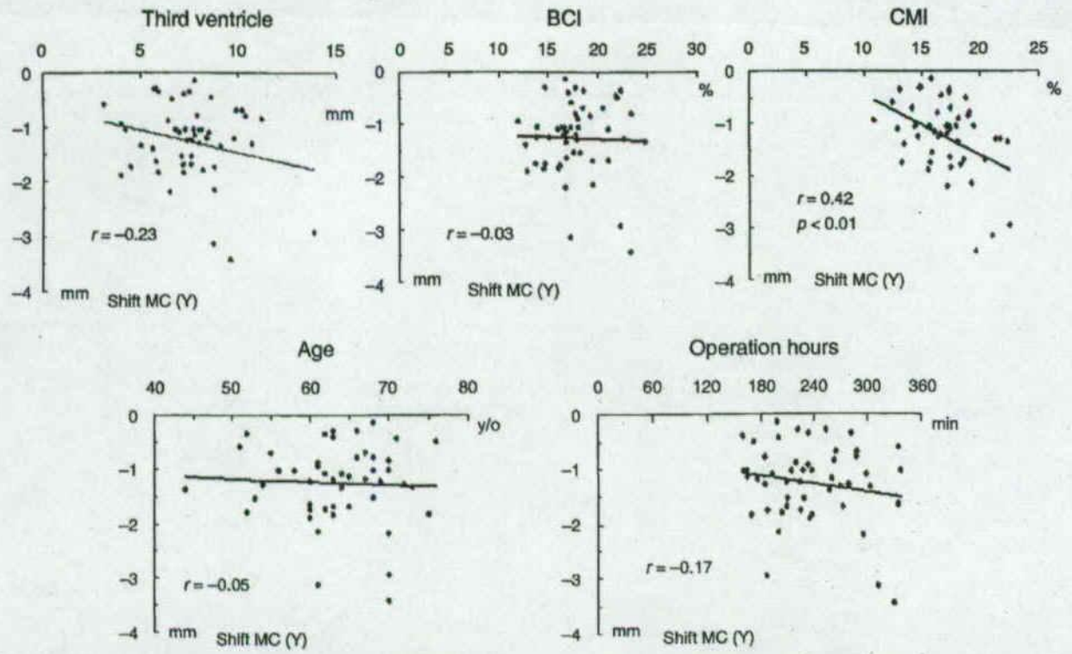

FIGURE 6. Comparison between the posterior shift of midcommissure (MC) and predicting factors for brain shift. Third ventricle, width of the third ventricle; BCI, bicaudate index; CMI, cella media index; age, patient's age; operation hours, from start of drilling the burr hole to the completion of deep brain stimulation electrode implantation.

the correlation of the shift of the MC with the width of the third ventricle, BCI, CMI, age, and operation hours. Among these items, only the CMI demonstrated a significant correlation with the shift of the MC. In our study, 16 of the 50 STN-DBS cases revealed a more than 1.5-mm brain shift in the posterior direction. Logistic regression analysis of the two different groups indicated that both groups showed a significant difference in CMI only. The width of the third ventricle and BCI demonstrated no significant differences. The BCI represents the anterior part of the lateral ventricle, but the CMI represents the body part of the lateral ventricle. Our findings suggest that the enlargement of the body part of the lateral ventricle, which represents the actual enlargement of the lateral ventricle, is the most reliable factor predicting an intraoperative brain shift.

There are several factors which can account for differences between the initial and intraoperative final targets: These include MR image distortion (16), brain shift (13,15) caused by CSF leakage and air influx, the neurophysiologic method (17–22) of finding the best target, and technical error. Zonenshayn et al. (23) reported that the average distance error between the final physiologic targets and the MRI-derived target was 2.6 ± 1.3 mm. Andrade-Souza et al. (24) reported that the mean distances between the optimal contact position and the planned target were 3.19 ± 1.19 mm using the red nucleus-based method, 3.42 ± 1.34 mm using indirect targeting, and 4.66 ± 1.33 mm using a modified direct targeting. These differences between the optimal contact position and the planned target involve not only brain shifts but also other factors as described above. We evaluated the differences in pre- and postoperative MC locations on three-dimensional MR images, and this difference in MC location proved useful for evaluating the brain shift itself during the stereotactic operation.

Once the location of the STN at the first side was identified by microelectrode recording and the chronic DBS electrode was implanted, the second side targeting of the STN was found to be almost the same as that of the first side in the present study. This result indicates that the difference in shift of the STN in the posterior direction is small between the first and second operated sides when our operation method is employed, including the head position, location of the burr hole, and early bilateral burr-hole formation with an intact dura. We have implanted unilateral chronic DBS electrodes by the same operation method in 12 cases which included dystonia, tremor, and Parkinson's disease. In these 12 cases, the shift of the MC in the posterior direction was 0.87 ± 0.87 mm. The shift of the MC to the posterior direction after the bilateral chronic DBS electrode implantation in this study was 1.27 ± 0.70 mm, and the difference of MC shift in the posterior direction as compared with the unilateral DBS electrode implantation with our method was thus only 0.40 mm.

In order to determine the brain shift in real time during the stereotactic operation, the use of intraoperative ultrasound and intraoperative MR imaging is considered promising. If the correlation of the brain shift between the STN and cortical surface or anterior horn is examined as in this study, intraoperative estimation of the brain shift of the cortical surface or anterior horn by intraoperative ultrasound or intraoperative MR imaging can be used as a method of real-time monitoring. In addition, direct targeting of the STN which can identify the whole shape of the STN employing intraoperative MR imaging may prove to be an ideal method in the future.

Conclusion

We utilized the same conditions for head elevation and burr-hole location in STN-DBS for cases of advanced Parkinson's disease, and compared the pre- and postoperative MR images employing SurgiPlan. The shift of the MC was mainly in the posterior direction, and the most reliable predictive factor for a brain shift was the CMI, which is helpful for evaluating the enlargement of the body part of the lateral ventricle. Determinations of the shift direction and predictive factors for a brain shift are useful for achieving accurate targeting during stereotactic surgery.

Acknowledgments

The present work was supported by grants from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan (Grants No. A-15209047 and No. C-18591614) and a grant for the promotion of industry–university collaboration at Nihon University.

Conflict of Interest

The authors reported no conflict of interest.

References

1. Katayama Y, Kasai M, Oshima H et al. Subthalamic nucleus stimulation for Parkinson's disease: benefits observed in levodopa-intolerant patients. *J Neurosurg* 2001;95:213–221.

2. Krack P, Batir A, Van Blercom N et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;349:1925–1934.

3. Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L. Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. *J Neurol Neurosurg Psychiatry* 2002;72:53–58.

4. Limousin P, Krack P, Pollak P et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;339:1105–1111.

5. The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med* 2001;345:956–963.

6. Priori A, Egidi M, Pesenti A et al. Do intraoperative microrecordings improve subthalamic nucleus targeting in stereotactic neurosurgery for Parkinson's disease? *J Neurosurg Sci* 2003;47:56–60.

7. Rodriguez-Oroz MC, Rodriguez M, Guridi J et al. The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. *Brain* 2001;124:1777–1790.

8. Romanelli P, Heit G, Hill BC et al. Microelectrode recording revealing a somatotopic body map in the subthalamic nucleus in humans with Parkinson's disease. *J Neurosurg* 2004;100:611–618.

9. Starr PA, Christine CW, Theodosopoulos PV et al. Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging-verified lead locations. *J Neurosurg* 2002;97:370–387.

10. Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C. Dual-floor burr hole adjusted to burr-hole ring and cap for implantation of stimulation electrodes. *J Neurosurg* 2003;99:783–784.

11. Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. *J Neurosurg* 2004;101:201–209.

12. Yamamoto T, Katayama Y, Fukaya C, Oshima H, Kasai M, Kobayashi K. New method of deep brain stimulation therapy with two electrodes implanted in parallel and side by side. *J Neurosurg* 2001;95:1075–1078.

13. Wester K, Krakenes J. Vertical displacement of the brain and the target area during open stereotaxic neurosurgery. *Acta Neurochirur (Wien)* 2001;143:603–606.

14. Pollo C, Vingerhoets F, Pralong E et al. Localization of electrodes in the subthalamic nucleus on magnetic resonance imaging. *J Neurosurg* 2007;106:36–44.

15. Winkler D, Tittgemeyer M, Schwarz J et al. The first evaluation of brain shift during functional neurosurgery by deformation field analysis. *J Neurol Neurosurg Psychiatry* 2005;76:1161–1163.

16. Bourgeois G, Magnin M, Morel A et al. Accuracy of MRI-guided stereotactic thalamic functional neurosurgery. *Neurosurgery* 1999;41:636–645.

17. Hamid NA, Mitchell RD, Mocroft P, Westby GW, Milner J, Pall H. Targeting the subthalamic nucleus for deep brain stimulation: technical approach and fusion of pre- and postoperative MR images to define accuracy of lead placement. *J Neurol Neurosurg Psychiatry* 2005;76:409–414.

18. Hutchison WD, Allan RJ, Opitz H et al. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. *Ann Neurol* 1998;44:622–628.

19. Lopez-Flores G, Miguel-Morales J, Teijeiro-Amador J et al. Anatomic and neurophysiological methods for the targeting and lesioning of the subthalamic nucleus: Cuban experience and review. *Neurosurgery* 2003;52:817–830.

20. Starr PA, Vitek JL, DeLong M, Bakay RA. Magnetic resonance imaging-based stereotactic localization of the globus pallidus and subthalamic nucleus. *Neurosurgery* 1999;44:303–313.

21. Sterio D, Zonenshayn M, Mogilner AY et al. Neurophysiological refinement of subthalamic nucleus targeting. *Neurosurgery* 2002;50:58–67.

22. Yokoyama T, Sugiyama K, Nishizawa S et al. Neural activity of the subthalamic nucleus in Parkinson's disease patients. *Acta Neurochir (Wien)* 1998;140:1287–1290.

23. Zonenshayn M, Rezai AR, Mogilner AY, Beric A, Sterio D, Kelly PJ. Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. *Neurosurgery* 2000;47:282–292.

24. Andrade-Souza YM, Schwalb JM, Hamani C et al. Comparison of three methods of targeting the subthalamic nucleus for chronic stimulation in Parkinson's disease. *Neurosurgery* 2005;56(2 Suppl.):360–368.

NEUROMODULATION: TECHNOLOGY AT THE NEURAL INTERFACE

Volume 11 • Number 4 • 2008
http://www.blackwell-synergy.com/loi/ner

ORIGINAL ARTICLE

Intrathecal Drug Delivery Device Infection and Meningitis due to *Mycobacterium Fortuitum*: A Case Report

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ABSTRACT

Intrathecal drug delivery device infection with *Mycobacterium fortuitum* has not been reported previously. We report a case of an implanted baclofen pump infection and associated mycobacterium meningitis due to *Mycobacterium fortuitum*. The entire pump system was removed and the patient was treated successfully with a prolonged regimen of antibiotics.

KEY WORDS: *Baclofen pump infection, intrathecal drug delivery device, meningitis,* Mycobacterium fortuitum.

Introduction

Baclofen is a muscle relaxant, antispastic agent, and γ-aminobutyric acid agonist that acts at the spinal cord level to inhibit the release of excitatory neurotransmitters (eg, glutamate, aspartate) by inhibiting Ca^{2+} influx into presynaptic terminal. Baclofen may be administered directly into the intrathecal space. Doing so allows for much smaller drug doses to achieve therapeutic effects compared with oral administration, which had bioequivalent doses may be associated with an increased incidence of side-effects.

Intrathecal baclofen therapy using programmable implantable pumps is widely acknowledged to be clinically effective in the treatment of intractable spasticity of either spinal or cerebral origin by reducing muscle tone and spasm (1–3). However, implantation of such intrathecal drug delivery devices (IDDD) is associated with complications (4). Such complications include skin breakdown and infection at the pump implantation site, meningitis, cerebrospinal fluid leak, or mechanical problems such as catheter kinking or break.

Intrathecal drug delivery device infection is reported to occur in 1–2% of cases (4). These infections are usually due to organisms of low virulence. The organisms most implicated in shunt infections are the coagulase-negative staphylococci, such as *Staphylococcus epidermidis* which accounts for 50–75% of infections. The next most frequent causes of infection include *Staphylococcus aureus*, Gram-negative enteric bacteria, and anaerobic diphtheroids.

Case Report

A 60-year-old man with a history of an incomplete cervical spinal cord injury from a fall presented with progressively worsening spasticity. He presented to the Duke University Medical Center with significant quadriparesis and he was started on intravenous methylprednisolone. Computed tomography (CT) of his cervical spine revealed severe central canal stenosis at C5–6 due to degenerative disease as well as moderate central canal stenosis at C4–5 and C6–7 secondary to central disc protrusions and focal osteophyte at C7 but no acute fractures. CT of his thoracic

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Clinical Neurophysiology 119 (2008) 993–1001

www.elsevier.com/locate/clinph

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

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Accepted 22 December 2007
Available online 10 March 2008

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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1388-2457/$34.00
doi:10.1016/j.clinph.2007.12.022

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.

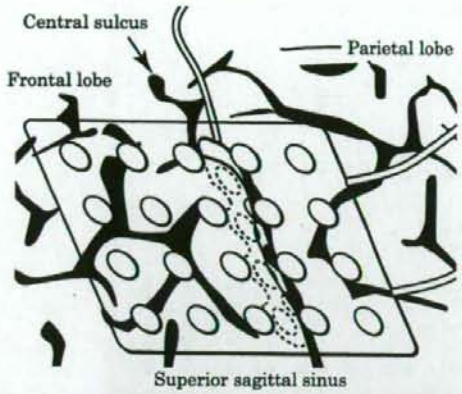

Fig. 1. Schematic drawing shows that a 4-plate electrode (Resume) implanted within the central sulcus, in addition to a 20-grid electrode placed on the brain surface. To reduce stiffness of a Resume electrode, that was trimmed off.

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 ⩾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 ⩾12 months. Effectiveness of MCS, as indicated by improvement in the VAS score of ⩾50%, was maintained in 12 of 32 patients (36%) with follow-up periods of ⩾12 months. The mean follow-up period in patients who used implanted MCS for ⩾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 ⩾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.

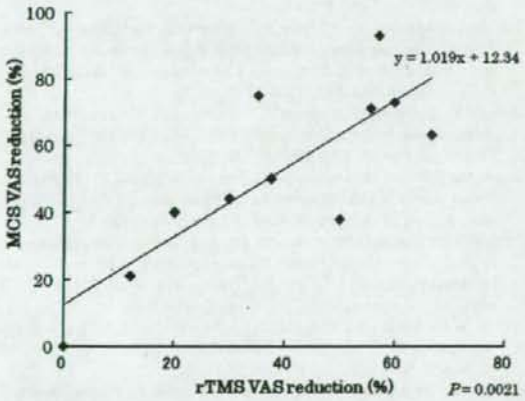

Fig. 2. Relation between short-term VAS reduction in response to rTMS and MCS. Simple linear regression indicated that the pain reduction in response to rTMS contributed to that in response to MCS on test stimulation or discharge ($p = 0.0021$).

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.

Reported predictive factors of MCS efficacy in post-stroke pain patients include the absence of severe motor weakness (Katayama et al., 1998), some types of pain, such as trigeminal neuropathic pain (Rasche et al., 2006), and good pain relief with rTMS of M1 (Andre-Obadia et al., 2006; Saitoh et al., 2006). In the present study, pain relief was not associated with patient characteristics (age, sex, presence or absence of cerebral lesion, treated painful region). The latest pain reduction in patients with longer pain duration history ($\geqslant$5 years) was statistically larger than that in the others (<5 years), however, this relationship might be confounded by other variables that were not tested in this study.

The effects of MCS differ according to the lesion causing intractable pain. Post-stroke pain and trigeminal neuropathic pain are both improved significantly by MCS. However, in several reports, trigeminal neuropathic pain appears to respond more favorably than post-stroke pain (Rasche et al., 2006; Saitoh and Yoshimine, 2007). We recently reported that subthreshold high-frequency rTMS of M1 was more effective in patients with spinal cord or peripheral lesions than in those with cerebral lesions (Saitoh et al., 2007). In the present study, MCS was also suggested to be more effective in patients with non-cerebral lesions than in those with cerebral lesions, although the difference was not significant.

The detailed mechanisms underlying the effect of MCS remain to be elucidated. Several positron emission tomography activation studies suggested that MCS might activate the thalamus, anterior cingulate, orbitofrontal cortex and upper brainstem which related the affective-emotional component of chronic pain and the descending inhibition of pain (Garcia-Larrea et al., 1999; Kishima et al., 2007). Katayama et al. (1998) speculated that the pain control afforded by MCS requires neuronal circuits maintained by the presence of intact corticospinal neurons originating from M1. These findings suggested several brain regions and pathways might somewhat play a role in pain relief provided by MCS. Our findings that MCS appeared to be more effective in patients without cerebral lesion were consistent with this concept.

Based on the success of MCS, rTMS is now being applied to intractable neuropathic pain. It was reported that high-frequency rTMS (5 Hz or 10 Hz) of M1 resulted in significant but transient relief of intractable neuropathic pain (Migita et al., 1995; Lefaucheur et al., 2001, 2004; Hirayama et al., 2006; Saitoh et al., 2007). It has been suggested that results with rTMS may predict the effectiveness of MCS in the treatment of neuropathic pain. In a few recent studies, a correlation between the efficacy of rTMS and that of MCS was reported (Migita et al., 1995; Lefaucheur et al., 2004; Andre-Obadia et al., 2006; Saitoh et al., 2006). In the present study, the rate of pain reduction in response to rTMS was significantly correlated with that of MCS over the short term. Although it needs a further study, our results suggested that preoperative rTMS would be helpful in selection of MCS candidates.

Acknowledgement

This study was supported by Ministry of Health, Labor and Welfare, Japan.

References

Andre-Obadia N, Peyron R, Mertens P, Mauguiere F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. Clin Neurophysiol 2006;117:1536–44.

Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 1999;83:259–73.

Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, et al. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain 2006;122:22–7.

Katayama Y, Fukaya C, Yamamoto T. Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 1998;89:585–91.

Kishima H, Saitoh Y, Osaki Y, Nishimura H, Kato A, Hatazawa J, et al. Motor cortex stimulation in patients with deafferentation pain: activation of the posterior insula and thalamus. J Neurosurg 2007;107:43–8.

Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport 2001;12:2963–5.

Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 2004;75:612–6.

Lende RA, Kirsch WM, Druckman R. Relief of facial pain after combined removal of precentral and postcentral cortex. J Neurosurg 1971;34:537–43.

Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P. Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl (Wien) 1993;58:150–3.

Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery 1995;36:1037–9, discussion 9–40.

Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, et al. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 1999;82:245–51.

Rasche D, Ruppolt M, Stippich C, Unterberg A, Tronnier VM. Motor cortex stimulation for long-term relief of chronic neuropathic pain: a 10 year experience. Pain 2006;121:43–52.

Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T. Motor cortex stimulation for central and peripheral deafferentation pain. Report of eight cases. J Neurosurg 2000;92:150–5.

Saitoh Y, Kato A, Ninomiya H, Baba T, Shibata M, Mashimo T, et al. Primary motor cortex stimulation within the central sulcus for treating deafferentation pain. Acta Neurochir Suppl 2003;87:149–52.

Saitoh Y, Hirayama A, Kishima H, Oshino S, Hirata M, Kato A, et al. Stimulation of primary motor cortex for intractable deafferentation pain. Acta Neurochir Suppl 2006;99:57–9.

Saitoh Y, Yoshimine T. Stimulation of primary motor cortex for intractable deafferentation pain. In: Sakas DE, Simpson BA, editors. Operative neuromodulation 2007;vol. 2. Wein: Springer; 2007. p. 51–6.

Saitoh Y, Hirayama A, Kishima H, Shimokawa T, Oshino S, Hirata M, et al. Reduction of intractable deafferentation pain due to spinal cord

or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex. J Neurosurg 2007;107:555–9.

Son UC, Kim MC, Moon DE, Kang JK. Motor cortex stimulation in a patient with intractable complex regional pain syndrome type II with hemibody involvement. Case report. J Neurosurg 2003;98:175–9.

Takahashi N, Kawamura M, Araki S. Isolated hand palsy due to cortical infarction: localization of the motor hand area. Neurology 2002;58:1412–4.

Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 1991;52:137–9.

Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 1993;78:393–401.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16.

White LE, Andrews TJ, Hulette C, Richards A, Groelle M, Paydarfar J, et al. Structure of the human sensorimotor system: I. Morphology and cytoarchitecture of the central sulcus. Cereb Cortex 1997;7:18–30.

15) Saitoh, Y., Hirayama, A., Kishima, H., Oshino, S., Hirata, M. Kato, A., Yoshimine, T., Stimulation of primary motor cortex for intractable deafferentation pain, Acta Neurochir. Suppl., 99 (2006) 57-59.
16) Saitoh, Y., Yoshimine, T., Stimulation of primary motor cortex for intractable deafferentation pain, Acta Neurochir. Suppl., 97 (2007) 51-56.
17) Speer, A.M., Kimbrell, T.A., Wassermann, E.M., Repella, J.D., Willis, M.W., Herscovitch, P., Post, R.M., Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients, Biol. Psychiatry, 48 (2000) 1133-1141.
18) Tamura, Y., Okabe, S., Ohnishi, T., Saito, D.N., Arai, N., Mochio, S., Inoue, K., Ugawa, Y., Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin, Pain, 107 (2004) 107-115.

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Mechanistic analysis of motor cortex stimulation for phantom limb pain

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[Received 7 December 2007, Accepted 22 January 2008]

Abstract

Phantom limb pain and other deafferentation pain are characterized by changes in cortical processing and organization (cortical reorganization), poor response to conventional treatments. Whereas several studies reported a close relationship between imagery movements of the amputated or paralyzed limb and the intractable pain, the alterations in the motor cortex related to the imagery movements has not yet been explored in detail. Here, we studied the electrocorticogram (ECoG) of sensorimotor cortex in deafferentation pain to reveal the relationship between some imagery movement tasks and the dynamical pattern of ECoG during the tasks. A clear correlation between the ECoG and imagery movements was observed in a patient who well responded to motor cortex stimulation (MCS). On the other hand, there was little correlation between them in a patient who did not respond to MCS. For the former patient, the optimal stimulation site for MCS located around the primary motor cortex, where the pattern of ECoG well differentiated among types of imagery movements. We will discuss the relation between imagery movements and the effects of MCS.

Key words: Cortical reorganization; Phantom limb pain; Deafferentation pain; Imagery movements, Motor cortex stimulation

幻肢痛に対する大脳皮質刺激療法のメカニズム解析

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はじめに

外傷などの神経損傷で四肢からの神経連絡が絶たれた後に，損傷した神経に関連した部位が激しく痛む求心路遮断性疼痛は多くの場合に難治性であり治療に苦慮する[12]．近年，動物実験やヒトでの観察から，求心路遮断後に体性感覚野や運動野で著明な大脳皮質再構築（cortical reorganization: CR）が生じることが明らかになり，求心路遮断性疼痛患者における疼痛とCRの程度との間に相関関係が報告されている[4,5,8,13,16]．また，求心路遮断性疼痛である幻肢痛患者に鏡を用いたリハビリテーション（鏡療法）などを行い，患者が切断肢（幻肢）の運動のイメージを取り戻すことで幻肢痛が改善されることから，運動想起の変化と幻肢痛，CRとの関係が検討されている[6,15]．難治性求心路遮断性疼痛の発生機序解明と治療には体性感覚野や運動野でのダイナミックな変化に注目する必要がある．

我々は難治性求心路遮断性疼痛に対して，感覚運動野上に硬膜下電極を留置し，大脳皮質を電気刺激（motor cortex stimulation: MCS）することで疼痛が軽減することを報告してきた[14]．しかし，MCSによる求心路遮断性疼痛軽減のメカニズムは明らかでなく，個人個人におけるMCSの効果を的確に予測することは難しい．今回，我々は求心路遮断性疼痛に対してMCSが著効した症例と無効であった症例について，運動想起を行った際の皮質脳波活動を比較検討した．MCS著効症例では，想起する運動種類毎に皮質脳波活動が特異的な活動パターンを示すのに対し，無効症例では想起する運動種類毎の特異的なパターンが認められなかった．運動想起時の皮質脳波活動パターンとMCSとの関係について論じる．

症例と方法

大阪大学脳神経外科でMCSを施行した末梢神経障害による難治性求心路遮断性疼痛患者12例中，特にMCSが有効であった症例と無効であった症例各1例を解析の対象とした．症例1は31歳男性，バイク事故による左腕神経叢引き抜き損傷の患者である．事故直後より左上肢にVisual analog scale（VAS: 視覚的アナログ尺度）6～8程度の痛みが出現し難治であった．発症より5年後に当科でMCSを施行し，VASは1～3まで低下しMCSが著効した．症例は患側上肢の神経移行術を受けていたが，運動の想起も行うことができた．症例2は46歳男性，転落事故による左上腕切断の幻肢痛患者である．VAS 8程度の幻肢痛が事故直後より発生し難治であったため，発症4年後に当科でMCSを施行したが，疼痛改善を認めなかった．症例は幻肢の指先を軽度屈曲させる程度の運動しか想起できなかった．

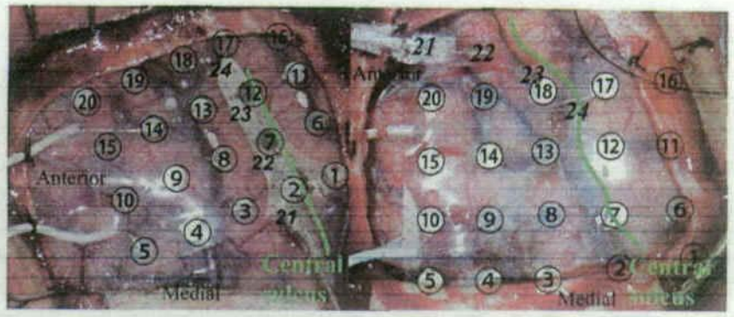


Fig.1 Location of implanted subdural electrodes.
Two pictures of brain surface and subdural electrodes were taken at the surgery of patient 1 (left) and 2 (right). For each patient, grid and strip arrays of planar surface platinum electrodes were temporarily placed over the sensorimotor cortices. Green curves indicate the location of the central sulcus. A four-strip electrode array was inserted on the anterior wall of the central sulcus after dissecting the sulcus. A twenty-pole grid electrode array (4 × 5 electrodes) was placed over the central sulcus to cover the sensorimotor area.

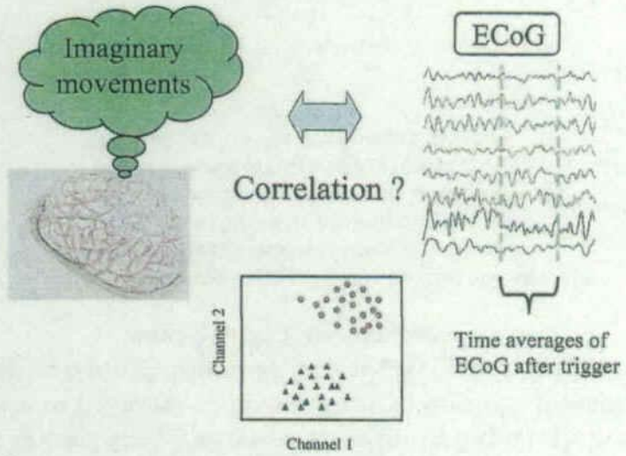


Fig.2 Schema of experiment.
Patients were instructed to image three types of upper limb movements: flexion of thumb, grasping of hand and flexion of elbow. The ECoG was recorded simultaneously with the image. A part of the ECoG was averaged by a time window of 100 ms. The values of averaged ECoG were plotted to clarify the difference of patterns of ECoG among the each movements. If there is a clear correlation between the imaginary movements and the pattern of ECoG, the plotted values will be divided into three groups.

両症例に対して直径3 mm，電極間隔1 cmのプラチナ製電極（Unique Medical Co., Tokyo, Japan）を硬膜下へ一時的に留置しMCSの最適刺激領域を検索した[14]．電極は中心溝内の運動野側に4極，脳表の感覚運動野を覆うように20極を留置した（**Fig.1**）．中心溝はMagnetic resonance image（MRI）による脳表再構成画像を用いて解剖学的に同定し，また術中正中神経刺激による体性感覚誘発電位（somatosensory evoked potential: SEP）を用いて電気生理学的にも同定した．

電極留置術後約10日目に，患者に運動想起

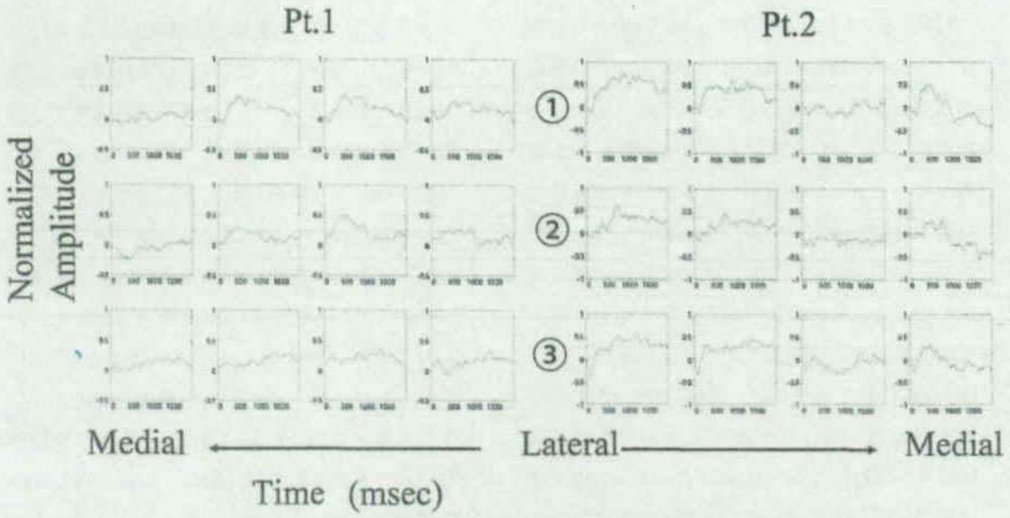


Fig.3 An example of averaged ECoG.
The ECoG of four-strip electrode on the anterior wall of the central sulcus was averaged for each type of imaginary movements. Each raw corresponds to the type of imaginary movements: ① flexion of thumb, ② grasping of hand, ③ flexion of elbow. Each column corresponds to the each electrode on the anterior wall of the central sulcus. Graphs show the normalized amplitude of averaged ECoG after the trigger.

課題を施行した．シールドルームにて患者を安静・座位とし，留置した硬膜下電極を 64 チャンネルデジタル脳波計（EEG2000, Nihon Koden, Japan）に接続した．患者に 5 秒間隔の視覚信号を与え，それをトリガーとして患側上肢の運動を 1 回ずつ想像させた．想起する運動は，①拇指屈曲，②握手，③肘屈曲の 3 種類とし，各種 20 ～ 100 回の運動想起を行った．脳波はフィルターをかけず抽出率（sampling rate）1000 Hz で計測した．トリガー前 500 msec の平均値と分散にて正規化し，トリガー後 1000 msec の脳波を計測した．

記録された脳波の振幅が最も大きい特徴的な時間区間を選び，その区間で各電極での時間平均値を計算した．全 24 電極毎の時間平均値から，3 種類の運動想起を分類するのに最適な電極を選択した（**Fig.2**）．つまり各電極の時間平均値を，選択した電極についてプロットすると，各プロットが想起した運動種類毎にできるだけ分かれて分布するように最適な電極を選択した．この際，スパース推定を用いた判別プログラムを用いた[7,17]．これにより，得られた皮質脳波のパターンが，想起した運動種類毎にどの程度異なるかを検討した．また，選択された電極と MCS による疼痛減弱効果を比較した．MCS の効果は施行前と施行直後での VAS の変化率【〔(施行前 VAS – 施行後 VAS)／施行前 VAS〕×100】にて評価した．

結　果

症例 1, 2 について，中心溝内運動野側へ留置された 4 極の硬膜下電極から記録された皮質脳波を運動想起課題毎に加算平均した．症例 1, 2 共に，トリガー後 400 ～ 500 msec にピークを持つゆっくりとした電位変化を認めた（**Fig.3**）．

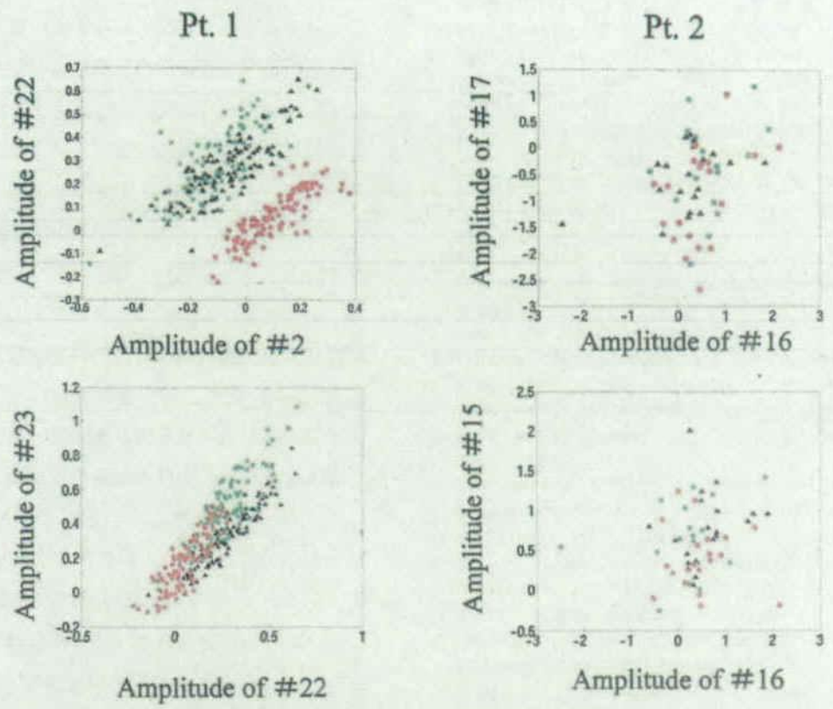
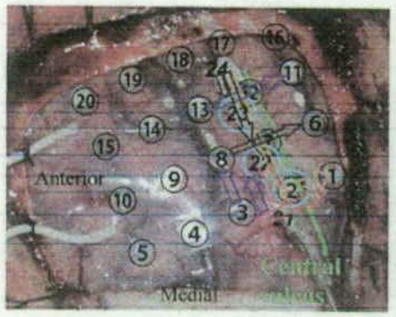


Fig.4 Distribution of time averaged ECoG.
The time averages of ECoG during 400 – 500 ms after the trigger were plotted. For patient 1, the electrodes 2, 22 and 23 were selected (left). The graphs show the distribution of the time averaged ECoG of electrodes 2 and 22 (upper left) and electrodes 22 and 23 (lower left). Green squares, black triangle and red circle correspond to the flexion of thumb, grasping of hand and flexion of elbow for each. As shown in the graphs, the plots of three types of imaginary movements were divided into three groups. For patient 2, the electrodes 15, 16 and 17 were selected (right). The graphs show the distribution of the averages of electrodes 16 and 17 (upper right) and electrodes 16 and 15 (lower right). As shown in the graphs, the plots of three types of imaginary movements were not divided into different groups.

これは運動に関連した課題を行う際に感覚運動野で認められる slow cortical potential（SCP）であると考えられる[2]．運動想起課題に伴い運動関連電位が記録され，そのピークはトリガー後 400 ～ 500 ms であった．

MCS が著効した症例 1 において電極 2, 22, 23（中心溝付近の電極）のトリガー後 400 ～ 500 msec での皮質脳波の時間平均値をプロットした（**Fig.4**）．3 種類の運動想起時の皮質脳波の時間平均値は各施行に対応して非常に明確に分離された．**Fig.1** 左上に示されるように，電極 2 と 22 の時間平均値の分布は，拇指屈曲もしくは握手を想起した際と肘屈曲を想起した際とで明らかに異なっていた．また，更に電極 22 と 23 についての分布も合わせて検討すると，3 種類の運動想起が皮質脳波だけから，ほぼ完全に予測できるほど分離した分布が得られた．つまり，MCS が著効した症例 1 では想起した運動種類毎に皮質脳波に特徴的なパターンがあり，皮質脳波が運動想起に関する明確な情報を持つことが明らかになった．一方，MCS が無効であった症例 2 では電極 15, 16, 17 を選



+	-	VAS reduction (%)
22	21	55
3	1	50
24	21	46
2	1	33
21	22	25
3	8	25
13	11	14
24	23	0
24	22	0
8	6	0

Fig.5 Effects of MCS.
Electrical stimulation was applied between several sets of electrodes of patient 1. For each sets of electrodes, the VAS reductions by MCS were represented by colored arrows on the picture. The arrow was drawn from positive to negative of stimulation. As shown in the figure, the stimulation around the selected electrodes (2, 22 and 23) revealed significant VAS reduction of 40 – 50%.

択したが，3種類の運動想起時の皮質脳波を分離することはできなかった．これは，全ての電極の組み合わせにつき行われたが，明らかな分離を得られなかった．つまり，MCSが無効であった患者では，留置した硬膜下電極にて，運動想起パターンに特異的な皮質脳波活動を捉えることができなかった．

MCSが著効した症例1について選択された電極とMCSの効果について検討した．**Fig.5**に示すように，選択された電極は中心溝内運動野側の内側とその直上にある．この周囲を刺激するとVASにて50%程度の低下を認め，他の領域と比較して高い疼痛減弱効果を認めた．ただし，同じ電極の組み合わせでも刺激の方向によって疼痛減弱効果は異なり，電極の場所のみから疼痛減弱効果を予測することは難しかった．

考　察

MCSが著効した患者と無効であった患者について，患側上肢の運動想起課題を行った際の皮質脳波パターンを比較した．皮質脳波は運動想起課題に伴ってSCPを示した．SCPが最大振幅を示す時間区間（トリガー後400～500 ms）において各電極からの皮質脳波の時間平均値を求め，運動想起課題毎に特徴的な分布を示す電極を選んで描画した．MCSが著効した患者では皮質脳波の時間平均値の分布が運動想起課題毎で明らかに異なり，皮質脳波のパターンが想起する運動に強く相関していることが示された．一方，MCSが無効であった患者では皮質脳波の時間平均値の分布に特徴的なパターンを認めなかった．またMCSが著効した患者では，想起する運動毎に特徴的な皮質脳波パターンを示す電極周囲で，MCSによる疼痛減弱効果が高かった．

求心路遮断性疼痛患者が運動を想起する際，一次運動野周辺で運動毎に特徴的な皮質脳波活動を認めた．求心路遮断性疼痛患者の運動野はCRにより正常とは異なる構造となっていると考えられるが，運動想起との関係は明らかではない[3,9,10,11]．幻肢患者に幻肢の運動を想起させると切断肢断端部の筋活動が生じることが知られている[12]．この際，幻肢の運動を想起できる患者では，切断部の筋電図が想起する運動毎に異なるパターンの活動を示す．一方，幻肢の運動を想起できない患者では断端の筋電図は想起する運動によらず常に同じパターンを示す．本研究でも，幻肢の運動を想起する能力と複数の運動想起を異なるパターンで表現する能力（切断部の筋反応もしくは一次運動野の皮質脳波活動）との間には関連が示唆された．今後症例を重ねることで，幻肢の運動想起という主観的現象を皮質脳波の活動パターンによって客観的に評価できるようになることが期待される．

幻肢の運動想起能力を回復させることで痛みが軽減する現象が多く知られているが，運動想起と疼痛との関係は明らかでない[1,6,10]．本研究では想起する運動に対して特異的に皮質脳波活動が変化する患者ではMCSの効果が高いことが示唆された．また，運動想起とCRによる皮質脳波活動パターンの変化を検討するために，ECoG計測が有用であることが示された．これらの知見から，運動想起と求心路遮断性疼痛との関係を明らかにするだけでなく，MCSの効果を運動想起能力から推測し，逆に運動想起能力を高めることでMCSの効果を高めることが期待される．

文　献

1) Altschuler, E.L., Wisdom, S.B., Stone, L., Foster, C., Galasko, D., Llewellyn, M.E., Ramachandran, V.S., Rehabilitation of hemiparesis after stroke with a mirror, The Lancet, 353 (1999) 2035-2036.
2) Blankertz, B., Dornhege, G., Krauledat, M., Muler, K.-R., Kunzmann, V., Losch, F., Curio, G., The Berlin Brain-computer interface: EEG-based communication without subject training, IEEE transactions on neural systems and rehabilitation engineering, 14 (2006) 147-152.
3) Ersland, L., Rosen, G., Lundervold, A., Smievoll, A.L., Tilung, T., Sundberg, H., Hugdahl, K., Phantom limb imaginary fingertaping causes primary motor cortex activation: an fMRI study, Neuroreport, 8 (1996) 207-210.
4) Flor, H., Phantom-limb pain: characteristics, causes, and treatment, Lancet Neurol., 1 (2002) 182-189.
5) Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Birbaumer, C.N., Lrbig, W., Taub, E., Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation, Nature, 375 (1995) 482-484.
6) Giraux, P., Sirigu, A., Illusory movements of the paralyzed limb restore motor cortex activity, Neuroimage, 20 (2003) S107-S111
7) Girolami, M., Rogers, S., Variational Bayesian multinomial probit regression with Gaussian process priors, Neural Comp., 18 (2006) 1790-1817.
8) Karl, A., Birbaumer, N., Lutzengerger, W., Cohen, L.G., Flor, H., Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain, J. Neuroscience, 21 (2001) 3609-3618.
9) Karl, A., Muhlnickel, W., Kurth, R., Flor, H., Neuroelectric source imaging of steady-state movement-related cortical potentials in human upper extremity amputees with and without phantom limb pain, Pain, 110 (2004) 90-102.
10) Moseley, G.L., Reilly, K.T., Vargas, C.D., Aballea, A., Sirigu, A., Mapping phantom movement representations in the motor cortex of amputees, Brain, 129 (2006) 2202-2210.
11) Reilly, K.T., Mercier, C., Schieber, M.H., Sirigu, A., Persistent hand motor commands in the amputees' brain, Brain, 129 (2006) 2211-2223.
12) Roux, F.-E., Lotterie, J.-A., Cassol, E., Lazorthes, Y., Sol, J.-C., Berry, I., Cortical areas involved in virtual movement of phantom limbs: comparison with normal subjects, Neurosurgery, 53 (2003) 1342-1353.
13) 齋藤洋一，住谷昌彦，真下節，吉峰俊樹，幻肢・幻肢痛の脳内メカニズム，痛みと臨床，7 (2007) 101-106.
14) Saito, Y., Yoshimine, T., Stimulation of primary motor cortex for intractable deafferentation pain, Acta Neurochir. Suppl., 97 (2007) 51-56.

15) Sumitani, M., Rossetti, Y., Shibata, M., Matsuda, Y., Sakaue, G., Inoue, T., Mashimo, T., Miyauchi, S., Prism adaptation to optical deviation alleviates pathologic pain, Neurology, 68 (2007) 128-133.
16) 柳澤琢史, 齋藤洋一, 押野悟, 貴島晴彦, 平田雅之, 谷直樹, 住谷昌彦, 加藤天美, 吉峰俊樹, 幻肢痛における大脳皮質再構築の経頭蓋磁気刺激, 脳磁図, 感覚誘発電位による検討, Pain Research, 22 (2007) 143-148.
17) Yamashita, O., Sato, M., Yoshioka, T., Kamitani, Y., Mapping voxels automatically selected by sparse classifier, 2007, HBM2007, Chicago.

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Spinal cord stimulation therapy for localized central pain

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[Received 7 December 2007, Accepted 31 January 2008]

Abstract

We studied the pathophysiology of localized central pain and the surgical result of spinal cord stimulation. There were 10 cases; 7 males and 3 females from 24 to 77 years old. Pain was caused by peripheral nerve injury in one case, spinal cord injury in two cases and cerebrovascular disease (CVD) (thalamic pain) in 7 cases. All cases were treated by epidural spinal cord stimulation and followed from 0.8 to 8.8 years. Sufficient pain relief was achieved in one case of peripheral nerve and spinal cord injury and in 4 cases of CVD. Moderate pain control was achieved in 2 cases of CVD. In one each case of spinal cord injury and of CVD, pain control was ineffective. In cases with thalamic pain, we studied the correlation between the surgical result of spinal cord stimulation and the clinical features, MRI, fluoro–deoxyglucose (FDG)–PET, and somatosensory evoked potentials (SEP) findings before operation. MRI revealed a small to moderate sized lesion on the thalamus or putamen in each case. PET also showed decreased accumulation of FDG on the affected thalamus. In all cases without one fair responder to spinal cord stimulation, we could recognize definite SEP originating in the sensory cortex ipsilateral side to the CVD lesion during contralateral median or posterior tibial nerve stimulation. In the good responders, we could recognize SEP originating in the sensory cortex of the lesion side with less delayed latency or decreased amplitude than in the moderate responders. In this group, test stimulation with low voltage on the spinal cord evoked a sensory effect (paresthesia) over the painful part of the body.

Spinal cord stimulation proved to be an effective treatment for localized central pain. In cases with localized central pain after CVD, we could expect to ameliorate the intractable pain in those cases in which SEP or spinal cord test stimulation revealed that the thalamo–cortical system was preserved.

Key words: Central pain; Localized pain; Thalamic pain; Spinal cord stimulation; SEP

PAIN RESEARCH 23 (2008) 35–44

中枢性疼痛局所痛の病態と脊髄刺激療法の効果

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Pain 140 (2008) 509–518

PAIN

www.elsevier.com/locate/pain

Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation

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Received 18 February 2008; received in revised form 8 July 2008; accepted 14 October 2008

Abstract

Central post-stroke pain (CPSP) is one of the most common types of intractable pain. We reported that repetitive transcranial magnetic stimulation (rTMS) of primary motor cortex relieves pain for patients who were refractory to medical treatment. But the mechanism is unclear. In the present study, we investigated relations between the characteristics of CPSP and the results of fiber tracking, which is the only noninvasive method of evaluating the anatomical connectivity of white matter pathways. Fiber tracking of the corticospinal tract (CST) and thalamocortical tract (TCT) was investigated in 17 patients with CPSP. The stroke lesion was located in a supratentorial region in all cases (corona radiata, one case; thalamus, seven cases; putamen, nine cases). Relations between the delineation ratio (defined as the ratio of the cross section of the affected side to that of the unaffected side) of the CST and of the TCT, manual muscle test score, pain score, region of pain, and efficacy of rTMS were evaluated. Fiber tracking was successful in 13 patients with the stroke lesion involving the TCT. The rTMS-effective group had higher delineation ratio of the CST ($p = 0.02$) and the TCT ($p = 0.005$) than the rTMS-ineffective group. Previous studies suggested that an intact CST allows pain control but did not discuss the TCT. Our results suggest that the TCT also plays a role in pain reduction by rTMS of the primary motor cortex and that the efficacy of rTMS for patients with CPSP is predictable by fiber tracking.

Keywords: Central pain; Fiber tracking; Repetitive magnetic stimulation; Corticospinal tract; Thalamocortical tract

1. Introduction

Central post-stroke pain (CPSP), characterized by constant or intermittent pain occurring after ischemic or hemorrhagic stroke and associated with sensory abnormalities, is one of the most common types of intractable pain. Typical associated abnormalities are decreased perception (hypoesthesia) and unusually high sensitivity (hyperesthesia), often accompanied by allodynia and hyperalgesia [4]. These features indicate lesions of the spinothalamocortical pathways relaying in the thalamic ventral posterolateral nucleus, whereas tactile and vibratory sensations are usually considered unrelated to CPSP [4].

Deafferentation pain, including CPSP, is sometimes difficult to control, and many cases of such pain are refractory to medical treatment. According to recent reports, repetitive transcranial magnetic stimulation (rTMS) successfully relieves pain. A majority of the reports show that pain relief is associated with rTMS of the primary motor cortex [1,6,14,23].

Diffusion tensor imaging (DTI) is a magnetic resonance (MR) imaging technique that allows measurement

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0304-3959/$34.00
doi:10.1016/j.pain.2008.10.009

of the restricted diffusion of water in tissue. The architecture of axons in parallel bundles facilitates the diffusion of water molecules along the length of the fibers [27]. It is possible to calculate a tensor for each voxel that describes the three-dimensional shape of diffusion and to display the results on such images as fractional anisotropy (FA) images, three-dimensional anisotropy contrast images, and apparent diffusion coefficient maps [28,30].

Fiber tracking is a relatively new method that applies DTI in vivo to reveal white matter pathways in three-dimensional images, and it is often used to evaluate the spatial relation between a lesion and a white matter pathway [8,18] and the quantity of tracked fibers [31]. Broad bundles such as the corticospinal tract (CST) and the thalamocortical tract (TCT) can be delineated clearly [20] and reproducibly [40], but it is difficult to delineate the fibers separately through each thalamic nuclei related to thermal, tactile, vibratory, and deep sensation [41] and in accordance with the distribution of motor function [40].

The mechanism underlying the efficacy of rTMS of the primary motor cortex in pain relief is still under discussion. While motor cortex stimulation (MCS), electrical stimulation of the brain surface with grid electrodes, has been reported to relieve pain, it provides unsatisfactory pain relief for patients with severe paresis [17]. Although the mechanism of pain relief through rTMS is not necessarily the same, participation of the CST in the pain relief is suspected. Participation of the TCT in pain relief is also suspected because impairment of the TCT causes CPSP. However, there have been few studies making use of fiber tracking to investigate the relations between these tracts and CPSP [34]. In this study, we evaluated the relations between fiber tracking and CPSP, emphasizing not the detailed symptoms, which cannot be represented by fiber tracking, but the efficacy of rTMS which is suspected to relate to the fibers, the CST and the TCT, delineated reproducibly by fiber tracking.

2. Materials and methods

2.1. Patients

We are conducting a clinical trial on efficacy of rTMS for the patients with deafferentation pain originating from stroke, spinal cord injury, root avulsion, or peripheral nerve injury. The present study involved 17 consecutive patients with CPSP who participated in that clinical trial (eight men and nine women; median age, 66 years; range, 44–73 years). Patients were recruited from the outpatient clinic for neurosurgery at the Osaka University Hospital between April 2004 and September 2007. Inclusion criteria were as follows: (1) the presence of central pain secondary to a supratentorial stroke lesion confirmed by clinical and neuroradiological data; (2) a causal relation between the lesion and the pain as indicated by clinical characteristics, notably regional pain distribution; (3) pain lasting more than 6 months; (4) pain not attributable to causes other than central causes (e.g., peripheral inflammation, diabetes); and (5) pain resistant to medication of various kinds (non-steroidal anti-inflammatory drugs, anti-anxiety drugs, anti-epileptic drugs, and antidepressants), and to physical and complementary medicine treatments. Exclusion criteria were as follows: (1) contradictions for rTMS (history of epilepsy, cardiac pacemaker, brain stimulation system, or unruptured aneurysm); (2) two or more stroke lesions; or (3) any other non-stroke lesion of the brain. Patient characteristics are listed in Table 1. Stroke originated from a thalamic lesion in seven cases, putaminal lesion in nine cases, and corona radiate lesion in one case. The mean pain duration was 5.1 years (range, 1.0–8.8 years). Written informed consent was obtained from all patients in accordance with the approval from the ethics committee of Osaka University Hospital.

2.2. rTMS

All patients underwent rTMS, and post-treatment pain relief was assessed. Magnetic stimulation was applied through a figure-eight coil (MC B-70, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark), which provides for focal cortical stimulation. The coil was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnostics A/S). The resting motor threshold of the affected muscles was determined by stimulation of the corresponding motor cortex, the position of which was confirmed by the use of the Brainsight Frameless Navigation System (Rouge Research Inc., Montreal, Quebec, Canada). We determined the resting motor threshold from EMGs of the affected area. Muscle twitches in painful areas were elicited when the motor cortex was stimulated carefully according to the cortical somatotopy. For the patients in whom muscle twitches in the painful areas were difficult to elicit owing to severe damage of the motor pathways, rTMS was applied at an intensity of 100 A/μs. A potential equivalent to 90% intensity of the resting motor threshold was used for treatment. Ten trains of 10-s 5-Hz TMS pulses, with 50-s intervals between trains, were applied to the motor cortex.

2.3. Neurological evaluations

Clinical characteristics of sensation over the painful areas were examined in all cases before rTMS with special emphasis on the level of pain. Somatosensory deficit was assessed by means of standard clinical methods: testing for tactile hypoesthesia with blunted needles.

Table 1
Patient characteristics and results of fiber tracking.

Patient	Age (years)	Sex	Lesion location	Symptom topography	MMT		Painful area	VAS before rTMS	Duration (years)	ΔNRS (%)	DRFT	
					Upper extremity	Lower extremity					CST (%)	TCT (%)
1	48	M	Putamen	L	5	5	F, U, T, L	9.0	1.0	67.0	75.0	100.0
2	73	F	Putamen	R	4	2	F, U, T, L	10.0	5.4	60.0	N/A	N/A
3	44	F	Putamen	R	5	5	L	9.0	7.1	57.0	78.6	75.0
4	59	F	Putamen	R	4	4	L	8.0	4.2	47.1	88.2	71.4
5	57	M	Thalamus	L	5	4	F, U, T, L	8.0	7.6	35.1	78.6	60.0
6	59	M	Corona radiata	R	5	5	F, U, T, L	6.0	6.0	33.3	N/A	N/A
7	71	F	Thalamus	R	5	5	U, T	5.0	8.8	30.0	N/A	N/A
8	66	F	Putamen	R	4	5	F, U, T, L	10.0	7.9	30.0	71.4	77.8
9	67	F	Putamen	L	3	4	U, T, L	10.0	4.2	23.1	13.3	35.3
10	60	F	Putamen	R	4	3	F, U, T, L	7.0	2.1	20.0	0.0	0.0
11	56	M	Thalamus	R	4	4	T, L	7.0	1.1	12.0	73.9	36.4
12	66	M	Thalamus	R	4	4	U, T, L	9.0	3.6	11.1	N/A	N/A
13	60	F	Putamen	R	4	4	L	10.0	3.1	0.0	72.7	44.4
14	68	M	Thalamus	R	4	4	U, L	4.0	6.3	0.0	N/A	0.0
15	73	M	Putamen	R	4	4	F, U, T, L	7.0	3.3	0.0	72.7	0.0
16	73	F	Thalamus	L	4	4	F, U, T, L	10.0	7.0	0.0	52.9	0.0
17	72	M	Thalamus	R	3	4	U, T, L	9.0	7.6	−10.0	64.3	30.0

M, male; F, female; R, right; L, left; MMT, manual muscle test (0: no movement and 5: normal); F, face; U, upper extremities; T, trunk; L, lower extremities; ΔVAS, reduction rate of VAS score after repetitive transcranial magnetic stimulation of the primary motor cortex to that before stimulation; DRFT, delineation ratio of fiber tracking; CST, corticospinal tract; TCT, thalamocortical tract; N/A, not available.

Thermal hypoesthesia was identified with the use of hot (42 °C) and cold (10 °C) tubes. The presence of abnormally provoked pain was tested systematically before rTMS. Allodynia was defined as pain arising in response to innoxious stimuli (i.e. stimuli that never caused pain in normal control subjects) [26]. Whenever possible, mechanical allodynia was tested by means of touch (static) or light rubbing of the skin (dynamic). Hyperalgesia was defined as abnormally enhanced pain sensations in response to noxious stimuli [26] and was tested by means of pinprick [38].

To assess motor weakness on the hemiplegic side, the manual muscle test (MMT) system was applied to the following: elbow flexion and extension, shoulder extension, knee flexion and extension, hip flexion. MMT score ranks function on a scale of 0, indicating that no contractile activity can be felt in a gravity-free position, to 5, if the patient can hold the position against maximum resistance and through the complete range of motion.

It is soon after rTMS that the most pain relief is shown [14]. Before and soon after rTMS, patients evaluated their own level of pain by visual analog scale (VAS), rating from 0 (no pain) to 10 (maximum pain). Stimulation was judged to be effective if the VAS score after stimulation decreased more than 30% from that before stimulation. Subjects were separated into two groups, those in whom rTMS was effective and those in whom rTMS was ineffective.

2.4. DTI

All diffusion tensor images were obtained with a 3.0-T whole-body MR imager (Signa VH/i, GE Medical Systems, Milwaukee, Wisconsin, USA). An acquisition time of approximately 3 min was used. Images were acquired by a single-shot echo-planar imaging technique with TE = 80, TR = 10,000. Diffusion gradient encoding in six directions with $b = 1000$ s/mm^2 and an additional measurement without diffusion gradient ($b = 0$ s/mm^2) were performed. A parallel imaging technique was used to record data with a 256 × 256 spatial resolution for a 260 × 260-mm field of view. A total of 50 sections were obtained, with a section thickness of 3.0 mm and no intersection gap.

2.5. Fiber tracking

The diffusion tensors were calculated, and three-dimensional fiber tracking of the CST and the TCT was performed using Volume-One and dTV software (free software by Masutani, URL: http://www.ut-radiology.umin.jp/people/masutani/dTV.htm). Interpolation along the z-axis was applied to obtain isotropic data (approximately 1.0156 × 1.0156 × 1.0156 mm). The diffusion tensor elements at each voxel were determined

by least-squares fitting and diagonalized to obtain three eigenvalues and three eigenvectors. For fiber tracking, two ROIs, seed and target, were manually placed on the three-dimensional anisotropy contrast image, which shows the diffusion direction in each voxel by color (red for left–right, green for anterior-posterior, and blue for craniocaudal). The seed ROI, from which fiber tracking starts, was placed on the cerebral peduncle (Fig. 1A). The target ROI, at which fiber tracking ends, was placed on the precentral gyrus for the CST and on the postcentral gyrus for the TCT on the basis of anatomical knowledge (Fig. 1B). The thresholds of tracking termination were set at 1.8 for the FA value and 30° for the angle between two contiguous eigenvectors (Fig. 1C).

After tracking the CST or the TCT, the three-dimensional fiber tracking data were converted to grayscale two-dimensional transverse images with the dTV software. Normalization of these images to normal space was performed with SPM2 software (Wellcome Department of Imaging Neuroscience, London, UK). The non-diffusion-weighted (b0) images were normalized to the Montreal Neurological Institute echo-planar imaging template supplied with the SPM2 software. The two-dimensional fiber tracking images were spatially transformed according to the normalized b0 images (Fig. 1D). Normalized images were reformatted into 69 slices with $2 \times 2 \times 2\,mm^3$ voxels. Corresponding slices that included the posterior peduncle of the internal capsule were selected for all patients, and the number of voxels making up the CST and the TCT was counted. The delineation ratio, i.e. the ratio of the cross section of the affected side to the cross section of the unaffected side, was calculated for the CST and the TCT.

2.6. Statistical analysis

Fiber tracking of the CST was successful in 12 patients, and tracking of the TCT was successful in 13 patients; data from these cases were analyzed. Correlation was assessed between the level of paresis and the delineation ratio of the CST and between the level of pain before rTMS and the delineation ratio of the TCT by means of Pearson's correlation coefficient. Difference in the delineation ratio of the fiber tracts between the rTMS-effective group and the rTMS-ineffective group was analyzed by Mann–Whitney U test.

3. Results

3.1. Fiber tracking

Fiber tracking of the CST was successful in 12 patients, and tracking of the TCT was successful in 13 patients. It was impossible to trace the tracts completely from the cerebral peduncle to the precentral gyrus or to the postcentral gyrus in some patients. The FA value was decreased by ischemic changes in the white matter of the corona radiata, resulting in an incomplete trace of the CST in four patients and of the TCT in three patients, and metal artifacts distorted the images, resulting in an incomplete trace of both the CST and TCT in two patients.

3.2. Symptoms before rTMS and fiber tracking

3.2.1. Area of pain

All patients had unilateral pain, which was localized on the right side in 13 patients, and on the left side in four patients. Pain involved the entire half of the body, including the face, in eight patients, an upper and lower extremity in four patients, upper extremity in one patient, and lower extremity in four patients.

Post-stroke lesions shown by b0 images affected the CST and the TCT delineated by fiber tracking. Conventional MR imaging and color-coded DTI show the locations of putaminal and thalamic lesions (Fig. 2). In the case of thalamic lesions, patients with a small lesion tended to have pain in a limited area of the body (Fig. 2A), whereas patients with a large lesion extending to the medial side tended to have pain in the entire half of the body, including the face (Fig. 2B). In the case of putaminal lesions, which damage the TCT from the lateral side, patients with a small lesion limited to the lateral side tended to have pain only in a lower extremity (Fig. 2C), whereas patients with a large lesion that extended to the wall of the lateral ventricle tended to have pain in the entire half of the body, including the face (Fig. 2D).

3.2.2. Intensity of pain

Before rTMS, the VAS score in the most painful area was 10 for five patients, 9 for four patients, 8 for two patients, 7 for three patients, and under 6 for three patients. The VAS score before stimulation did not correlate with the delineation ratio of the TCT (Fig. 3B).

3.2.3. Sensory abnormalities

Hyperesthesia in response to pinprick in the painful area was found in seven patients, and hypoesthesia was found in five patients. The kind of sensory disturbance was not related to the volume of fiber tracking or the location of the stroke lesion.

3.2.4. Paresis

The MMT score was 5 for four patients, 4 for nine patients, 3 for three patients, and 2 for one patient; that is, the paresis tended to be mild. The MMT score correlated with the CST delineation ratio (correlation coefficient 0.69, $p < 0.05$; Fig. 3A), but there was no apparent relation between the lesion location and the region of the paresis.