Motor cortex stimulation in patients with deafferentation pain: activation of the posterior insula and thalamus

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Objective. The mechanisms underlying deafferentation pain are not well understood. Motor cortex stimulation (MCS) is useful in the treatment of this kind of chronic pain, but the detailed mechanisms underlying its effects are unknown.

Methods. Six patients with intractable deafferentation pain in the left hand were included in this study. All were right-handed and had a subdural electrode placed over the right precentral gyrus. The pain was associated with brainstem injury in one patient, cervical spine injury in one patient, thalamic hemorrhage in one patient, and brachial plexus avulsion in three patients. Treatment with MCS reduced pain; visual analog scale (VAS) values for pain were 82 ± 20 before MCS and 39 ± 20 after MCS (mean ± standard error). Regional cerebral blood flow (rCBF) was measured by positron emission tomography with H215O before and after MCS. The obtained images were analyzed with statistical parametric mapping software (SPM99).

Results. Significant rCBF increases were identified after MCS in the left posterior thalamus and left insula. In the early post-MCS phase, the left posterior insula and right orbitofrontal cortex showed significant rCBF increases, and the right precentral gyrus showed an rCBF decrease. In the late post-MCS phase, a significant rCBF increase was detected in the left caudal part of the anterior cingulate cortex (ACC).

Conclusions. These results suggest that MCS modulates the pathways from the posterior insula and orbitofrontal cortex to the posterior thalamus to upregulate the pain threshold and pathways from the posterior insula to the caudal ACC to control emotional perception. This modulation results in decreased VAS scores for deafferentation pain.

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Key Words • deafferentation pain • motor cortex stimulation • posterior insula • posterior thalamus • regional cerebral blood flow
In the present study, we used \(H_{2}^{15}O\) PET to investigate the pattern of MCS-related neuronal activation and/or attenuation before and after MCS; \(H_{2}^{15}O\) PET shows rCBF, which reflects focal neuronal activation.\(^\text{11}\) We also used a recently developed method of statistical analysis involving parametric mapping of normalized brain images. Six patients with chronic deafferentation pain in the left hand and with electrodes placed on the right precentral gyrus corresponding to the M1 of the left hand were studied. This method provides more accurate results than those reported previously because the M1 is precisely and specifically stimulated.

**Clinical Material and Methods**

**Patients and Surgical Procedure**

Six right-handed patients (four men and two women, age range 50–67 years) with intractable deafferentation pain in the left hand were included in this study (Table 1). Deafferentation pain had resulted from brainstem injury (one patient), cervical spine injury (one patient), thalamic hemorrhage (one patient), and brachial plexus avulsion (three patients). The patients had suffered from intractable pain for 3 to 27 years, and medication had been ineffective. All of the patients showed slight to moderate motor weakness in the left arm. The VAS (grading range 0–100) and the short form of the McGill Pain Questionnaire were used to evaluate the degree of pain.

The surgical procedure was performed as described previously.\(^\text{29,30}\) In brief, the location of the central sulcus was approximated with the use of preoperative magnetic resonance images and confirmed by intraoperative phase reversal of the N20 component of the somatosensory evoked potential upon stimulation of the left median nerve,\(^\text{41}\) recorded with an evoked potential recorder (Neuropack 8, Nihon Kohden Co. Ltd.). A 20-grid set of electrodes (4 × 5 array, 0.3-cm-diameter electrode, 0.7-cm separation; Unique Medical Co. Ltd.) was implanted subdurally, covering the convexities of the pre- and postcentral gyr of the left hemisphere. After confirmation of pain reduction in response to stimulation for 10 to 14 days, a permanent four-array stimulating electrode (Resume II, model 3587A, Medtronic, Inc.) was placed subdurally at the surface of the right precentral gyrus at the site associated with the most effective pain reduction. The electrode was controlled by a subcutaneously implanted stimulator (Itrel III, Medtronic, Inc.).

Bipolar stimulation\(^\text{39}\) was used for pain relief, and stimulation parameters varied in each patient. The general ranges were: voltage, 0.6 to 3.5 V; frequency, 25 to 40 Hz. The pulse width was 210 microseconds, and stimulation was administered for 30 minutes one to four times a day. The patients used MCS for at least 6 months.

**The PET Scanning Procedure and Activation Task**

The PET study was performed 1 to 3 years after implantation of the stimulation electrode. A Headtome V PET scanner (Shimadzu Co.) was used to scan in the 3D acquisition mode with a head shield. Patients went without cortical stimulation for more than 12 hours before the PET study. The patients lay with eyes closed in a silent and dim room. A 15-minute transmission scan was performed first with \(^{68}\text{Ge}\) sources to correct for \(\gamma\)-ray attenuation. Relative cerebral blood flow was measured based on the distribution of radioactivity after slow bolus intravenous injection of \(H_{2}^{15}O\) (7 mCi/scan, each lasting 90 seconds). Six PET scans corresponding to six \(H_{2}^{15}O\) injections were performed before MCS; MCS was performed for approximately 30 minutes; and six PET scans were performed after confirmation of pain reduction. The PET protocol was as described previously.\(^\text{29}\)

**Data Analysis**

Attenuation-corrected data were reconstructed into an image (voxel sizes: \(2 \times 2 \times 3.125\) mm; field of view: \(256 \times 256 \times 196\) mm) with a resulting resolution of \(4 \times 4 \times 5\) mm at FWHM. The images were analyzed with SPM software (SPM99; Wellcome Department of Cognitive Neurology).\(^\text{17}\) The PET images were anatomically normalized in 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\(^\text{6}\) to account for variation in gyral anatomy and interindividual variability in structure–function relationships, and to improve the signal-to-noise ratio. This procedure was used for image realignment, anatomical normalization, smoothing (12 mm at FWHM), and statistical analysis.\(^\text{15}\) Data were normalized to global blood flow (average 50). The effect of state-dependent differences in global blood flow was tested with analysis of covariance.

All six patients were included in the same statistical analyses, with voxel-to-voxel comparison. Statistical parametric maps were generated with an analysis of variance model using the General Linear Model formulation of SPM99.\(^\text{8}\) We analyzed the main effect of MCS by comparing images obtained after MCS with those obtained before MCS with the statistical threshold set at a probability value of less than 0.005 for peak height, corrected for spatial extent (\(>\) eight voxels per cluster). We also categorized post-MCS sessions as follows: the first two scans in the 20 minutes just after MCS were denoted as the early post-MCS phase and the last two scans more than 40 minutes after MCS were denoted as the late post-MCS phase. We generated SPM (t) maps of rCBF changes associated with each comparison. For between-group comparisons, the SPM (t) maps were transformed into SPM (Z) maps, and the levels of significance of areas of activation were assessed according to peak height of foci estimation based on the theory of random Gaussian fields. Significance was accepted if a cluster showed a corrected probability value of less than 0.05. Data are presented as means ± standard errors.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Associated Lesion</th>
<th>Duration of Pain (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50, F</td>
<td>brainstem injury</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>50, F</td>
<td>cervical spine injury</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>59, M</td>
<td>thalamic hemorrhage</td>
<td>8.3</td>
</tr>
<tr>
<td>4</td>
<td>67, M</td>
<td>brachial plexus avulsion</td>
<td>27.0</td>
</tr>
<tr>
<td>5</td>
<td>57, M</td>
<td>brachial plexus avulsion</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>56, M</td>
<td>brachial plexus avulsion</td>
<td>3.0</td>
</tr>
</tbody>
</table>

H. Kishima et al.
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.

Results

Pain Reduction in Response to MCS

After MCS, all six patients showed various degrees of pain reduction according to VAS data (from a mean of 82 ± 20 to a mean of 39 ± 20). The duration of the MCS effect differed between the patients, ranging from 2 to 12 hours. In this study, we found that the pain reduction began during MCS and continued for at least 30 minutes after MCS. The pain reduction was stable during the six post-MCS PET scans. The results of the short form of the McGill Pain Questionnaire agreed for the most part with the VAS scores.

Brain Activation Profiles in Response to MCS

Comparison of rCBF before and after MCS showed significant rCBF increases after MCS in the left posterior thalamus (pulvinar) and left posterior insula (the six cases were analyzed together, corrected cluster p = 0.044; Table 2, Fig. 1A and B). No areas of significant rCBF decrease were identified. When we compared the scans obtained in the early post-MCS phase with the six pre-MCS scans, we found significant rCBF increases in the left posterior insula (p = 0.011) and the right orbitofrontal cortex (BA 11) (p = 0.047) (Table 2, Fig. 1C and D). Significant decreases in rCBF were identified between the right middle frontal gyrus (BA 9) and the right precentral gyrus (BA 4) (p = 0.048) (Table 3, Fig. 2).

When scans obtained in the late post-MCS phase were compared with the six pre-MCS scans, the left caudal part of the ACC (BA 24) showed significant increases in rCBF (p = 0.005; Table 2, Fig. 1E). Comparing rCBF in the early post-MCS phase with that in the late post-MCS phase, rCBF in the left medial frontal gyrus (supplementary motor area; BA 6) was increased in the late phase (p = 0.033, cluster size, 309; Talairach coordinates, x = 3, y = −5, z = 59).

Discussion

All of the right-handed patients in this study complained of left-hand pain, and the nondominant (right) precentral gyrus was stimulated electrically. Preoperative MR images and intraoperative somatosensory evoked potentials were used to determine the location of the central sulcus. Thus, we were able to precisely stimulate the area of the precentral gyrus corresponding to the left hand. We observed changes in neuronal activity with H.\(^{15}\)O PET, and all PET images were normalized and then analyzed using SPM.\(^7,8,9,15\) Therefore, the results of this study were based on anatomically well-standardized samples and equal stimulation of identical brain regions.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>p Value (corrected)</th>
<th>Size (voxel)</th>
<th>Talairach Coordinates (x, y, z in mm)</th>
<th>Equivalent Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-MCS compared w/ all phases of post-MCS</td>
<td>0.044</td>
<td>685</td>
<td>−31, −19, 15</td>
<td>3.57</td>
</tr>
<tr>
<td>lt insula</td>
<td></td>
<td></td>
<td>−25, −26, 11</td>
<td>3.38</td>
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<tr>
<td>pre-MCS compared w/ early phase of post-MCS</td>
<td>0.011</td>
<td>593</td>
<td>−33, −19, 15</td>
<td>4.44</td>
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<tr>
<td>lt orbitofrontal cortex (BA 11)</td>
<td>0.047</td>
<td>420</td>
<td>15, 26, −15</td>
<td>4.32</td>
</tr>
<tr>
<td>pre-MCS compared w/ late phase of post-MCS</td>
<td>0.005</td>
<td>406</td>
<td>−8, −15, 38</td>
<td>4.47</td>
</tr>
<tr>
<td>lt cingulate cortex (BA 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In this study, neither sham stimulation nor a control study was indicated. We used test stimulations of 10 to 14 days prior to the second surgery. Patients who had showed no effect or sham effect were excluded. And all of the patients in this study had used MCS for at least 6 months and had confirmed the effectiveness of MCS. We believe that there was no placebo effect associated with MCS in these cases.

It is not clear whether electrical stimulation activates or suppresses neurons around the point of stimulation. Some researchers have reported that low-frequency (5 Hz) stimulation of the cortex results in long-term potentiation of corticostriatal neuron activity in rats, but the relationship between frequency of stimulation and effect on surrounding neurons has not been clarified. In our study, all patients showed the most pain reduction at frequencies between 25 and 40 Hz. Thus, we conclude that 25 to 40 Hz is a suitable range for MCS treatment of intractable pain. We found that stimulation in this frequency range decreased rCBF in the M1 for at least 20 minutes after MCS, indicating that the level of electrical stimulation used in this study inhibits neuronal activity under the electrode.

In this study, MCS did not alter rCBF in the postcentral gyrus (primary sensory cortex). This finding supports reports that MCS-induced pain reduction does not involve normal sensory pathways. In fact, Drouot et al. reported that MCS for control of chronic pain improves abnormal sensory thresholds. Thus, relief of chronic pain by MCS does not depend on sensory suppression and does not involve neuronal activity of the primary sensory cortex.

The rCBF in the right dorsolateral prefrontal cortex (BA 9) was also decreased after MCS. The prefrontal cortex is considered to include attentional and memory networks activated by noxious stimulation. Lorenz et al. also reported that BA 9 exerts active control of pain perception by modulating corticosubcortical and corticocortical pathways. Furthermore, repetitive transcranial magnetic stimulation of BA 9 has been reported to be effective in the treatment of depression. Reduced BA 9 neuronal activity in the early post-MCS phase may reflect attenuation of attention and perception of chronic pain and may control psychological state.

The left posterior insula was activated in the early post-MCS phase. The posterior insula as well as the secondary somatosensory cortex are well described as reflecting pain perception and are parametrically activated by nociceptive input. It was recently reported that in the rostral agranular insula, γ-aminobutyric acid can alter pain thresholds in rats and that locally increasing the level of this neurotransmitter in the insula induces analgesia by enhancing descending inhibition of spinal nociceptive neurons. The posterior insula has connections to the periaqueductal gray matter, the area around the locus caeruleus, the rostroventral medulla, and the mesolimbic/mesocortical ventral forebrain. Schlereth et al. speculated that the left dorsal insula plays a dominant role in the early sensory-discriminative phase of pain processing. Thus, MCS appears to activate the left dominant posterior insula, resulting in upregulation of the pain threshold.

We found significantly increased rCBF in the right orbitofrontal cortex in the early post-MCS phase. Jasmin et al. reported that the rostral agranular insula possesses reciprocal connections with the orbital infralimbic cortex and ACC in rats. It has also been reported that the cingulofrontal cortex, including the orbitofrontal cortex and the ACC in the area around the genu of the corpus callosum, exerts

<table>
<thead>
<tr>
<th>Area</th>
<th>Condition &amp; Areas</th>
<th>p Value (corrected)</th>
<th>Size (voxel)</th>
<th>Talairach Coordinates (x, y, z in mm)</th>
<th>Equivalent Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>rt prefrontal cortex (BA 9)</td>
<td>pre-MCS compared w/ early phase of post-MCS</td>
<td>0.048</td>
<td>406</td>
<td>29, 16, 29</td>
<td>4.10</td>
</tr>
<tr>
<td>rt precentral cortex (BA 4)</td>
<td></td>
<td></td>
<td></td>
<td>22, −11, 48</td>
<td>3.48</td>
</tr>
</tbody>
</table>
Brain modulation with MCS for deafferentation pain

a topdown influence on the posterior thalamus and periaqueductal gray matter to gate pain modulation during distraction. The left posterior thalamus was activated in the early post-MCS phase in our study. Thus, it is possible that the activated orbitofrontal cortex, together with the posterior or insula, excites the dominant posterior thalamus to upregulate the pain threshold.

The area of rCBF increase included the pulvinar of the thalamus (according to the atlas of Talairach and Tournoix). In the 1970s, the posterior thalamus (pulvinar) was a target of lesioning surgery for cancer pain, and pulvinotomy resulted in early relief of cancer pain in most patients, but the pain often recurred. Although the function of the posterior thalamus is not well characterized, we speculate that the dominant posterior thalamus is involved in chronic deafferentation pain.

Garcia-Larrea et al. reported that the ipsilateral motor thalamus (ventrolateral and ventroanterior thalamus) and brainstem regions are activated by MCS. The ipsilateral thalamus shows hypometabolism in cases of central pain. In our study, the ipsilateral (right) thalamus was not affected. In addition, one patient had poststroke pain but not severe motor dysfunction; others in this study had brainstem, spinal cord, or peripheral nerve injuries. Thus, corticostriatothalamic connections relating to movements were preserved in all patients, resulting in preserved right motor thalamus function.

The posterior insula projects efferent fibers to the amygdala in rats. The bilateral caudal ACC and the posterior insula/secondary somatosensory cortex have been reported to be specific to the experience of pain. It has also been reported that the caudal part of the right ACC is activated when the right M1 is stimulated magnetically in a capsaicin-induced pain model, and the ACC is also activated by thalamic stimulation in patients with chronic pain. The amygdala and cingulate gyrus belong to the limbic system and play important roles in emotional control. The caudal ACC (BA 24) contains the cingulate motor area, which is associated with emotional behavior. Our data showed that not only the posterior insula but also the caudal ACC (BA 24) were activated in response to MCS. Thus, MCS for treatment of chronic deafferentation pain modulates pain-related emotion and mood, resulting in pain relief. The caudal ACC, which was activated in the late post-MCS phase, contributes to long-lasting pain relief (several hours of relief) induced by MCS.

Conclusions

The use of MCS for the treatment of deafferentation upregulates the pain threshold by modulating pathways from the posterior insular and orbitofrontal cortex to the posteri or thalamus. Treatment with MCS also controls pain-related emotion by modulating the pathway from the posterior insula to the caudal ACC. These findings support the use of MCS for treatment of deafferentation pain.

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