PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION

Original Research Article

Pain-Related Brain Activity Evoked by Active and Dynamic Arm Movement: Delayed-Onset Muscle Soreness as a Promising Model for Studying Movement-Related Pain in Humans

Yoichi Matsuda, MD,* Shigeyuki Kan, PhD,[†]
Hironobu Uematsu, MD, PhD,*
Masahiko Shibata, MD, PhD,[†]
and Yuji Fujino, MD, PhD*

*Department of Anesthesiology & Intensive Care Medicine; and [†]Pain Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Reprint requests to: Masahiko Shibata, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. Tel. +81-6-6879-3745; Fax: +81-6-6879-3495; E-mail: mshibata@pain.med.osaka-u.ac.jp.

Methods. DOMS was induced in the left upper-arm flexor muscles by an eccentric elbow contraction exercise. Movement-evoked pain in the affected muscles was evaluated just before (day 0) and after (days 1–7 and 30) the exercise using a visual analog scale. Subjects underwent functional magnetic resonance imaging scans while performing repeated elbow flexion on day 2 (DOMS condition) and day 30 (painless condition). We compared brain activity between the DOMS and painless conditions.
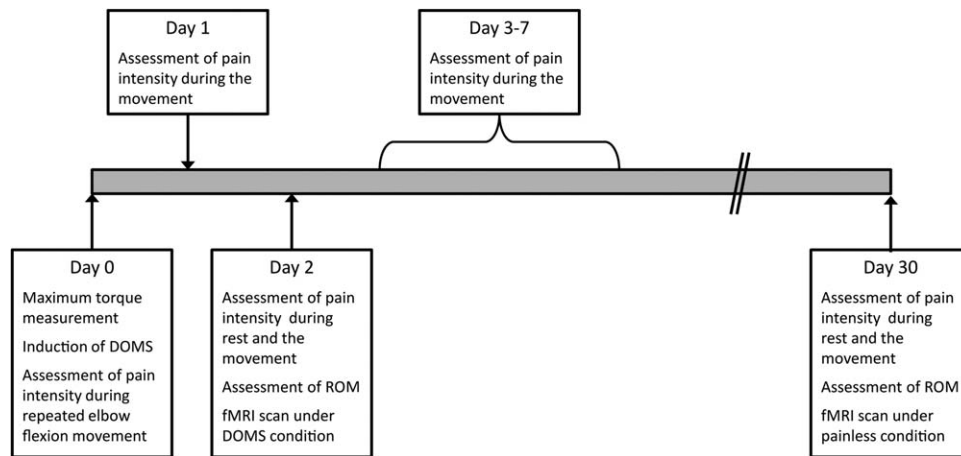
Results. Movement-evoked pain reached peak intensity on day 2 and disappeared by day 30 in all subjects. No subject felt pain at rest on either of these days. Contralateral primary motor cortex (M1), parietal operculum and bilateral presupplementary motor area (pre-SMA) showed greater activity during active and dynamic arm movement with DOMS than during the same movement without pain. There was no difference in activation of brain regions known collectively as the "pain matrix," except for the parietal operculum, between the two conditions.

Conclusion. Active and dynamic movement with pain selectively evoked activation of M1, pre-SMA, and parietal operculum, as assessed using DOMS. Our results demonstrate that DOMS is a promising experimental model for the study of movement-evoked pain in humans.

Key Words. Functional Magnetic Resonance Imaging; Movement-Evoked Pain; Delayed-Onset Muscle Soreness; Motor Adaptation

Introduction

Many people suffer from musculoskeletal pain such as low-back pain and osteoarthritis [1], and the personal and social costs of pain conditions have become a serious concern in our society [2]. Movement-related pain including musculoskeletal pain impairs activities of daily

Abstract

Objective. To demonstrate delayed-onset muscle soreness (DOMS) is a suitable model for the study of movement-evoked pain, we attempted to identify brain regions specifically involved in pain evoked by active and dynamic movement under DOMS condition.

Subject. Twelve healthy volunteers

Figure 1 Timeline of this study. At day 0, we began the DOMS induction procedure. From day 0 to day 7, we assessed subjects' pain intensity during repeated elbow flexion and contraction movement daily. We also assessed pain intensity at rest and left upper limb range of motion (ROM) on day 2 and day 30. We conducted fMRI scans on day 2 (DOMS condition) and day 30 (painless condition).

living and quality of life and is, therefore, an important therapeutic target for health care. Musculoskeletal pain is caused by overuse as well as muscle injury and tissue inflammation. For example, low back pain from overuse is a common work-related diagnosis. It is estimated that one-third of adults have pain from overuse. Considering the clinical and social importance of treating movement-related pain, a better understanding of its underlying brain processing is needed to develop effective and efficient therapeutic strategies.

Several recent studies reported the influence of pain on the motor system. For example, nociceptive stimuli to a muscle elicit the redistribution of motoneuron discharges in the surrounding muscles [3,4]. Furthermore, pain suppresses the electromyographic response of an affected muscle to stimulation of the peripheral nerve or the motor cortex [5,6]. Based on these findings, Hodeges et al. [7] proposed a model of how the central nervous system sustains our motor functions when we have musculoskeletal pain. To maintain motor performance, plastic changes for adapting to pain occur at various level of the central nervous system, especially the brain. In their model, the pain-related plastic changes of the central motor system are a specific feature of movement with pain. To date, however, no study has directly demonstrated brain plasticity related to movement with pain.

In previous studies that investigated the relationship between pain and movement, either the nociceptive stimulus was not directly related to the movement, or pain was evoked by isometric contraction. Although pain directly evoked by active and dynamic movement closely resembles the clinical condition of chronic pain, studies for pain with active and dynamic movement are scarce. Indeed, a suitable experimental model for pain evoked by active and dynamic movement has not been established in humans. Such an experimental model would have to satisfy the following requirements: subjects feel pain only when they make a body movement, and they have no pain at rest. Stimulation techniques such as injection of hypertonic saline into the muscle do not meet the requirements. Delayed-onset muscle soreness (DOMS) is an unpleasant sensation after strenuous exercise to which the muscles are unaccustomed [8]. In DOMS, there is no spontaneous pain at rest, and muscle pain is only evoked by movement of the affected muscles [9–12]. DOMS, therefore, meets the requirements for an experimental model of movement-evoked pain. Using DOMS, Zimmermann et al. [13] reported brain activation related to DOMS-related pain. In their study, however, muscle pain was evoked by mechanical muscle stimulation or isometric contraction. They did not investigate brain activation related to pain evoked by active and dynamic movement.

The purposes of this study are (1) to examine whether DOMS is a suitable model for the study of movement-evoked pain and (2) to identify brain regions specifically involved in pain evoked by active and dynamic movement. We, therefore, used functional magnetic resonance imaging (fMRI) to compare brain activations between a DOMS condition in which subjects felt pain in DOMS-affected muscles and a painless condition in which there was no movement-evoked pain at all.

Materials and Methods

Subjects

Twelve healthy right-handed volunteers (9 males, 3 females, age range 23–48 years) participated in this study. They had no physical or neurological illness or detectable MRI abnormalities in the brain. They
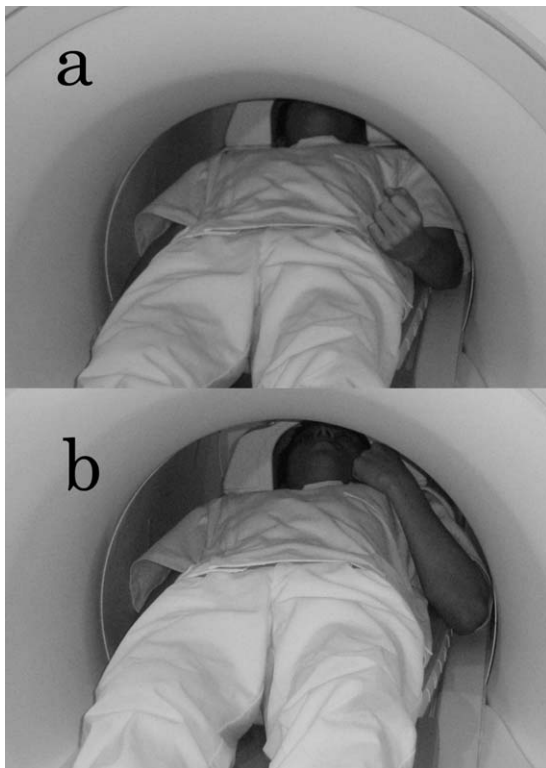
Figure 2 In the activation phases (a), subjects performed left elbow flexion and extension movement inside the MRI gantry at a frequency of 0.5 Hz (paced by a metronome and transmitted to them by headphones). Range of the motion during the fMRI recording session was identical with the maximum range of the motion that was measured just before the first session. In the rest phases (b), subjects lay with their left arm folded on their chest.

underwent DOMS induction, assessment of pain intensity during rest and repeated elbow flexion, assessment of range of motion, and fMRI scans (Figure 1). This study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board on Human Studies at the Osaka University Medical Hospital. Written informed consent was obtained from each subject before the experiment.

Induction and Evaluation of DOMS

DOMS was induced in the left upper-arm flexor muscles of each subject by an exercise using an isokinetic dynamometer similar to a procedure adopted in a previous study [14]. The dynamometer (Biodex System 3, Biodex Medical Systems, NY, USA) was set in isokinetic mode. The exercise for induction of DOMS consisted of two parts: pre-exercise elbow flexion torque measurement

and eccentric contraction exercise. Subjects were seated on the machine with their left forearm in a supinated position, and the elbow was aligned with the axis of the dynamometer lever arm.

First, subjects performed five maximal left biceps contractions (elbow flexion) to measure elbow flexion torque. In this part, the dynamometer was adjusted to $30°/$ seconds with a range of $10°–110°$. We measured maximum elbow flexion torque for each trial and calculated average torque across five trials after discarding the minimum and maximum values.

After the torque measurement, subjects performed three sets of eccentric elbow flexion exercise with a 30-second rest to induce DOMS. In a set, each subject repeated eccentric elbow flexion 10 times. Angular velocity and motion range of the dynamometer were identical to those in the pre-exercise. Torque of the dynamometer was adjusted for each subject to their average torque, which was determined in the pre-exercise.

To confirm that the eccentric elbow flexion exercise-induced DOMS, we assessed movement-evoked pain in all subjects from just before (day 0) to 7 days after the exercise (day 7). Using a 100-mm-visual analog scale (VAS, where $0 =$ No Pain; $100 =$ Worst Possible Pain), subjects evaluated the level of pain in the left upper-arm flexor muscles during left elbow flexion and extension movement each day. We also evaluated pain at 30 days after the exercise (day 30) using the same procedure, to confirm that fMRI data acquisition was performed without movement-evoked pain at that day. We questioned all subjects about the presence of pain at rest on day 2 and day 30.

Experimental Protocol

We obtained fMRI data using a block design. The experimental paradigm consisted of three 30-second rest phases (blocks) interleaved with three 30-second activation phases, and consequently total scanning time was 3 minutes. In rest phases, subjects lay with their left arm folded on their chest. In activation phases, subjects performed left elbow flexion and extension movement at a frequency of 0.5 Hz (paced by a metronome and transmitted to them by headphone; Figure 2). Range of motion during the fMRI recording session was identical with the maximum range of motion that was measured just before the first fMRI session using a goniometer. We cued subjects to switch between the activation and rest phases by a short beep sound. Subjects performed the same task on day 2 (DOMS condition) and day 30 (painless condition).

fMRI Procedures

We used a 1.5 T MRI scanner (Signa EXCITE XI 11.0, GE Healthcare, Milwaukee, WI, USA). The fMRI data were acquired by gradient echo single-shot echo-planar imaging (EPI) sequences. Parameters of the EPI
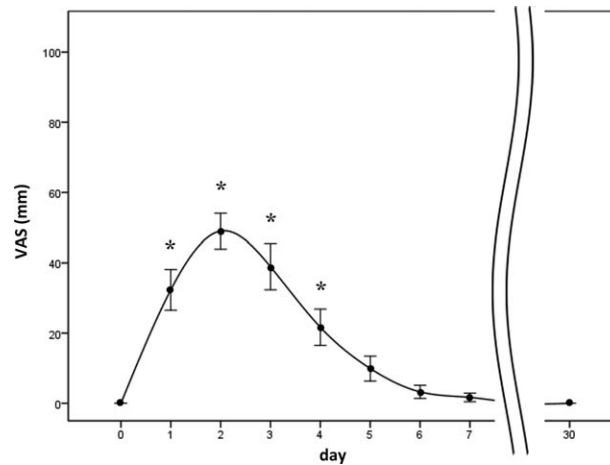
Figure 3 Visual analog scale (VAS) ratings (0–100 mm: 0 = No Pain, 100 = Worst Possible Pain) for pain evoked by active and dynamic arm movement (mean ± SEM, n = 12) from day 0 (just before the exercise that induced DOMS) to day 7 (7 days after the exercise) and day 30 (30 days after the exercise). We evaluated pain on day 30 to confirm that fMRI data acquisition was performed without pain on that day. *$P < 0.01$, Dunnett's test, compared with rating on day 0. SEM = standard error of the mean.

sequence were as follows: repetition time, 2500 ms; echo time, 60 ms; flip angle, 90; field of view, 300 mm; in-plane resolution, 4.69×4.69 mm^2; the number of slices, 30 slices; slice thickness, 5 mm thickness with no gap; acquisition order, interleaved. All subjects were positioned in the scanner with a foam rubber pad to minimize head movement and instructed simply to lay with their eyes closed without talking. High-resolution T1-weighted anatomical images were also collected from each subject.

Data Analysis

We compared the VAS ratings for movement-evoked pain on day 1 or later with that on day 0 (baseline) by Dunnett's test. SPSS statistics version 19 (IBM corporation, Somers, NY, USA) was used to analyze the data. The threshold of the test was $P < 0.05$.

Statistical parametric mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) was used for preprocessing and statistical analysis of the fMRI data. Preprocessing steps consisted of realignment, normalization and smoothing. For the smoothing process, we used an 8-mm isotropic full width half maximum Gaussian kernel. For statistical analysis, we used block design analysis for first-level individual analysis, and random effect analysis for second-level group analysis. Using a one-sample t-test, we first examined task-related brain activations in DOMS and the painless condition, respectively. Then, we performed a paired t-test (DOMS vs. No pain) to find brain activity specific to pain evoked by active and dynamic arm movement. In both statistical tests, the significance threshold was set at $P < 0.001$ (uncorrected for multiple comparisons).

Results

Pain Ratings

Maximum VAS ratings for movement-evoked pain (49.0 ± 5.1 mm, mean ± standard error of the mean (SEM)) after DOMS induction were recorded on day 2. Movement-evoked pain clearly decreased by day 7 (VAS = 1.7 ± 1.2 mm), and it completely disappeared in all subjects by day 30 (VAS = 0 mm; Figure 3). No subject reported pain at rest on day 2 or day 30.

Head Motion During fMRI Scans

In this study, subjects performed repeated eccentric elbow flexion during fMRI scans. Such body movement likely causes head movement, which in turn could produce false activation signals. This head motion-evoked false activation points out the possibility that our results merely reflect differences in head movement between the DOMS and painless conditions. To evaluate this possibility, we calculated the mean volume-to-volume difference of each of the six rigid body transformation parameters (x-, y-, and z-translation, pitch, roll, and yaw) and compared these values between the two conditions (DOMS and painless) by paired t-test. Although all parameters were greater in the DOMS condition, the average and maximum volume-to-volume motion were both less than 0.1 mm. In addition, only differences of y- and z-translation reached significance (y-translation, DOMS: 0.0278 ± 0.0075 mm, mean ± standard deviation (SD), painless: 0.0227 ± 0.0077 mm, $P < 0.05$; z-translation, DOMS: 0.0592 ± 0.0223 mm, painless: 0.0354 ± 0.0160mm, $P < 0.01$). Because the sizes of

**Table 1** MNI coordinates and *Z*-scores of regions activated by condition

Region	Cluster Size	*x*	*y*	*z*	*Z*-Score
			DOMS Condition		
Left cerebellum	2895	−2	−52	−18	4.85
		−26	−60	−28	4.81
Right cerebellum		2	−58	−26	4.75
Right superior temporal sulcus	32257	40	−32	6	5.72
Right parietal operculum		50	6	12	5.29
Left thalamus		−16	−28	14	5.27
Left superior temporal gyrus		−44	−26	10	5.24
Right primary motor cortex/primary somatosensory cortex		28	−30	62	5.18
Left secondary somatosensory cortex		−54	−32	20	5.15
Right post central gyrus/inferior parietal lobule		28	−40	40	5.14
Right superior parietal lobule		24	−54	64	5.13
Right superior temporal gyrus		56	−22	6	4.99
Left post central gyrus/inferior parietal lobule		−24	-44	50	4.98
Mid-cingulate cortex		16	−28	46	4.98
Right thalamus		18	−22	4	4.97
Right secondary somatosensory cortex		50	−28	24	4.91
Left supramarginal gyrus		−52	−34	32	4.77
Right thalamus		14	−16	10	4.59
Right anterior insula		50	14	−4	4.57
Left operculum	405	−48	4	10	4.35
Right inferior frontal gyrus	35	42	38	4	3.48
			Painless Condition		
Right superior temporal gyrus	18970	58	−28	20	5.45
Right supramarginal gyrus/precentral gyrus		66	−16	20	5.30
Right insula		42	6	−4	5.22
Right primary motor cortex		32	−26	56	5.01
Right precentral gyrus		28	−14	64	4.90
Mid-cingulate cortex		6	−10	44	4.87
Right inferior frontal gyrus		54	10	18	4.78
Supplementary motor area		8	−8	54	4.77
Right thalamus		20	−28	10	4.30
Right superior parietal gyrus		26	−52	60	4.29
Right thalamus		18	−16	52	4.27
Left inferior parietal lobule		−28	−44	48	4.25
Right hippocampus		24	−34	2	4.23
Left cerebellum	1051	−6	−50	−22	4.80
Cerebellum		0	−58	−28	4.58
		0	−48	−12	4.31
Right inferior frontal gyrus	25	48	46	−2	4.35
Left superior temporal gyrus	366	−54	−30	22	4.14
Left supramarginal gyrus		−64	−32	28	3.46
Left parietal operculum	116	−50	4	4	3.75
Left parietal operculum	27	−42	−14	24	3.68

motion were quite small, we think that body movement did not affect our fMRI result even though the *y*- and *z*-translation were significantly different in the uncorrected *P* value analysis.

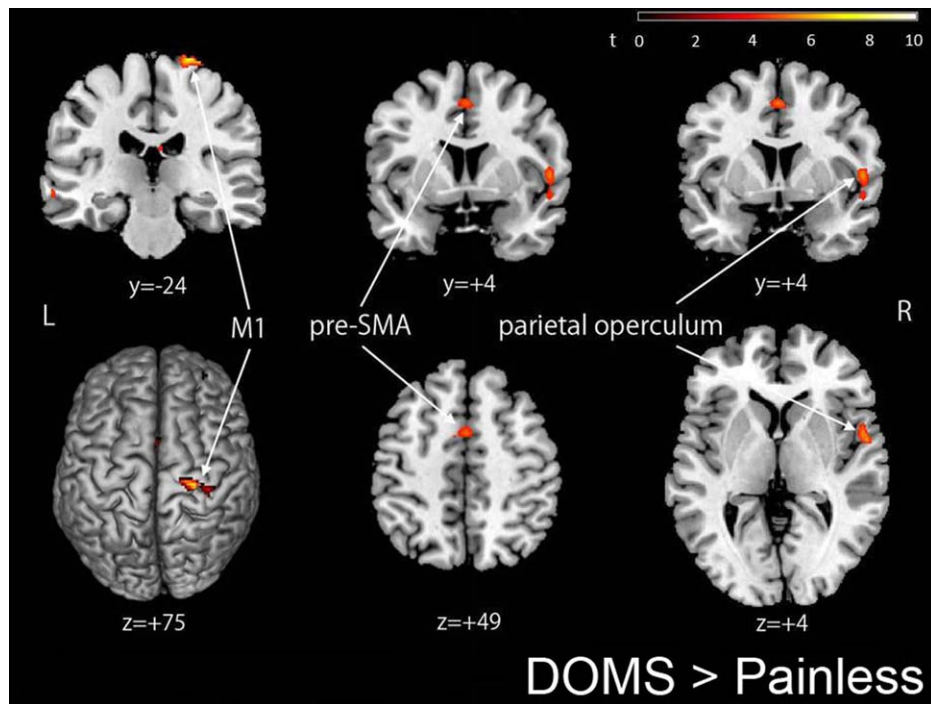*Brain Activation*

As shown in Figure 3 and Table 1, active and dynamic left arm movement activated contralateral primary motor
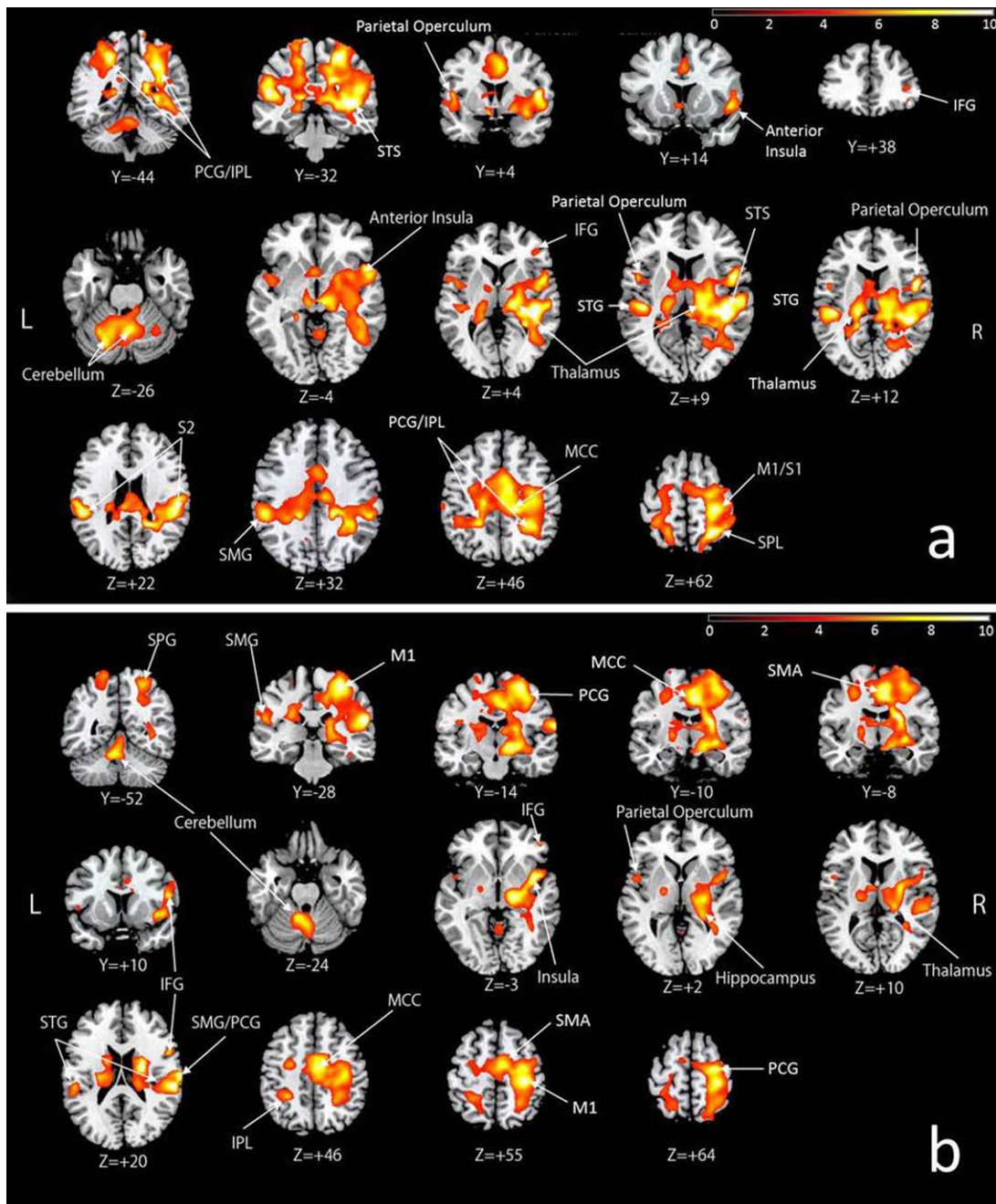
Figure 4 Brain regions activated during active and dynamic arm movement in DOMS (a) and the painless condition (b). Activated regions were overlaid on the T1-weighted Montreal Neurological Institute (MNI) single-subject template. The color of each activated voxel corresponds to its T-value, as per the color bar scales (random effect analysis, n = 12, thresholds; $P < 0.001$, uncorrected). IFG, inferior frontal gyrus; M1, primary motor cortex; MCC, mid-cingulate cortex; IPL, inferior parietal lobule; PCG, precentral gyrus; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; SMG, supra-marginal gyrus; SPG, superior parietal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus; L, left side (ipsilateral to the moving arm); R, right side (contralateral to the moving arm).

Figure 5 Brain regions showing stronger activation with active and dynamic arm movement in the DOMS condition than in the painless condition. Activated regions were overlaid on a T1-weighted MNI single-subject template. The color of each activated voxel corresponds to its *T*-value, as per the color bar scales (Paired *t*-test, n = 12, threshold; $P < 0.001$, uncorrected). M1, primary motor cortex; pre-SMA, presupplementary motor area; L, left side (ipsilateral to the arm with movement); R, right side (contralateral to the arm with movement).

cortex (M1), mid-cingulate cortex (MCC), inferior frontal gyrus, thalamus, ipsilateral supramarginal gyrus (SMG), parietal operculum, bilateral superior temporal gyrus, and cerebellum in both the DOMS and painless conditions.

Contralateral parietal operculum, superior temporal sulcus, superior parietal lobule, anterior insula, ipsilateral thalamus, bilateral secondary somatosensory cortex (S2), and precentral gyrus (PCG)/inferior parietal lobule (IPL) were activated by the arm movement with DOMS (Figure 4a; Table 1). In contrast, arm movement in the painless condition induced activity in contralateral SMG/PCG, insula, supplementary motor area (SMA), thalamus, superior parietal gyrus (SPG), hippocampus, and ipsilateral IPL (Figure 4b; Table 1).

As shown in Figure 5 and Table 2, comparison of brain activity between DOMS and the painless condition revealed that contralateral M1, parietal operculum, and bilateral pre-SMA were significantly more activated by active and dynamic left arm movement with DOMS than by the same movement without pain. According to the somatotopic organization of the brain, the activated area in M1 corresponded to the presumed arm area (medial side of the "hand knob" area of M1). In contrast, no

regions showed significantly more activation in the painless condition than in the DOMS condition.

We found no significant difference in activation of the "pain matrix," except the parietal operculum, between the two conditions.

Discussion

DOMS

All subjects experienced pain perceived in their left upper-arm flexor muscles with elbow flexion and extension movement, and all subjects felt no spontaneous pain at rest. The movement-evoked pain reached maximum intensity 2 days after the eccentric contraction exercise, and the pain mostly disappeared by day 7. This process is consistent with the known time course of DOMS [8], indicating that we were able to adequately induce DOMS in the targeted muscles.

Furthermore, we were able to identify brain regions that showed differential activation between DOMS and the painless condition using DOMS as an experimental model for movement-evoked pain. Although our findings

Table 2 MNI coordinates and *Z*-scores of the regions significantly more activated during movement with DOMS vs the same movement without pain

Region	DOMS > Painless Condition				
	Cluster Size	*x*	*y*	*z*	*Z*-Score
Right primary motor cortex	112	26	−24	78	4.55
Right parietal operculum	86	56	0	2	4.01
Pre-supplementary motor area	36	2	4	50	3.75

are different from those reported by Zimmermann et al. [13] in several respects, both studies were able to find brain activations related to the condition of DOMS. This supports the notion that DOMS is a promising experimental model for the study of movement-evoked pain in humans.

Brain Activations Related to Arm Movement with Pain

M1

We observed that active and dynamic left arm movement with DOMS in flexor muscles significantly activated contralateral M1 compared with the same movement without pain. If motor parameters were different between the two conditions, this could have led to a difference in M1 activation. In this study, however, subjects performed the same task with the same motor parameters regardless of pain. A difference in motor parameters between the two conditions, therefore, was not the cause of the differential brain activations observed in this study.

The main role of M1 is to encode movement parameters such as force, speed, and direction by signaling excitatory and inhibitory motor commands to multiple muscle groups [15]. Previous fMRI studies reported that muscle pain activated M1 but skin pain did not [16–18]. Although the association between muscle pain and M1 activation remains unclear, recent studies suggest that M1 plays a role in motor adaptation to pain [3–7] and in the activation of descending inhibitory neurons to nociceptive muscle afferents [19–22]. These previous findings provide two plausible explanations for the activation of M1 in our study.

One explanation for the M1 activation observed in this study is that it reflects motor adaptation to pain in M1. The theory is that muscle pain elicits the redistribution of activity within muscles by changing the nervous system at multiple levels, to prevent further damage in an injured muscle and to maintain motor activities in pain conditions as well as in painless conditions [7]. Motor-evoked potentials and electromyogram (EMG) responses in an affected muscle elicited by transcranial magnetic stimulation to M1 are inhibited in the presence of muscle pain [5,6]. Other previous studies

also demonstrated that activities within muscles were redistributed under muscle pain conditions. That is, EMG signals from the affected muscle decrease, while those from the opposing muscle without pain increase during movement [3,4]. Zedka et al. [4] argued that supraspinal regions (i.e. M1) play a role in this redistribution. Based on these findings, stronger activation of M1 in the DOMS condition may be associated with the redistribution of activities within left upper-arm flexor muscles to maintain the same movement as in the painless condition.

Another possible explanation is that the activation of M1 reflects the activation of descending inhibitory neurons to nociceptive muscle afferents. It is well known that the descending pain modulatory system inhibits pain sensation. Nociceptive stimuli elicit activation of the descending pain modulatory system, which inhibits nociceptive transmission by descending inhibitory neurons projecting from the brain, midbrain, and medulla to the dorsal horn of the spinal cord [19]. Canedo [20] reported that M1 also directly projects to the contralateral dorsal horn and suggested that this projection plays a role in modulation of somatosensory ascending systems. Senapati et al. provided further evidence for this notion. They showed in rats that electrical stimulation of the motor cortex significantly inhibits the response of spinal cord dorsal horn neurons to mechanical noxious stimuli without any effect on their response to innocuous stimuli, and they concluded that activation of the motor cortex leads this inhibition directly and indirectly through activation of the inhibitory interneurons in the dorsal horn [21]. Actually, stimulation to human motor cortex reduces clinical pain [22]. These findings, therefore, support our explanation for the stronger activation of M1 in the DOMS condition.

Presupplementary Motor Area

Our data show that active and dynamic left upper-arm flexor movement with DOMS significantly activated the pre-SMA compared with the same movement without pain. We assume that this activation of the pre-SMA is associated with motor adaptation to pain as with M1. The pre-SMA is one of the higher motor areas and plays various roles in the control of action (e.g., intention to move, preparation of action, motor planning) [23].

Furthermore, a previous study pointed out that upstream areas of M1 associated with motor planning play a role in motor adaptation to pain as well as M1 [24]. Although the pre-SMA does not have a direct projection to M1 [23], this area has functional connectivity with and a modulating effect on M1 [25]. These facts support our explanation for the activation of the pre-SMA in this study.

In addition to the relationship between the pre-SMA and motor control, a recent study showed that pre-SMA is related to pain processing as well as motor control. Perini et al. [26] conducted meta-analysis to investigate regions related to both pain processing and motor control, and they showed that the SMA and the MCC were activated across experiments involving pain, action execution, and action preparation. Although they regarded activation located on the midline surface of the hemisphere just above the cingulate sulcus as the SMA, this region is nearer to the pre-SMA than the SMA because the local maximum of this area was located in front of the vertical line that passes through the caudal-most point of the anterior commissure (vertical commissure anterior line). Therefore, this result suggests that the pre-SMA is related to pain processing as well as motor control. Another study demonstrated that the pre-SMA is related to motor control with cognition of sensory input [27]. In our study, the task in the DOMS condition requires subjects to control their movement with cognition of a muscle pain sensation, and the mechanism of motor adaptation to pain is regarded as part of this movement control with cognition of pain. From this point of view, these previous findings support our explanation.

Parietal Operculum

Active and dynamic left-arm movement with DOMS in flexor muscles also significantly activated contralateral parietal operculum. In general, the parietal operculum corresponds to human secondary somatosensory cortex (S2) [28], and S2 is involved in the processing of tactile sensation including pain and discrimination of pain [28,29]. However, we assume that the activation of the parietal operculum is associated with the motor adaptation to pain in the same way as M1 and pre-SMA.

Eickhoff et al. [28] classified human parietal operculum into four subregions, OP 1–4. OP 1, corresponding to posterior S2, is associated with higher-order somatosensory processing [30]. In contrast, OP 4, corresponding to anterior S2, is associated with the integration of basic sensorimotor processing and action control [30]. According to Eickhoff's probability map [28,31,32], the activated regions of the parietal operculum of this study corresponded to OP 4. Because the motor adaptation to pain can be interpreted as the integration mechanism of muscle nociceptive input and action control, the activation in the parietal operculum evoked by active and dynamic movement with pain would be related to this process.

Taking into account the fact that the parietal operculum is a member of the "pain matrix," this area may be activated in response to muscle nociceptive stimuli. However, the widely accepted activation pattern of S2 to nociceptive stimuli is inconsistent with such an interpretation. Although a wide range of imaging studies for pain reported that bilateral S2 activation is associated with pain sensation [33], we observed activation of the parietal operculum only in the contralateral side. Furthermore, OP4 in the parietal operculum has a strong anatomical and functional connection with ipsilateral M1 [30]. This fact further supports our explanation that activation of the parietal operculum reflects motor adaptation to pain in synergy with contralateral M1.

Why was not the "Pain Matrix" Activated in This Study?

Our study found no significant difference in activation of the "pain matrix" between the DOMS and painless conditions. Many previous studies reported that nociceptive stimuli elicit activation within certain brain regions called the "pain matrix," which consists of S1, S2, insula, and anterior cingulate cortex [34]. However, Mouraux et al. demonstrated that response of the "pain matrix" to nociceptive stimuli can be largely explained by somatosensory-specific but not nociceptive-specific neural activities. They also showed that the saliency of a received sensory stimulus determined how much the stimulus activates the "pain matrix" [35]. The saliency of pain with active movement is lower than that of rest pain because subjects pay attention to not only pain sensations but also to execution of the movement. Furthermore, the saliency of pain with active movement can be attenuated compared with that of passive pain. The saliency of passive pain is large because subjects cannot predict the onset of painful stimuli, whereas the saliency of active movement-evoked pain is less because the onset of pain is predictable. Therefore, the pain evoked by active and dynamic movement may be insufficient to activate the "pain matrix."

Differences Between Our Data and a Previous DOMS Study

Zimmermann et al. [13] examined cortical activation related to DOMS. They induced DOMS in the right quadriceps muscle of healthy volunteers, and attempted to identify brain activations evoked by mechanical stimulation and isometric contraction of quadriceps muscles, respectively. Their study showed that contralateral M1 and the "pain matrix" were more activated during both mechanical stimulation and isometric contraction of the thigh with DOMS compared with those without pain. In addition, contralateral M1 were widely activated far beyond the area corresponding to the thigh [13]. We think that these differences were probably due to the different experimental procedures, in particular type of

movement and stimulation site, adopted in our and Zimmermann's studies. In addition, the differences may be partly due to the greater static strength (and sensitivity) of their 3T MRI vs. our 1.5T MRI.

Although both studies demonstrate activation in contralateral M1 related to painful movement with DOMS, the activation of M1 observed in this study was limited to the arm region. Subjects in Zummermann's study performed maximal isometric contraction of the affected muscle, whereas those in our study performed dynamic movement of the affected muscle. Previous studies report that the influence of muscle pain on muscle coordination is different between static and dynamic muscle contraction. In dynamic movement, muscle pain causes alteration of muscle co-ordination between agonistic and antagonistic muscles [36]. In contrast, muscle pain during isometric exercise does not modulate such a co-ordination between them [37]. Therefore, localized activation of M1 with DOMS in our study was probably associated with motor adaptation to pain evoked by dynamic movement, whereas widespread activation of M1 observed in Zimmermann's study likely reflected cooperative contraction of various muscles including thigh, lower leg, or trunk involved in sudden onset of maximal isometric contraction of the affected muscle.

In addition to types of movement, the stimulated sites were different between the two studies. The previous study found a significant difference in activation of the "pain matrix" between the DOMS and painless conditions. In that study, they stimulated different legs between the DOMS and painless condition, and they did not control the movement with and without DOMS. In this study, by contrast, subjects performed the same left arm movement in the DOMS and painless conditions. Thus, the difference in activation of the "pain matrix" between the two studies may reflects whether the movement was controlled or not between the two conditions.

Limitations

This study has two main limitations. One is that movement may not have been identical between the two conditions. The other is that we did not use a randomized crossover design.

In this study, extrinsic motion parameters were the same between the two conditions, but the intention of movement may have differed between the two conditions. The brain activation differences between the two conditions, therefore, may reflect a difference in intention associated with movement between the DOMS and painless conditions.

Pain restricts the range of motion. To make extrinsic motion parameters including the range of motion equal between the two conditions, consequently, we measured the range of motion in DOMS first, and then sub-

jects performed the movement with the same range of motion in the painless condition. We, therefore, needed to conduct fMRI scan in the DOMS condition before doing so in the painless condition in each subject. Thus, a crossover design was not possible. The differences in brain activations observed in this study could possibly reflect an order effect.

In addition, we note several limitations related to the reliability of our fMRI experiment. DOMS is a promising model of movement-related pain because people with DOMS do not typically report pain while at rest. It is possible, however, that a subject may feel certain uncomfortable sensations such as soreness in the affected limb with DOMS even during rest. Although our subjects did not report uncomfortable sensations at rest, and our results demonstrate brain activation evoked by movement with muscle pain, uncomfortable sensations at rest might have affected the brain activities we observed. Further consideration of this point is needed to confirm whether DOMS is an appropriate experimental model of movement-related pain.

Subjects performed repeated elbow flexion and contraction movements during fMRI scans. Such movement causes head motion, which in turn produces false activation. Comparing the amount of head motion between the DOMS and painless conditions, we found that two of six motion parameters were significantly different. Therefore, although maximum values of head motion were too small to produce false activation (less than 0.1 mm), false activation resulting from head motion cannot be ruled out entirely.

In this study, we adopted a voxel level threshold of $P < 0.001$ without multiple comparison correction. Further cluster level thresholding with multiple comparison correction has been used in similar studies; thus, our threshold was relatively liberal.

Conclusion

Using artificially induced DOMS as an experimental model for movement-evoked pain and/or movement with pain, we were able to identify differences in brain activation in several brain regions between active and dynamic movement with and without DOMS. Our results indicate that DOMS is a promising experimental model for studies in this field.

We showed that contralateral M1, parietal operculum, and bilateral pre-SMA were significantly more activated by active and dynamic arm movement with DOMS compared with the same movement without pain. Furthermore, there was no significant difference in activation of the "pain matrix" between the DOMS and painless conditions. These results may indicate that the brain processing of pain evoked by active and dynamic movement is different from that of passive pain without movement. Considering previous findings, the difference in activation of contralateral M1, parietal operculum and bilateral

pre-SMA suggests that these areas are involved in motor adaptation to pain.

References

1 Nakamura M, Nishiwaki Y, Ushida T, Toyama Y. Prevalence and characteristics of chronic musculoskeletal pain in Japan. J Orthop Sci. 2011;16:424–32.

2 Gaskin DJ, RichardP. The economic costs of pain in the United States. J Pain. 2012;13:715–24.

3 Ervilha UF, Farina D, Arendt-Nielsen L, Graven-Nielsen T. Experimental muscle pain changes motor control strategies in dynamic contractions. Exp Brain Res. 2005;164:215–24.

4 Zedka M, Prochazka A, Knight B, Gillard D, Gauthier M. Voluntary and reflex control of human back muscles during induced pain. J Physiol. 1999; 520:591–604.

5 Svensson P, Miles TS, McKay D, Ridding MC. Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation. Eur J Pain. 2003;7:55–62.

6 Le Pera D, Graven-Nielsen T, Valeriani M, et al. Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. Clin Neurophysiol. 2001;112:1633–41.

7 Hodges PW, Tucker K. Moving differently in pain: A new theory to explain the adaptation to pain. Pain. 2011;152:S90–8.

8 Armstrong RB. Mechanisms of exercise-induced delayed onset muscle soreness: A brief review. Med Sci Sports Exerc. 1984;16:529–38.

9 Graven-Nielsen T, Arendt-Nielsen L. Induction and assessment of muscle pain, referred pain, and muscular hyperalgesia. Curr Pain Headache Rep. 2003;7:443–51.

10 Clarkson PM, Nosaka K, Braun B. Muscle function after exercise-induced muscle damage and rapid adaptation. Med Sci Sports Exerc. 1992;24:512–20.

11 Jones DA, Newham DJ, Obletter G, Giamberardino MA. Nature of Exercise-Induced Muscle Pain. In: Tiengo M, Eccles J. Cuello AC, Ottson D, eds. Advances in Pain Research and Therapy. New York: Raven Press; 1987:207–18.

12 Miles MP, Clarkson PM. Exercise-induced muscle pain, soreness, and cramps. J Sports Med Phys Fitness. 1994;34:203–16.

13 Zimmermann K, Leidl C, Kaschka M, et al. Central projection of pain arising from delayed onset muscle soreness (DOMS) in human subjects. PLoS One. 2012;7:e47230.

14 Zainuddin Z, Newton M, Sacco P, Nosaka K. Effects of massage on delayed-onset muscle soreness, swelling, and recovery of muscle function. J Athl Train. 2005;40:174–80.

15 Kalaska JF. From intention to action: Motor cortex and the control of reaching movements. Adv Exp Med Biol. 2009;629:139–78.

16 Henderson LA, Bandler R, Gandevia SC, Macefield VG. Distinct forebrain activity patterns during deep versus superficial pain. Pain. 2006; 120:286–96.

17 Nash PG, Macefield VG, Klineberg IJ, et al. Changes in human primary motor cortex activity during cutaneous and muscle orofacial pain. J Orofac Pain. 2010;24:379–90.

18 Schreckenberger M, Siessmeier T, Viertmann A, et al. The unpleasantness of tonic pain is encoded by the insular cortex. Neurology. 2005;64:1175–83.

19 Millan MJ. Descending control of pain. Prog Neurobiol. 2002;66:355–474.

20 Canedo A. Primary motor cortex influences on the descending and ascending systems. Prog Neurobiol. 1997;51:287–335.

21 Senapati AK, Huntington PJ, Peng YB. Spinal dorsal horn neuron response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. Brain Res. 2005;1036:173–9.

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

23 Nachev P, Wydell H, O'Neill K, Husain M, Kennard C. The role of the pre-supplementary motor area in the control of action. Neuroimage. 2007;36:T155–63.

24 Hodges PW, Moseley GL. Pain and motor control of the lumbopelvic region: Effect and possible mechanisms. J Electromyogr Kinesiol. 2003;13:361–70.

25 Mars RB, Klein MC, Neubert FX, et al. Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci. 2009;29:6926–31.

26 Perini I, Bergstrand S, Morrison I. Where pain meets action in human brain. J Neurosci. 2013;33:15930–9.

27 Ikeda A, Yazawa S, Kunieda T, et al. Cognitive motor control in human pre-supplementary motor area studies by subdural recording of discrimination/selection-related potentials. Brain. 1999;122:915–31.

28 Eickhoff SB, Amunts S, Mohlberg H, Zilles K. The human parietal operculum II. Cerebral Cortex. 2006;16:268–79.

29 Maihöfner C, Herzner B, Otto Handwerker H. Secondary somatosensory cortex is important for the sensory-discriminative dimension of pain: A functional MRI study. Eur J Neurosci. 2006;23:1377–83.

30 Eickhoff SB, Jbabdi S, Caspers S, et al. Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. J Neurosci. 2010;30:6409–21.

31 Eickhoff SB, Stephan KE, Mohlberg H, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage. 2005;25:1325–35.

32 Eickhoff SB, Schleicher A, Zilles K, Amunts. The human parietal operculum I. Cerebral Cortex. 2006;16:254–67.

33 Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: A bilateral, distributed mechanism. J Neurophysiol. 1999;82:1934–43.

34 Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9:463–84.

35 Mouraux A, Diukova A, Lee MC, Wise RG, Iannettiet GD. A multisensory investigation of the functional significance of the "pain matrix". Neuroimage. 2011;54:2237–49.

36 Graven-Nielsen T, Svensson P, Arendt-Nielsen L. Effects of experimental muscle pain on muscle activity and co-ordination during static and dynamic motor function. Electroencephalogr Clin Neurophysiol. 1997;105:156–64.

37 Ciubotariu A, Arendt-Nielsen L, Graven-Nielsen T. The influence of muscle pain and fatigue on the activity of synergistic muscles of the leg. Eur J Appl Physiol. 2004;91:604–14.