

Virtual Pain Stimulation of Allodynia Patients Activates Cortical Representation of Pain and Emotions: A Functional MRI Study

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Summary: The present study investigated neural correlates of affect processing in allodynia patients (n=8) and healthy controls (n=12) with the aid of virtual tactile stimulation. Whole brain functional magnetic resonance imaging was performed for allodynia patients and healthy volunteers while they were shown a video demonstrating light stimulation of the palm and another stimulation aimed at producing anticipation of palm stimulation. Contrasting with controls, patients displayed activation of the cortical areas related to pain and emotions: prefrontal cortex (Brodmann's area BA 10) and anterior cingulate cortex (BA 24). These findings may indicate involvement of an emotional component of pain perception in allodynia patients.

Key words: Allodynia; fMRI; Virtual tactile stimulation; Pain; Emotions.

Introduction

Patients with neuropathic pain show various types of pain-related neurological and psychological symptoms. More than a third of patients suffering mental disorders reportedly display some form of chronic pain condition (Von Korff et al. 2005). Pain evoked by non-noxious stimulation, known as allodynia, represents a commonly observed feature in patients with chronic neuropathic pain. This type of pain represents a serious health problem, strongly impacting quality of life and influencing psychological condition in patients who experience it.

Several neurophysiological mechanisms in the spinal cord and peripheral nervous system have been proposed to explain the development of allodynic pain. Indeed, Woolf et al. (1992) reported that large myelinated A β fibers, which normally convey tactile sensations, sprout to lamina I of the dorsal horn, where the majority of pain-related C-fibers terminate. Andrew et al. (1999) reported that sensitized and hyperactivated C-fibers start responding to not only noxious signals, but also innocuous gentle tactile stimuli. In contrast, few studies have focused on the brain mechanisms of allodynic pain regardless of how such pain is recognized and experienced inside the brain.

Functional neuroimaging techniques like functional magnetic resonance imaging (fMRI) offer informative tools for detecting neurological activation in the brain in response to various tasks (Apkarian 1999). Importantly, fMRI can be used in clinical settings to assess pain conditions of clinical relevance. Although various methods for acquiring functional activation of the brain have been developed, blood oxygenation level-dependent contrast (BOLD)-fMRI is considered the principal tool for mapping studies of the human brain (Apkarian et al. 1999; Fox et al. 1988). However, no previous studies have used fMRI to examine functional anatomy in the brains of patients with allodynia in relation to the emotional aspects of pain using virtual tactile stimulation.

The present study investigated whether anticipation of painful stimulation can cause activation of cortical areas responsible for pain and emotions in allodynia pa-

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tients. Allodynia patients are known to often display guarding of the painful limb and intense aversion to touching various objects to avoid pain. We therefore hypothesized that in neuropathic pain patients with allodynia, visualization of a painful experience could provoke unpleasant emotions, and these emotions might be closely related to the maintenance of chronic pain conditions. We also wondered whether any distinctions would exist in the activation of cortical brain areas between normal subjects and allodynia patients in response to virtual tactile stimulation.

Methods

Subjects

Activation of the brain was studied in 12 normal individuals (9 male, 3 female; mean age 41.9 years) and 9 allodynia patients (8 male, 1 female; mean age 46.4 years) in response to the 2 types of virtual experiences described below. All examined patients displayed right hand allodynia resulting from right arm/hand trauma or minor cervical spine injury and were diagnosed with complex regional pain syndrome ($n=7$) or partial spinal cord injury ($n=2$). Neither volunteers nor patients had any previous history of cerebrovascular disease or head trauma. Self-diagnostic depression score (SDS) was obtained for all patients to exclude the possibility of depression. All protocols were approved by the ethics committee of Kochi Medical School. Participants were given full information on the purposes of the study and provided written consent. Prior to the functional imaging study, a plain T2-weighted MRI was performed to check for non-symptomatic brain lesions. However, no abnormal lesions were detected from any of the participants used in this study.

Experimental Design and Procedure

Virtual tactile stimulation was used to evoke experiences of tactile and/or unpleasant feelings and anticipation of such feelings in normal volunteers and neuropathic pain patients with allodynia. The design of the experiment aimed to reproduce sensations evoked by expectation of pain as close to reality as possible. At the time of fMRI, tasks were applied in a fixed block design. All participants were exposed to virtual tactile stimulation, using a digital video clip demonstrating random tactile stimulation of the palm using a horse-hair brush (Task 1) and similar serial movements of the brush without touching the palm (Task 2). Task 1 imitated painful stimulation itself, while Task 2 was supposed to produce the anticipation of this stimulation. Before and between these tasks, participants were

shown two static hands (palms) on a screen, providing the baseline stimulation (control condition). Distance between eyes and screen was 110 cm. The hand projected on screen was 18 cm wide and 24 cm high, subtending a visual angle of $12.6^\circ \times 9.4^\circ$ (figure 1). Tasks were applied randomly and the experiment lasted 336 s (see details of paradigms, figure 1). At 7-10 days after first fMRI, all volunteers underwent a second fMRI scan. Prior to the second fMRI, an actual brush was applied to the right palm of volunteers for 10 min (preconditioned volunteer study), to familiarize subjects with the feelings evoked by the shown stimulation. Prior to this experiment, subjects again underwent Tasks 1 and 2 (both tasks were shown within a single scanning session, lasting 336 s; figure 1) for 10 min, and thus could recall the type of feelings accompanied by the stimulation. Feelings evoked by tasks, such as discomfort or anxiety, were subjectively qualified using a visual analogue scale after fMRI.

Image Acquisition

Acquisition of images was performed for the entire brain using a SIGNA 1.5-T scanner (GE, Tokyo) with a BOLD T2-weighted multislice gradient EPI sequence (TE 40 ms; TR 4000 ms; flip angle 90° ; slice width 7 mm; interslice gap 1 mm; 17 slices). Subjects underwent imaging in a supine position in the standard manner with a sponge placed under the lower half of the head, which was immobilized using a vacuum splint to minimize movement artifacts. During imaging, subjects were instructed to view a video on a screen via a mirror. Noise generated by the MRI apparatus was suppressed using earplugs. Respiratory conditions and O_2 saturation were monitored during the session.

Image Analysis

Results were analyzed on a Unix workstation using SPM99 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London <http://www.fil.ion.ucl.ac.uk/spm>). Acquired images were realigned, spatially normalized using a standard EPI template and finally smoothed with an isotropic Gaussian kernel of 8 mm FWHM. Statistical significance was assessed using the delayed box-car reference convolved with a hemodynamic response function. Linear contrasts between different conditions provided the results as activated areas by creating a spatially distributed map of the t-statistic (SPM{t}). To detect neural substrates for virtual visual experience, we compared the 2 task conditions and control condition in allodynic patients and volunteers. Thresholds for activation were set at $p < 0.001$ for voxel level of activation, which was corrected for multiple comparisons at the extent threshold

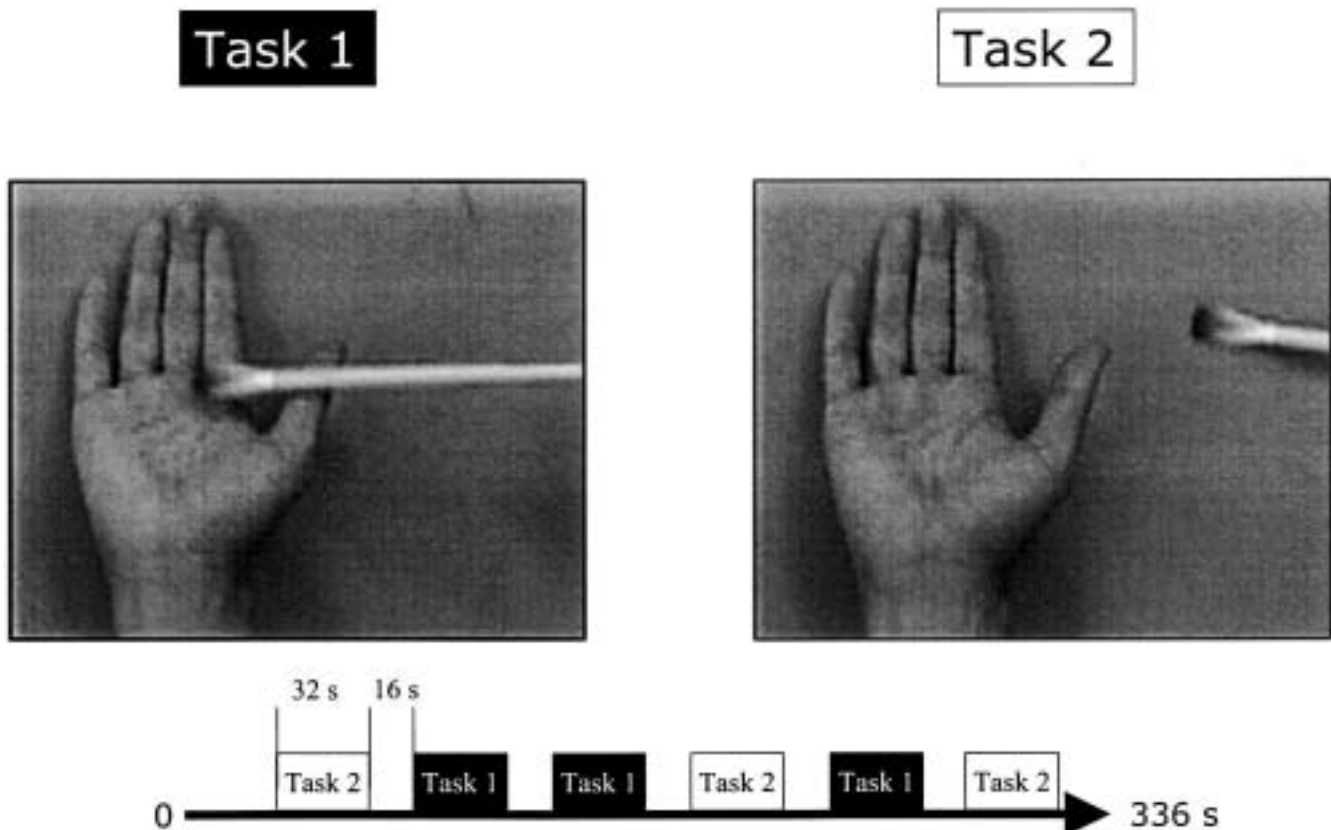


Figure 1. Experimental design. Subjects enrolled in the experiment were shown a digital video clip demonstrating random tactile stimulation of the palm using a horse hair brush (task 1) and similar serial movements of the brush without touching the palm (task 2).

of $p < 0.05$. The atlas of Talairach and Tournoux was used to anatomically localize foci of significant activation (Talairach 1988).

Results

Evaluations of Task-Related Pain and Discomforts

Neither patients nor volunteers reported actual painful feelings (mean visual analog scale (VAS) score, 2.9; range, 0-5.5; table I). However, 8 of the 9 patients described discomfort and irritation. While 8 patients completed the study, 1 patient experienced severe discomfort during scanning and abandoned the study. Discomfort in this patient lasted 2 days and impacted on activities of daily life (ADL) despite normal findings for ADL and psychological status on pre-fMRI evaluation. No volunteers reported any discomfort during both non-preconditioned and preconditioned studies, but 6 of the 12 volunteers reported unusual emotional experiences during the preconditioned study. In contrast, no

non-preconditioning controls reported any emotional experiences (table I).

O_2 saturation and heart rate remained unchanged during fMRI in all subjects.

fMRI Results

Group Analysis (Table II)

In allodynia patients, the superior frontal gyrus (Brodmann's area (BA) 10) and anterior cingulate cortex (ACC; BA 24) were more activated under Task 1 conditions than under Task 2 conditions (figure 2). In contrast, no areas were more significantly activated under Task 2 compared to Task 1 (figure 2). Compared with the control condition, both Task 1 and Task 2 activated BA 3.

In response to Task 1, controls in the preconditioning subgroup displayed activation of BA 39 and the parietal angular gyrus (figure 3). No significant activation was detected in Task 2 (figure 3). Controls in the non-preconditioning subgroup displayed no significant activation in response to Tasks 1 and 2.

Table I. Allodynic pain cases.

Age	Sex	Diagnosis	Pain Symptom	Pain Intensity (VAS)			
				Disease duration (months)	Spontaneous Pain	Allodynic pain by real stim	Discomfort evoked by visual task (VAS)
35	M	CRPS	Right hand allodynia, hand contracture, finger motion pain	11	2.5	4.5	1.5
64	M	CRPS	Right hand allodynia, hand contracture	26	5	7.5	4
55	M	CRPS	Right elbow-hand allodynia, hand contracture	23	4	7	3.5
25	M	CRPS	Right hand allodynia, hand contracture, finger motion pain	14	6	8	4
55	M	Partial spinal cord injury	Both hand allodynia	24	3.5	5.5	0
44	M	CRPS	Right hand allodynia, wrist and finger contracture	15	2.5	6.5	5.5
48	F	Partial spinal cord injury	Both hand allodynia, finger contracture	12	4.5	8	2
45	M	CRPS	Right hand allodynia, hand contracture, finger motion pain	9	4	7	2.5
40 (could not complete study)	M	CRPS	Right hand allodynia, hand contracture, finger motion pain	35	4.5	6	8

Table II. Talairach coordinates and Brodmann's areas for regions of significant activation ($p < 0.05$ at voxel level, corrected for multiple comparisons) in response to virtual visual stimulation (tasks 1 and 2) in allodynia patients and normal volunteers with and without preconditioning.

	Task Type	Activated Cortical Areas
Patients	Task 1	BA10 (-6, 66, -4): Prefrontal cortex (T=6.15) BA24 (4, 14, 26): Anterior cingulate cortex (T=4.93)
	Task 2	No significant activation
Volunteers (non-preconditioned)	Task 1	No significant activation
	Task 2	No significant activation
Volunteers (preconditioned)	Task 1	BA39 (-48, 68, 32): Parietal angular gyrus (T=4.96)
	Task 2	No significant activation

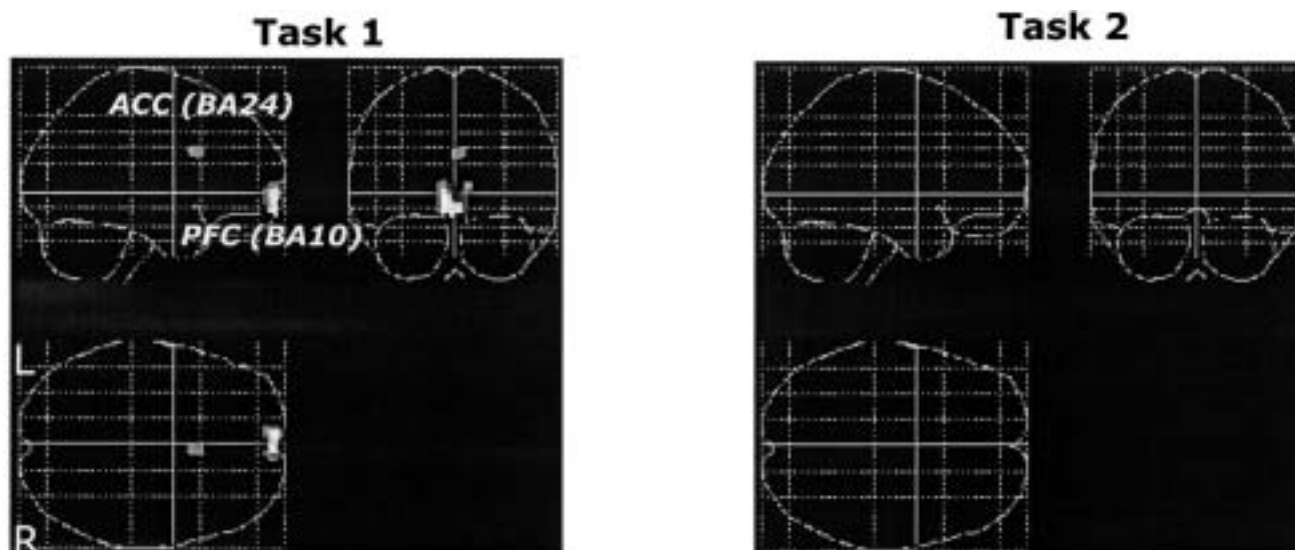


Figure 2. Areas of cortical activation in allodynia patients in response to the 2 tasks of virtual visual stimulation detected by fMRI. Patients showed activation of ACC (BA24), and prefrontal cortex (BA10) in response to task 1 (left). In contrast, no significant activation was detected in response to task 2 (right). Statistical threshold was voxel level $p < 0.05$ corrected for multiple comparisons.

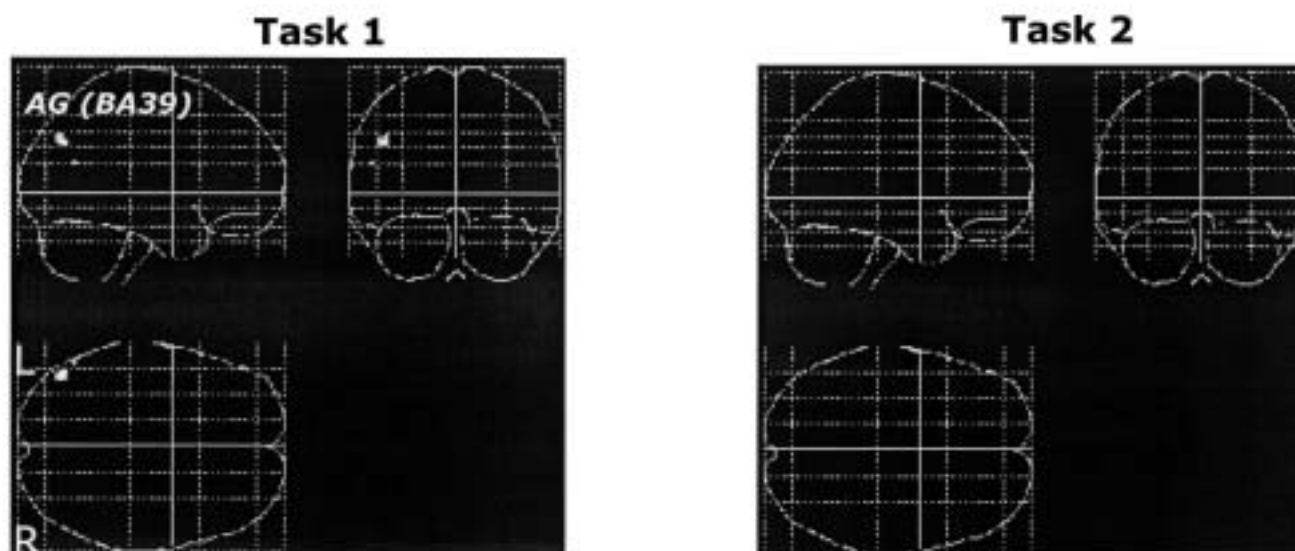


Figure 3. Areas of cortical activation in preconditioned normal volunteers in response to the 2 tasks of virtual visual stimulation detected by fMRI. Volunteers showed activation of left parietal angular gyrus (AG: BA39) in response to task 1 (left). In contrast, no significant activation was detected in response to task 2 (right). Statistical threshold was voxel level $p < 0.05$ corrected for multiple comparisons.

Table III. Talairach coordinates and Brodmann's areas for regions of significant activation ($p < 0.0001$, T score > 4.0 , uncorrected threshold) in response to virtual visual stimulation (Tasks 1 and 2) in allodynia patients.

		Task Type	Activated Cortical Areas
Case 1	25y M	Task 1	BA10 (-26, 52, 2): Prefrontal cortex (T=5.24) BA47 (-40, 24, -18): Inferior-frontal cortex (T=4.74) BA24 (4, 12, 32): Anterior cingulate cortex (T=4.21) (-14, -14, 18): Caudate (T=5.73)
		Task 2	No significant activation
Case 2	64y M	Task 1	BA10 (-30, 62, -10): Prefrontal cortex (T=5.42) BA11 (-44, 38, -12): Middle-frontal cortex (T=4.93) (12, -2, -2): Lentiform Nucleus (T=4.25)
		Task 2	No significant activation

A direct comparison between the patient group and the preconditioned group showed activities in ACC, insula and prefrontal cortex respectively.

Case Analysis (Table III)

Case 1: A 25-year-old man experienced injury to the right hand in an accident involving a compressing machine in September 2002. The right middle finger was amputated at the distal phalanx and radiological examination revealed index, middle and ring finger fractures. The patient subsequently developed allodynia and spontaneous, unendurable pain in the injured hand, particularly in the index and middle finger (VAS: 8). Feelings of discomfort were reported during both fMRI scans (VAS: 4).

First-level individual fMRI analysis revealed activation of the left prefrontal cortex, left inferior frontal cortex, right ACC and caudate nucleus during Task 1. In contrast, no significant activation was detected during Task 2 (figure 4, left).

Case 2: A 64-year-old man with existing asymptomatic cervical ossification of the posterior longitudinal ligament (OPLL) accidentally fell down a stairwell and sustained injury to the cervical spinal cord. The patient subsequently developed allodynic pain and minor sensory deficit on both palms without major motor paresis (VAS: 7.5). Feelings of discomfort were reported during fMRI (VAS: 4).

First-level individual fMRI analysis revealed activation of the left prefrontal cortex, left middle frontal cortex and right lentiform nucleus during Task 1. In contrast, no

significant activation was detected during Task 2 (figure 4, right).

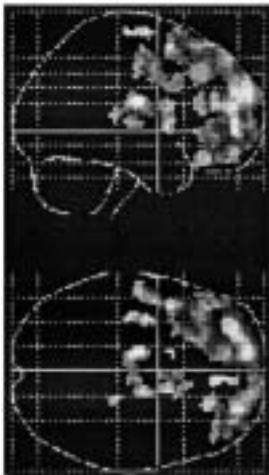
Discussion

Our results demonstrate that fMRI can be used to identify regions of the brain activated by unique visual stimulation in both normal volunteers and patients with allodynia. In contrast to normal volunteers, virtual tactile stimulation of allodynia patients caused activation of the ACC and prefrontal cortex.

Recent neuroimaging studies in humans have documented real-pain-related activation in limbic sites such as the ACC and rostral insula, and in the primary sensory regions SI and SII (Talbot et al. 1991; Rainville et al. 1997; Ringler et al. 2003). In our previous study of allodynia patients, real painful stimulation to the allodynic site also produces activation in the ACC, SI, SII and supplementary motor area (Ikemoto et al. 2003). A similar finding was reported by pin-prick stimulation of mechanical hyperalgesia areas in patients with complex regional pain syndrome (Maihofner et al. 2005). The present findings support observations that real-pain-related activation of the ACC is determined by the specific emotional and behavioral reactions of allodynia patients to pain (Bushnell et al. 1984). This area has been classified as part of the limbic system of the brain, which is thought to control emotions and affective responses to pain (Maclean 1955; Vogt et al. 1979). Resection of the ACC has been found to reduce distress associated with chronic intractable

Case 1: 25-y.o. M

Task 1



Task 2



Case 2: 64-y.o. M

Task 1



Task 2



Figure 4. Areas of cortical activation in individual allodynia patients in response to the 2 tasks of virtual visual stimulation detected by fMRI. Case 1 showed activation of left prefrontal cortex (BA10), left inferior-frontal cortex (BA47), right anterior cingulate cortex (BA24) and left caudate in response to task 1 (left). Case 2 showed activation of left prefrontal cortex (BA10), left middle frontal cortex (BA11) and right lentiform nucleus in response to task 1 (right). Statistical threshold was $p < 0.0001$ (uncorrected) for voxel level activation.

ble pain (Foltz and White 1962; Hurt and Ballantine 1974). Neurosurgeons have resected this area (usually bilaterally) in cases of intractable pain with a strong emotional component, finding that patients subsequently complain less about pain, although still acknowledging its existence (Talbot et al. 1991). This also supports our findings that emotional arousal or anxiety are among factors activating the ACC in allodynia patients.

Our finding of the activation of prefrontal cortex (BA 10) in allodynia patients in response to virtual visual stimulation supports other clinical and imaging reports demonstrating the involvement of various cerebral prefrontal areas in processing of pain (Grachev and Apkarian 2000). This has received further confirmation in animal experiments showing the involvement of these areas in the modulation of neuropathic manifestations in awake rats (Baliki et al. 2003). In addition, surgical lesions of the orbital cortex in patients have been shown to provide relief from chronic pain (Grantham and Spurling 1953). Furthermore, normal subjects with high anxiety reportedly display increased concentrations of chemicals (inositol complex, N-acetylaspartate, GABA, etc.) in the orbital frontal cortex than subjects with lower anxiety (Grachev and Apkarian 2000; Grachev et al. 2000).

Despite these previous reports describing the neurophysiological involvement of the ACC and prefrontal cortex, the role of these regions in pain modulation remains unclear. Valet et al. (2004) reported distraction during the pain experience significantly increases activation of the cingulo-frontal cortex, including the orbitofrontal region, ACC and periaquaeductal gray (PAG). Those results suggest that the cingulo-frontal cortex may exert top-down influence on PAG and posterior thalamus to gate pain modulation. However, pain relief following creation of a surgical lesion in the ACC or orbital cortex appears inconsistent with Valet's findings and further research is needed to improve our understanding of cortical pain mechanisms.

In response to Task 1, activation of BA 39 (angular gyrus) was observed in preconditioned controls. Similar observation has been the result of a direct comparison between preconditioned vs non-preconditioned study. Angular gyrus is known as a multimodality area and is known to be involved in spatial attention and writing/reading abilities (Chambers et al. 2004; Milne et al. 2002). In other studies, activation of angular gyrus has been observed when the task requires connecting different types of sensory modalities (Calvert et al. 1997;

Capek et al. 2004). Similar findings were also observed in functional tasks which require visual-tactile cross-modal information integrations (Saito et al. 2003). Therefore, the activation of angular gyrus observed in our study may be related to visual-tactile cross-modal integrations and possibly affect unusual emotional feelings.

In conclusion, the present results suggest interactions between brain cortical structures responsible for pain and emotions in allodynia patients. The model of virtual pain stimulation described herein may offer a useful tool for evaluating the efficacy of pharmacological or psychological interventions directed specifically at minimizing either responses to pain or its anticipation in patients with allodynia.

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