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Differential brain activity in subjects with painful trigeminal neuropathy and painful temporomandibular disorder

Andrew M. Youssef [a], Sylvia M. Gustin [a], Paul G. Nash [a], Jenna M. Reeves [a], Esben T. Petersen [b], Chris C. Peck [c], Greg M. Murray [c], Luke A. Henderson [a,*]

[a] Department of Anatomy and Histology, University of Sydney, Sydney, NSW 2006, Australia
[b] Departments of Radiology and Radiotherapy, University Medical Center Utrecht, The Netherlands
[c] Jaw Function and Orofacial Pain Research Unit, Faculty of Dentistry, University of Sydney, Westmead Hospital, Westmead, NSW 2006, Australia

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ABSTRACT

Human brain imaging investigations have revealed that acute pain is associated with coactivation of numerous brain regions, including the thalamus, somatosensory, insular, and cingulate cortices. Surprisingly, a similar set of brain structures is not activated in all chronic pain conditions, particularly chronic neuropathic pain, which is associated with almost exclusively decreased thalamic activity. These inconsistencies may reflect technical issues or fundamental differences in the processing of acute compared with chronic pain. The appreciation of any differences is important because better treatment development will depend on understanding the underlying mechanisms of different forms of pain. In this investigation, we used quantitative arterial spin labeling to compare and contrast regional cerebral blood flow (CBF) patterns in individuals with chronic neuropathic orofacial pain (painful trigeminal neuropathy) and chronic nonneuropathic orofacial pain (painful temporomandibular disorder). Neuropathic pain was associated with CBF decreases in a number of regions, including the thalamus and primary somatosensory and cerebellar cortices. In contrast, chronic nonneuropathic pain was associated with significant CBF increases in regions commonly associated with higher-order cognitive and emotional functions, such as the anterior cingulate and dorsolateral prefrontal cortices and the precuneus. Furthermore, in subjects with nonneuropathic pain, blood flow increased in motor-related regions as well as within the spinal trigeminal nucleus.

1. Introduction

Over the past decade, many human functional magnetic resonance imaging (fMRI) investigations have explored brain activation during acute noxious stimuli. These investigations have led to the concept that the perception of acute pain results from coactivation of multiple brain regions, including the thalamus, somatosensory, insular, cingulate and prefrontal cortices [10,16,53]. In the orofacial system, a number of investigations report discrete activations within the spinal trigeminal nucleus and even within the trigeminal ganglion during acute thermal noxious stimuli [3,6,22,36,53]. Despite this consistent pattern of brain activation during acute pain, some evidence suggests that a similar pattern does not consistently occur in individuals with chronic pain. For example, positron emission tomography (PET) investigations have found that chronic neuropathic pain is not associated with increased blood flow in these brain regions [18,20] but instead is associated with almost exclusively decreased thalamic blood flow [18,20,31]. Moreover, single-photon emission tomography (SPECT) studies have revealed that fibromyalgia is associated with blood flow decreases in the thalamus, caudate, and pontine tegmentum [25,33]. In contrast, individuals with painful osteoarthritis and chronic low back pain display increased blood flow in a number of brain areas also activated by acute pain [23,52].

This inconsistent brain activation pattern is surprising given that, as with acute pain, individuals with chronic pain can localize and describe the intensity and sensory qualities of their pain. If, for example, the somatosensory cortices codes intensity, location, and sensory qualities of pain, one would expect increases in activity within these regions in both acute and chronic pain conditions. However, PET investigations in chronic pain patients report mixed results in somatosensory activity, reporting an increase, decrease,

* Corresponding author. Tel.: +61 2 9351 7063; fax: +61 2 9351 6556.
E-mail address: lukeh@anatomy.usyd.edu.au (L.A. Henderson).

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or no change in blood flow [19,23,54]. It is possible that the reported inconsistencies in cerebral blood flow (CBF) patterns in chronic pain conditions result from technical issues such as the relatively poor spatial resolution and insensitivity of brain imaging techniques such as PET and SPECT compared with techniques such as fMRI. Alternatively, it could be that different chronic pain conditions are in fact represented by activity changes in different brain regions. To overcome some of the potential technical issues, a recently developed magnetic resonance imaging (MRI) technique, quantitative arterial spin labeling (qASL), allows for the quantitative measurement of ongoing CBF with more accurate signal source localization and spatial resolution [39].

The aim of this investigation was to use qASL to compare and contrast regional CBF patterns in 2 different chronic pain conditions. We aimed to investigate regional CBF in individuals with chronic neuropathic orofacial pain (painful trigeminal neuropathy; PTN) and in individuals with chronic nonneuropathic orofacial pain (painful temporomandibular disorder; TMD). We hypothesized that TMD, a condition thought to result from primarily nociceptive activation [28,41,43], would be associated with CBF increases in brain structures that are also activated during acute muscle pain, whereas PTN, a neuropathic pain condition, would be associated with primarily decreased thalamic blood flow.

2. Methods

2.1. Subjects

Eighteen subjects with PTN (14 women; mean ± SEM age 50.4 ± 2.1 years; range, 34–67 years), 15 subjects with painful TMD (12 women; mean ± SEM age 44.9 ± 3.1 years; range, 25–67 years) and 54 pain-free control subjects (41 women; mean ± SEM age 46.9 ± 2.1 years; range, 20–80 years) were recruited for the study. There was no significant difference in age (2-sample t test; $P > .05$) or gender composition (chi-square test, $P > .05$) between the subject groups. All chronic orofacial pain subjects were recruited by the Faculty of Dentistry, Westmead Hospital, University of Sydney, Australia. PTN subjects were diagnosed using the Liverpool criteria [37], and TMD subjects were diagnosed in accordance with the research diagnostic criteria for TMD [9]. During the 7 days before the MRI session, each PTN and TMD subject reported 3 times a day, with a vertical pen stroke, their pain intensity on a 10-cm horizontal visual analogue scale, with 0 cm indicating no pain and 10 cm indicating the worst pain imaginable. These pain intensity scores were averaged to create a mean diary pain intensity score. On the day of the MRI scanning session, patients rated their pain using the same intensity scale (“scan pain”), illustrated the distribution of their ongoing pain, and completed the McGill Pain Questionnaire [29]. All procedures were approved by the Institutional Human Research Ethics Committees of Westmead Hospital and the University of Sydney. Written consent was obtained from all subjects in accordance to the Declaration of Helsinki, with all subjects informed that they may withdraw at any time. A subset of subjects used in this study was also used in previous investigations [13,14,17].

2.2. MRI acquisition

All subjects lay supine on a 3 T MRI scanner (Philips, Achieva) bed, with their head fixed in a tight-fitting head coil. A 3-dimensional qASL series encompassing the entire brain was collected using a gradient echo, quantitative STAR-labeled (Quasar) sequence (TR/TE/DTI/TI1, 400/23/300/40 ms; 84 reps; 64 × 64 matrix; 14 slices; FOV, 240 × 240; flip angle, 35/11.7°; SENSE, 2.5; Venc, [∞,4 cm/s]; 82 (48 @ Venc = 4 cm/s, 24 @ Venc = ∞, 10 low flip angle, all implemented in 2 separate sequences, raw voxel size, 3.75 × 3.75 × 10 mm) [39]. In addition, a T1-weighted anatomical image set was collected (echo time, 2.5 ms; repetition time, 5600 ms; 256 × 256 matrix; 14 slices; flip angle, 8°; FOV, 240 × 240) at the same slice locations as the qASL images. The total acquisition time was 15 min, during which subjects were instructed to keep their eyes closed to standardize visual processing.

2.3. MRI analysis

CBF and grey–white matter images were extracted using custom software [39] and then processed by SPM8 [11]. The T1-weighted image sets were coregistered to the resliced (voxel size, 2 × 2 × 2 mm) grey–white images and then spatially normalized to the Montreal Neurological Institute template. These normalization parameters were then applied to the CBF maps, and the resulting spatially normalized CBF maps were then spatially smoothed using a 6-mm full-width-at-half maximum (FWHM) Gaussian filter. For PTN subjects with unilateral right-sided pain ($n = 3$), TMD patients with unilateral right-sided pain ($n = 3$), and bilateral right-dominant pain ($n = 2$), the smoothed images were reflected across the midline so that each individual’s brain represented pain on the same (left) side of the face.

In 12 of the 18 PTN, 10 of the 15 TMD, and 24 of the 54 controls (PTN: 9 women, mean ± SEM age 52.5 ± 2.1 years; TMD: 9 women, mean ± SEM age 44.7 ± 4.8 years; controls: 21 women, mean ± SEM age 42.5 ± 3.5 years; no significant difference in age or gender), CBF maps also encompassed the entire brain stem caudally to the spinomedullary junction. In these individuals, the T1-weighted image set was isolated, spatially normalized, and resliced (voxel size, 2 × 2 × 2 mm) using a spatially unbiased brain stem template within the SUIT toolbox [7]. The normalization parameters were applied to the grey–white and CBF maps, and the resulting spatially normalized CBF maps were smoothed using a 3-mm FWHM Gaussian filter. These smoothed images were then reflected as described above so that each individual’s brain represented pain on the left side. Global CBF values were then calculated for each subject and significant differences between groups determined ($P < .05$, 2-sample t test).

For both whole-brain and brain stem analyses, significant differences in blood flow between both TMD and PTN subjects and controls were determined by 2-sample t tests (random effects, $P < .05$ false discovery rate corrected for multiple comparisons, age and gender as nuisance variables). Because no significant differences occurred in PTN subjects at this stringent threshold, a lower threshold was used (uncorrected $P < .001$; minimum cluster size 10 voxels, age and gender as nuisance variables) followed by multiple comparison correction at the cluster level ($P < .05$ false discovery rate corrected for multiple comparisons). For each comparison, global CBF effects were factored out by modeling them as nuisance variables. Significant clusters were overlaid onto an individual’s T1-weighted image (for whole-brain analysis) or SUIT template (for brain stem analysis). For each cluster, absolute blood flow values were extracted from all 3 groups and for those CBF values not compared during the voxel-by-voxel analysis, significant differences were determined using 2-sample t tests ($P < .05$). In addition, significant correlations between CBF and pain intensity and duration were determined ($P < .05$, Bonferroni corrected for multiple comparisons).

3. Results

3.1. Psychophysics

Individual PTN and TMD subject characteristics, pain duration, and pain intensity are shown in Table 1. The mean diary pain, scan