# Changes in Human Primary Motor Cortex Activity During Acute Cutaneous and Muscle Orofacial Pain

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***Aims:*** *To use functional magnetic resonance imaging (fMRI) to determine whether orofacial cutaneous or muscle pain is associated with changes in primary motor cortex (M1) activity that outlast the duration of perceived pain, and whether these M1 changes are different during cutaneous pain compared with muscle pain.* ***Methods:*** *fMRI was used in healthy subjects experiencing orofacial muscle (n = 17) or cutaneous (n = 15) pain induced by bolus injections of hypertonic saline (4.5%) into the belly of the masseter muscle (0.5 ml) or subcutaneously (0.2 ml) into the overlying skin, respectively. To determine the effects of the injection volume, isotonic saline (n = 4) was injected into the masseter muscle.* ***Results:*** *Similar pain scores were observed following subcutaneous (mean [± SEM]; 4.73 ± 0.51) or intramuscular injections (4.35 ± 0.56). Orofacial muscle but not cutaneous pain was associated with a transient increase in signal intensity in the contralateral M1. Cutaneous and muscle orofacial pains were associated with similar signal intensity decreases within the contralateral M1 that continued to decrease for the entire scanning period. Isotonic saline did not evoke pain or changes in M1 signal intensity.* ***Conclusion:*** *The transient contralateral M1 signal intensity increase during orofacial muscle pain may underlie escape-like motor patterns. However, once the initial threat has subsided, longer-term reductions in M1 activity and/or excitability may occur to aid in minimizing movement of the affected part, an effect consistent with the general proposals of the Pain Adaptation Model.* J OROFAC PAIN 2010;24:379–390

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It is generally accepted that pain serves to alter an individual's behavioral state in an attempt to deal with the current threat. As a result, pain has a short-term effect on motor output, typically evoking behavioral states such as "fight or flight."[1] In addition to these short-term changes in motor activity, it has been suggested that acute pain is associated with longer-term changes in motor activity. A popular, but not clinically proven, hypothesis—referred to as the Johansson-Sojka hypothesis—suggests that muscle metabolites released by underlying muscle contraction evoke a "vicious cycle," reciprocally aggravating muscle pain and muscle tone.[2] Experiments in anesthetized cats have demonstrated that group III and group IV afferents excite γ motoneurones (fusimotor neurones) and thereby increase the background firing of the muscle spindles.[3,4] According to this hypothesis, muscle spindle excitation may lead to an increased activation level of the homonymous α motoneurone pool, the sustained muscle tone or contraction-induced ischemia resulting in accumulation of metabolites.[2] Accordingly, if the production of

metabolites is high enough to excite nociceptors, or if the nociceptive input from joints[5] and ligaments[6] also contributes, a process sustaining a "vicious cycle" might be initiated, resulting in chronic muscle pain. However, whether this model, established from studies in anesthetized experimental animals, applies to awake human subjects is controversial. The authors recently showed that bolus intramuscular or subcutaneous injections of hypertonic saline had no effect on the background discharge of muscle spindles in relaxed human leg muscles[7,8]; in the anesthetized cat, muscle spindle firing rate increased by ~80% in response to the same noxious stimulus.[4] Furthermore, Simons and Mense[9] reported that painful muscles in humans mostly show no electromyographic activity and, if present, the electromyogram did not correlate with pain either in the time or intensity domain. Svensson et al[10] also concluded that human experimental muscle pain is unable to induce longer-lasting muscle hyperactivity.

Lund and colleagues[11] reviewed a wide range of clinical literature and experimental studies and came to the conclusion that chronic pain tends to inhibit, not facilitate, voluntary and reflex contractile activity of a painful muscle or its agonists. They suggest that these effects are beneficial and provide protective adaptation (the Pain Adaptation Model) and are definitely not the cause of pain. Indeed, experimentally induced pain and clinical pain are associated with smaller and slower movements and inhibition of agonist muscle activity.[12–14] The Pain Adaptation Model suggests that, during muscle pain, increased antagonist and decreased agonist muscle activity limit movement and prevent further muscle damage. The validity of this model, and the involvement of brain regions underlying changes in motor output during acute pain, remain vigorously debated.[15] In addition to the well-documented modulatory effects of pain on motor function in the spinal cord and brainstem,[11,16–18] recent evidence in rats has shown that glutamate infusion into the tongue results in a long-term decrease in primary motor cortex (M1) excitability.[19] Others have also reported decreased M1 excitability in humans during noxious limb stimulation.[20,21] Evidence is emerging, therefore, that noxious stimuli have motor effects not only at the level of the brainstem and spinal cord, as previously documented,[5] but also at suprabulbar and supraspinal levels, including the cerebral cortex.

In contrast to these reports of altered M1 excitability during pain, two recent human transcranial magnetic stimulation studies reported that the area of M1 which projects to brainstem motoneurones supplying orofacial muscles was not affected during acute orofacial pain induced by topical capsaicin to the tongue and cheek as well as hypertonic saline infusion into the masseter.[22,23] However, capsaicin-evoked tongue mucosal pain did interfere with M1 neuroplasticity associated with novel tongue-task motor training.[24] It has also been suggested that the effects of pain on motor function may vary depending on the tissue stimulated, since previous studies have revealed that noxious stimulation of muscle and joint results in greater central sensitization than that which occurs during noxious skin stimulation.[25,26] The possibility of different central neural effects with noxious stimulation of different tissues may help explain the differences between studies. Consistent with this, it has been reported in a functional magnetic resonance imaging (fMRI) study that acute cutaneous and muscle pains are associated with differential increases in blood oxygen level dependent (BOLD) signal intensity in an area that appeared to encompass the region of M1 that projects to motoneurones supplying muscles of the lower limbs. Following intramuscular injection of hypertonic saline into tibialis anterior, signal intensity increased in a manner that followed the profile of the pain; conversely, it did not change during cutaneous pain induced by injection of hypertonic saline into the overlying skin.[27] In contrast, using positron emission tomography, Kupers and colleagues reported M1 signal intensity changes during allodynic orofacial cutaneous stimulation but not during masseter muscle pain, also induced by injection of hypertonic saline.[28]

In a previous investigation, the authors searched for signal intensity changes that were relatively brief, ie, that matched the temporal profile of pain intensity. However, a recent study by Le Pera and colleagues[21] suggested that muscle pain is associated with longer-lasting depression of M1 excitability that did not follow the profile of the painful stimuli, but instead persisted well beyond the period of perceived pain. These findings are consistent with observations in rats following noxious lingual stimulation.[19] While these studies indicate that M1 activity is altered during acute noxious stimuli, the precise nature of the signal changes during acute orofacial pain in humans remains unclear. If M1 signal intensity changes persist beyond the period of perceived pain, then this may suggest that acute pain has longer-term effects on M1 excitability and would provide added support for the Pain Adaptation Model. Furthermore, an improved understanding of the cortical mechanisms underlying orofacial pain may provide additional insights that may aid the development of improved therapeutic strategies.

The aims of this study were to use fMRI to determine whether orofacial cutaneous or muscle

pain is associated with changes in M1 activity that outlast the duration of perceived pain and whether these M1 changes are different during cutaneous pain compared with muscle pain. Two hypotheses were tested: firstly, that M1 signal intensity would increase in a pattern similar to the pain intensity change during acute orofacial muscle pain but not cutaneous pain, and secondly, that both cutaneous and muscle orofacial pain would induce long-term changes in signal intensity that outlasted the period of perceived pain.

## Materials and Methods

### Subjects

Thirty healthy subjects (22 males, 8 females) aged 19 to 52 years participated in this study. All procedures were carried out with the understanding and written informed consent of each subject. All procedures were approved by institutional Human Research Ethics Committees (University of New South Wales, University of Sydney, Westmead Hospital) and were conducted in accordance with the conditions established by the Declaration of Helsinki.

### Stimulation and MRI

Subjects were randomly allocated into two groups. In each group, two fMRI scans were performed. One group received subcutaneous injection (0.2 ml) of hypertonic saline (4.5%) during the first fMRI scan and intramuscular injection (0.3 ml) of hypertonic saline during the second fMRI scan. The second group received intramuscular injection in the first scan and subcutaneous injection in the second scan. The subjects were not aware of the time and type of injection they had received.

At the beginning of the fMRI scanning session, each subject was placed in a supine position and a fine plastic cannula (23 gauge), attached to a 1-ml syringe containing sterile hypertonic saline, was inserted deep into the central belly of the right masseter muscle and another into the skin overlying the right masseter muscle. The syringe, connected by a 2-m extension tube to the injection cannula, was located out of sight of each experimental subject, and each subject was asked to lie still. A continuous series of 130 volumes of gradient echo, echo planar images (EPI) using BOLD contrast was then collected using a 3 Tesla, Phillips Intera scanner (57 axial slices = 1 volume, TR = 4 s, TE = 30 ms, flip angle = 90 degrees, FOV = 250 mm, raw voxel size = 1.95 × 1.62 × 3.3-mm thick). In each fMRI scan, following 40 volumes, subjects received either an intramuscular or subcutaneous hypertonic saline injection (ie, only one painful injection in each fMRI scan). Simultaneous injections into the masseter and skin were not performed.

Each subject was instructed to press a buzzer with their left thumb to indicate when *(1)* they felt the onset of pain, *(2)* the pain began to subside from its peak, and *(3)* the pain had ceased. The time of the buzzer was recorded as the scan number being acquired. To ensure that pain intensity had returned to 0 after a painful injection, there was at least a 20-minute interval before the next painful injection. During this interval, three 3-D T1-weighted anatomical scans (voxel size = 0.8 × 0.8 × 0.8 mm) were collected. Immediately following each fMRI scan, subjects were asked to rate the maximum pain intensity and unpleasantness as well as describe the sensory and affective qualities of the stimulus through the McGill Pain Questionnaire.[29] Thus, immediately following each fMRI scan and while still lying stationary inside the scanner, subjects were read aloud a Modified Borg Scale for pain intensity and unpleasantness and asked to respond verbally (pain intensity; 0 = no pain, 1 = minimal, 2 = mild, 3 = moderate, 4 = considerable, 5 = large, 7 = very large, 10 = maximal. Pain unpleasantness; 0 = not unpleasant, 1 = mild, 3 = discomforting, 5 = distressing, 7 = horrible, 10 = excruciating).[30] Subjects were read the number and corresponding word cue and were made aware that they were to choose a number between 0 and 10 that best reflected the maximum intensity and unpleasantness of the pain. In addition, subjects were read a long-form McGill Pain Questionnaire and asked to choose the words that most accurately described the quality of the pain (eg, was the pain hot or cold, sharp or dull).

Following the scanning session, subjects were asked to draw on a line representing the baseline period, point of injection, and end of scanning, the pain-intensity profile (ie, how quickly the pain rose to its peak, how long it remained elevated, and how quickly it subsided). Using this approximate pain-intensity profile, in combination with the times at which each subject pressed the buzzer, a pain-intensity profile for each stimulus was created for each subject. These individual pain intensity curves were then averaged across subjects to create a mean pain intensity curve for the cutaneous and muscle noxious stimuli. In addition, each subject was asked to draw the area over which they experienced pain on a standardized anterolateral drawing of a face. All subjects reported unilateral pain; therefore, only drawings of the right side of the face were collected. However, a drawing of the left side of the face was

available had patients reported bilateral pain. Each individual's pain spread was overlaid onto a standard anterolateral picture of the face to gauge the pain spread during cutaneous and muscle pain. A detailed metric analysis was not performed on these pain drawings.

In five subjects who had received both the intramuscular and subcutaneous hypertonic saline injections and who rated both injections as painful (ie, pain rating ≥ 3, mean [± SEM]; muscle pain, 6.5 ± 1.1; cutaneous pain, 5.8 ± 1.2) an additional fMRI scanning session was performed within 1 month (at least 1 week) of the initial session. During this additional fMRI scanning session, an isotonic saline (0.9%, 0.3 ml) injection was made into the masseter in accordance with the protocol described above. The rationale for including this additional scanning session was to ensure that any signal intensity changes that occurred within M1 during the intramuscular hypertonic saline injections were the result of the noxious stimulation *per se* and not the activation of muscle stretch receptors due to the volume injected. A continuous series of 130 volumes of gradient echo EPI images were collected using the same MRI parameters described above. Brainstem data from the same experimental sessions have been published previously.[31]

### MRI Analysis

The software package SPM5[32] was used to correct all functional images for motion errors, and only subjects with movement parameters less than 1 mm in the X, Y, and Z planes were used for analysis. In addition, for the cutaneous and muscle pain series, all subjects experienced pain, but only those subjects who rated the pain intensity as 3 or greater were used for further analysis. From the 30 subjects who participated in the study (all of whom received both intramuscular and subcutaneous injections), 15 subjects had acceptable pain ratings (pain ≥ 3) and movement (≤ 1 mm) parameters for inclusion in the cutaneous pain group (8 subjects were excluded due to movement > 1 mm, 7 subjects were excluded due to pain < 3). Of the 30 subjects, 17 had acceptable pain ratings and movement parameters for inclusion in the muscle pain group (8 excluded due to movement > 1 mm, 5 excluded due to pain < 3). Ten of the 30 subjects had acceptable pain and movement criteria to be included in both the cutaneous and muscle pain analyses. Of the 30 subjects, 4 were included in the intramuscular isotonic saline analysis (1 subject was removed from the initial group of 5 due to excessive head movement).

After the images were realigned, the remaining subjects' functional images were normalized to the Montreal Neurological Institute (MNI) template, spatially smoothed with a 6 mm full-width-at-half-maximum Gaussian filter and temporally smoothed (10 seconds). Following the removal of the first 10 volumes (to allow for scanner equilibration), significant changes in signal intensity were determined on a voxel-by-voxel basis using the remaining 120 volumes. To determine those brain regions that responded in a manner similar to the change in reported pain intensity, a box-car model (convolved with a hemodynamic delay), which approximated the period of perceived pain (30-volume baseline, 30-volume on, 60-volume off), was used. One-sample *t* tests were performed to determine significant signal intensity increases and decreases during the two primary stimulation paradigms (cutaneous pain; muscle pain; $P < .05$ random effects, False Discovery Rate [FDR] corrected for multiple comparisons, minimum cluster size 10 voxels). The resulting statistical maps were then overlaid onto a T1-anatomical image. In addition, an analysis was performed that was restricted to the contralateral M1 ($P < .05$, FDR corrected for multiple comparisons). A two-sample *t* test ($P < .05$ random effects, FDR corrected for multiple comparisons, minimum cluster size 10 voxels) was also performed to ascertain if there were significant differences in M1 signal intensity changes during cutaneous and muscle pain.

To determine whether M1 signal intensity changed in a longer-term pattern, a box-car model, which included the entire 90-volume period following each saline injection, was used (30-volume baseline, 90-volume on). A voxel-by-voxel analysis restricted to the M1 was also performed using this box-car model and significant signal intensity changes during each of the three stimulation paradigms were determined using one-sample *t* tests ($P < .05$ random effects, FDR corrected for multiple comparisons, minimum cluster size 10 voxels). The resulting statistical maps were then overlaid onto a T1-anatomical image, and the percentage change in signal intensity over time (relative to baseline) for each subject was calculated for each significant cluster and then averaged across subjects to give a plot of overall mean (± SEM) percentage change in signal intensity over time. A two-sample *t* test ($P < .05$ random effects, FDR corrected for multiple comparisons, minimum cluster size 10 voxels) was also performed to ascertain if there were significant differences in M1 signal intensity changes during cutaneous and muscle pain.

In addition to the group M1 analysis, the most significantly activated voxel within the contralateral M1 was determined in each individual subject. The location of these voxels was then plotted onto a rendered view of an individual subject's T1-image

and the percentage change in signal intensity plotted over time. Finally, to determine if the changes in signal intensity in the contralateral M1 during muscle pain were a result of the injection volume, M1 signal intensity changes during intramuscular isotonic saline injections were assessed in the four subjects who had received both the intramuscular and subcutaneous hypertonic saline injections (see above). Since the authors were interested in determining whether the isotonic saline injections evoked a signal intensity change within the M1 region that was activated by muscle pain, a region of interest (ROI) was created from significant M1 activation determined by the intramuscular hypertonic saline injection analysis; no random effects analysis was performed on these four subjects, as the sample size was too small. The percentage change in signal intensity over time (relative to baseline) was calculated for this M1 cluster and averaged across subjects to give an overall mean (± SEM) percentage change in signal intensity over time.

## Results

### Pain Perception and Spread

Subcutaneous (n = 15) and intramuscular (n = 17) hypertonic saline injections evoked pain that started within 10 seconds of the injection onset, reached a peak at approximately 50 seconds, and returned to preinjection levels within approximately 420 seconds. The mean (± SEM) maximum pain scores, calculated from all subjects included in the fMRI analysis (ie, those with a pain rating of "3" or greater and with minimal head movement), following subcutaneous and intramuscular hypertonic saline injections, were 4.73 ± 0.51 and 4.35 ± 0.56, respectively. Subcutaneous hypertonic saline evoked pain that was described as "sharp and hot," whereas intramuscular hypertonic saline injections evoked pain that was "dull and cramping." Both cutaneous and muscle pain spread rostrally to encompass most of the right cheek. In contrast, intramuscular isotonic saline injection evoked a pain rating of "0" in four subjects and "1" in the remaining subject.

### fMRI Signal Intensity Changes

When a statistical model that followed the pattern of perceived pain intensity was initially used, group analysis revealed that both cutaneous and muscle orofacial pains were associated with significant increases in signal intensity in a number of brain regions. Signal increases occurred in the thalamus, primary and secondary somatosensory cortices, midcingulate cortex, insula, and cerebellum (Fig 1). In none of these regions was either cutaneous pain or muscle pain associated with a significant decrease in signal intensity that matched the perceived change in pain intensity.

#### M1

Within the contralateral M1, group analysis revealed that orofacial muscle pain was associated with a transient, immediate increase in signal intensity in the region, which projects to brainstem motoneurones supplying orofacial muscles (Fig 2, Table 1). Orofacial cutaneous pain was not associated with a similar transient increase in signal intensity.

In contrast, when a statistical model was used that followed longer-term changes in signal intensity, group analysis restricted to M1 revealed that both cutaneous and muscle orofacial pains were accompanied by significant signal intensity decreases within the contralateral M1 cortex in the region that projects to brainstem motoneurones supplying orofacial muscles (Fig 3, Table 1). Similar to those signal increases described above, the contralateral M1 signal intensity decreases began almost immediately following each hypertonic saline injection.However, in contrast to the signal intensity increases accompanying orofacial muscle pain, the M1 signal decreases did not return to baseline in a pattern similar to the perceived pain, but instead continued to decrease throughout the entire scanning period. It appeared that, at the earliest, these declines may have reached their nadir during the last few volumes of the scanning period, ie, 360 seconds following the hypertonic saline injection. At this point, the magnitudes of the signal intensity decreases were similar following both the intramuscular and subcutaneous hypertonic saline injections (cutaneous pain [mean ± SEM]: –1.47 ± 0.38, muscle pain: –1.41 ± 0.27; $P > .05$). Neither muscle nor cutaneous pain was associated with significant signal intensity changes in the ipsilateral M1, and no significant difference was found between the changes in M1 signal intensity during cutaneous and muscle pain.

Analysis of individual data revealed that the decreases in signal intensity associated with orofacial pain were consistent between subjects (Fig 3). In all subjects, both orofacial cutaneous and muscle pains were associated with signal intensity decreases within the facial M1 region. Moreover, these signal decreases were protracted, not reaching the maximum fall until near the end of the scanning period, when the perceived pain intensity had returned to near zero. A lack of significant relationship between M1

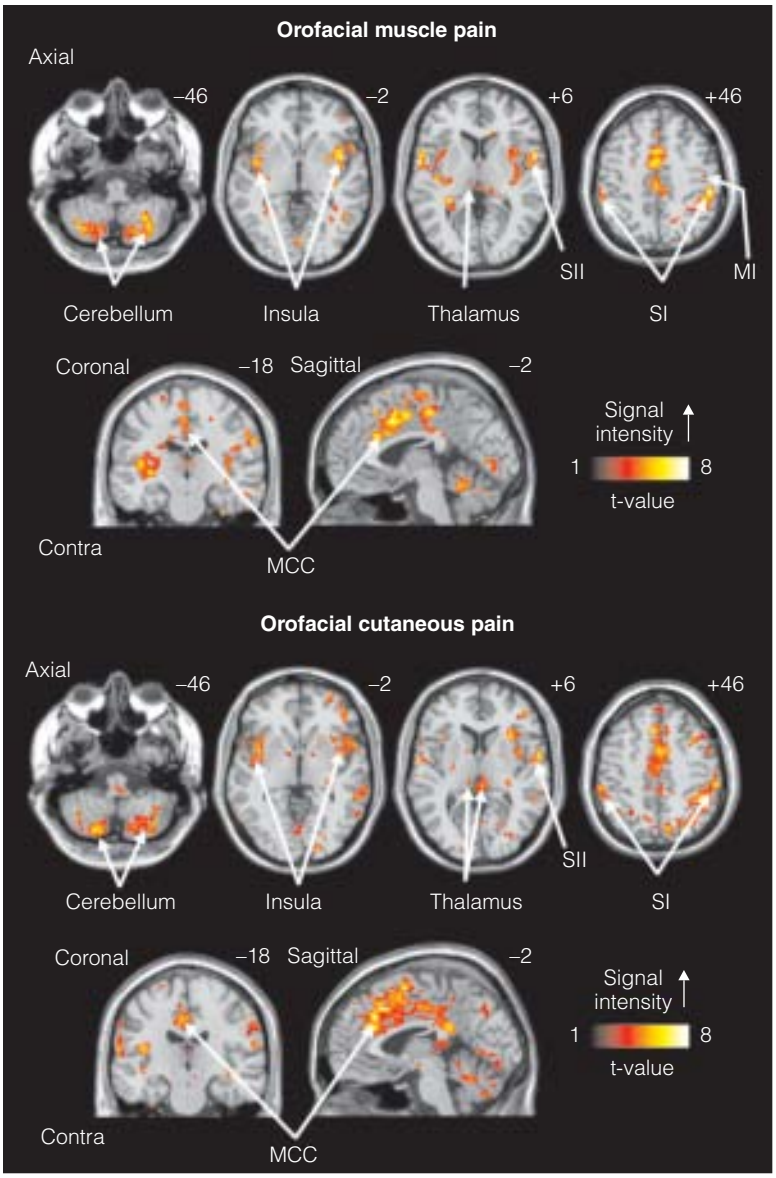



**Fig 1** Cortical and subcortical regions showing increases (hot color scale) in signal intensity during orofacial muscle pain *(top)* and orofacial cutaneous pain *(bottom)* induced by injection of hypertonic saline into the right masseter muscle or overlying skin. The slice locations in MNI space are indicated in the top right of each image. MCC: mid-cingulate cortex; SI: primary somatosensory cortex; SII: secondary somatosensory cortex; contra: contralateral to the side of the injection (ie, left).

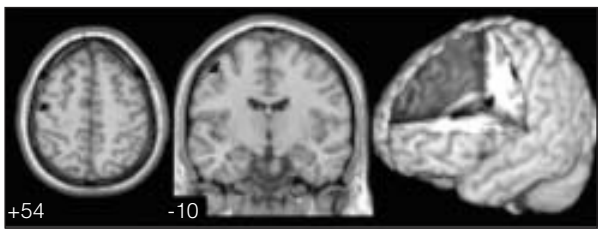
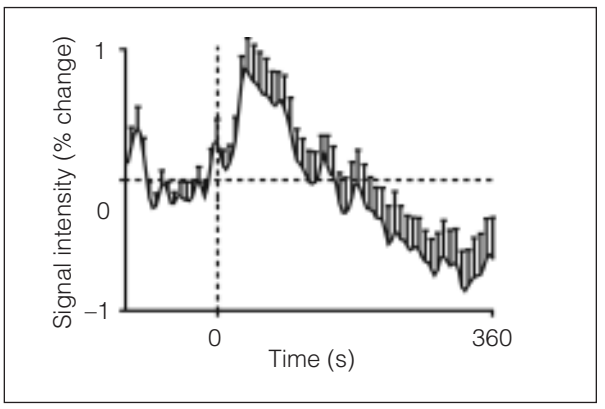



**Fig 2** Region within the contralateral M1 in which signal intensity increased during muscle pain in a pattern similar to the pain intensity. The significantly activated region is shown in black, overlaid onto a rendered T1-weighted anatomical image. The mean (± SEM) percentage changes in signal intensity within this cluster are shown to the right.



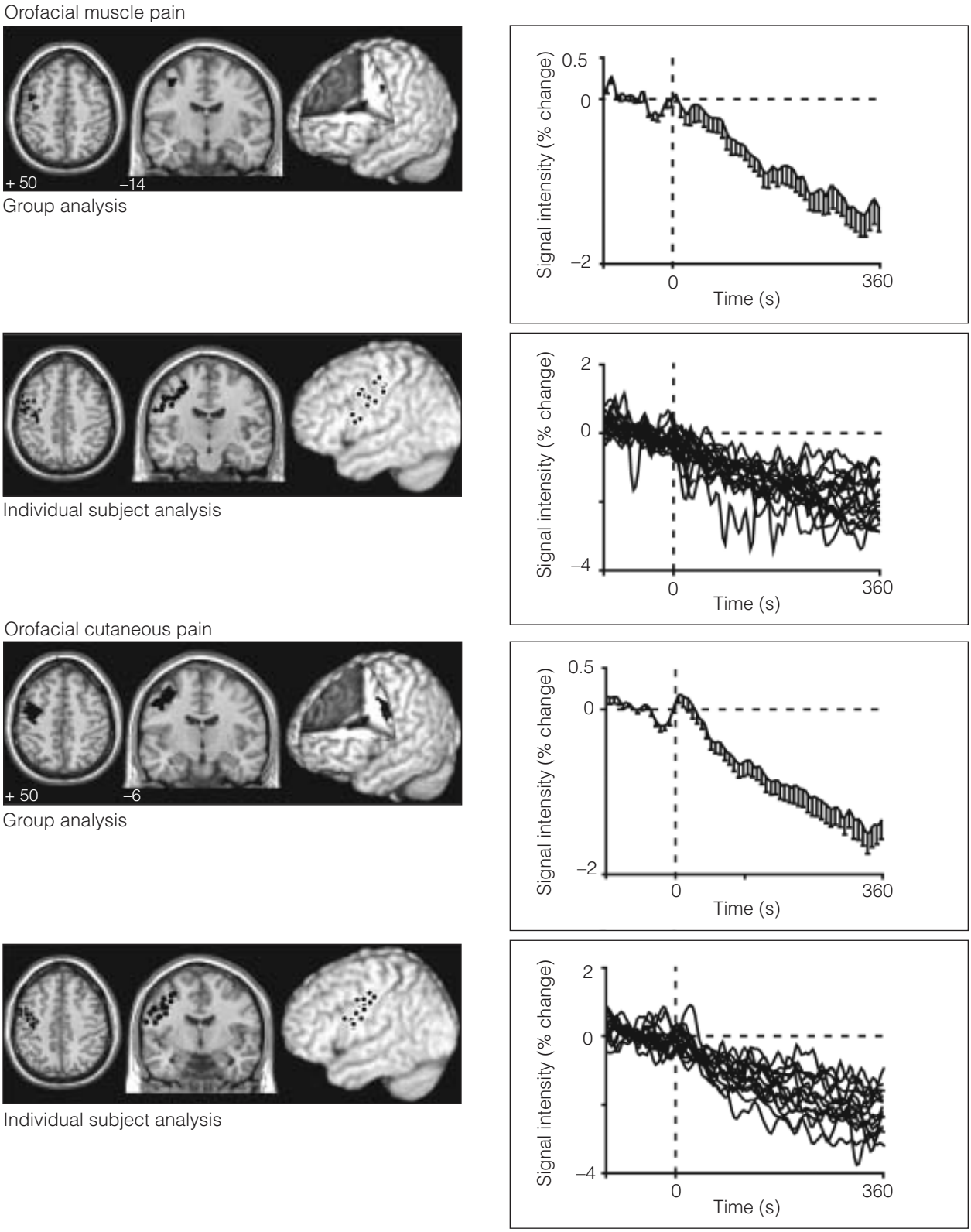



**Fig 3** Regions within the contralateral M1 in which signal intensity decreased slowly over the entire scanning period. The significantly activated region obtained from the group analysis, as well as the most significantly activated voxel in each individual subject, are shown for both orofacial muscle (top four images) and cutaneous (lower four images) pain. Significantly activated regions are shown in black, overlaid onto a rendered T1-weighted anatomical image. The mean (± SEM) percentage changes in signal intensity within each cluster are shown to the right. Note the consistency in the decreases in M1 signal intensity in each subject.

Table 1 MNI Coordinates, T-Values, and Sizes of M1 Clusters in Which Signal Intensity Increased and Decreased Significantly During Orofacial Muscle Pain and Decreased Significantly During Orofacial Cutaneous Pain

| | MNI coordinates | | | | |
|---|---|---|---|---|---|
| | X | Y | Z | T value | Cluster size |
| Muscle pain | | | | | |
| Signal increases | –44 | –10 | 54 | 3.41 | 14 |
| Signal decreases | –38 | –14 | 50 | 5.08 | 277 |
| Cutaneous pain | | | | | |
| Signal decreases | –50 | –6 | 46 | 6.47 | 1,437 |

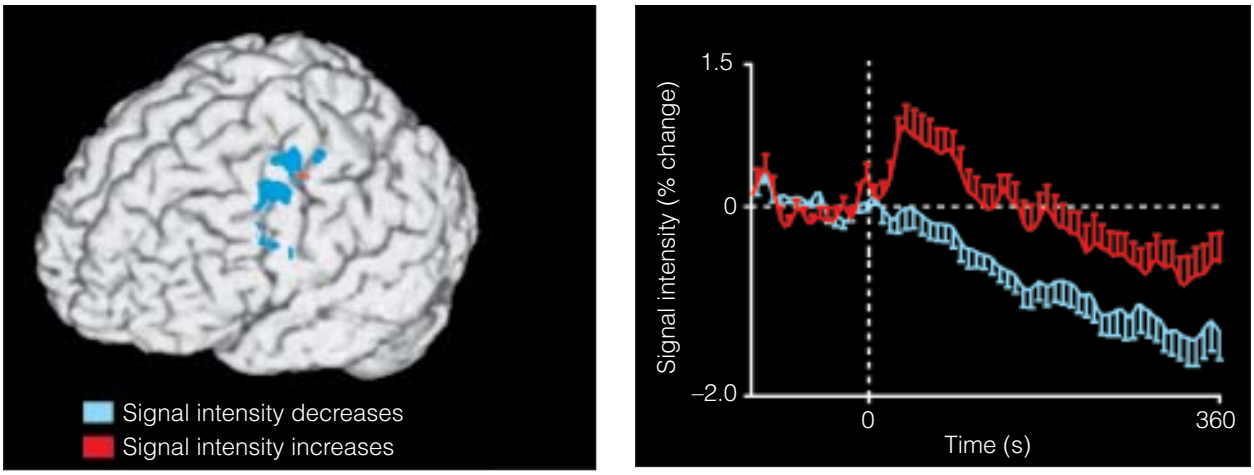


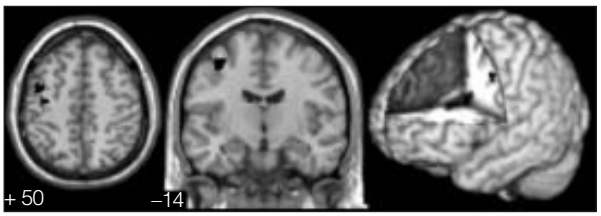

**Fig 4** Regions within the contralateral M1 in which signal intensity increased in a pattern similar to the pain intensity *(red)* and gradually decreased *(blue)* during orofacial muscle pain. The significantly activated regions are overlaid onto a rendered T1-weighted anatomical image. The mean (± SEM) percentage changes in signal intensity within these clusters are shown to the right. Note that the discrete region in which signal intensity increased is surrounded by a larger region in which signal intensity decreased.

signal intensity change and perceived pain intensity was further strengthened by the finding that there was no significant correlation between the maximum decrease in M1 signal intensity and the maximum perceived pain intensity (muscle pain: $R = 0.19$; cutaneous pain: $R = 0.15$).

An overlay of the transient M1 signal intensity increases and the prolonged M1 signal intensity decreases accompanying orofacial muscle pain revealed that the signal increases were surrounded by the signal intensity decreases (Fig 4). There was no significant change in M1 signal intensity following isotonic saline injections ($P > .05$, one-sample $t$ test). Furthermore, isotonic saline injections were not associated with a significant change in signal within the region of M1 that was significantly activated during muscle pain (Fig 5).

## Discussion

Consistent with the hypothesis that pain alters M1 excitability, acute orofacial muscle and cutaneous pains were associated with significant and prolonged decreases in signal intensity within the contralateral M1. Although this decrease in signal began almost immediately after the onset of the perceived pain, it continued to fall for the entire scanning period and did not follow the profile of perceived pain intensity. Furthermore, a brief increase in signal intensity occurred in the contralateral M1 during orofacial muscle pain. These data support the idea that while acute pain may initially evoke escape-like motor patterns (as evidenced by the transient increase in M1 signal intensity), once the initial threat has subsided, longer-term reductions in M1 activity and/or excitability may occur. If these changes truly reflect reductions in M1 excitability, then the findings sug-



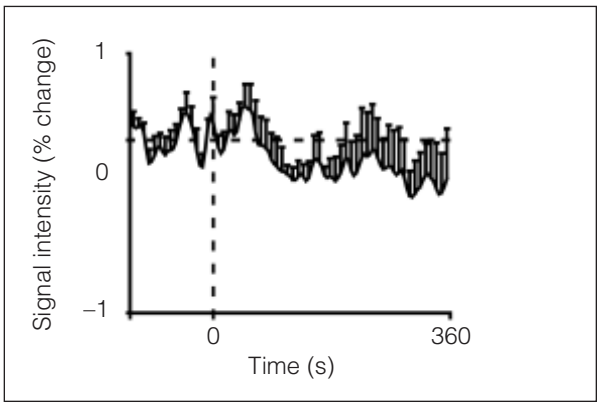




**Fig 5** Percentage change (mean ± SEM) in signal intensity *(black)* in contralateral M1 in subjects who received isotonic saline injections into the right masseter muscle. Signal changes were derived from the most activated cluster evoked by intramuscular hypertonic saline injection.

gest that orofacial pain has longer-term inhibitory effects on face M1 activity that may reduce voluntary orofacial movements during orofacial pain. Such effects are consistent with the general proposals of the Pain Adaptation Model that pain acts to limit movement so as to prevent further damage and thus aid healing.[11] Furthermore, the data suggest that the neural circuitry of the Pain Adaptation Model extends to suprabulbar regions and does not simply reside in the brainstem as originally proposed.

### M1 and Acute Pain

Similar to their previous investigation,[27] the authors found that acute muscle pain, but not cutaneous pain, was accompanied by a transient increase in M1 signal intensity in a pattern similar to pain intensity. Although some human brain imaging investigations have reported M1 signal intensity increases during acute pain, many have not.[33–36] Contrary to the present data, Porro and colleagues reported signal intensity increases that followed the pattern of pain intensity within the somatotopically appropriate M1 during subcutaneous injections of ascorbic acid into the dorsum of the foot.[37] However, these authors also reported signal intensity decreases within M1 and did not investigate longer-term changes in M1 signal intensity. In general, the inconsistencies with respect to M1 signal intensity changes in response to noxious stimuli may be due to the different methods of noxious stimulation, the close proximity of the primary motor and somatosensory cortices in conjunction with the relatively poor spatial resolution of other brain imaging techniques, such as positron emission tomography (PET). Furthermore, since the vast majority of pain imaging investigations have used cutaneous noxious stimuli to explore nociceptive pathways, and the present study found that only muscle pain was associated with an increase in M1 signal intensity, it is not surprising that most of these studies have not reported increases in M1 signal intensity. However, the present results are consistent with a previous investigation showing M1 signal intensity increases during muscle but not cutaneous pain applied to the leg.[27]

It is well established that the primary role of acute pain is to alter an individual's behavior in order to deal with the current threat, with the precise nature of the response being governed by the tissue from which the noxious stimulus originates. For example, acute cutaneous pain typically evokes fight or flight behaviors and hyperreactivity, whereas muscle and visceral pains typically evoke quiescence and hyporeactivity.[1] Although it is likely that these patterned motor responses to orofacial pain are generated entirely within the brainstem, the present data suggest that M1 plays a role in generating and/or modulating these patterned changes in motor output during orofacial muscle pain. An alternative interpretation is simply that the increases in M1 signal intensity resembled the ongoing pain intensity and therefore the change in sensory qualities associated with orofacial muscle pain. The authors have previously reported that hypertonic saline injection into the masseter muscle evokes a pain that is most often described as "aching" and "cramping" in quality.[31] It has been previously shown that M1 displays highly localized and significant signal intensity increases during the somatic perception of limb movement[38]; thus, it is possible that the signal intensity increases within M1 during orofacial muscle pain reflect each subject's perception of muscle cramp.

In contrast to the differential effects of muscle and cutaneous pain on M1 signal intensity increases, both acute orofacial cutaneous and muscle pains were accompanied by a slow and profound *decrease*

in M1 signal intensity. Although many brain imaging investigations have explored the central processing of acute pain, until now, no study has reported signal intensity decreases within M1 during either cutaneous or muscle pain. This is likely due to the fact that the vast majority of these studies has employed brief cutaneous heat as the noxious stimulus and has subsequently searched for signal intensity changes that matched these brief pain periods. The present data clearly demonstrate that during acute cutaneous and muscle orofacial pain, M1 signal intensity decreases slowly and continues to decrease for at least 6 minutes following the onset of pain and therefore after the pain has subsided to baseline levels. Most studies have not been designed to explore such longer-term signal changes and, as a result, would not have looked for a gradual signal decrease.

It has been suggested that during muscle pain in particular, muscles surrounding the noxious stimulus alter their activities so as to prevent further pain and muscle damage, ie, the Pain Adaption Model.[11] This model proposes that, via segmental brainstem or spinal cord motor circuits, pain leads to alterations in muscle activity that limit movement and protect the skeletomotor system from further injury and thereby promote healing. Consistent with this model, many previous studies have shown that acute pain is associated with changes in motor output. For example, experimental pain results in movements that are smaller and slower during static and dynamic activity.[12–14] Although these alterations in motor output may originate from changes within the brainstem and/or spinal cord and have been considered to exert their predominant effects there,[11] there is growing evidence that pain also alters activity within the MI. It has recently been shown in the rat that noxious stimulation by glutamate infusion into the tongue is associated with long-term depression of M1 excitability.[19] Furthermore, this depression was restricted to the M1 region that represented the muscle at the injection site.

In addition to human brain imaging studies, several groups have used transcranial magnetic stimulation to determine the effects of acute pain on the amplitude of motor evoked potentials (MEPs). Farina and colleagues[20] reported a significant reduction in the amplitude of MEPs during capsaicin-induced cutaneous pain and further reported that these MEP reductions were restricted to the musculature directly related to the site of noxious stimulation. Similarly, Le Pera and colleagues reported a reduction in H-reflex amplitude as well as M1 excitability during acute muscle pain,[21] indicating a decreased excitability of spinal, as well as cortical, motoneurones.[39] Consistent with the gradual and sustained M1 signal intensity changes reported here, both groups reported a longer duration of the M1 inhibitory effect that persisted well after the pain had ceased. In light of these earlier studies, the present findings suggest that the neural circuitry for the Pain Adaptation Model may involve not only segmental brainstem circuits but also suprabulbar regions, such as M1.

The present analysis revealed that the M1 region in which signal intensity increased during muscle pain was surrounded by a more diffuse region of signal intensity decrease. This pattern appears consistent with the idea that acute muscle pain is associated with a change in motor activity within the immediate area of pain and a more diffuse change in motor output to the areas surrounding the painful region. While it is thought that positive BOLD signal intensity changes are related to increased neuronal activation,[40,41] the meaning of a negative BOLD response remains unclear. Negative BOLD responses have been attributed to several different mechanisms, such as an increase in the cerebral metabolic rate of oxygen which exceeds arterial blood compensation,[42] a decrease in neuronal activity,[43,44] as well as a "vascular-steal" effect.[44] Although it appears that the present results may be explained by a vascular-steal effect, in which blood flow is redirected to the area of increased neuronal activation, this is unlikely, since the M1 signal increases and decreases did not follow similar temporal patterns. In addition, since previous studies[19–21] reported inhibition of M1 during acute pain, the authors believe that the negative BOLD response in the present study is a result of a decrease in neuronal activity and not as a result of other nonneuronal factors.

It is feasible that the transient increase in M1 signal intensity that occurred during orofacial muscle pain was related to facial movements, such as grimacing, or an excitatory effect on motoneurones from the hypertonic saline. However, it has previously been reported that hypertonic saline infusion into the masseter muscle of healthy subjects has no significant effect on resting electromyographic activity in the masseter, posterior temporalis, anterior digastric, or the inferior head of the lateral pterygoid muscles.[45] Also, grimacing or other facial movements were never observed during the infusion of hypertonic saline in the present study; subjects knew that they had to remain still and those subjects who managed to do so (and were included in the data set) did so without any facial movements whatsoever. Furthermore, previous studies have shown that painful injections of hypertonic saline into the masseter[10] or the tibialis anterior muscles[16] are not associated with a change in α-motoneurone excitability, as determined by

H-reflex amplitude assessments, nor do they evoke any electromyographic activity,[7] so these data argue against any direct excitatory effects of hypertonic saline on motoneurones.

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