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Central representation of hyperalgesia from myofascial trigger point

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The aim of the study was to investigate if an abnormal brain response to pain exists in patients with myofascial pain syndrome (MPS) when stimulated in a hypersensitive myofascial trigger point (MTP). Event-related functional magnetic resonance imaging was used to characterize the brain response to pain evoked from an MTP. Activation patterns from patients were compared with those evoked from an equivalent site in healthy controls with stimulus intensity matched and pain intensity matched stimuli. Compared to healthy controls at matched stimulus intensity, patients experienced significantly higher pain intensity (hyperalgesia). The corresponding brain response revealed significantly enhanced somatosensory (SI, SII, inferior parietal, mid-insula) and limbic (anterior insula) activity and suppressed right dorsal hippocampal activity in patients compared with controls. At matched pain intensity, enhanced activity was found in the same somatosensory areas but not in limbic areas. Our results show that the hyperalgesic state observed in MPS patients was associated with abnormal hyperactivity in regions processing stimulus intensity and negative affect. We speculate that suppressed hippocampal activity might reflect stress-related changes in relation to chronic pain as an effective physical and emotional stressor.

Keywords: Functional MRI; Hippocampus; Intramuscular electrostimulation; Myofascial pain; Stress

Introduction

Myofascial pain syndrome (MPS) is a highly prevalent chronic pain condition (Skootsky et al., 1989). It is characterized by regional musculoskeletal pain emanating from focal hyperalgesic contractures in the muscle termed myofascial trigger points (MTP) (Harden et al., 2000; Travell and Simons, 1983). Other signs and symptoms associated with MPS include taut muscular bands, palpable nodules, pain exacerbated by stress and referred pain patterns (Harden et al., 2000; Travell and Simons, 1983). Although still controversial, MTPs and the associated pain are thought to arise from acute or chronic muscular stress resulting in local ischemia and peripheral and central sensitization (Mense, 2004; Travell and Simons, 1983).

Little is known about the central contribution to hyperalgesia in MPS and to what extent hyperalgesia of muscular origin share the same central characteristics as for skin and viscera. Converging evidence from brain imaging studies points to a substantial supraspinal contribution to the development and maintenance of chronic pain states. Such contributions range from compromised structural integrity (Apkarian et al., 2004; Oosterman et al., 2006; Schmidt-Wilcke et al., 2006) to abnormal changes in neuronal chemistry (Grachev et al., 2000, 2002) as well as altered processing across multiple brain regions (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; Hsieh et al., 1995, 1999; Maihofner et al., 2005; Verne et al., 2003). Where experimentally induced hyperalgesia (allodynia) has been associated with enhanced sensory-discriminative and motivational-affective processing (Hess et al., 2007; Lorenz et al., 2002; Maihofner et al., 2004), clinical studies are less equivocal. This might be due to the fact that the experimental models used mostly mimicked inflammatory or neuropathic pain. In contrast, the clinical states investigated have had different etiologies with different peripheral mechanisms (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; Maihofner et al., 2005; Petrovic et al., 1999; Verne et al., 2003). Also, clinical pain is often associated with an altered psychological state that interacts with the pain experience. Mood alterations such as depression, anxiety, and catastrophizing frequently develop as sequelae to pain and can cause further exacerbation of the pain (Giesecke et al., 2005; Gracely et al., 2004; Ploghaus et al., 2001). In addition, chronic stress can induce a state of hyperalgesia (Gameiro et al., 2006b). Since MPS has been associated with abnormal stress responses (Yoshihara et al., 2005), it

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is reasonable to hypothesize the presence of altered central pain processing in patients with MPS.

The aim of the study was, by means of event-related functional magnetic resonance imaging (fMRI) and intramuscular electrostimulation (IMES), to characterize the brain responses to pain from a hypersensitive MTP. Activation patterns from patients with an MTP were compared with those evoked from an equivalent site in healthy controls with stimulus intensity matched and pain intensity matched stimuli. The same approach has been used in patients with fibromyalgia (Gracely et al., 2002). Also, discrete painful IMES has previously been shown to engage the pain network in the brain of healthy subjects (Niddam et al., 2002) and MPS patients (Niddam et al., 2007).

Patients and methods

Patients and controls

A total of 16 patients (PTS) referred from the Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, were enrolled in the study. Patients were diagnosed with myofascial pain syndrome by a clinically experienced physician. Inclusion criteria were (1) palpable band or hardened nodules in upper left trapezius muscle; (2) myofascial pain emanating from a well-localized area (MTP) in the palpable band; (3) local muscle twitches evoked by manipulation of needle electrode into MTP. None of the patients had received medication or any other treatment for the myofascial pain. 16 Healthy volunteers were enrolled in the control group (CTR). None fulfilled any of the above listed criteria. All participants gave informed consent to the experimental protocol which had been approved by the Institutional Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki.

Experimental paradigm

During functional scans, painful IMES (1-ms square wave pulse) was applied to the MTP or the equivalent area within the upper left trapezius muscle with a pair of needle electrodes (20-mm length, 0.35-mm diameter, 2-mm^2 stimulation area, tip uninsulated; Model 9013R0271, Medtronic Dantec, Denmark) separated by 1 cm. Prior to the experiment, subjects were familiarized with a combined numerical descriptor scale of pain intensity used for individual calibration of stimulus intensities (Niddam et al., 2002). Each patient received a single functional scan session (P) in which a constant stimulus current corresponding to "moderate painful" intensity was applied. Two stimulus levels were applied to controls in separate (counter balanced) sessions. The levels matched the mean stimulus intensity (CI) and subjective pain rating (CP) of the patient group. Following each scanning session, the stimuli were evaluated by an overall rating of pain intensity. In each session, 48 stimuli were delivered with temporally jittered presentation (mean interval: 9.8 s; range: 2–21 s).

Subjective pain thresholds to IMES and to pressure were registered at the MTP or the equivalent site for controls prior to functional scanning. Pain thresholds were found from 6 series of ascending stimuli with the first series being discarded.

Data acquisition

Data were acquired on a 3-T imaging system (Bruker MedSpec S300, Kalsruhe, Germany) with a quadrature head coil. Patients' heads were placed in the scanner after being immobilized with a vacuum-beam pad. Functional data were acquired with a T2*-weighted gradient-echo EPI using blood oxygenation level-dependent contrast (TR/TE/θ = 2008 ms/50 ms/90°) with the parameters: matrix, 64 × 64 × 20; field of view (FOV), 230 × 230 mm^2 with a 120-mm coverage in the slice direction (5-mm thickness plus 1-mm gap). For each slice 247 images were acquired per session. The anatomical image was acquired using a T1-weighted, 3D gradient-echo pulse sequence (modified driven equilibrium Fourier transform: TR/TE/TI = 88.1 ms/4.12 ms/650 ms) with the following parameters: matrix, 256 × 256 × 192; FOV, 230 × 230 mm^2; slice thickness, 1.5 mm.

Image processing and statistical analysis

Functional data were preprocessed and analyzed with statistical parametric mapping (SPM5 software from Welcome Department of Cognitive Neurology, London). Scans were slice time corrected, realigned and co-registered to the individual anatomical image before normalization to standard space (Ashburner et al., 1999). Scans were further re-sampled (2-mm^3 voxel), smoothed (8-mm), high-pass filtered, and corrected for temporal serial correlations (Friston et al., 2000).

For image statistics, each event was modeled using a canonical hemodynamic response function with temporal derivatives. Individual contrasts from each condition entered into a second-level random effect analyses accounting for both intrasubject and intersubject variability. Comparisons within main conditions (P, CI, CP) and between groups (P–CI, P–CP, CI–P, CP–P) were assessed by one-sample and two-sample *t*-tests, respectively. From these, statistical parametric maps were created. Since a priori knowledge existed on the brain network engaged in response to painful IMES (Niddam et al., 2002) an uncorrected voxel threshold of $P \leq 0.005$ (extend threshold = 10 voxels) was implemented for evaluation of main conditions (P, CI, CP). Comparisons between groups were first performed in pre-specified regions of interests to tests for larger activations in patients under matched stimulus intensity (P–CI). This corresponds to the hyperalgesic state in patients. Regions were selected according to a previous fibromyalgia report (Gracely et al., 2002) and encompassed somatosensory cortices, inferior parietal lobule, insula, superior temporal gyrus, anterior and posterior cingulate as well as cerebellum. Peak activations in these regions were considered significant when passing $P \leq 0.05$ after a small volume correction of their respective clusters (thresholded at $P \leq 0.005$). For whole brain comparisons between groups, maps were thresholded at $P \leq 0.05$ (corrected for entire volume). To further provide indication of effects in other brain regions trends passing an uncorrected voxel threshold of $P \leq 0.005$ (extend threshold = 10 voxels) were reported as well. Local maxima were localized and labeled on the SPM template by means of Talairach Daemon (Research Imaging Center, University of Texas) after being transformed into Talairach space (Brett et al., 2001).

Results

Behavioral results

Data from two subjects in the control group were discarded due to excessive head motion during data acquisition. Analysis was performed on the remaining data from 16 patients (PTS: 10 females/6 males) and 14 controls (CTR: 8 females/6 males). Self-report of

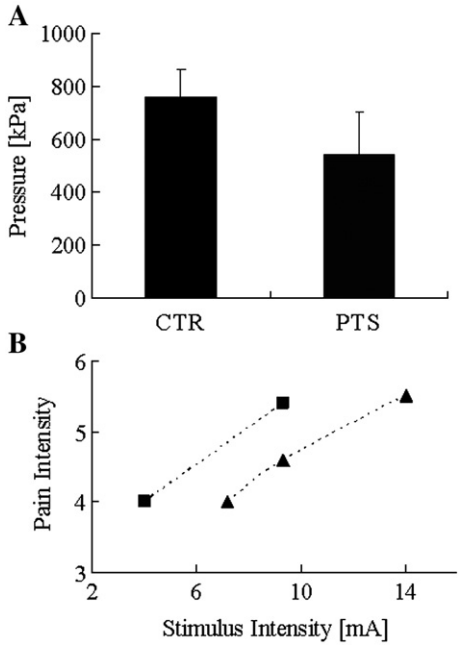

Fig. 1. Psychophysical responses. (A) Significant lower pressure pain thresholds at the MTP in patients (grey) than at an equivalent site in controls (black). (B) Stimulus–response functions for IMES at two intensities for patients (grey squares) and three intensities for controls (black triangles). Characteristic for hyperalgesia, the curve is shifted to the left for patients. That is, lower stimulus current in patients to reach pain threshold (pain intensity=4); higher pain intensity in patients at equivalent stimulus current intensity; and higher stimulus current for controls to reach equivalent pain intensity as for patients.

clinical pain emanating from the MTP corresponded to moderate pain (5.9±1.2 on scale). No significant difference was found in age of the two groups (PTS: 32.6±7.2 years [mean±SD]; CTR: 30.6±9.0 years; *t*-test: $P=0.587$). Patients displayed significant lower pain thresholds at the MTP to both IMES (PTS: 4.0±3.6 mA; CTR: 7.2±2.4 mA; one-tailed *t*-test: $P<0.001$) and pressure (PTS: 544.3±155.9 kPa; CTR: 757.9±102.6 kPa one-tailed *t*-test: $P<0.001$) compared with controls (Fig. 1). Patients received a single functional scan session with a mean stimulus intensity of 9.3±3.8 mA which evoked a moderately painful sensation (5.4±0.7 on VAS scale). At the same stimulus intensity, healthy controls experienced the stimulus as significantly less intense (VAS=4.6±0.6; one-tailed: $P=0.001$). Further on, a significantly larger stimulus current (current=14.0±0.9 mA; one-tailed: $P<0.001$) had to be applied in order to induce pain of equivalent intensity (CTR: VAS=5.5±1.0; $P=0.758$) to that of the patients (Fig. 1B).

Functional MRI results

Fig. 2 shows the pain networks engaged in the three main conditions. Table 1 lists the brain regions activated in the high stimulus intensity condition for controls (CP) as well as loci common with the other two conditions (P, CI). A substantial overlap was observed between responses in patients and those in the high-intensity condition in controls. Bilaterally these regions encompassed middle frontal gyrus, somatosensory cortices, inferior parietal lobule, anterior insula, thalamus, and caudate. Contralaterally, common activity was observed in superior temporal gyrus, anterior (Brodmann area [BA] 24) and posterior cingulate (BA 23) as well as in cerebellum. Ipsilaterally, the regions included inferior and medial frontal gyri, precentral gyrus, paracentral lobule, precuneus, anterior (BA 32) and posterior cingulate (BA 31), and mid and posterior portions of insula. The brain regions activated in the low-intensity condition in controls (CI) could be considered as a subset of those activated in the high-intensity condition (CP).

Deactivations were only found in the patient group and covered bilateral parahippocampal (right: [32, −51, −1], $P<0.001$, $Z=3.93$; left: [−32, −41, −5], $P<0.001$, $Z=4.15$) and precentral gyri (BA 6; right: [59, 0, 31], $P=0.003$, $Z=2.8$; left: [−57, 0, 30], $P<0.001$, $Z=3.08$) as well as contralateral (right) hippocampus ([28, −41, 4], $P<0.001$, $Z=3.69$) and postcentral gyrus (BA 2; [48, −26, 55], $P=0.002$, $Z=2.81$).

Based on a previous report (Gracely et al., 2002), regions of interest were a priory defined for which we hypothesized that patients would exhibit greater activity than controls. In these regions

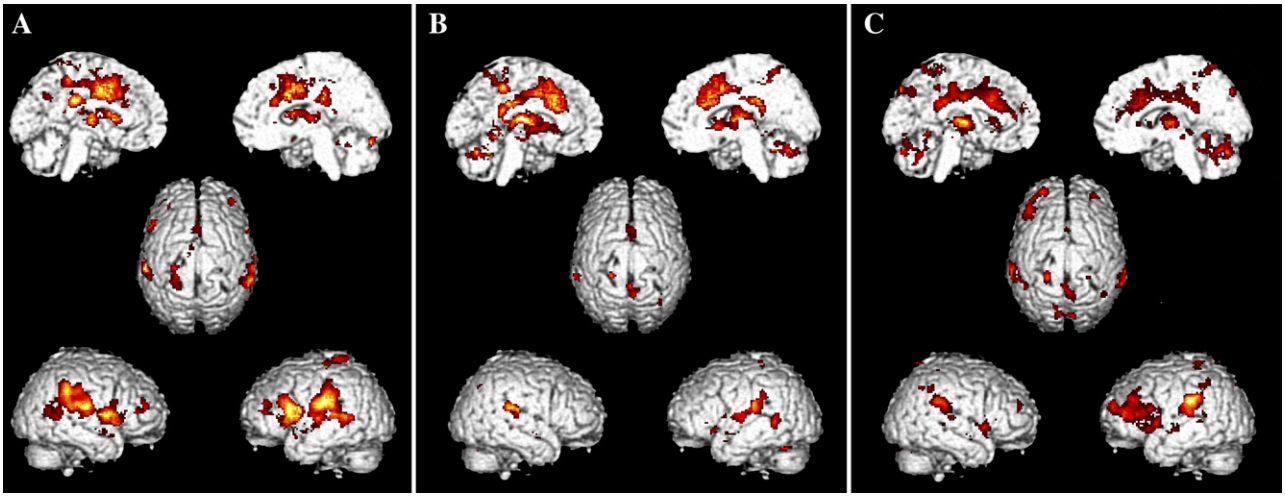

Fig. 2. Rendered views of brain responses overlaid on a standard SPM-MNI template. Responses from (A) patients at low stimulus intensity and high pain intensity, (B) controls at low stimulus intensity and low pain intensity, and (C) controls at high stimulus intensity and high pain intensity, are thresholded at $P<0.005$ (extend=10 voxels; one-sample *t*-test).

Table 1
Significant brain responses in normal controls at matched pain intensity (one-sample *t*-test thresholded at uncorrected $P<0.005$; extend = 10 voxels)

Anatomical region	Left hemisphere (ipsilateral)					Right hemisphere (contralateral)				
	BA	*x*	*y*	*z*	Zmax	BA	*x*	*y*	*z*	Zmax
Superior frontal G	–	–	–	–	–	10	24	44	20	3.81
Inferior frontal G	47	−32	17	−3	4.27[a,b]	–	–	–	–	–
Middle frontal G	10	−40	45	12	4.41[a]	10	30	50	21	3.72[a]
	46	−42	30	24	4.04[a]	–	–	–	–	–
	9	−38	27	35	3.87	–	–	–	–	–
Medial frontal G	6	0	14	47	3.46[a,b]	–	–	–	–	–
Precentral G	44	−51	2	9	3.34[a]	–	–	–	–	–
Paracentral L	5	−2	−44	59	3.91[a,b]	5	14	−35	46	3.38
Postcentral G										
(SI)	2	−22	−35	63	4.27[a,b]	3	24	−34	59	3.47[a]
(SII)	40	−53	−26	16	4.56[a,b]	40	63	−26	20	4.39[a,b]
	–	–	–	–	–	7	4	−53	67	3.82
Inferior parietal L	40	−57	−28	27	5.89[a,b]	40	63	−30	27	4.52[a]
	40	−44	−46	47	3.63	40	40	−52	41	3.77
Precuneus	7	−12	−64	38	3.95[a,b]	7	6	−78	43	4.29[b]
Superior temporal G	22	−51	13	−4	3.81[b]	22	50	2	4	3.23[a,b]
	21	−53	−16	−4	3.61	22	48	−31	5	3.75[a]
Anterior cingulate	32	−2	43	11	3.74[a]	24	4	19	23	4.07[a,b]
	24	−4	28	17	4.07	24	4	−8	30	4.94[a,b]
	32	−4	21	28	4.68[a]	–	–	–	–	–
Posterior cingulate	31	−14	−21	43	4.15[a,b]	23	2	−32	27	4.31[a,b]
Insula	Ant	−38	13	14	4.51[a,b]	Ant	44	13	−2	4.11[a]
	Mid	−34	5	13	4.36[a,b]	–	–	–	–	–
	Post	−40	−16	−1	5.25[a,b]	Post	40	−18	−1	5.52[b]
Thalamus	VAN	−6	−8	2	4.67[b]	VAN	14	−7	11	4.04
	VLN	−14	−13	4	4.34[a]	VLN	14	−13	6	4.01[a,b]
	–	–	–	–	–	MDN	6	−15	3	3.41[b]
Lentiform nucleus	MGP	−20	−12	−4	4.19[b]	Put	16	10	3	3.34[b]
Caudate	CB	−14	20	8	4.01[a,b]	CH	14	22	4	3.48[a,b]
Cerebellum	–	–	–	–	–	Culmen	18	−46	−18	4.87[a,b]
	Declive	−2	−73	−20	3.63[b]	Declive	26	−63	−20	4.56[a,b]

Note. Zmax is peak *Z* value. BA, Brodmann area; G, gyrus; L, lobule; Ant, anterior; Post, posterior; CB, caudate body; CH, caudate head; MDN, medial dorsal nucleus; MGP, medial globus pallidus; Put, putamen; VAN, ventral anterior nucleus; VLN, ventral lateral nucleus; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; coordinates (*x*, *y*, *z*) are given in Talairach space and are expressed in millimeters. [a] and [b] denote common with patient and control (CI) group, respectively.

a less strict statistical criterion was implemented (voxel threshold, $P<0.005$ and correction for cluster volume at $P<0.05$). At matched stimulus intensity, patients showed a more pronounced activity than controls in several of these pre-specified regions (Table 2). Significant differences were found in bilateral primary somatosensory cortices (SI), ipsilateral secondary somatosensory cortex (SII), and contralateral inferior parietal lobule as well as in anterior and mid portions of insula. Sub-significant trends ($P<0.005$, extend > 10 voxels) were found in bilateral inferior frontal and precentral gyri (primary motor cortex [MI]) and contralaterally in middle temporal gyrus and claustrum. At matched perceived pain intensity, all regions found to respond more in patients than controls were also found to be responding at matched stimulus intensity. Significant differences were found in the following pre-specified regions of interest: bilateral SI, ipsilateral SII and contralateral mid portion of insula. Sub-significant trends were also found in bilateral MI, but not in anterior insula and inferior frontal gyri (Table 2).

Since no a priory hypothesis was defined for regions in which patients exhibited smaller activity than controls, significance was only considered at a threshold corrected for the entire brain volume ($P<0.05$). A single region passed this threshold when comparing brain responses in patients and controls at matched stimulus intensity but different pain ratings. This region corresponded to the right dorsal hippocampus (Fig. 3). Trends common to conditions at matched stimulus intensity and matched pain intensity included contralateral angular gyrus and hippocampal formation as well as ipsilateral parahippocampal gyrus, thalamus and claustrum. To post hoc test whether the hippocampal response was related to the stimulus order for controls, e.g., more anxiety or stress in the first session than the second session, all initial sessions and last session were pooled separately despite of stimulus intensity. However, no hippocampal response was found when comparing first with second session (uncorrected $P\leq0.005$, paired *t*-test).

Discussion

By means of event-related fMRI we investigated the central representation of hyperalgesia from a myofascial trigger point in MPS patients. In order to probe both the hyperalgesic and adaptive cerebral responses, patients were compared to healthy controls at matched stimulus intensity as well as matched subjective pain intensity. Psychophysically, the present study showed that MPS patients have hyperalgesia to pain evoked by both IMES and the more commonly used pressure to an MTP. As delineated below abnormal central processing was observed in several brain regions in the patient group reflecting the muscular hyperalgesia.

Table 2
Patients (PTS) versus controls (CTR), thresholded at uncorrected $P<0.005$ (extend = voxel 10; two-sample *t*-test)

Anatomical region	Left hemisphere (ipsilateral)					Right hemisphere (contralateral)				
	BA	*x*	*y*	*z*	Zmax	BA	*x*	*y*	*z*	Zmax
PTS>CTR: matched stimulus intensity										
Inferior frontal G	44	−46	16	10	3.39	44	48	14	7	2.99
Precentral G (MI)	*4*	*−51*	*−12*	*26*	*3.17*	*4*	*53*	*−12*	*25*	*2.85*
Postcentral G										
(SI)	*2*	*−51*	*−25*	*44*	*3.31**	*2*	*53*	*−22*	*34*	*2.85**
(SII)	*43*	*−57*	*−11*	*19*	*2.99**					
Inferior parietal L						40	50	−35	39	3.23*
Middle temporal G						39	48	−67	24	3.6
Insula						Ant	38	11	−10	3.35*
						Mid	*42*	*3*	*18*	*2.57**
Claustrum							36	−5	11	2.68
PTS>CTR: matched perceived pain intensity										
Precentral G (MI)	*4*	*−50*	*−12*	*25*	*2.93*	*4*	*57*	*−13*	*27*	*2.81*
Postcentral G										
(SI)	*2*	*−53*	*−25*	*45*	*2.92**	*2*	*51*	*−24*	*33*	*3.11**
(SII)	*43*	*−57*	*−11*	*19*	*2.7**					
Insula						*Mid*	*40*	*−3*	*17*	*3.34**
PTS<CTR: matched stimulus intensity										
Angular G						*39*	*34*	*−58*	*38*	*3.05*
Hippocampal F	Hip	−28	−39	5	3.91	*Hip*	*32*	*−31*	*−3*	*4.57***
Parahippocampal G	*36*	*−22*	*−37*	*−7*	*2.93*					
Thalamus	Pul	−14	−25	10	3					
Claustrum		*−36*	*−20*	*−2*	*3.25*					
Lentiform Nucleus	LGP	−20	−10	4	2.77					
PTS<CTR: matched perceived pain intensity										
Precuneus	7	−10	−68	35	2.89	7	16	−74	35	3.08
Angular G						*39*	*36*	*−57*	*34*	*3.01*
Hippocampal F						*Hip*	*32*	*−29*	*−2*	*2.85*
Parahippocampal G	*36*	*−22*	*−37*	*−7*	*3.32*					
Thalamus	VPLN	−18	−17	5	3.44	VPLN	14	−15	6	2.88
Claustrum		*−38*	*−16*	*−3*	*3.17*					

Note. Loci in italics are activated at both matched stimulus intensity and pain intensity; *Denotes significance at $P<0.05$ corrected for cluster volume. **Denotes significance at $P<0.05$ corrected for entire brain volume. Hip, hippocampus; LGP, lateral globus pallidus; Pul, pulvinar; VPLN, ventral posterior lateral nucleus; MI, primary motor cortex. See Table 1 for further details.

Central representation of painful IMES in normal subjects

For normal controls, high-intensity painful IMES of the upper left trapezius muscle evoked activity in bilateral cortical and subcortical regions consistent with a previous study of ours using painful IMES applied to the hand (Niddam et al., 2002). The high degree of bilaterality observed in the present study can be explained by the high stimulus intensity applied (Coghill et al., 1999; Niddam et al., 2002) as well as the close to midline stimulus site. As previously observed (Niddam et al., 2002), lower intensity IMES engaged a subset of regions activated at higher stimulus intensity. Overall, painful IMES to the trapezius muscle activated brain regions most commonly activated in other pain studies (Apkarian et al., 2004; Peyron et al., 2000). These included thalamus, SI, SII, inferior parietal, anterior and posterior portions of insula and cingulate cortex as well as prefrontal cortex and cerebellum.

Enhanced activity in patients with MPS

A substantial overlap in muscle pain representations between MPS patients and normal controls was observed. However, hyperalgesia in patients was associated with enhanced activity (condition: P>CI) in somatosensory (SI, SII, mid-insula, inferior parietal) and limbic regions (anterior insula) and trends towards significance were observed in motor (MI) and associative regions (inferior frontal). At matched subjective pain intensity (condition: P>CP) enhanced activity was observed in the same somatosensory regions indicating adaptive sensory-discriminative responses to pain in patients with MPS.

Hyperactivity in somatosensory regions has previously been observed in a wide range of pain conditions such as, e.g., fibromyalgia, complex regional pain syndrome, irritable bowel syndrome and mononeuropathy as well as in experimental hyperalgesia (allodynia) using matched stimulus intensities (Gracely et al., 2002; Hess et al., 2007; Maihofner et al., 2005, 2004; Petrovic et al., 1999; Verne et al., 2003). Enhanced anterior insula and inferior frontal activity was also observed in several of these studies. Whereas activation of somatosensory areas, anterior insula and inferior frontal cortices is not unique for pain, hyperactivity in these areas suggests altered stimulus coding and increased negative affect (Price, 2000) in patients with MPS congruent with the presence of hyperalgesic MTPs in this group. This notion gains further support

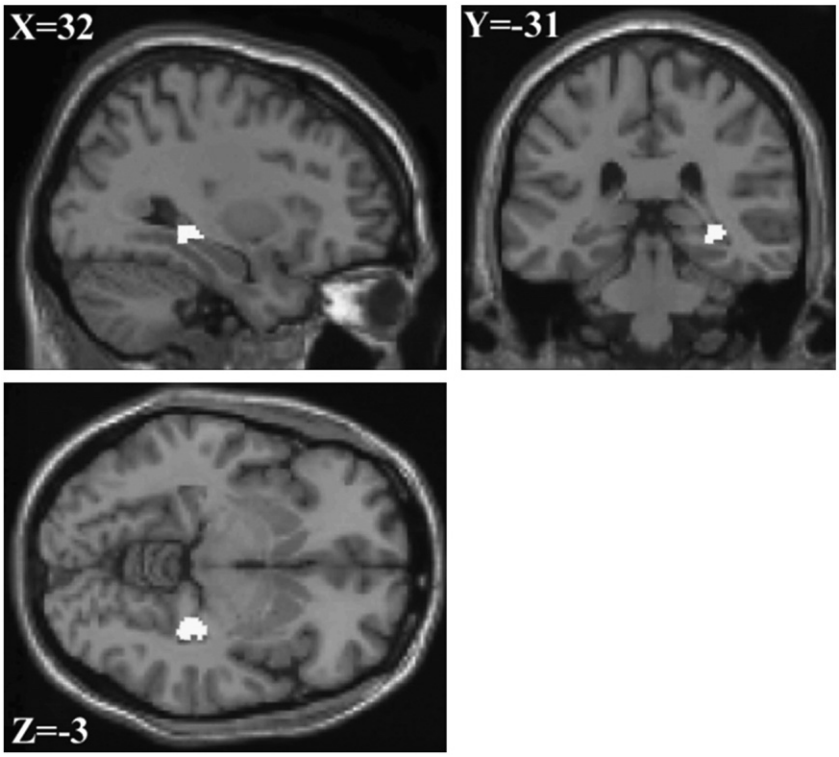

Fig. 3. Localization of activity where MPS patients have lower activity than controls at matched stimulus intensity. The only locus passing a corrected threshold ($P \leq 0.05$) was found at hippocampus. Activity is superimposed over sagittal, coronal and horizontal slices of an anatomical MRI (MNI template from SPM). Images show location of peak activity at $X=32$ mm, $Y=-31$ mm and $Z=-3$ mm. For illustrative purpose the activity is shown with lowered threshold (uncorrected height threshold, $P \leq 0.001$).

from our finding at matched pain intensity, which presumably equates the affective state, where no difference in anterior insula and inferior frontal activity was found.

It is noteworthy to mention that other studies have found enhanced activity in the medial thalamic pathway and in regions such as, e.g., posterior cingulate and medial and superior frontal cortices (Gracely et al., 2002; Hess et al., 2007; Lorenz et al., 2002; Maihofner et al., 2005; Verne et al., 2003). Indications of enhanced medial and superior frontal activities (BA 8, 9 and 10) were in fact also found in the present study at lower thresholds ($Z=2.55$). Other differences might partially be explained by the different etiologies of the pain including the sensitized tissue systems and peripheral receptors in conjunction with the stimulus modality applied. Also, different pain conditions likely induce different psychological states especially influencing the affective component of pain.

Decreased hippocampal activity in patients with MPS

Hyperalgesia in patients was also associated with a prominent hypoactivity in right (contralateral) dorsal hippocampus. A similar result has previously been found for allodynia in patients with mononeuropathy (Petrovic et al., 1999). However, the meaning of this suppressive effect is unknown. Hippocampus is a limbic structure known to process nociceptive-related information. In humans, it is possible to evoke painful sensations by direct electrical stimulation (Halgren et al., 1978) as well as pain relief by partial ablation (Gol and Faibisch, 1966). In contrast, antinociception can also be evoked by direct electrical stimulation (Prado and Roberts, 1985). This dual role in analgesia and hyperalgesia can be explained by hippocampus being an integral part of a stress-related neural circuit capable of modulating nociceptive responses under acute and chronic stress (Bodnar et al., 1980; Gameiro et al., 2006a,b).

Hippocampus, stress and MPS

MPS has been associated with both physical and emotional stress. A self-perpetuating cycle has been hypothesized to lead to the chronic state observed in MPS (Gameiro et al., 2006a). In this cycle, stress induces muscular tension which then leads to MPS symptoms such as MTPs and regional pain. However, pain is an effective physical and emotional stressor by itself leading to physical and psychological adjustments causing further stress and pain. Emotional stress such as anxiety has been found to exacerbate pain via hippocampal mechanisms (Ploghaus et al., 2001).

During acute stress the hippocampus exerts inhibitory feedback on to the amygdala and hypothalamus resulting in stress-hormone levels returning to resting state levels (Feldman and Conforti, 1980; Fendler et al., 1961; Herman and Cullinan, 1997; McQuade et al., 2006). In addition, hippocampal NMDA mechanisms could be responsible for terminating behavioral responses associated with acute stress via the mesolimbic dopaminergic system (Floresco et al., 2001; Lodge and Grace, 2006; Thierry et al., 1976). Such responses include analgesia of preferentially tonic inescapable pain (Altier and Stewart, 1999; McKenna and Melzack, 2001). Our finding of hippocampal hypoactivity in MPS patients might therefore indicate altered feedback on to the stress system. In accord with this, patients with myofascial pain exhibit exaggerated stress responses in the

hypothalamus–pituitary–adrenocortical system (Yoshihara et al., 2005).

The mechanisms by which prolonged stress induces hyperalgesia remain unknown. It has been hypothesized that a hippocampal induced disruption of mesolimbic dopaminergic transmission is involved (Wood, 2006). In support of this, reduced presynaptic hippocampal and ventral tegmental dopamine release was recently observed in patients with fibromyalgia (Wood et al., 2007). Prolonged stress is also known to affect hippocampal dendritic morphology as well as enhance dendritic atrophy rendering hippocampal functions highly susceptible to disruption by stress (Sousa and Almeida, 2002; Sousa et al., 2000). Recently, the same stress-like hippocampal alterations have been observed in response to persistent pain (Duric and McCarson, 2006). Hippocampal hypoactivity in MPS patients could thus also reflect altered functionality as a result of stress-related atrophy after prolonged pain.

Conclusions

Overall, MPS patients and normal controls showed overlapping brain representations of pain. However, at matched stimulus intensity hyperalgesia observed in patients was associated with enhanced activity in somatosensory and limbic regions suggesting altered stimulus coding and increased negative affect. Hyperalgesia was also associated with prominent suppressed hippocampal activity. Although speculative, this could reflect stress-related changes in relation to chronic pain as an effective physical and emotional stressor. Finally, together with related literature our results suggest that hyperalgesia (allodynia) with different etiologies is associated with hyperactivation of regions involved in sensory-discriminative processing. The variable expression of regions responsible for affective-motivational processing could reflect the different etiologies of the pain in conjunction with different psychological states.

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