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ORIGINAL REPORT

CORRELATION OF MOTOR FUNCTION WITH TRANSCALLOSAL AND INTRACORTICAL INHIBITION AFTER STROKE

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Objective: **The inhibitory role of neuronal networks in motor recovery after stroke remains to be elucidated. We examined the influence of transcallosal inhibition and short intracortical inhibition on motor recovery after stroke. We also investigated the correlation between transcallosal inhibition and mirror activity.**

Design: **A cross-sectional study.**

Subjects: **Thirty-eight chronic stroke patients.**

Methods: **Transcallosal inhibition was evaluated using single transcranial magnetic stimulation, and short intracortical inhibition was assessed using paired-pulse transcranial magnetic stimulation. Mirror activity was measured during tonic contraction of the contralateral hand.**

Results: **Transcallosal inhibition from the contralesional to the ipsilesional motor cortex correlated positively with motor function of the paretic hand; in contrast, transcallosal inhibition to the ipsilesional motor cortex correlated negatively with mirror activity of the paretic hand in both cortical and subcortical stroke patients. Short intracortical inhibition of the ipsilesional motor cortex correlated negatively with motor function of the paretic hand in only the subcortical stroke patients.**

Conclusion: **Transcallosal inhibition from the contralesional to the ipsilesional motor cortex may inhibit mirror movements in stroke patients with good motor function. The weak transcallosal inhibition in patients after stroke with poor motor function may be ineffective for inhibiting mirror movement; however, it may have the advantage of facilitating motor recovery.**

Key words: stroke; rehabilitation; reorganization; mirror movement; transcallosal inhibition; intracortical inhibition.

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INTRODUCTION

Stroke alters the neuronal function of the motor cortex adjacent to or distant from the lesion through neuronal networks (1). Transcranial magnetic stimulation (TMS) has been used to detect changes in neuronal function after stroke. Several studies have reported the loss of inhibition in the ipsilesional and the contralesional motor cortex of stroke patients using TMS (2, 3). A decrease in the inhibition contributes to the cortical reorganization by unmasking the latent networks (4); however, whether the disinhibition after stroke is caused by the lesion, whether it reflects a compensatory mechanism, or both, is still poorly understood (1). The change in transcallosal inhibition (TCI) after subcortical stroke has also been assessed using TMS (5). While a recent study has examined the changes in both TCI and intracortical inhibition after stroke (6), it remains unknown whether these neurophysiological parameters are correlated with motor function in both cortical and subcortical stroke and whether the parameters of cortical stroke differ from those of subcortical stroke.

In this study, we evaluated TCI and short intracortical inhibition (SICI) to determine whether these TMS parameters influence motor recovery in both cortical and subcortical stroke. It has been demonstrated previously that although SICI may be reduced in appearance, the inhibitory function may be normal if the excitability function increases (7). Therefore, we measured not only SICI but also short interval cortical excitability (SICE) to evaluate inhibitory and excitatory function in more detail. In addition, we investigated the correlation between TCI from the contralesional to the ipsilesional motor cortex and the mirror activity of the paretic hand. We hypothesized that the change in TCI to the ipsilesional motor cortex after stroke could influence the mirror activity of the paretic hand during non-paretic hand movement.

METHODS

The study population comprised 38 first-time chronic stroke patients. Motor function was evaluated using the upper limb subset of the Fugl-Meyer scale (FMS) (8). All the subjects gave written informed consent, and the experimental protocol was approved by the local ethics committee of Hokkaido University Graduate School of Medicine. The patients were classified into the following two subgroups according to brain computed tomography (CT) or MRI findings (Table I): (*i*) the cortical group, which had stroke lesions involving the sensorimotor cortex or both sensorimotor cortex and subcortical structure; and (*ii*) the subcortical group, which had lesions located caudal to the *corpus callosum*, indicating that the *corpus callosum* was intact.

TCI was performed using a 70-mm figure-8 coil and Magstim 200 (Magstim Company, Dyfed, UK), and paired-pulse TMS was applied

Table I. *Clinical characteristics*

	Age, year Mean (SD)	Gender		Paretic side		Duration after stroke, month Mean (SD)	Fugl-Meyer scale, Mean (SD)	*EMG activity of first dorsal interosseous	
		Male *n*	Female *n*	Right *n*	Left *n*			Non-paretic, μV Mean (SD)	Paretic μV Mean (SD)
Cortical group (n=20)	61.7 (10.1)	12	8	12	8	46.3 (34.2)	68.0 (23.4)	350.8 (210.2)	155.0 (140.8)
Subcortical group (n=18)	61.6 (10.3)	11	7	10	8	56.9 (51.9)	63.9 (21.7)	395.4 (220.1)	154.6 (155.5)

*Mean rectified EMG activity during maximal tonic contraction.
SD: standard deviation; EMG: electromyography.

using the same coil and a Bistim device (Magstim Company) that triggered two magnetic stimulators. The coil was placed tangentially over the motor cortex at an optimal site for the first dorsal interosseous (FDI) muscle. The optimal site was defined as the location where stimulation at a slightly suprathreshold intensity elicited the largest motor-evoked potentials (MEPs) in the FDI. The resting motor threshold (rMT) was determined separately for each stimulator and defined as the lowest stimulator output that could activate MEPs with a peak-to-peak amplitude greater than 50 μV in at least half of the 10 trials. We excluded patients for whom MEPs were not detected in the ipsilesional hemisphere from the ipsilesional TMS study section, i.e. patients in whom MEPs were not induced even at 100% stimulator output.

We performed paired-pulse TMS at inter-stimulus intervals (ISIs) of 2, 3, 10 and 15 ms. The intensity of the first conditioning stimulus was 80% rMT and that of the test stimulus was 120% rMT. Ten trials were performed for each ISI and unconditioned trials (controls) were recorded during complete relaxation. The paired stimulation with each ISI was randomly mixed with the control stimulation. The mean peak-to-peak amplitude of the control MEPs and paired MEPs at each ISI was calculated. The mean amplitudes of paired MEPs at ISIs of 2 and 3 ms were averaged to obtain a representative value for SICI and that at ISIs of 10 and 15 ms intervals for intracortical facilitation (ICF). SICI is expressed as the percentage of the degree of inhibition (1 − (paired/control)), and ICF is expressed as the percentage increase (paired/control) in MEPs amplitude. SICE was measured using paired-pulse TMS at an ISI of 2 ms. The intensity of the conditioning stimulus varied between 30% and 80% of MT and was administered randomly at 10% increments; whereas, the intensity of the test stimulus was the same as that for the SICI measurement. MEPs amplitudes at each conditioning stimulus in SICE were expressed as a percentage of the mean amplitude of the control MEPs.

In the TCI procedure, each hemisphere was stimulated 20 times (intensity, 150% rMT) during unilateral maximal tonic contraction of the ipsilateral FDI, while keeping the contralateral upper limb relaxed as described previously (9). Twenty electromyography (EMG) signals of the FDI were rectified and averaged for evaluation of TCI. The mean amplitude of EMG signals prior to the stimulus for 100 ms was defined as the background activity. TCI was quantified by the period of relative EMG suppression after the stimulus, i.e. from the point at which the EMG activity clearly decreased below the background activity to that at which the EMG activity again increased to equal the background activity. The area of suppressed EMG activity was also averaged. TCI was then defined as the percentage of this mean suppressed activity in the background activity. This indicates that the greater the EMG activity suppression, the greater the TCI.

Mirror activity was calculated from the data in the TCI section to avoid the fatigue of stroke patients by additional tests. We rectified and averaged 20 EMG signals of the contralateral FDI muscles (mirror condition) prior to TMS for 100 ms during a maximal tonic contraction of the FDI muscle (active condition). Finally, mirror activity was expressed as a percentage of the mean amplitude of the mirror condition in the mean amplitude of the active condition at the same FDI.

Clinical data were compared between the cortical and subcortical groups by using the Mann-Whitney U test or the χ^2 test, depending on the type of variable assessed. For the comparison of TMS parameters, the Kruskal-Wallis test was used. The changes in SICE were evaluated using analysis of variance (ANOVA) for repeated measures, with INTENSITY as a within-subjects factor and STIMULATION SITE as a between-subjects factor. A *post-hoc* analysis was performed with Bonferroni's correction. Possible correlations among the various parameters were determined using the Spearman's correlation test.

RESULTS

There was no significant difference between the cortical and subcortical groups with regard to age, gender, paretic side, duration after stroke, FMS, EMG activity of non-paretic, or EMG activity of paretic (Table I). Table II shows TMS parameters of each hemisphere in the subcortical and cortical groups. We obtained ipsilesional TMS data from 9 patients in the cortical group and 9 patients in the subcortical group. There was no significant difference between the 4 stimulation sites with regard to rMT, amplitude of MEPs, SICI, ICF, or TCI (Table II).

Table III shows the correlations between TMS parameters and motor function of the paretic hand. SICI of the ipsilesional motor cortex was negatively correlated with the FMS score

Table II. *Transcranial magnetic stimulation parameters*

Stimulation site	rMT, % Mean (SD)	Amplitude of MEPs, μV Mean (SD)	SICI, % Mean (SD)	ICF, % Mean (SD)	TCI, % Mean (SD)
Ipsilesional hemisphere in cortical group (n=9)	52.8 (12.2)	921.9 (463.6)	38.4 (50.6)	169.2 (71.8)	50.1 (14.0)
Ipsilesional hemisphere in subcortical group (n=9)	50.9 (9.7)	556.8 (348.7)	23.6 (41.7)	182.6 (160.8)	53.7 (14.3)
Contralesional hemisphere in cortical group (n=20)	51.9 (9.1)	895.0 (451.7)	25.7 (65.8)	192.2 (93.6)	46.2 (15.1)
Contralesional hemisphere in subcortical group (n=18)	52.9 (8.6)	813.6 (670.0)	22.0 (49.6)	239.6 (139.5)	58.7 (14.6)

rMT: resting motor threshold; MEPs: motor evoked potentials; SICI: short intracortical inhibition; ICF: intracortical facilitation; TCI: transcallosal inhibition; SD: standard deviation.

Table III. *Correlations between transcranial magnetic stimulation parameters (TMS) and Fugl-Meyer scale (correlation coefficient and* p*-values)*

	Fugl-Meyer scale			
	Ipsilesional hemisphere (stimulation site)		Contralesional hemisphere (stimulation site)	
TMS parameters	Cortical (n=9)	Subcortical (n=9)	Cortical (n=20)	Subcortical (n=18)
rMT	–0.497 (0.173)	–0.033 (0.933)	0.038 (0.873)	0.143 (0.570)
MEPs	0.267 (0.488)	–0.183 (0.637)	–0.251 (0.285)	–0.060 (0.813)
SICI	–0.483 (0.187)	–0.783 (0.013)*	–0.121 (0.612)	–0.162 (0.521)
ICF	0.300 (0.433)	0.550 (0.125)	0.403 (0.078)	0.054 (0.832)
TCI	–0.200 (0.606)	–0.250 (0.516)	0.502 (0.024)*	0.649 (0.004)**

*p<0.05; **p<0.01.

rMT: resting motor threshold; MEP: motor-evoked potentials; SICI: short intracortical inhibition; ICF: intracortical facilitation; TCI: transcallosal inhibition.

of the paretic hand in the subcortical (Fig. 1a; r=–0.783, p=0.013), but not the cortical group (r=–0.483, p=0.187). TCI from the contralesional to the ipsilesional motor cortex was positively correlated with the FMS score of the paretic hand in both the cortical (Fig. 1b; r=0.502, p=0.024) and the subcortical groups (Fig 1c; r=0.649, p=0.004). There was a negative correlation between TCI to the ipsilesional motor cortex and mirror activity of the paretic hand in both the cortical (Fig. 2a; r=–0.508, p=0.022) and the subcortical groups (Fig 2b; r=–0.600, p=0.009). There was no significant correlation between TCI from the ipsilesional to the contralesional motor cortex and mirror activity of the non-paretic hand in either group.

Fig. 3 shows the change in SICE in the cortical and the subcortical group. A repeated-measures ANOVA for SICE showed no significant interaction between INTENSITY and STIMULATION SITE (F (15, 260) = 0.884, p=0.582) or STIMULATION SITE (F (3, 52) = 0.142, p=0.935), but a significant effect of INTENSITY (F (5, 260) = 21.462, p<0.001), reflecting that SICE had not been influenced by the stimulation site. *Post-hoc* analysis revealed that a strong conditioning stimulus could reduce SICE (Fig. 3).

DISCUSSION

This study revealed that the inhibitory function of the ipsilesional motor cortex correlated negatively with motor function of the paretic hand in subcortical stroke patients. The inhibition from the contralesional to the ipsilesional motor cortex correlated positively with motor function of the paretic hand; in contrast, the inhibition from the contralesional to the ipsilesional motor cortex correlated negatively with mirror activity of the paretic hand in both cortical and subcortical stroke patients.

Several studies have reported disinhibition of the ipsilesional motor cortex in the acute stage of both cortical and subcortical stroke (2, 10). However, whether the inhibitory function of the ipsilesional motor cortex normalizes or remains decreased in the chronic stage remains controversial (11, 12). The correlation between inhibitory function and motor function is also poorly understood. In this study, we have revealed that the inhibitory function of the ipsilesional motor cortex was correlated negatively with the motor function of the paretic hand in only

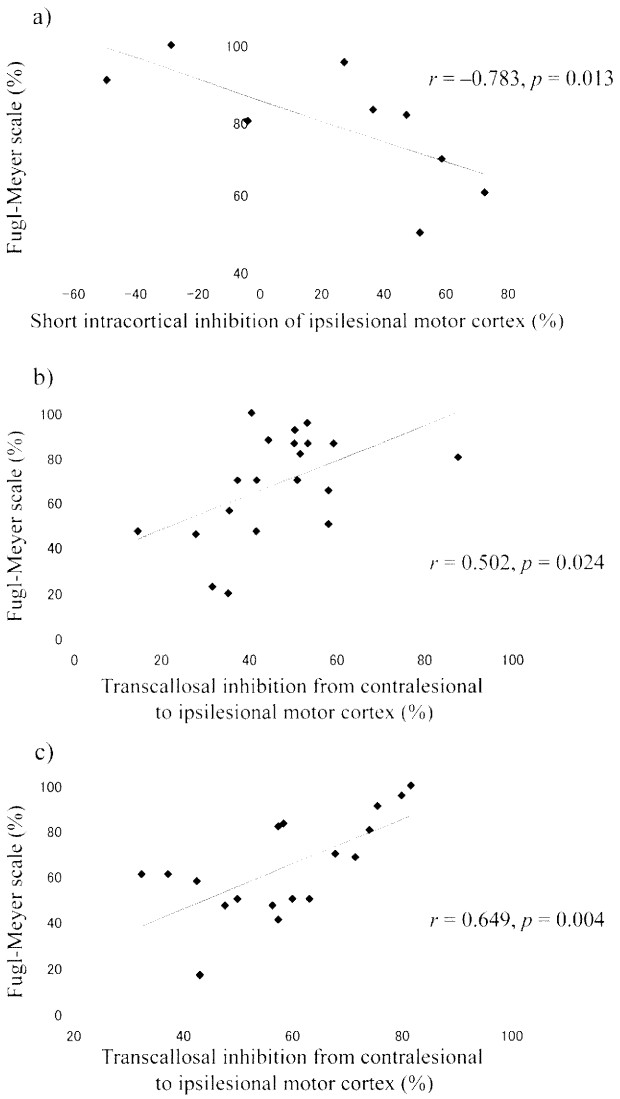

Fig. 1. Correlation between inhibitory function and motor function. (a) There was a negative correlation between intracortical inhibition of the ipsilesional motor cortex and the Fugl-Meyer Scale score in the subcortical group. There was a significant positive correlation between transcallosal inhibition from the contralesional to the ipsilesional motor cortex and the Fugl-Meyer Scale score in both (b) the cortical and (c) the subcortical groups.

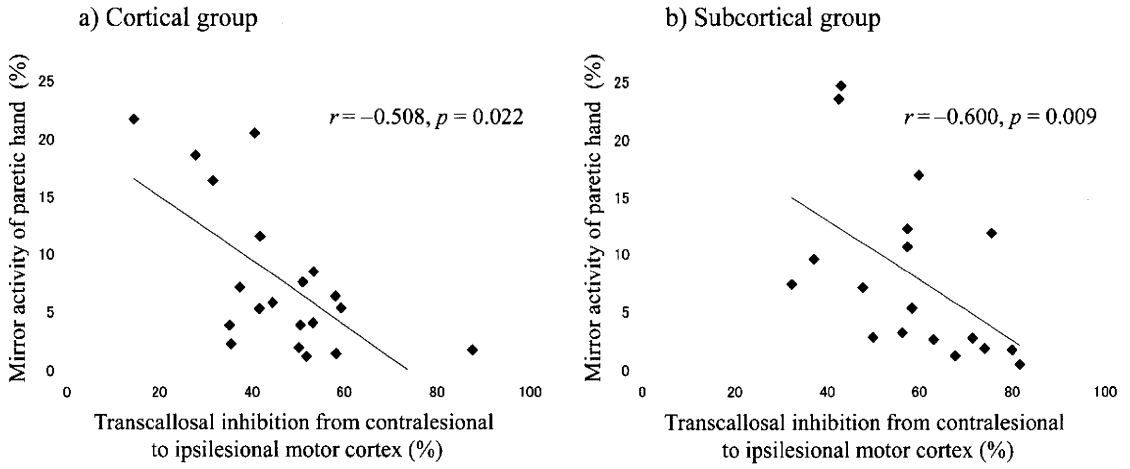

Fig. 2. The correlation between transcallosal inhibition and mirror activity of the paretic hand. There was a negative correlation between transcallosal inhibition from the contralesional to the ipsilesional motor cortex and mirror activity of the paretic hand in both (a) the cortical and (b) the subcortical groups.

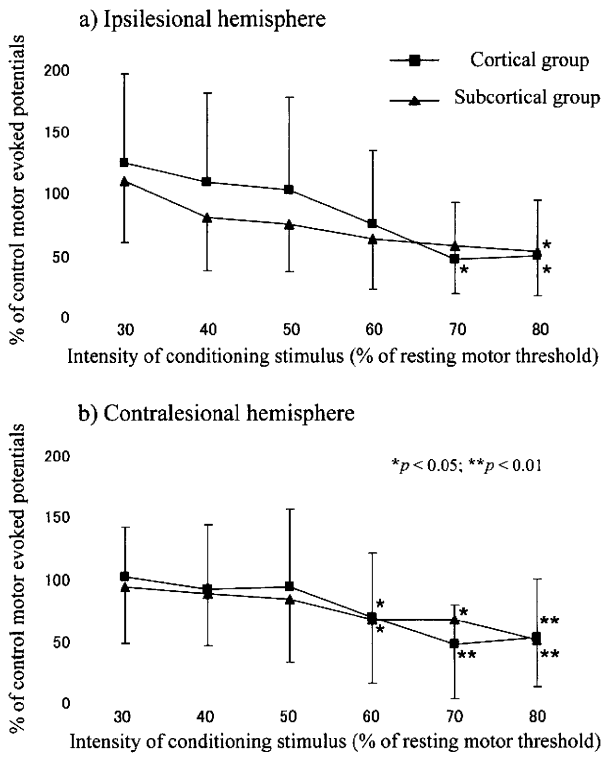

Fig. 3. Short interval cortical excitability. The strong conditioning stimulus reduced the amplitude of motor evoked potentials (MEPs) in short interval cortical excitability in all groups. A significant reduction in the amplitude of the MEPs is indicated by asterisks. Error bar: standard deviation.

subcortical stroke patients, but not cortical stroke patients, in the chronic stage. Considering these findings, the continuous disinhibition of the ipsilesional motor cortex in subcortical stroke patients may promote the best possible recovery of motor function by facilitating the plasticity of the non-damaged motor cortex in the ipsilesional hemisphere (4); in contrast, the inhibitory function of the ipsilesional motor cortex in cortical stroke patients may be influenced more by direct cortical damage than compensatory mechanisms in the chronic stage.

The problem with the SICI methods is that it was difficult to decide whether a reduced SICI indicated weak inhibitory or strong excitatory cortical function solely on the basis of the SICI paradigm. To avoid this problem, we used the SICE paradigm that could evaluate the inhibitory and excitatory circuits in more detail. The influence of the excitatory function has been shown to be superior to that of the inhibitory function at a strong conditioning stimulus in the SICE paradigm (7). If only the excitatory function increases and the inhibitory function remains unchanged, the amplitude of SICE is small at a weak conditioning stimulus and large at a strong conditioning stimulus (7). However, the amplitude of SICE was reduced according to the intensity of the conditioning stimulus in this study. Therefore, the reduction in SICI of the ipsilesional motor cortex implies the loss of inhibitory function and not an epiphenomenon caused by modified neuronal circuits shifting toward excitatory activity.

TCI from the contralesional to the ipsilesional motor cortex was more prominent in patients with greater motor function during movement. This finding is not consistent with that of previous study, which reported a negative correlation between TCI at pre-movement and the motor function of the paretic hand (5). These differences may have resulted from the differing methods and TCI mechanisms employed in our and previous study (13). A recent study reported that TCI could inhibit unwanted mirror activity during intended unimanual motor tasks (14). Consistent with this report, TCI to the ipsilesional motor cortex was correlated negatively with the mirror activity of the paretic hand in our study. Therefore, TCI to the ipsilesional motor cortex during movement may play a neurophysiological role in the inhibition of mirror movement of the paretic hand. To clarify this hypothesis, further studies are required to evaluate the change in mirror activity when TCI to the ipsilesional motor cortex is reduced by using inhibitory repetitive TMS over the contralesional motor cortex (14). We propose that TCI to the ipsilesional motor cortex may

be important for mirror movement of the paretic hand; however, we agree with the hypothesis that TCI to the ipsilesional motor cortex may inhibit motor function in some stroke patients (5). Considering these findings, TCI to the ipsilesional motor cortex may be influenced by a balance between motor function and mirror movement in the paretic hand during the process of reorganization after stroke. That is to say, TCI to the ipsilesional motor cortex may be strong to inhibit mirror movement in patients with good motor function; in contrast, TCI in patients with poor motor function may be weak to improve motor function without inhibition of mirror movement.

The neurophysiological results of this study may help improve individualized rehabilitation strategies after stroke. Recent study has reported that inhibitory neuromodulation of the contralesional motor cortex could improve the motor function of the paretic hand by a reduction in TCI to the ipsilesional motor cortex (9). Therefore, inhibitory neuromodulation of the contralesional motor cortex may be especially effective for stroke patients with good motor function who had strong TCI, although the mirror activity of the paretic hand may increase. In addition, for subcortical stroke patients with disinhibition of the ipsilesional motor cortex, intense use of the paretic limb, such as constraint-induced movement therapy, may promote motor recovery by inducing use-dependent reorganization (15). In contrast, inhibitory neuromodulation of the contralesional motor cortex may be less effective in stroke patients with poor motor function, because these patients already have weak TCI before the neuromodulation interventions. The functional imaging study has reported that the contralesional motor cortex is engaged during paretic hand movements in stroke patients with poor motor function (16). Therefore, therapy aimed at increasing the excitability of the contralesional motor cortex may be effective for motor recovery of stroke patients with poor motor function. However, to our knowledge, there is no report that a neuromodulatory approach that increases the excitability in only the contralesional motor cortex can enhance motor recovery, ignoring the importance of the balance between bilateral hemispheres (17). If excitability is increased only in the contralesional motor cortex, the weak TCI to the ipsilesional motor cortex in stroke patients with poor motor function may become strong and inhibit the function of the ipsilesional motor cortex. Therefore, bilateral movement training that engages and balances both hemispheres may be effective for stroke patients with poor motor function (18).

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Modulation of neuronal activity after spinal cord stimulation for neuropathic pain; $H_2{}^{15}O$ PET study

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ABSTRACT

Spinal cord stimulation (SCS) is an effective therapy for chronic neuropathic pain. However, the detailed mechanisms underlying its effects are not well understood. Positron emission tomography (PET) with $H_2{}^{15}O$ was applied to clarify these mechanisms. Nine patients with intractable neuropathic pain in the lower limbs were included in the study. All patients underwent SCS therapy for intractable pain, which was due to failed back surgery syndrome in three patients, complex regional pain syndrome in two, cerebral hemorrhage in two, spinal infarction in one, and spinal cord injury in one. Regional cerebral blood flow (rCBF) was measured by $H_2{}^{15}O$ PET before and after SCS. The images were analyzed with statistical parametric mapping software (SPM2). SCS reduced pain; visual analog scale values for pain decreased from 76.1 ± 25.2 before SCS to 40.6 ± 4.5 after SCS (mean $\pm$ SE). Significant rCBF increases were identified after SCS in the thalamus contralateral to the painful limb and in the bilateral parietal association area. The anterior cingulate cortex (ACC) and prefrontal areas were also activated after SCS. These results suggest that SCS modulates supraspinal neuronal activities. The contralateral thalamus and parietal association area would regulate the pain threshold. The ACC and prefrontal areas would control the emotional aspects of intractable pain, resulting in the reduction of neuropathic pain after SCS.

Introduction

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system (Loeser and Treede, 2008). It is generally more severe and more likely to be drug-resistant and persistent than nociceptive pain (Finnerup et al., 2005; Dworkin et al., 2003). Thus, chronic pain is often under-diagnosed and under-treated (Taylor, 2006), and it impairs quality of life. The causes of neuropathic pain vary and include such conditions as failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), central post-stroke pain, phantom limb pain, peripheral and central nerve system injury, and post-spinal cord injury pain (Dworkin et al., 2003). Chronic neuropathic pain is most common in the back and legs.

Shealy et al. (1967) were the first to report that electrical stimulation of the dorsal spinal cord relieves cancer pain. Spinal cord stimulation (SCS) has since been applied not only to numerous cases of intractable pain but also to other conditions such as angina pectoris (AP), ischemic pain, and persistent vegetative state (Morita et al., 2007; Börjesson et al., 2008; Pedrini and Magnoni, 2007). Taylor (2006) reported that SCS not only reduces the pain but also improves quality of life in patients with FBSS or CRPS. He also reported that SCS is a cost-saving therapy. Kumar et al. (2007) reported that SCS provides better pain relief than conventional medical management alone in FBSS patients, and this was supported by a multicenter trial (Manca et al., 2008). Furthermore, the European Federation of Neurological Society guidelines support the effect of SCS in patients with FBSS or CRPS (Cruccu et al., 2007). For the central pain (spinal cord or brain lesions), SCS was reported to have some effect for pain relief. Katayama et al. (2001) reported that 7% of post-stroke pain patients revealed pain reduction with SCS and Kumar et al. (2006) also reported that SCS relieved 79% of the chronic pain due to multiple sclerosis. Thus, SCS is an essential treatment for relief of chronic neuropathic pain.

Oakley and Prager (2002) investigated some of the mechanisms underlying relief of pain by SCS. SCS was shown to stimulate the neurons of the dorsal horn of the spinal cord to release increased amount of acetylcholine and GABA and decreased amounts of aspartate and glutamate in rat models (Meyerson and Linderoth,

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2000; Schechtmann et al., 2008). SCS was also shown to induce neurophysiological change, normalizing neuronal hyperexcitability in the dorsal horn (Yakhnitsa et al., 1999). In addition to these spinal mechanisms, functional alteration at the supraspinal level has been suggested to play an important role in pain reduction. Physiological study revealed cortical modulation during SCS (Polácek et al., 2007; Schlaier et al., 2007). However, the mechanism of pain relief by SCS is not fully understood. Brain activation during SCS has been analyzed by means of $H_2{}^{15}O$ positron emission tomography (PET) in patients with AP (Hautvast et al., 1997) and by means of functional magnetic resonance imaging (fMRI) in patients with FBSS (Kiriakopoulos et al., 1997; Stancák et al., 2008).

The investigators reported that SCS activates the primary and secondary sensorimotor cortex, cingulate cortex, insula, thalamus, and premotor cortex. Pain relief continues for several hours after SCS, so most patients with chronic pain use SCS intermittently, for example, several times per day. The modulation of brain activity after SCS has not been thoroughly examined.

In the present study, we used $H_2{}^{15}O$ PET to investigate the pattern of SCS-related neuronal activation and/or attenuation before and after SCS. $H_2{}^{15}O$ PET visualizes regional cerebral blood flow (rCBF), which reflects focal neuronal activation (Kapur et al., 1994). We also used statistical parametric mapping of normalized brain images to identify functionally specialized brain responses.

Materials and methods

Patients and surgical procedure

Nine patients (six men and three women) with intractable neuropathic pain in their lower extremities were included in this study (Table 1). Patients ranged in age from 28 to 65 years. The intractable neuropathic pain was due to FBSS in three patients, CRPS in two, cerebral hemorrhage in two, spinal cord infarction in one, and spinal cord injury in one. Pain was left-sided in five patients, right-sided in two patients, and bilateral in two patients. One of two patients with bilateral pain (patient 3) had more severe pain in right leg and the other (patient 8) had more severe pain in left leg. Their purposes of SCS were to reduce the pain in the more painful leg. Medical therapy had not been satisfactory, and the nine patients suffered from the intractable pain for 31 to 147 months before SCS was tried. Five of the nine patients showed slight to moderate motor weakness, and all had slight to severe sensory disturbance in the affected legs (Table 1). A visual analog scale (VAS), ranging from 0 to 100, and the short form of the McGill Pain Questionnaire (SF-MPQ) were used to evaluate the degree of pain.

The standard surgical procedure was used to place the SCS lead. In brief, under local anesthesia, a quadripolar electrode lead (Pisces Quad, 3487A; Medtronic, Inc., Minneapolis, MN, USA) was inserted percutaneously into the epidural space of the lumbar or thoracic spine by fluoroscopic guidance. The electrode was finally positioned after electrical sensation was detected in the region of pain upon stimulation. After confirmation of pain reduction in response to stimulation for 5–10 days, the electrode was connected to a subcutaneously implanted stimulator (Itrel III; Medtronic, Inc.).

Habitual bipolar stimulation was used for pain relief, and stimulation parameters varied between patients. General stimulation parameters were as follows: voltage, max 10 V; frequency, 10–85 Hz; pulse width, 210 to 450 μs; and duration of stimulation, 30 min. The patients controlled the stimulation at will and used SCS for at least 6 months before the PET study.

PET scanning procedure and activation task

The PET study was performed 6 to 12 months after implantation of the stimulation electrode. A Headtome-V PET scanner (Shimadzu, Kyoto, Japan) was used to scan in the three-dimensional acquisition mode with a shield to protect against scattered rays. Patients went without spinal cord stimulation for more than 12 h before the PET study. The patients lay with eyes closed in a silent and dim room. A 15-min transmission scan was acquired first with ^{68}Ge sources to correct for γ-ray attenuation. Relative CBF was measured based on the distribution of radioactivity after a slow bolus i.v. injection of $H_2{}^{15}O$ (7 mCi/scan, each lasting 90 s). Six PET scans corresponding to six $H_2{}^{15}O$ injections were obtained before SCS, SCS was performed for 30 min under the habitual condition, and six PET scans were obtained after pain reduction was confirmed. The PET protocol was the same as the motor cortex stimulation (MCS) protocol described previously (Kishima et al., 2007).

Data analysis

Attenuation-corrected data were reconstructed into an image (voxel sizes, $2\times2\times3.125$ mm; field of view, $256\times256\times196$ mm) with a resulting resolution of $4\times4\times5$ mm at FWHM (full width at half maximum). The images were analyzed with statistical parametric mapping (SPM) software (SPM2; Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1991). PET images were anatomically normalized to fit with ICBM coordinates of the Montreal Neurological Institute. Images from each patient were realigned to the first volume of PET images and normalized to the template (Friston et al., 1995a) to account for variation in gyral anatomy and inter-individual variability in the structure–function relation and to improve the signal-to-noise ratio. This procedure was used for image realignment, anatomic normalization, smoothing (12 mm at FWHM), and statistical analysis (Kiebel et al., 1997). Data were normalized to global blood flow (average = 50). State-dependent differences in global blood flow were subjected to ANCOVA.

All nine patients were included in the same statistical analyses, with voxel-to-voxel comparison. Statistical parametric maps (SPM) were generated with an ANOVA model with the General Linear Model formulation of SPM2 (Friston et al., 1995b). We analyzed the main effect of SCS by comparing images obtained after SCS with those

Table 1
General characteristics of patients with deafferentation pain.

Patient	Age (years), sex	Etiology of pain	Pain laterality	Motor (0–5)	Sensory (0–10)	Duration of pain (months)	Pre-SCS VAS	Post-SCS VAS
1	44, M	Spinal infarction	Rt	4	4	36	80	40
2	60, F	Putaminal hemorrhage	Lt	4	10	99	100	55
3	65, F	FBSS	Bi (Rt > Lt)	5	10	147	90	30
4	45, M	CPRS	Lt	2	2	65	60	20
5	41, M	FBSS	Rt	3	5	54	85	25
6	28, F	CRPS	Lt	2	2	31	70	60
7	59, M	Putaminal hemorrhage	Lt	5	1	59	55	50
8	50, M	Spinal injury	Bi (Rt < Lt)	5	6	42	60	40
9	38, M	FBSS	Lt	5	10	57	85	45

FBSS, failed back surgery syndrome; CRPS, complex regional pain syndrome; Rt, right; Lt: left; Bi, bilateral; Motor, MMT score (0, complete paresis; 5, normal); Sensory, sensory scores (0, anesthesia; 10, normal); Pre-SCS VAS, VAS of pre-SCS; Post-SCS VAS, VAS of post-SCS.

Table 2
Increased rCBF after SCS.

Area	Cluster		Talairach coordinates (*x*, *y*, *z* mm)	Voxel equiv. *Z*
	p (corrected)	Size (voxels)		
(A) Rt thalamus	0.006	197	11.9, −15.6, 0.0	4.64
(B) Rt orbitofrontal (BA11)	0.040	161	43.6, 51.8, −12.7	4.70
(C) Lt Inf. parietal (BA7)	0.009	178	−33.7, −61.8, 45.5	4.39
(D) Rt Sup. parietal (BA7)	0.014	158	37.6, −45.9, 53.9	4.57
(E) Lt anterior cingulate (BA24)	0.001	301	−7.98, 38.1, 23.4	4.64
(F) Lt dorsolateral prefrontal (BA10)	0.050	100	−33.7, 36.0, 18.4	4.27

Rt, right; Lt, left; Inf, inferior; Sup, superior.

obtained before SCS, with the statistical threshold set at $p<0.02$ (corrected for multiple comparisons) in False Discovery Rate (FDW) for peak height, corrected for spatial extent (>8 voxels per cluster), and the cluster size was set at 100 contiguous voxels.

This method was used to generate SPM (*t*) of rCBF changes associated with each comparison. For between-group comparisons, the SPM (*t*) maps were transformed into SPM (*z*), and the levels of significance of areas of activation were assessed according to the peak height of foci estimation based on the theory of random Gaussian fields.

Three patients had been treated to reduce the right lower limb pain (patients 1, 3, and 5). MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html) was used to invert the images obtained from these patients from the right to the left so that statistical analysis would be consistent with that of other patients. The images were then realigned, normalized, and analyzed as previously described. Furthermore, to detect the correlation of the rCBF change and SCS efficacy, these images were performed covariance analysis with the VAS reduction rate after SCS ((pre-VAS – post-VAS) / pre-VAS).

Significance was accepted if a cluster showed a cluster corrected threshold of $p<0.05$. Anatomical locations were indicated according to the atlas of Talairach and Tournoux (1988).

This study adhered to the guidelines of the Declaration of Helsinki on the use of human subjects in research, and the patients provided written informed consent. This study was approved by the ethics committee of Osaka University Hospital.

Results

Pain reduction after SCS

After SCS, all nine patients showed various degrees of pain reduction according to VAS data (76.1 ± 25.2 to 40.6 ± 4.5) (Table 1). The pain reduction began during SCS and continued for at least 120 min after SCS. The degree of pain reduction remained stable for 60 min during the post-SCS PET scanning phase. In general, results of the SF-MPQ were for the most part compatible with VAS scores.

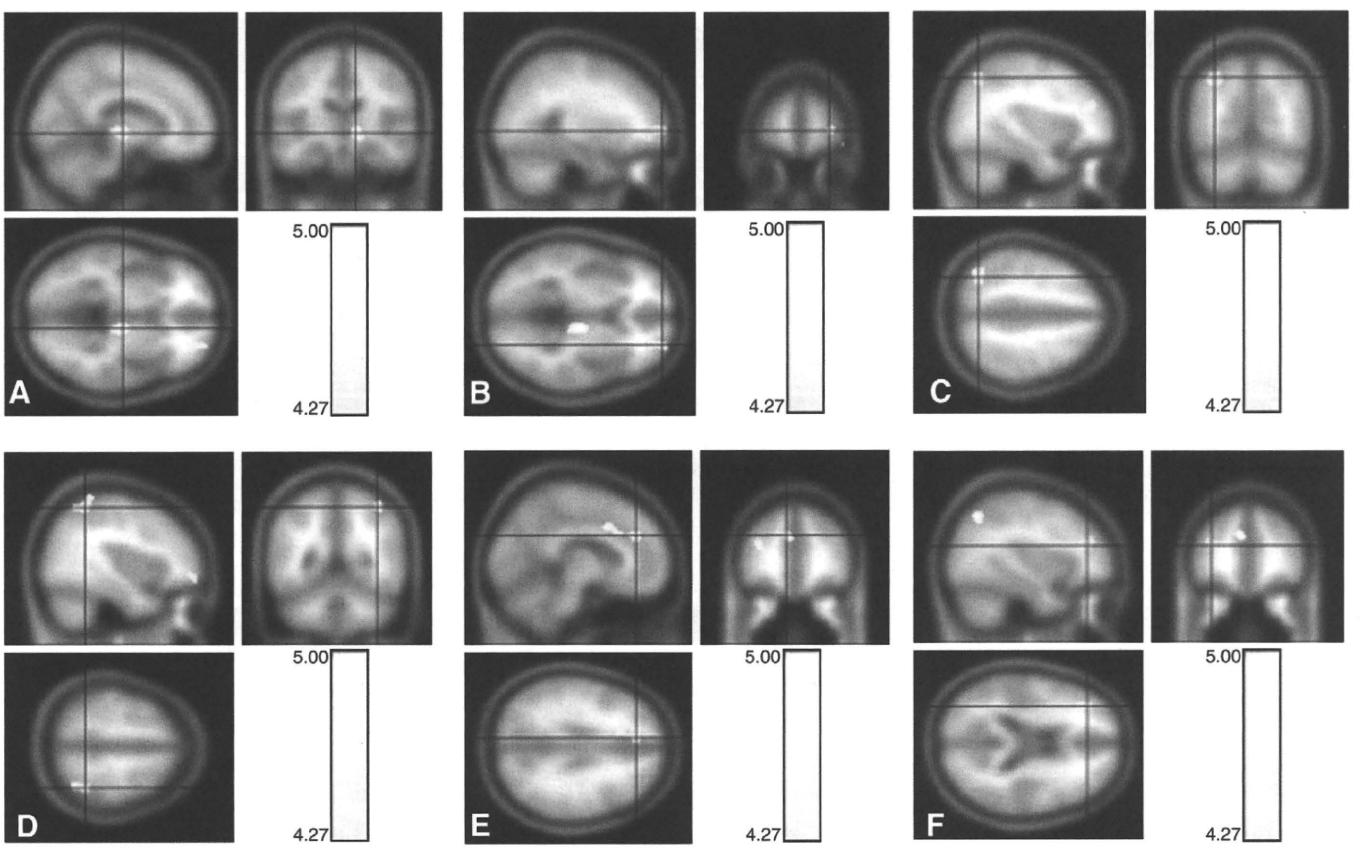

Fig. 1. Statistical parametric maps (*Z* maps) of intensity in normalized images. Comparison of rCBF before and after SCS shows that rCBF is increased after SCS in the right thalamus (A), right orbitofrontal cortex (BA11) (B), left inferior parietal lobule (C), right superior parietal lobule (D), left anterior cingulate cortex (E), and left dorsolateral prefrontal cortex (F). Colored bar indicates *Z* value (threshold, $p<0.05$). Panels A–F correspond to Table 2.

Table 3
Increased rCBF after SCS in reference to the affected side.

Area	Cluster		Talairach coordinates (*x*, *y*, *z* mm)	Voxel equiv. *Z*
	p (corrected)	Size (voxels)		
(A) C. Inf. parietal (BA40)	0.002	207	30.9, −47.9, 53.5	5.48
(B) C. Inf. parietal (BA40)	0.003	432	43.2, −46.0, 30.8	4.96
(C) C. dorsolateral prefrontal (BA10)	0.004	169	25.6, 56.8, 6.2	4.78
(D) C. anterior cingulate (BA24)	0.005	183	8.0, 18.0, 30.6	4.55
(E) I. lateral precentral (BA6)	0.01	109	−46.6, 0.6, 10.3	4.22
(F) C. thalamus	0.011	108	8.0, −16.9, −1.14	4.17
(G) I. dorsolateral prefrontal (BA9)	0.013	128	−27.2, 25.8, 25.7	4.06
(H) I. orbitofrontal (BA10)	0.014	143	−34.2, 43.2, −8.6	4.02
(I) I. Sup. parietal (BA7)	0.018	127	−27.2, −67.3, 35.0	3.85

I, ipsilateral to affected side; C, contralateral to affected side; Bi, bilateral; Inf, inferior; Sup, superior.

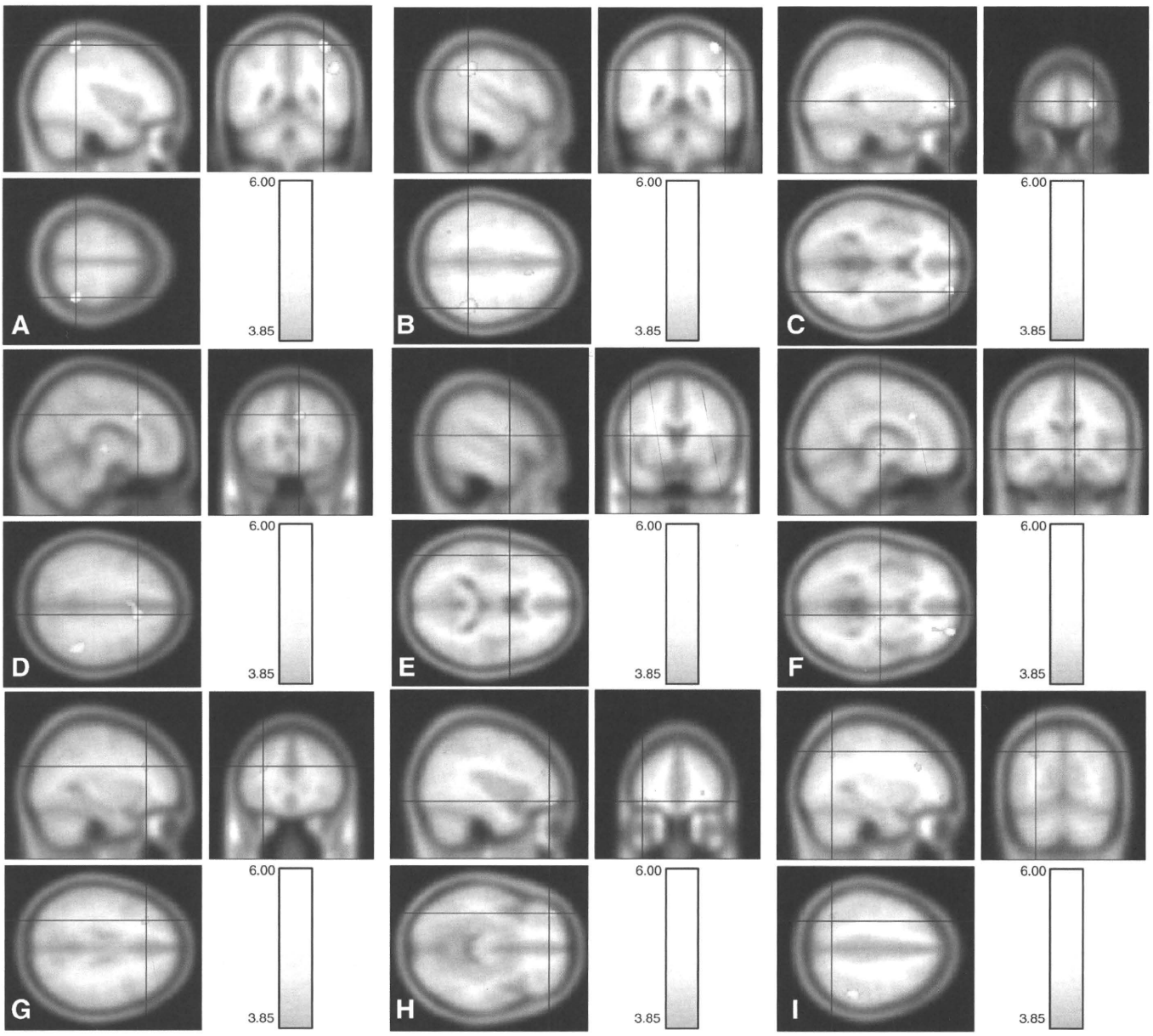

Fig. 2. Statistical parametric maps (*Z* maps) of intensity in normalized images. Comparison of rCBF before and after SCS by positioning the affected sides on the left shows that rCBF is increased after SCS in the contralateral inferior parietal lobules ($Z=5.48$, 4.96) (A, B), contralateral dorsolateral prefrontal cortex (BA10) ($Z=4.78$) (C), contralateral anterior cingulate cortex (BA24) ($Z=4.55$) (D), contralateral orbitofrontal cortex (BA10) ($Z=4.63$) and contralateral medial prefrontal cortex (BA10) ($Z=4.56$), ipsilateral lateral precentral cortex (BA6) ($Z=4.22$) (E), contralateral thalamus ($Z=4.17$) (F), ipsilateral dorsolateral prefrontal (BA9) ($Z=4.06$) (G), ipsilateral orbitofrontal cortex (BA10) ($Z=4.02$) (H), and ipsilateral superior parietal lobule (BA7) ($Z=3.85$) (I). Colored bar indicates *Z* value. Colored bar indicates *Z* value (threshold, $p<0.05$). Panels A–I correspond to Table 3.

Brain activation profiles in response to SCS

Comparison of rCBF before and after SCS showed significant rCBF increases in the right thalamus ($Z=4.64$), right orbitofrontal cortex (BA11) ($Z=4.70$), left inferior parietal lobule (BA7) ($Z=4.39$), right superior parietal lobule (BA7) ($Z=4.57$), and left anterior cingulate cortex (ACC) (BA24) ($Z=4.64$), and left lateral prefrontal cortex (BA10) ($Z=4.27$) (Table 2, Fig. 1). There was no region where rCBS decreased after SCS.

The result analyzed after three images of patients 1, 3, and 5 were inverted so that the affected side appeared on the left, showed that rCBF was increased in the contralateral (right) inferior parietal lobules ($Z=5.48$, 4.96), contralateral dorsolateral prefrontal cortex (BA10) ($Z=4.78$), contralateral ACC (BA24) ($Z=4.55$), contralateral thalamus ($Z=4.17$), and ipsilateral lateral precentral cortex (BA6) ($Z=4.22$), dorsolateral prefrontal (BA9) ($Z=4.06$), ipsilateral orbitofrontal cortex (BA10) ($Z=4.02$), and ipsilateral superior parietal lobule (BA7) ($Z=3.85$) (Table 3, Fig. 2). There was no region where rCBF decreased after SCS. When these images were performed covariance analysis with VAS reduction rate after SCS, increased rCBF in ipsilateral dorsolateral prefrontal cortex (BA9) ($Z=5.59$), ipsilateral lateral precentral cortex (BA6) ($Z=5.18$), ipsilateral medial prefrontal cortex (BA8) ($Z=4.08$), and contralateral medial prefrontal cortex (BA8) ($Z=4.18$) were positively correlated with pain reduction rate (Table 4, Fig. 3).

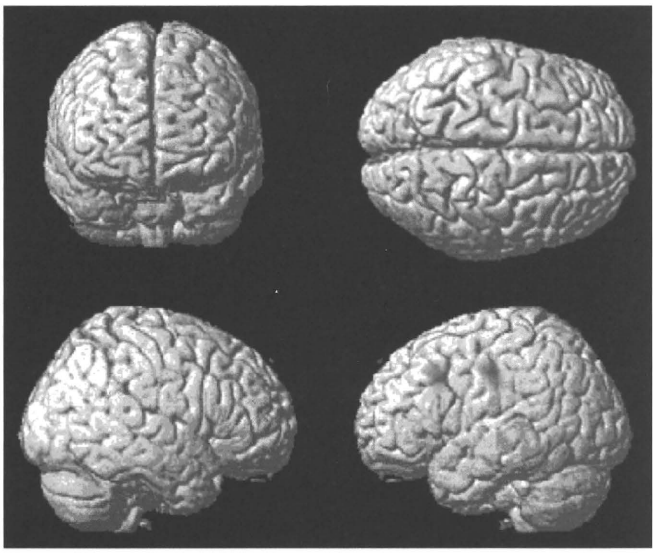

Fig. 3. Areas of significantly increased rCBF correlated to the VAS reduction rate after SCS, rendered in the normalized images, indicate ipsilateral to affected side of dorsolateral prefrontal cortex (BA9), ipsilateral lateral precentral cortex (BA6), and bilateral medial prefrontal (BA8) (threshold, $p<0.05$).

Discussion

This is the first report that rCBF is modified after SCS for chronic neuropathic pain as shown by $H_2{}^{15}O$ PET. rCBF is thought to reflect focal neuronal activation (Kapur et al., 1994). Thus, we concluded that there is a change in neuronal activation after SCS in patients with neuropathic pain. Our study included nine patients who underwent SCS to relieve their neuropathic pain. Although the etiology of chronic pain varied, all nine patients experienced some pain relief with SCS, and all used SCS everyday for more than several months. So we categorized them as SCS responders based on their pain reduction, and we report that the observed rCBF changes may be involved in the pain relieving mechanism of SCS.

We measured neuronal activity with $H_2{}^{15}O$ PET before and after SCS, and all PET images were normalized and then analyzed by SPM (Friston et al. 1991; 1995a,b; Kiebel et al., 1997). Therefore, the results of this study were based on anatomically well-standardized samples. Furthermore, images of three patients having only right-sided pain were reversed to move the affected side to the left and were analyzed with the others. This method statistically enhances the results, especially in pain cognition-related regions.

We found that rCBF increased in the right thalamus and superior parietal lobule (BA7) and left inferior parietal lobule (BA7) after SCS. rCBF was also shown to be increased in the contralateral thalamus and contralateral inferior parietal lobule (BA40), and ipsilateral superior parietal lobule (BA7) when we moved the affected side to the left. BA7 is the secondary somatosensory area (S2), and BA40 is the parietal association area. These areas play important roles for cognition of the somatosensory input.

One interesting finding of this study is that neither the contralateral primary motor cortex (M1) nor S1 corresponding to the affected leg showed rCBF change after SCS. This finding is contrary to previous reports that the contralateral S1 and the contralateral paracentral regions are activated during SCS as shown by electrophysiological methods (Polácek et al., 2007) and fMRI (Stancák et al., 2008). We attribute this difference to the fact that we performed PET scanning before and after SCS rather than during SCS as in the previous studies. During SCS, the patient often feels a stimulating sensation, and this might influence S1. After SCS, this sensation might diminish quickly; consequently, activation of S1 and paracentral regions would normalize. Moreover, the pain relief continues for several hours after SCS. Thus, S2 and the parietal association area are modulated by SCS and would control the threshold of the chronic pain for several hours after SCS.

An important finding is that the contralateral thalamus was shown to be activated in the post-SCS phase after the affected side was adjusted to the left. This finding is contrary to that of a previous report based on fMRI that did not describe thalamic activation during SCS (Stancák et al., 2008). It is also reported that the thalamus contralateral to the painful side shows hypometabolism in cases of central pain (De Salles and Bittar, 1994; Laterre et al., 1998). Hsieh et al. (1995) reported that rCBF in the contralateral thalamus was decreased by the peripheral nerve block with lidocaine in the mononeuropathy patients. We suppose this method might inhibit the sensory input of the peripheral to spinal cord and it might reduce the spino-thalamic information, resulting to the reduction of the contralateral thalamic activity. In our study, however, SCS never blocks the sensory input and it just controls the pain. So the result in this study is different from the previous report of Hsieh et al. Although the detailed role of the contralateral thalamus in the pathology of

Table 4
Increased rCBF after SCS covariate with pain reduction rate.

Area	Cluster		Talairach coordinates (x, y, z mm)	Voxel equiv. Z
	P (corrected)	Size (voxels)		
(A) I. dorsolateral prefrontal (BA9)	0.001	396	−44.8, 14.1, 32.1	5.59
(B) I. lateral precentral (BA6)	0.002	559	−44.8, −18.8, 34.0	5.18
(C) C. Sup. prefrontal (BA8)	0.008	168	13.3, 20.0, 53.6	4.18
(D) I. Sup. prefrontal (BA8)	0.01	112	−18.4, 14.1, 49.7	4.08

I, ipsilateral to affected side; C, contralateral to affected side; Bi, bilateral; Sup, superior.

neuropathic pain remains unclear, it is possible that SCS induces neuronal activity in contralateral thalamus, resulting in pain relief, and that the thalamus alters the pain threshold and sensory cognition after SCS, as previously reported (Garcia-Larrea et al., 1999).

It was shown that the ACC, dorsolateral prefrontal cortex, and orbitofrontal cortex were activated after SCS. The ACC and prefrontal cortex are reported to be involved in the modulation of pain and emotion. The activation of prefrontal cortex and ipsilatearl lateral precentral cortex was correlated with the degree of SCS efficacy (Table 4, Fig. 3). A previous report on MCS showed correlation between pain relief and ACC activation (Kishima et al., 2007; Peyron et al., 2007). Peyron et al. (2007) also reported that the prefrontal region, orbitofrontal region, and ACC act as descending (top–down) inhibitory controls for pain threshold in patients treated with MCS. Ochsner et al. (2004) reported that the prefrontal region and ACC recruit the up- and down-regulation of negative emotion. It has been reported that the activity of the right ventrolateral prefrontal region correlates with reduced negative emotional experience (Wager et al., 2008) and that fear of various types of physical pain predicts activation of the ventrolateral frontal region and anterior and posterior cingulate regions (Ochsner et al., 2006). Furthermore, because the ACC and prefrontal area are components of the brain reward system, it is possible that this system is also activated by SCS. In line with these findings, SCS itself and/or pain relief induced by SCS would control the emotional aspects of pain, resulting in a long lasting effect. The role of ipsilateral precentral area activated after SCS is not clear. The activation of dorsolateral prefrontal regions would reflect the most of the patients' satisfaction.

It was reported that rCBF increases to noxious stimuli are observed in S2, S1, thalamus, ACC, dorsal parietal, and prefrontal area (Peyron et al. 2000). SCS during heat stimuli increased rCBF in S2, S1, and posterior insula (Stancák et al. 2008). Thalamus, ACC, dorsal parietal, S2 and prefrontal regions were activated after SCS with neuropathic pain in this study. In line with those results, we could suppose that both acute pain stimuli and pain reduction by SCS would induce the neuronal activation in the similar regions. After SCS for patients with neuropathic pain, the change of sensory input, pain cognition, attention, and memory network would activate thalamus, parietal areas, ACC, and prefrontal areas.

Conclusions

For treatment of neuropathic pain, SCS controls pain cognition by modulating the thalamus and parietal association area. SCS also controls the emotional aspects of pain by modulating the prefrontal region and ACC. These findings support the use of SCS for treatment of neuropathic pain.

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Spinal Cord Stimulation for Central Poststroke Pain

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BACKGROUND: Although spinal cord stimulation (SCS) has been shown to be effective for treating neuropathic pain of peripheral origin, its effectiveness for central poststroke pain (CPSP) is not well established.

OBJECTIVE: We report our experience with SCS in 30 consecutive patients with intractable CPSP.

METHODS: All patients underwent a percutaneous SCS trial. When patients decided to proceed, they received a permanent SCS system. Pain intensity was evaluated by a visual analogue scale (VAS). The Patient Global Impression of Change (PGIC) scale was also assessed at the latest follow-up visit as an indicator of overall improvement.

RESULTS: During trial stimulation, pain relief was good (≥50% VAS score reduction) in 9 patients (30%), fair (30%-49% reduction) in 6 patients (20%), and poor (<30% reduction) in 15 patients (50%). Ten patients elected to receive a permanent SCS system. Nine of these 10 patients were followed long-term (mean, 28 months; range, 6-62 months). Seven patients reported significant pain relief on the VAS (5 = good and 2 = fair). On the PGIC scale, 6 of these 7 patients reported a rating of 2 (much improved) and 1 reported a rating of 3 (minimally improved). Of the remaining 2 patients, 1 reported a rating of 4 (no change) and 1 reported a rating of 5 (minimally worse). The median VAS score in the 9 patients decreased significantly from 8.6 (range, 6.0-10.0) to 4.5 (range, 3.0-8.0; $P = .008$). There were no significant reported complications.

CONCLUSION: SCS may provide improved pain control in a group of patients with intractable CPSP and may have therapeutic potential for intractable CPSP.

KEY WORDS: Central poststroke pain, Medically refractory, Neurostimulation, Spinal cord stimulation

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Central poststroke pain (CPSP) is a type of neuropathic pain that affects approximately 1% to 8% of patients after stroke[1,2] and is characterized by pain and sensory dysfunction involving the area of the body that has been affected by the stroke.[3] Once present, CPSP rarely abates, causing a considerable long-term impact on patient's quality of life.[4] Although amitriptyline and gabapentin are usually the drugs of first choice, they are often ineffective. In addition, the utility of amitriptyline is limited by its intolerable side effects, including dry mouth, urinary retention, arrhythmias, and sedation, especially in elderly stroke patients.[5]

The use of neurostimulation techniques has been proposed for severe medically refractory CPSP.[6] Deep brain stimulation has yielded variable results,[7] whereas motor cortex stimulation (MCS) has been reported to achieve pain relief in approximately half of patients.[8] MCS involves implanting electrodes over the motor strip through a craniotomy. Its use is correspondingly restricted to well-established functional neurosurgical centers.[6]

Spinal cord stimulation (SCS) is the most widely used neurostimulation technique for chronic pain because it is minimally invasive, has a low complication rate, and is generally effective.[9] SCS has been proven effective for various types of neuropathic pain of peripheral origin, in particular, failed back surgery syndrome and peripheral neuropathy.[9] In contrast, SCS is considered ineffective for central neuropathic pain, including CPSP.[7] However, the efficacy of SCS for CPSP has not been adequately explored, and there are only a few reports of its use in a small number of patients.[6,7,10,11] To evaluate the efficacy of SCS in CPSP, we retrospectively reviewed our clinical data from SCS in 30 consecutive

ABBREVIATIONS: CPSP, central poststroke pain; **MCS,** motor cortex stimulation; **SCS,** spinal cord stimulation; **VAS,** visual analogue scale

patients with intractable CPSP and report the results of trial as well as long-term stimulation.

PATIENTS AND METHODS

Patient Population

Between May 2002 and July 2009, 87 patients with medically refractory CPSP underwent one or more of the following neuromodulatory procedures at the Department of Neurosurgery of Osaka University Hospital: MCS (13 patients), repetitive transcranial magnetic stimulation (59 patients), or SCS (30 patients). We reviewed the records of the 30 consecutive patients with medically refractory CPSP who underwent SCS trials or implantations. They included 21 men and 9 women, with a mean ± standard deviation age of 64.8 ± 7.4 years and a mean duration of pain before surgery of 44.8 ± 35 months.

All patients were diagnosed with CPSP according to the following findings[12]: (1) development of pain after stroke, (2) sensory disturbance correlated with the cerebrovascular lesion, (3) pain located within the territory of sensory disturbance, and (4) exclusion of other causes of nociceptive and peripheral neuropathic pain, especially lumbar canal stenosis and poststroke shoulder pain caused by contracture deformity. Comprehensive neuropsychological assessment was performed in all patients to rule out serious psychiatric disorder or severe cognitive dysfunction. All patients had a poor response to medical treatment for at least 6 months before the SCS treatment, including antidepressants and anticonvulsant drugs.

We used to recommend MCS as a primary neurostimulation option for patients with medically refractory CPSP. However, we found that some patients refused MCS because of the need for a craniotomy. Another group of patients had a poor response to repetitive transcranial magnetic stimulation, which predicted a poor response to MCS.[13] In these situations, we discussed an SCS trial as an alternative and less invasive option. Moreover, because SCS is most effective in well-localized pain,[12] we considered SCS in patients with restricted pain distribution or when pain had a wide distribution but the area with greatest pain and disability was restricted to a small area like a foot or hand (Figure 1).

The most frequent cause of stroke was putaminal hemorrhage (n = 12; 40%), followed by thalamic hemorrhage (n = 9; 30%). Other less frequent causes (n = 9; 30%) are listed in Table 1. All patients had unilateral pain, which varied in distribution from single limb to hemibody pain (Figure 1). Allodynia was observed in 18 patients (60%) and hyperpathia in 11 patients (37%). Motor weakness was mild in 20 patients (Manual Muscle Test grade 4; 67%) and moderate in 3 patients (Manual Muscle Test grade 3; 10%).

Trial Stimulation

With the patient under local anesthesia and in the prone position, a percutaneous lead with quadripolar electrodes (Pisces Quad, Model 3487A; Medtronic, Inc, Minneapolis, Minnesota) was inserted into the epidural space using a Touhy needle. The tip was advanced to the required spinal level: C4 to C7 for upper limb pain or T9 to T12 for lower limb pain. The electrodes were manipulated with fluoroscopic guidance so that the stimulation-induced paresthesia covered the entire region affected by pain.[14]

Using an externalized temporary lead connected to a test stimulator (Model 3625; Medtronic, Inc), trial stimulation was performed to evaluate the efficacy of pain relief before permanent implantation. During the trial period (2-7 days), patients were allowed to test the pain-relieving effects of several stimulation parameters and combinations of active electrodes. Thereafter, the temporary electrodes were removed, and patients were discharged. After counseling the patients in the outpatient clinic, those who decided to proceed were scheduled for implantation of a permanent SCS system.

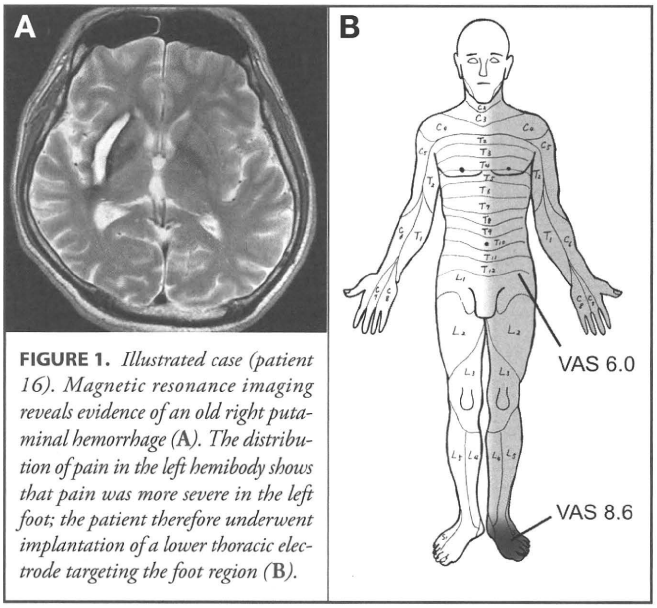

FIGURE 1. *Illustrated case (patient 16). Magnetic resonance imaging reveals evidence of an old right putaminal hemorrhage (A). The distribution of pain in the left hemibody shows that pain was more severe in the left foot; the patient therefore underwent implantation of a lower thoracic electrode targeting the foot region (B).*

Implantation of Permanent SCS System

A permanent lead was implanted in a similar manner as used for the trial lead and was anchored subcutaneously. A second trial stimulation was performed to verify consistent efficacy. Finally, an implantable pulse generator (Itrel III Model 7425 or Synergy Model 7427 V; Medtronic, Inc) was implanted in the left lower abdomen or anterior chest with the patient under general anesthesia.

Evaluation of Pain Relief

Pain intensity was evaluated using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst possible pain) at baseline, during the trial, and at follow-up visits every 6 months. In patients with wide regions of pain, the VAS score was assessed independently for each region, and the target area for SCS was determined based on the area with greatest pain and disability (Figure 1).

In addition, the Patient Global Impression of Change (PGIC) scale was assessed at the latest follow-up visit after the permanent implant. The PGIC scale indicates overall improvement according to a 7-point categorical scale: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse. The ratings 2 and 1 were considered clinically significant improvement.[15]

During data analysis, the degree of pain relief was classified into 3 categories: good (≥50%), fair (30%-49%), or poor (<30%) based on the percentage of reduction of the VAS score: [% reduction = ($VAS_{pre\text{-}stimulation}$ − $VAS_{post\text{-}stimulation}$/$VAS_{pre\text{-}stimulation}$) × 100%].[13] Pain relief of fair or better was considered clinically significant based on a report documenting that a pain reduction as low as 30% corresponds to clinically meaningful success.[15]

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

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

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

Clinical Factors Related to the Outcome of Trial Stimulation

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

Statistical Analysis

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

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

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

[a] Allod, allodynia; Hyperp, hyperpathia; VAS, visual analogue scale; PGIC, Patient Global Impression of Change (scale) (2, much improved; 4, no change; 5, minimally worse); L, left; thal, thalamic; hem, hemorrhage; R, right; UL, upper limb; LL, lower limb; put, putaminal; inf, infarction; ND, not determined.

[b] These patients had 2 electrodes implanted, but in the statistical analysis, only results for the thoracic electrode are included.

[c] This patient had less than 6 months of follow-up at the time of latest follow-up and was therefore excluded from long-term-follow-up analysis.

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

Ethical Issues

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

RESULTS

Trial Stimulation

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

Permanent Implantation

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

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

Results at Latest Follow-up

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

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

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

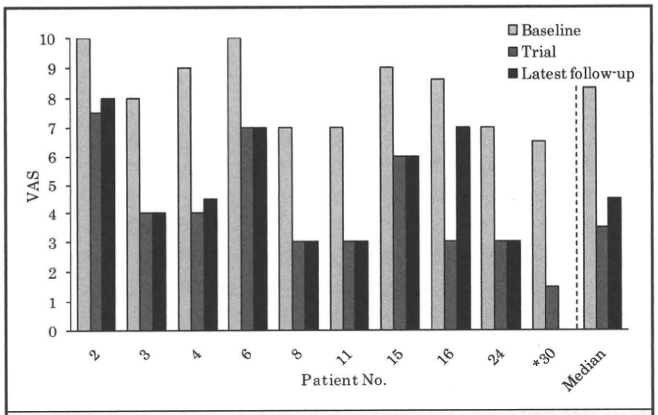

FIGURE 2. *Bar graph showing changes in visual analogue scale (VAS) scores for 10 permanently implanted patients during trial stimulation and latest follow-up The median VAS score in target areas decreased significantly from 8.3 (range, 6.5-10.0) to 3.5 (range, 1.5-10.0) after the trial (P < .001) and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

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

Complications

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

Clinical Factors Related to the Outcome of Trial Stimulation

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

DISCUSSION

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

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

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

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

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

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

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

Study Limitations

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

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

CONCLUSION

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

Disclosure

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

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COMMENT

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

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

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

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

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

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JA SYMPOSIUM

Phantom limb pain in the primary motor cortex: topical review

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Introduction: what is a phantom limb and phantom limb pain?

Following limb amputation, 80% or more of patients perceive the existence of their lost limb, or sensations such as hot–cold or tingling, in the space where their lost limb once existed. The experience of the existence of this lost limb and sensations is known as "phantom limb". Even without limb amputation, phantom limb can develop as a result of motor palsy or sensory deafferentation by cerebral stroke, spinal cord injury, or peripheral nerve injury; in these cases, such a condition is called supernumerary phantom limb. The perception of phantom body parts has also been reported to occur after breast, penis, or eyeball excision. In patients who have had a limb amputated, the incidence rate of phantom limb complicated by pathological pain (phantom limb pain) is 50–80%. According to some reports, a majority of patients continue to suffer from phantom limb pain for several years after onset [1].

In animal experiments, it has been shown that the mechanisms underlying phantom limb pain are induced by various factors, such as neuroma-derived abnormal impulses resulting from peripheral nerve injury, hyperexcitability of neurons on the spinal dorsal horn, and hyperexcitability of neurons in the supraspinal central nervous system. Functional brain imaging studies suggest, however, that functional reorganization of the supraspinal central nervous system plays an important role in the onset of phantom limb pain. Brain regions within the primary somatosensory cortex (S1) correspond to a specific part of the body, constituting a somatotopic map (somatotopy). After amputation of an upper limb, for example, reorganization is observed in S1: the brain region corresponding to the affected upper limb shrinks, and the adjacent area in

S1 corresponding to the mouth/facial surface area expands [2]. Furthermore, a somatotopic map also exists in the primary motor cortex (M1). After amputation of an upper limb in patients with phantom limb pain, both shrinkage of the upper-limb area and expansion of the mouth/facial surface area are observed in M1, and the excitability of neurons in the upper-limb area increases excessively. Because the reorganization of the somatotopic map observed in S1/M1 (the sensorimotor cortex) is observed not only in cases of phantom limb pain but also in cases of pain following spinal cord injury [3] or complex regional pain syndrome [4], it seems to be a common underlying mechanism of neuropathic pain.

Motor control of phantom limbs: involuntary and voluntary movements of phantom limbs

Patients who have phantom limb pain complain of various kinds of pain. In a study involving 1,250 patients with phantom limb pain who lost a limb during the civil war in Bosnia and Herzegovina [5], approximately 58% of patients complained of pain associated with sensations on the skin surface, such as being cut with a knife, receiving an electrical shock, or feeling a stinging sensation. Approximately 42% of patients complained of pain associated with a sensation of movement (i.e., proprioceptive sensation), such as spasms or cramps in the phantom limb, or feeling that the phantom limb was twisted. Thus, almost half of patients with phantom limb pain perceived unpleasant involuntary movements of their phantom limb. Which neural substrates could underlie movement sensations of phantom limbs? Among phantom-limb patients, there are persons who can voluntarily "move" the phantom limb; that is, they can clearly perceive that the phantom limb is moving voluntarily. Functional brain imaging studies on phantom limb movements show activation of M1/S1 and the supplementary motor area (SMA) similar to that which occurs during voluntary movements of healthy limbs [6]. In the case of involuntary "movements" accompanied by an unpleasant feeling in the phantom limb, in addition to activation of S1/M1 and SMA, activation of the cerebellum, anterior cingulated cortex (ACC), and posterior parietal cortex (PPC) are observed [7]. Both ACC and PPC are known to relate with limb-movement control and the perception of this movement [8]. In one phantom limb study, however, ACC and PPC activations were correlated linearly with the degree of pain and discomfort arising from phantom-limb involuntary movements [9]. The patterns of brain activations (including ACC and PCC activations) accompanying phantom limb movements and healthy limb movements appear to be similar, regardless of whether the phantom limb movements are voluntarily or involuntarily. In terms of the perception of limb movements in the brain, there may be no discrimination between phantom and healthy limbs.

It has recently been revealed that motor commands to the phantom limb are generated from the hand area in M1, which is invaded and submerged by the mouth/facial surface area through M1 reorganization following the limb amputation [10]. It has also been reported that a combination of somatosensory feedback of muscle contractures in the residual limb and motor commands to the phantom limb can produce movement sensations in the phantom limb [11].

Up to this point in this review, we have described movement sensations of phantom limbs. The perception of phantom limb movements, posture (position), and size can fluctuate from moment to moment [12]. The phantom limb is often perceived to be intact, resembling a normal limb, or telescoped and shrunken so that the proximal portion of the limb is perceived to be missing or shortened, with the more distal portion floating near the stump. Occasionally, patients with phantom limbs perceive that the missing limb is swollen or enlarged compared with the intact limb. These phenomena are known as "telescoping". The degree to which telescoping is perceived (how short the phantom limb is felt to be) correlates with the degree of reorganization. As such, phantom hand movements of a completely telescoped phantom limb create activity in the S1/M1 cortical region that normally manifests the shoulder somatotopy, indicating enlargement of the hand region in S1/M1, while phantom hand movements of partially telescoped phantom limbs create activity in the S1/M1 region of the arm under normal circumstances, and those of a non-telescoped phantom limb activate the hand region [2]. Thus, the neural substrates for moving the phantom limb seem to be closely related with those for producing phantom limb sensations.

Phantom limb pain and the primary motor cortex

Movement sensations of phantom limbs are closely related with activity in M1, but what is the relationship between M1 and pathologic pain occurring in the phantom limb? As described in the Introduction, reorganization in the S1/M1 cortices is one of the underlying mechanisms of phantom limb pain, and the reorganization in M1 is not observed in patients who do not suffer from phantom limb pain following amputation of an upper limb [13]. It has been reported that repeated transcutaneous magnetic stimulation of M1 and electrical motor cortex stimulation (MCS) are effective in cases of neuropathic pain, such as phantom limb pain [14, 15]. Further, in order to produce such analgesic effects, the M1 somatotopic map area related to