) had phantom limb pain, while the remaining 7 (group II) had pain without phantom sensation after root or nerve injury.

Under local anesthesia a burr hole was cut at 30–35 mm anterior to the coronal suture and 20–25 mm lateral to the midline. Each electrode then approached the target point at an angle of 40–50° to the horizontal plane of the anterior-posterior commissure (AC-PC) line and 0–12.5° to the sagittal plane. A tungsten semimicroelectrode (about 200–400 kΩ) guided by an outer cannula was inserted into the Vc region through a frontal burr hole to check the receptive field and the projected fields. A permanent DBS electrode (model 387; Medtronic, Minneapolis, Minn., USA) with 4 contact points, sequentially numbered 0 through 3 from the most distal (0) to the most proximal contact point (3), was inserted and placed in such a way that contact point 0 was located in the Vc (11–15 mm lateral to the PC) and contact point 3 in the thalamic nucleus ventralis intermedius.

The stimulation parameters for the pulse width and stimulation frequency were 0.15–0.21 ms and 20–135 Hz, respectively. The contact points for bipolar stimulation and the stimulation intensity were selected to induce paresthesia with covering of the painful area.

Results

We evaluated cases with Vc-DBS as effective when the visual analogue scale (VAS) score was reduced by >60%. Long-term satisfactory pain control was achieved in 8 of the 11 patients of group I (73%) and in 6 of the 7 patients of group II (86%). Thus, 14 (78%) of the 18 cases in total showed pain control (table 1). The best effects for inducing pain reduction and paresthesia covering the painful area were usually obtained by bipolar stimulation of wide areas from the anterodorsal part to the center of the Vc, rather than by focal stimulation of a restricted area.

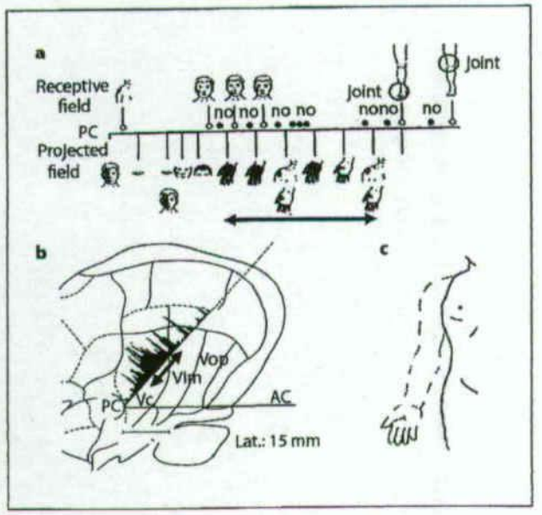

Fig. 1. a Distribution of the receptive and the projected field along the track shown in **b**. Note the site of mismatches between the receptive and the projected field. Double arrow: Microstimulation of this area induced paresthesia within the area of phantom sensation. **b** Single-cell recording showing hyperactivity in the same area where microstimulation induced paresthesia in the part with phantom sensation. Vim = Thalamic nucleus ventralis intermedius; Vop = thalamic nucleus ventralis oralis posterior. **c** The phantom limb area in this case (dotted line).

In group I the spike density markedly increased in the same area of the Vc where the microstimulation induced paresthesia in the part with phantom sensation. Reorganization of the receptive field representation within the Vc was also demonstrated by microrecording and microstimulation (fig. 1). In group II oscillating neural hyperactivity appeared when allodynia was induced during single-cell recording in the Vc (fig. 2). In both groups, however, stimulation of these areas of the Vc did not induce pain at all. Chronic stimulation of these areas with the DBS electrode (Vc-DBS) was useful for achieving pain reduction. In effective cases the required stimulation period for pain control gradually decreased, and the

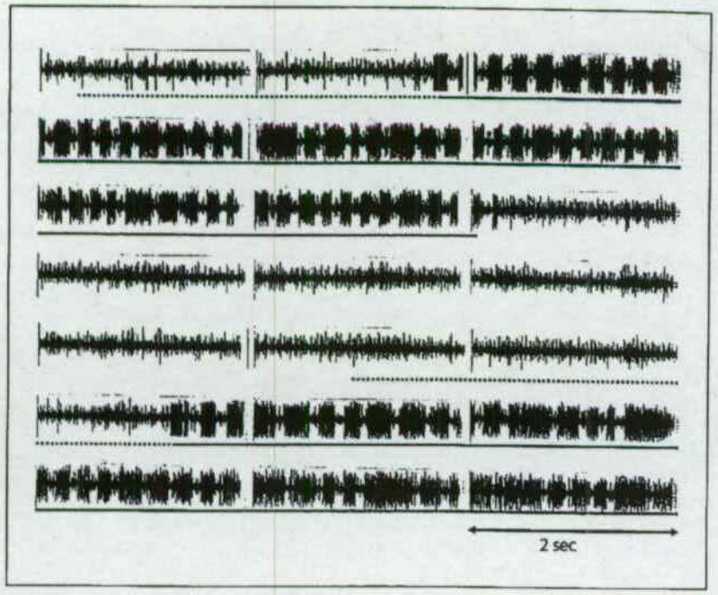

Fig. 2. Allodynia-related bursting activity recorded in the Vc in a case of root injury pain (upper extremity) without phantom sensation. Allodynia was repeatedly induced during continuous recording of the neural activity (from upper left to lower right). The dotted lines indicate tapping of the hand for activation of allodynia. The solid lines indicate that allodynia was induced: the patient complained of severe pain of the upper extremity in this period.

pain completely disappeared after long-term stimulation in 2 cases of phantom limb pain. In these 2 cases pain reappeared after long-term cessation of the Vc-DBS, and they underwent Vc-DBS again, which subsequently reduced the pain.

Discussion

The present investigation confirmed that Vc-DBS has a significant potential for controlling peripheral deafferentation pain. In our results 14 (78%) of 18 cases showed >60% of pain reduction by the VAS. The success rate for long-term pain control by Vc-DBS reported in the literature varies from 20 to 97% [5–8]. In most studies the long-term success rate ranged from 50 to 65% [7, 8] and was lower than in our results. There are 2 points of difference between our Vc-DBS for the treatment of peripheral deafferentation pain and previous reports. The first involves the drug challenge test, and the second is the area of stimulation with the DBS electrode. We carried out a pharmacological classification [9] by the morphine, thiopental and ketamine tests. Such pharmacological classification provides data that are useful as exclusion criteria for Vc-DBS and for the selection of additional therapy which may include ketamine drip infusion or morphine intake. If the patient continues complaining of pain even at the time of falling asleep with thiamylal, we excluded the individual as a candidate for Vc-DBS. The DBS electrode was not located under the AC-PC line, and the stimulation point of our Vc-DBS covered a relatively wide area, which extended from the anterodorsal part to the center of the Vc.

In group I patients with phantom limb pain, the primary somatosensory cortex may undergo a reorganization of the receptive field representation (invasion of the phantom limb area by the adjacent area). It has been reported that such reorganization is highly correlated with the development of phantom limb pain and unrelated to the nonpainful phantom sensation [10]. These findings suggest the hypothesis that chronic Vc-DBS can induce restoration of the original organization and diminish phantom limb pain. A similar reorganization of the receptive field representation within the Vc has been demonstrated by microrecordings and microstimulation during surgery for therapeutic electrode implantation. In group II patients without phantom sensation, oscillating neural hyperactivity appeared when the allodynia was induced during single-cell recording. Based on these findings, inhibition of spinothalamic tract neurons, restoration of the original receptive field representation and modulation of thalamocortical rhythmic oscillations are considered important as possible factors in the mechanism of Vc-DBS for the treatment of peripheral deafferentation pain.

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Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain

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Abstract

Objective: To assess the pain-relieving effects of motor cortex electrical stimulation (MCS) within the central sulcus and the predictive factors retrospectively.
Methods: Thirty-four patients with intractable neuropathic pain underwent MCS; 19 patients had cerebral lesions, and 15 had non-cerebral lesions. In selected 12 patients, test electrodes were implanted within the central sulcus and on the precentral gyrus. Twelve patients received both MCS and repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex.
Results: Pain reduction of $\geqslant 50\%$ was observed in 12 of 32 (36%) patients with $\geqslant 12$ months follow-ups (2 patients were excluded because of short follow-up). In 10 of the 12 patients who received test electrodes within the central sulcus and on the precentral gyrus, the optimal stimulation was MCS within the central sulcus. In 4 of these (40%) patients, positive effects were maintained at follow-ups. The pain reduction of rTMS significantly correlated with that of MCS during test stimulation.
Conclusions: The test stimulation within the central sulcus was more effective than that of the precentral gyrus. In the selected patients, chronic stimulation within the central sulcus did not significantly improve long-term results.
Significance: The present findings suggest that an intra-central sulcus is one of the favorable targets for MCS.

Keywords: Motor cortex stimulation; Deafferentation pain; Neuropathic pain; Post-stroke pain; Phantom-limb pain; Repetitive transcranial magnetic stimulation

1. Introduction

Neuropathic pain is very difficult to treat and is usually refractory to medical treatment. In 1991, Tsubokawa et al. reported that post-stroke pain can be reduced by motor cortex stimulation (MCS) (Tsubokawa et al., 1991). In 1993, trigeminal neuropathic pain was successfully treated with MCS (Meyerson et al., 1993). Other types of neuropathic pain (phantom-limb pain, pain due to brachial plexus avulsion or spinal cord injury and complex regional pain syndrome type II) also respond well to MCS (Nguyen et al., 1999; Saitoh et al., 2000; Son et al., 2003). MCS is effective in 50–75% of patients with these types of intractable chronic neuropathic pain (Tsubokawa et al., 1993; Katayama et al., 1998; Rasche et al., 2006; Saitoh and Yoshimine, 2007).

In most of the early studies on MCS, the electrodes were implanted epidurally via a burr hole. Such an epidural method might not provide optimal pain relief because both the method and the area subjected to test stimulation are restricted by the brief operative period and the single burr

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hole. The main portion of the primary motor cortex (M1, Brodmann's area 4), particularly the area corresponding to the hand, is located within the central sulcus, and only a small portion of M1 appears on the precentral gyrus (White et al., 1997; Takahashi et al., 2002). Therefore, we modified the epidural method to a subdural method and incorporated implantation within the central sulcus. These modified methods are applied to the patients with neuropathic pain who had severe motor dysfunction, because dissection of the central sulcus may develop new motor deficit. We already reported the preliminary results (Saitoh et al., 2000, 2003).

Recently, repetitive transcranial magnetic stimulation (rTMS) of M1 has been applied in the treatment of neuropathic pain (Migita et al., 1995; Lefaucheur et al., 2004; Hirayama et al., 2006). In a few studies, a correlation between the efficacy of rTMS and that of MCS was reported, and it was suggested that rTMS trials had the potential to predict the efficacy of MCS (Andre-Obadia et al., 2006; Saitoh et al., 2006).

In this retrospective and exploratory study, we report the results, including long-term follow-up, obtained with our modified method with subdural electrodes placed on the precentral gyrus or within the central sulcus, in a consecutive series of 34 patients with intractable chronic neuropathic pain. The exploratory analyses of the relations between MCS efficacy and several clinical factors, including underlying disease and the pain reduction of rTMS of M1, are reported.

2. Methods

2.1. Subjects

Subjects comprised consecutive 34 patients (28 men, 6 women; mean age, 57.0 years; range, 28–76 years) suffering from intractable neuropathic pain. In a patient with an epidural electrode, the electrode was later changed to a subdural electrode because of a diminished stimulation effect (Saitoh et al., 2000). Patient characteristics and clinical data are summarized in Table 1. The mean history of pain was 5.4 years (range, 0.5–28 years). Eighteen patients had post-stroke pain; strokes were due to thalamic hemorrhage or infarction ($n = 11$), putaminal hemorrhage ($n = 3$), brainstem hemorrhage or infarction ($n = 3$), or temporoparietal subcortical infarction ($n = 1$). One patient had pain related to pontine injury. Other origins of pain included brachial plexus avulsion ($n = 7$), phantom-limb pain (all of lower limbs; $n = 4$), spinal cord lesion ($n = 2$), trigeminal neuropathic pain ($n = 1$) and peripheral nerve injury ($n = 1$). Patients were assigned to 1 of 2 groups according to the type of lesion: cerebral lesion group (patients C1–C19; 15 men, 4 women; mean age, 61.1 years; range, 50–76 years) or non-cerebral lesion group (patients N1–N15; spinal cord or peripheral lesion; 13 men, 2 women; mean age, 51.8 years; range, 28–74 years). Patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs), anti-anxiety drugs, anti-epileptic drugs and anti-depressants as required. Pain topography was localized on the right side in 14 patients, on the left side in 18 patients and bilaterally in 2 patients and concerned the entire half body in 2 patients, the face and upper limb in 2 patients, the upper limb and lower limb in 4 patients, the face in 2 patients, the upper limb in 14 patients and the lower limb in 10 patients. Twenty-nine of these patients were partly reported (Saitoh et al., 2000, 2003, 2006).

Eleven patients (10 men, 1 woman; mean age, 52.8 years; range, 28–74 years) underwent both rTMS and MCS. Of these, 5 had post-stroke pain; strokes were due to thalamic hemorrhage or infarction ($n = 2$), putaminal hemorrhage ($n = 2$) or brainstem infarction ($n = 1$). Other origins of pain included phantom-limb pain ($n = 2$), brachial plexus avulsion ($n = 1$), spinal cord lesion ($n = 1$), trigeminal neuropathic pain ($n = 1$) and peripheral nerve injury ($n = 1$). All patients treated with MCS underwent previous rTMS at Osaka University Hospital. Three of these patients were reported previously (Hirayama et al., 2006).

This study was approved by the Ethics Committee of Osaka University Hospital, and written informed consent was obtained from all patients participating in this study.

2.2. Surgical procedures

The surgical procedures used in this study were similar to those reported previously (Saitoh et al., 2000, 2003). The location of the central sulcus was identified with preoperative magnetic resonance (MR) imaging. Under general anesthesia, craniotomy of a 5×6 cm area was performed over the sensorimotor cortex corresponding to the painful area. A 20-grid electrode (4×5 array; 0.3-cm electrode diameter; 0.7-cm separation; Unique Medical Co., Tokyo, Japan) was placed subdurally, and the location of the central sulcus was confirmed by records of sensory-evoked potentials (SEPs). For upper limb and/or face pain in selected 12 patients, the arachnoid membrane of the central sulcus was carefully dissected and the vessels within that sulcus were made to be free with microsurgical procedure to expose the hidden lateral walls of precentral and postcentral gyri. One or two 4-plate electrodes [(0.3-cm electrode diameter; 0.7-cm separation; Unique Medical Co., Tokyo, Japan) or (Resume; Medtronic, Inc., Minneapolis, MN)] were implanted within the central sulcus, and a 20-grid electrode was implanted over the precentral gyrus corresponding to the painful region. To reduce stiffness of a Resume electrode, that was trimmed off (Fig. 1). Most of the implantations within the central sulcus were limited to patients with severe motor weakness or lack of hand function, avoiding deterioration of the sensorimotor function. Nine patients with lower limb pain underwent placement of a 4-plate electrode in the interhemispheric fissure. Two patients (C1 and N1) received epidural MCS.

After the implantation of test electrodes, electrical stimuli were delivered to various parts of the grid electrode and the 4-plate electrode at the hospital. One or 2 weeks after

Table 1
Patient characteristics and clinical data

Patient	Age (year)	Sex	Underlying disease	Treated painful region	History of pain (year)	Previous treatment	Current medication
C1	68	M	Lt thalamic hemorrhage	Rt hemi body	1.1	P	AA
C2	60	M	Lt putaminal hemorrhage	Rt lower limb	5.9	P, SCS	NSAID, AA, AE, AD
C3	68	M	Rt thalamic hemorrhage	Lt upper limb	1.3	P	AA, AD
C4	52	M	Rt thalamic infarction	Lt face, upper and lower limb	8.3	P, B	AA
C5	53	F	Pontine hemorrhage	Rt face, upper limb	2.5	P	AD
C6	67	M	Lt thalamic hemorrhage	Rt upper limb	1.4	P	AE
C7	59	M	Lt temporoparietal subcortical infarction	Rt lower limb	1	P	NSAID, AE
C8	58	M	Rt thalamic hemorrhage	Lt upper limb	7	P	AE, AD
C9	50	F	Rt pontine injury	Lt upper limb	3	P	AA
C10	64	M	Rt thalamic infarction	Lt upper limb	2	P	AA
C11	76	F	Lt pontine infarction	Lt face	2.1	P, TMS	AA
C12	66	M	Lt thalamic hemorrhage	Rt upper limb	4	P, B	AE
C13	64	M	Rt thalamic hemorrhage	Lt face, upper limb	3	P, B	NSAID, AA, AE
C14	54	F	Lt thalamic infarction	Rt upper and lower limb	2.3	P, SCS	
C15	71	M	Lt thalamic hemorrhage	Rt upper and lower limb	0.5	P, TMS	AA, AE
C16	62	M	Brainstem infarction	Rt upper limb	1.8	P, TMS	AA, AE
C17	56	M	Rt putaminal hemorrhage	Lt lower limb	15	P, B, TMS	
C18	55	M	Lt thalamic infarction	Rt upper and lower limb	1.5	P, TMS	AE
C19	57	M	Rt putaminal hemorrhage	Lt lower limb	6	P, SCS, TMS	AE, AD
N1	56	M	Lt brachial plexus avulsion	Lt upper limb	4.3	P, B, SCS, DREZ	NSAID, AE
N2	64	M	Lt brachial plexus avulsion	Lt upper limb	28	P, B, SCS	AA, AD
N3	62	M	Rt phantom-limb pain	Rt lower limb	6	P, B, SCS	NSAID, AA, AD
N4	53	M	Lt phantom-limb and stump pain	Lt lower limb	1.3	P, B, SCS	AD
N5	67	M	Rt brachial plexus avulsion	Rt upper limb	0.8	P, B	AA, AE, AD
N6	55	M	Lt brachial plexus avulsion	Lt upper limb	2.5	P, SCS	NSAID, AD
N7	51	F	Spinal cord injury	Lt upper limb, rt lower limb	1.5	P, B	NSAID, AE, AD
N8	59	M	Lt brachial plexus avulsion	Lt upper limb	10.2	P, B	NSAID, AA
N9	30	M	Lt brachial plexus avulsion	Lt upper limb	23	P	AE, AD
N10	28	M	Lt trigeminal pain	Lt face	1.8	P, B, TMS	AA
N11	28	M	Spinal cord injury	Rt lower limb	5	P, B, SCS, TMS	AA
N12	62	M	Bil phantom-limb pain	Bil lower limb	9	P, B, SCS, TMS	AE
N13	57	M	Lt phantom-limb pain	Lt lower limb	5.5	P, B, SCS, TMS	AA, AE, AD
N14	31	M	Lt brachial plexus avulsion	Lt upper limb	5.9	P, B, SCS, DREZ, TMS	AA, AD
N15	74	F	Rt peripheral nerve injury	Rt lower limb	10	P, B, SCS, TMS	AE, AD

M, male; F, female; lt, left; rt, right; bil, bilateral; P, pharmacologic therapy; SCS, spinal cord stimulation; B, nerve or ganglion block; TMS, transcranial magnetic stimulation; DREZ, surgery of the dorsal root entry zone; NSAID, non-steroidal anti-inflammatory drugs; AA, antianxiety drugs; AE, antiepileptic drugs; AD, antidepressants.

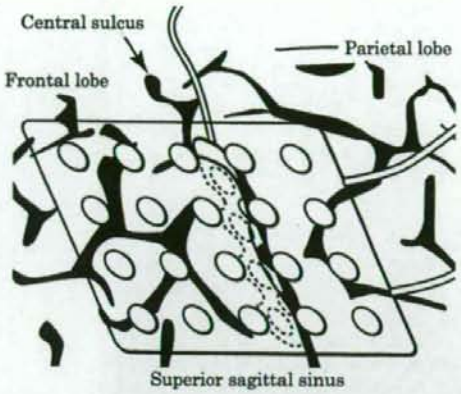

Fig. 1. Schematic drawing shows that a 4-plate electrode (Resume) implanted within the central sulcus, in addition to a 20-grid electrode placed on the brain surface. To reduce stiffness of a Resume electrode, that was trimmed off.

the surgery, a second surgery was performed under general anesthesia. The test electrodes were removed and a Resume electrode (Medtronic, Inc., Minneapolis, MN) was implanted after identification of the best location for pain relief. An implantable pulse generator (ITREL III; Medtronic, Inc.) was then placed subcutaneously in the chest or abdomen.

After implantation of all devices for MCS, electrical stimulation was performed on demand by the patients themselves. Chronic stimulation was usually applied continuously for 15–30 min on each occasion and 3–6 times a day.

2.3. rTMS

rTMS was applied through a navigation-guided figure-8 coil (MC B-70, Medtronic Functional Diagnosis A/S, Skovlunde, Denmark) which was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnosis A/S), more than 2 weeks before MCS in 11 patients. First, the resting motor threshold based on the electromyography in the affected muscle area was determined by stimulation of the corresponding M1 area. Muscle twitches in painful areas can be elicited, if stimulated carefully according to the somatotopy. This is possible even with trigeminal lesion and lower limbs. For the patients in whom muscle twitches in the painful areas were difficult to elicit due to severe damage of motor pathways, rTMS was applied with an intensity at 100 A/μs. In our study, 100 A/μs was the maximum tolerable intensity for most patients, with higher intensities resulting in scalp pain (Hirayama et al., 2006). An intensity of 90% of the resting motor threshold was used for treatment. Ten trains of 10-s 5-Hz TMS pulses, with a 50-s intertrain interval, were applied to the M1 area corresponding to the painful area. Thus, a total of 500 stimulations were applied. This protocol is in compliance with the guidelines for the safe use of rTMS (Wassermann, 1998). The TMS coil was held and positioned by an articulated coil holder. The Brainsight™ Frameless Navigation system (Rogue Research Inc., Montreal, Canada) was used to monitor the position and direction of the coil, and the position of the patient's head, as described previously (Hirayama et al., 2006).

2.4. Evaluation of pain relief

Pain intensity was evaluated in all patients before surgery, during the test stimulations and every 6 month on an outpatient basis by means of the visual analogue scale (VAS) and the short form of the McGill Pain Questionnaire (SF-MPQ). For patients who underwent rTMS, pain intensity was similarly evaluated before and after rTMS by VAS and SF-MPQ.

2.5. Statistical analysis

We evaluated the effectiveness of stimulation for each patient according to the reduction of VAS scores (reduction: $[1\text{-}VAS_{post\text{-}stimulation}/VAS_{pre\text{-}stimulation}] \times 100$). The difference in the positive effect (latest VAS reduction $\geqslant 50\%$) between the cerebral lesion group and the non-cerebral lesion group was analyzed by Fisher's exact test. Comparison of the VAS reduction in response to rTMS and MCS was made by two sided Wilcoxon's signed rank test. Linear relationship between VAS reduction in response to rTMS and MCS was analyzed by simple linear regression. Mann–Whitney test (the number of group = 2) or Kruskal–Wallis test (the number of group $\geqslant 3$) was applied to the comparison of VAS reduction in response to MCS and patient characteristics (age, sex, treated painful region, history of pain, presence or absence of cerebral lesions).

3. Results

3.1. Perioperative results

Twenty-seven of 34 patients showed various degrees of pain control in response to test stimulation. In the other 7 patients, various patterns of stimulation were tried without success. Results are summarized in Table 2. In 28 patients, one or two Resume electrodes were implanted in the optimal location as determined by test stimulation; one patient (N6) for whom test stimulation did not result in pain reduction (the mean reduction in VAS scores was 10%), nonetheless desired permanent Resume implants. In 27 patients, various stimulation patterns were evaluated with the use of grid electrodes to determine the optimal point for pain relief. M1 was identified as the optimal site for pain relief in all of these patients. In 12 selected patients, test electrodes were implanted both within the central sulcus and over the precentral gyrus. In 10 of these patients, test stimulation of M1 within the central sulcus

Table 2
Results of VAS after MCS

Patient	Treated painful region	Permanent electrodes	VAS reduction in test stimulation (%)	Latest VAS reduction (%)	Follow-up (month)	
C1	Rt hemi body	–	0	–	–	Not implanted
C2	Rt lower limb	I	60	60	88	
C3	Lt upper limb	S	30	20	23	Vegetative (ICH)
C4	Lt face, upper and lower limb	–	0	–	–	Not implanted
C5	Rt face, upper limb	–	0	–	–	Not implanted
C6	Rt upper limb	–	0	–	–	Not implanted
C7	Rt lower limb	I	30	10	72	
C8	Lt upper limb	S	88	60	75	
C9	Lt upper limb	CS	40	40	73	
C10	Lt upper limb	CS	100*	–	–	Removal (11 month)
C11	Lt face	CS	25	15	58	
C12	Rt upper limb	CS	25	10	54	
C13	Lt face, upper limb	CS	80	80	50	
C14	Rt upper and lower limb	CS, I	90	0	49	
C15	Rt upper and lower limb	–	0	–	–	Not implanted
C16	Rt upper limb	S	63	50	33	
C17	Lt lower limb	S	73	15	15	Removal (15 month)
C18	Rt upper and lower limb	S, I	21	20	14	
C19	Lt lower limb	S	75	50	13	
N1	Lt upper limb	E → S	75	10	112	
N2	Lt upper limb	S	90	80	36	Death (ICH)
N3	Rt lower limb	I	90	90	54	Death (gastric cancer)
N4	Lt lower limb	I, S	30	–	–	Removal (6 month)
N5	Rt upper limb	–	0	–	–	Not implanted
N6	Lt upper limb	S	10	5	76	Removal (76 month)
N7	Lt upper limb, rt lower limb	CS, I	89	65	75	
N8	Lt upper limb	CS	30	–	–	Removal (9 month)
N9	Lt upper limb	CS	50	50	50	
N10	Lt face	S	93	–	–	<6 month follow
N11	Rt lower limb	S	50	60	27	
N12	Bil lower limb	I, I**	38	–	–	<6 month follow
N13	Lt lower limb	S	44	–	–	Removal (5 month)
N14	Lt upper limb	CS	71	57	19	
N15	Rt lower limb	I	40	60	17	

lt, left; rt, right; bil, bilateral; S, subdural precentral gyrus surface; I, interhemispheric fissure; CS, central sulcus; E, epidural space; *, without stimulation; **, bilateral implant.

was more effective than that on the precentral gyrus, and a Resume electrode was implanted within the central sulcus. To reduce lower limb pain in 9 patients, a Resume electrode was implanted in the interhemispheric fissure. Among the 34 patients, improvement in the VAS score of $\geqslant 50\%$ was observed in 16 patients (47%) at the time of discharge.

Some patients experienced paresthesias of the painful region in response to MCS. The patients for whom stimulation was successful experienced paresthesias of the painful region. Most of the patients in this study experienced persistent pain before MCS. Patients N8 and N9 complained of both persistent and shooting pain. MCS was only effective against persistent pain.

MCS and rTMS did not make a constant change in SF-MPQ scores. In the patients with a high SF-MPQ score of pre-stimulation, the results of VAS and SF-MPQ tended to be similar. In those with a low SF-MPQ score of pre-stimulation, scores changed little, despite the reduction in VAS scores.

3.2. Postoperative follow-up

Two patients (N10 and N12) with peripheral neuropathic pain were excluded from the evaluation of latest pain relief because they could not be followed up for $\geqslant 12$ months. Effectiveness of MCS, as indicated by improvement in the VAS score of $\geqslant 50\%$, was maintained in 12 of 32 patients (36%) with follow-up periods of $\geqslant 12$ months. The mean follow-up period in patients who used implanted MCS for $\geqslant 12$ months was 50.7 months (range, 13–112 months). In 6 patients, the implants, including electrodes and pulse generator, were removed because of insufficient pain relief. Among the 10 patients with electrodes placed within the central sulcus, improvement in the VAS score of $\geqslant 50\%$ was observed in 6 patients (60%) at the time of the test stimulation and in 4 patients (40%) in the follow-up period. Patient C10 showed excellent pain reduction without electrical stimulation just after the electrode was implanted within the central sulcus. This pain relief in response to dissection

Table 3
Relationship between clinical factors and MCS efficacy

		VAS reduction in test stimulation (%)		Latest VAS reduction (%)	
		Mean (*n*)	*p* value	Mean (*n*)	*p* value
Age (year)	<60	50.5 (19)	0.508	34.0 (13)	0.122
	⩾60	42.7 (15)		51.7 (9)	
Sex	Male	47.0 (28)	0.982	42.8 (17)	0.753
	Female	47.3 (6)		36.0 (5)	
Cerebral lesion	+	42.1 (19)	0.243	33.1 (13)	0.131
	−	53.3 (15)		53.0 (9)	
Face pain	+	33.0 (6)	0.266	47.5 (2)	0.688
	−	50.1 (28)		40.6 (20)	
Upper limb pain	+	43.3 (22)	0.320	39.1 (14)	0.583
	−	54.0 (12)		45.0 (8)	
Lower limb pain	+	45.6 (16)	0.849	43.0 (10)	0.642
	−	48.3 (18)		39.8 (12)	
Pain laterality	Right	33.5 (14)	0.135	40.0 (9)	0.492
	Left	55.8 (18)		40.2 (12)	
	Bilateral	63.5 (2)		65.0 (1)	
History of pain (year)	<5	40.1 (20)	0.135	27.1 (12)	0.013*
	⩾5	57.1 (14)		58.2 (10)	

No significant differences were observed between improvement in VAS score and age, sex, presence or absence of cerebral lesion or treated painful region (Mann–Whitney test and Kruskal–Wallis test). The history of pain (⩾5 years or <5 years) contributed to the latest pain reduction as determined by the reduction of VAS scores (*$p = 0.013$, Mann–Whitney test).

of the central sulcus was maintained for several months, but the pain gradually returned. In patient N1, granulation tissue under the epidural electrode resulted in a decreasing level of pain relief over time, and the electrode was repositioned in the subdural space 6 months after the first placement.

There was no death related to MCS, but patients N2 and C3 developed cerebral hemorrhage during the follow-up period. Patient N2 died, and patient C3 remains in a vegetative state.

3.3. Correlation between MCS effectiveness and clinical factors

In the cerebral lesion group, improvement in the VAS score of ⩾50% was observed in 8 of 19 patients (42%) at the time of the test stimulation and in 5 of 19 patients (26%) during follow-up periods of ⩾12 months. In the non-cerebral lesion group, improvement in the VAS score of ⩾50% was observed in 8 of 15 patients (53%) at the time of the test stimulation and in 7 of 13 patients (54%) during follow-up periods of ⩾12 months. The absolute numbers suggested that MCS was more effective in the non-cerebral lesion group than in the cerebral lesion group. However, this difference did not reach significance (latest VAS reduction ⩾50%; $p = 0.15$).

No significant differences were observed between improvement in the VAS score and age, sex, presence or absence of cerebral lesion or treated painful region. The history of pain (⩾5 years or <5 years) contributed to the latest pain reduction value as determined by the reduction of VAS scores ($p = 0.013$) (Table 3).

3.4. Correlation between effectiveness of MCS and that of rTMS

Eleven patients underwent preoperative rTMS of M1 (Table 4). Ten showed some pain reduction with MCS and rTMS (mean VAS reductions were 51.6% and 38.6%, respectively, $p = 0.019$). The effect of rTMS lasted for 3 h after the stimulation in most of patients. Simple linear regression indicated that the pain reduction obtained with rTMS contributed to that obtained with MCS during test stimulation ($p = 0.0021$) (Fig. 2).

3.5. Complications

Postoperative infection occurred in 3 patients (N7, N8 and N11). They received antibiotics and in two of them devices were removed. After infection was cured, MCS device was implanted again in one of them. Transient mild paresis and numbness occurred in response to dissection of the central sulcus in 2 patients (C10 and C14), and patient C19 showed transient mild paresis of lower limb after implantation in the interhemispheric fissure, which was improved several weeks later. Patients C12 and C17 experienced uncomfortable paresthesias with MCS.

Table 4
Summary of 11 patients who underwent rTMS before MCS

Patient	Age (year)	Sex	Underlying disease	Treated painful region	MCS VAS reduction in test stimulation (%)	rTMS (5 Hz) VAS reduction (%)
C15	71	M	Lt thalamic hemorrhage	Rt upper and lower limb	0	0
N10	28	M	Lt trigeminal pain	Lt face	93	57
C16	62	M	Brainstem infarction	Rt upper limb	63	67
C17	56	M	Rt putaminal hemorrhage	Lt lower limb	73	60
N11	28	M	Spinal cord injury	Rt lower limb	50	38
N12	62	M	Bil phantom-limb pain	Bil lower limb	38	50
N13	57	M	Lt phantom-limb pain	Lt lower limb	44	30
N14	31	M	Lt brachial plexus avulsion	Lt upper limb	71	56
N15	74	F	Rt peripheral nerve injury	Rt lower limb	40	20
C18	55	M	Lt thalamic infarction	Rt upper limb	21	12
C19	57	M	Rt putaminal hemorrhage	Lt lower limb	75	35

M, male; F, female; lt, left; rt, right; bil, bilateral.

4. Discussion

In this study, MCS was effective in 47% of patients just after implantation and in 36% after a follow-up period of ⩾12 months. Test stimulation of M1 within the central sulcus was more effective than subdural stimulation on the precentral gyrus in 10 of 12 cases. However, chronic stimulation within the central sulcus did not improve long-term results in these selected cases. Neuropathic pain caused by cerebral lesion was suggested to be more refractory to MCS than that caused by non-cerebral lesion, although the difference was not significant. The short-term pain reduction of rTMS correlated well with that of MCS.

Katayama et al. (1998) reported a positive effect of MCS (pain reduction ⩾60%) in 15 of 31 patients (48%) with post-stroke pain over a follow-up period of >2 years. A positive effect (pain reduction ⩾50%) in 7 of 12 patients (58%) with trigeminal neuropathic pain was reported by Nguyen et al. (1999). Pain relief (pain reduction ⩾30%) in 5 of 10 patients (50%) with trigeminal neuropathic pain and 3 of 7 patients (43%) with post-stroke pain were reported by Rasche et al. (2006). In a recent review of 28 studies involving 271 patients, ⩾50% pain relief by MCS was provided in nearly 60% of patients: 82 of 159 (52%) post-stroke pain patients and 33 of 45 (73%) trigeminal neuropathic pain patients with follow-up periods of several months to a few years (Saitoh and Yoshimine, 2007). Our modified MCS method (subdural electrode implantation on the precentral gyrus or within the central sulcus) did not seem to improve long-term results.

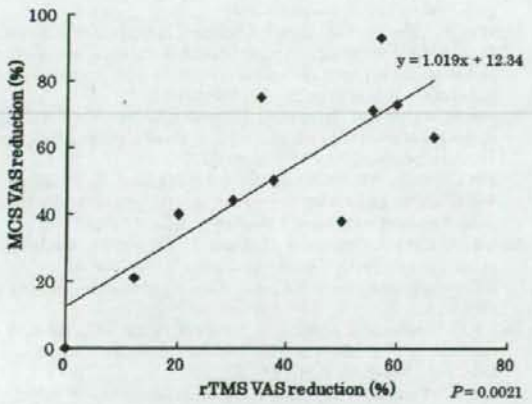

Fig. 2. Relation between short-term VAS reduction in response to rTMS and MCS. Simple linear regression indicated that the pain reduction in response to rTMS contributed to that in response to MCS on test stimulation or discharge ($p = 0.0021$).

Previous reports have described the implantation of epidural electrodes over the precentral gyrus (Meyerson et al., 1993; Tsubokawa et al., 1993; Katayama et al., 1998; Nguyen et al., 1999; Rasche et al., 2006). The main portion of M1 (Brodmann's area 4), particularly the area corresponding to the hand, is located within the central sulcus, with a small portion on the precentral gyrus surface (White et al., 1997; Takahashi et al., 2002). In our series, test stimulation of M1 within the central sulcus, which made it possible to stimulate M1 directly, was more effective than subdural stimulation on the precentral gyrus in most cases (10 of 12 cases). This result did not mean merely advantage of stimulation within the central sulcus in all cases, because transient mild paresis and numbness did occasionally occur in response to dissection of the central sulcus. In this study, selected patients with severe motor weakness or lack of hand function underwent MCS within the central sulcus, avoiding deterioration of the sensorimotor function. For these selected patients, stimulation within the central sulcus showed better results during the test stimulation, whereas chronic stimulation within the central sulcus did not improve long-term results. Therefore a further study is needed to elucidate the effect of the stimulation within the central sulcus. Initial surgical reports showed that combined removal of the precentral and postcentral cortices produced long-term pain relief in 2 patients (Lende et al., 1971). That report may consist with our findings that transient pain relief without electrical stimulation was obtained in the present study by intraoperative manipulation to dissect the central sulcus.