

# Multiple faces of pain: effects of chronic pain on the brain regulation of facial expression

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## Abstract

Pain behaviors are shaped by social demands and learning processes, and chronic pain has been previously suggested to affect their meaning. In this study, we combined functional magnetic resonance imaging with in-scanner video recording during thermal pain stimulations and use multilevel mediation analyses to study the brain mediators of pain facial expressions and the perception of pain intensity (self-reports) in healthy individuals and patients with chronic back pain (CBP). Behavioral data showed that the relation between pain expression and pain report was disrupted in CBP. In both patients with CBP and healthy controls, brain activity varying on a trial-by-trial basis with pain facial expressions was mainly located in the primary motor cortex and completely dissociated from the pattern of brain activity varying with pain intensity ratings. Stronger activity was observed in CBP specifically during pain facial expressions in several nonmotor brain regions such as the medial prefrontal cortex, the precuneus, and the medial temporal lobe. In sharp contrast, no moderating effect of chronic pain was observed on brain activity associated with pain intensity ratings. Our results demonstrate that pain facial expressions and pain intensity ratings reflect different aspects of pain processing and support psychosocial models of pain suggesting that distinctive mechanisms are involved in the regulation of pain behaviors in chronic pain.

**Keywords:** Chronic pain, Facial expression, fMRI, Frontal cortex, Pain behaviors

## 1. Introduction

Pain is an unpleasant sensory experience that motivates protective and communicative behavioral responses. Seminal neuroimaging studies have identified regional brain responses that code the intensity of the stimulus<sup>31</sup> and the amount of pain reported,<sup>10</sup> and more recent studies have indicated neurological patterns that can quantitatively predict reported pain intensity.<sup>35</sup> Others have examined how nociception translates into motivation,<sup>6,8</sup> how the pain system contributes to making predictions about upcoming aversive events,<sup>25,28</sup> and how these systems predispose the transition from subacute to chronic pain.<sup>7</sup> These studies have provided an integrative neurophysiological view of the pain system, but they have neglected the diversity of pain

manifestations in healthy individuals and, perhaps more importantly, in patients with chronic pain.

Pain facial expressions have traditionally been considered as a means for understanding affective states<sup>24</sup> and pain communication.<sup>38</sup> Spontaneous facial expressions are generally considered automatic and involuntary, and their distinctive role seems to be communicative, suggesting that their primary function may be social in nature. In contrast, pain ratings are generally used as a proxy for pain perception and involve controlled cognitive processes underlying cross-modality matching and voluntary report.<sup>21,29,32</sup>

The relationships between facial expression and reported pain intensity are at best moderate in healthy individuals undergoing acute pain tests and are generally weaker in patients with chronic pain.<sup>19</sup> The neural systems underlying pain perception and nonverbal facial expression may therefore be largely dissociable. The extent to which these patterns of activation can be dissociated remains largely unknown. Even less is known about the effects of pain chronicity on the neural processes underlying the generation of facial expressions of pain. The known dissociation between pain ratings and facial expressions observed in patients with chronic pain has been hypothesized to reflect the social reinforcement of pain behaviors, where associative learning of sociocontextual factors would gradually place the generation of facial expressions under the control of reward and sociocognitive systems.<sup>13,18,30</sup> Brain activity generating pain facial expressions might therefore reflect changes associated with patients with chronic pain spontaneously expressing their pain to obtain social support. In this study, we combined functional magnetic resonance imaging (fMRI) with in-scanner video recordings of spontaneous facial expressions of pain elicited by individually calibrated heat pain delivered to the leg. Pain expression intensity was quantified with the Facial

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Action Coding System (FACS), and pain ratings were obtained with a visual analogue scale (VAS) after each trial. We then identified brain activity varying with facial expressiveness and pain reports on a trial-by-trial basis using multilevel mediation analyses.<sup>5,37</sup> Whole-brain multilevel mediation analysis is a linear approach applied in this study to relate the brain responses elicited by thermal painful stimuli with facial expressions and pain ratings within a single model. The principal advantage of the mediation analysis is that the model considers several regressions permitting the dissociation of brain responses more strongly associated with pain perception or facial expressions and testing the possible mediating effect of facial expressions on pain reports. This further allowed identifying the moderating effects of chronic pain on these neural systems. Although the neural basis of pain facial expressions has been examined in one previous study (Kunz et al., 2011), the neural systems governing pain expression in chronic pain are, to our knowledge, studied here for the first time.

## 2. Materials and methods

### 2.1. Participants

Twenty-one patients with chronic back pain (CBP) {11 women; age (range [mean]): 23–49 (36) years} and twenty-one healthy control participants {10 women; age (range [mean]): 21–53 (36) years} participated in this study. Patients experiencing symptoms of back pain for more than 6 months (mean duration of 11 years; SD 10 years) were recruited through local pain treatment centers and newspaper advertisements in Montreal and invited to participate in the study after a medical evaluation. Healthy controls were matched with patients with CBP based on age and sex. Participants displaying facial expressions in response to painful thermal stimulations in less than 25% of the trials were rejected from the analyses because mediation analyses depended on the variability between trials within each participant. Of the 42 participants, 5 healthy individuals and 6 patients with CBP were rejected for showing little or no facial expression, and 1 patient with CBP was rejected because of large instantaneous head movements (more than 3 mm). The final sample consisted of 14 patients with CBP (7 women; age [mean  $\pm$  SD]: 36  $\pm$  10.90 years) and 16 matched controls (7 women; age [mean  $\pm$  SD]: 36  $\pm$  10.94 years) for examining the relationship between brain activity, pain ratings, and facial expression.

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of our institution (“Comité mixte d’éthique de la recherche du Regroupement Neuroimagerie Québec; CMER-RNQ”). All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice, and they received compensation for their travel expenses, time, and commitment.

### 2.2. Experimental pain procedure and material

The brain imaging session consisted of two runs of phasic thermal pain applied to the lower leg of the participants. Each functional scan consisted of eight noxious and eight innocuous (control) thermal stimulations. Thermal stimulations were administered with a computer-controlled thermal stimulator using a magnetic resonance imaging (MRI)-compatible 3  $\times$  3 cm<sup>2</sup> contact probe (Medoc TSA-II; Medoc). Baseline

temperature between successive stimuli was set at 38°C. Before the fMRI experimentation, pain sensitivity was assessed in each participant by a magnitude estimations procedure to determine the pain-eliciting temperature for each person ( $\leq 50.5^\circ\text{C}$ ; aiming at 75/100 on the pain scale). Using an individualized temperature generated comparable moderate to high-perceived pain intensities (self-report) across all participants. All thermal pain stimuli were administered at the same individually adjusted temperature across all pain trials (ie, within-subject). The control stimuli were also adjusted individually to produce a clearly perceptible but nonpainful warm sensation. During scanning, the rate of temperature increase from baseline (38°C) was adjusted on an individual basis to reach the target temperature in 2 s, and the following plateau lasted 5 s before temperature returned to baseline in 2 s. The order of the conditions was pseudorandomized to introduce some uncertainty regarding the intensity of the upcoming stimulus.

At the beginning of each trial, a fixation cross appeared for 3, 4, or 5 seconds before the noxious or innocuous stimulation, which was then followed by a long interval (18–25 s) to prevent sensitization and allow the participants to rate their pain. Each thermal sensation was evaluated with a VAS displayed on a screen using E-Prime (Psychology Software Tools Inc.; <http://www.pstnet.com>) and viewed through a mirror. After each stimulus, the participant indicated whether the thermal stimulus was warm or painfully hot with the right hand by using the index and middle finger keys of an MRI-compatible response box. The participant rated successively the intensity and the unpleasantness of the painful experience on two separate computerized VAS scales ranging from “no pain” or “not unpleasant” at 0 (left extremity) and “extreme pain” or “extremely unpleasant” at 100 (right extremity); the nonpainful VAS ranged from “0—no sensation” (left) to “100—very warm” (right). The scales were displayed for 12 seconds in the painful stimulations and for 18 seconds in the nonpainful conditions. The participant rated the pain level using the index and middle finger keys of the MRI-compatible response box.

### 2.3. Facial expression of pain

The facial expressions were videotaped using a small MRI-compatible camera (MRC Systems) that was mounted onto the headcoil to capture the face of the subject. Participants were told about the video recording in the information and consent form they signed before the scanning session. However, they were not informed that we were generally interested in the multiple responses evoked by pain, and facial expression was not discussed explicitly as a specific variable of interest in this study. The camera was positioned in a way that it was not in the center of the visual field of the subject. The onset of each thermal stimulus was automatically marked on the video recording using a signal sent from the stimulator to the sound card to identify the occurrence of facial expressions during the stimuli. The facial responses were quantified using the FACS.<sup>12</sup> The frequency and the intensity (5-point scale) of the different action units (AUs) were identified by two trained FACS-coders. Time segments of 9 s beginning at the onset of each stimulus were selected for scoring. Pain-relevant AUs were selected based on previous studies.<sup>17</sup> The mean AU frequency and mean AU intensity values of the selected AUs were combined (product terms) to form a composite score of pain-relevant facial responses. Importantly, we have previously reported that facial expression recorded in an MRI scanner does not

influence the spontaneous facial expressiveness of the participants.<sup>17</sup> The FACS composite scores were then used as an index of pain expression for each painful trial.

## 2.4. Behavioral analyses

Groups were first compared on pain intensity and FACS responses to the noxious heat stimuli using t-tests. Multilevel modeling was then used to determine the moderating effect of chronic pain on the relation between trial-by-trial fluctuations in FACS score and pain intensity ratings. Behavioral data were analyzed using custom Matlab scripts (MathWorks) to implement a linear mixed-effects model using robust regression (the scripts are available at <http://wagerlab.colorado.edu/tools>). The first level tested the within-subject effects of pain ratings on the FACS score, whereas the second level accounted for group effects (healthy controls vs patients with CBP). The significance of regression coefficients was estimated using a bootstrap test of 5000 samples.

## 2.5. Functional magnetic resonance imaging acquisition and preprocessing

Imaging was performed on a 3.0-T whole-body scanner (Siemens TRIO), using an 12-channel head coil, at the Unité de Neuro-imagerie Fonctionnelle (UNF), Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM) in Montréal, QC, Canada. Blood oxygenation level-dependent (BOLD) signal was acquired using a standard T2\*-weighted gradient-echo EPI sequence (TR = 3000 milliseconds, TE = 30 milliseconds; flip angle = 90°; FOV = 220 × 220 mm<sup>2</sup>; matrix = 40 interleaved, axial slices per whole-brain volume at 3.4 × 3.4 mm for isotropic voxels; 227 volumes). Structural images were acquired using a high-resolution T1-weighted MPRAGE sequence (TR = 2300 milliseconds; TE = 2.99 milliseconds; flip angle = 9°; FOV = 256 mm; matrix = 256 × 256; 1 × 1 × 1.2 mm voxels; 160 slices per whole-brain volume). All preprocessing was done using SPM 8 (Statistical Parametric Mapping, Version 8; Wellcome Department of Imaging Neuroscience, London, United Kingdom, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) executed in Matlab 7.8 (MathWorks,

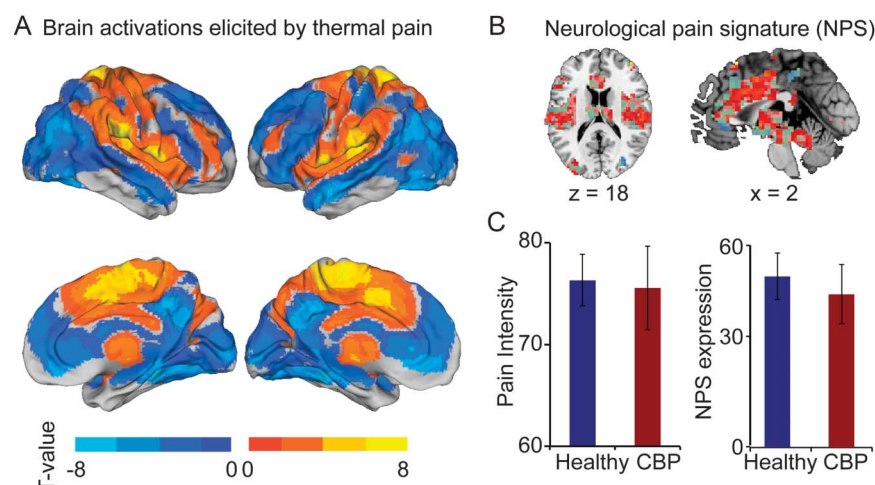
Sherborn, MA). Offline preprocessing of functional images included slice-time correction, realignment of functional time series, coregistration of each subject's functional and anatomical data, spatial normalization to the Montreal Neurological Institute space, and spatial smoothing (8-mm FWHM Gaussian kernel).

## 2.6. Functional magnetic resonance imaging analyses

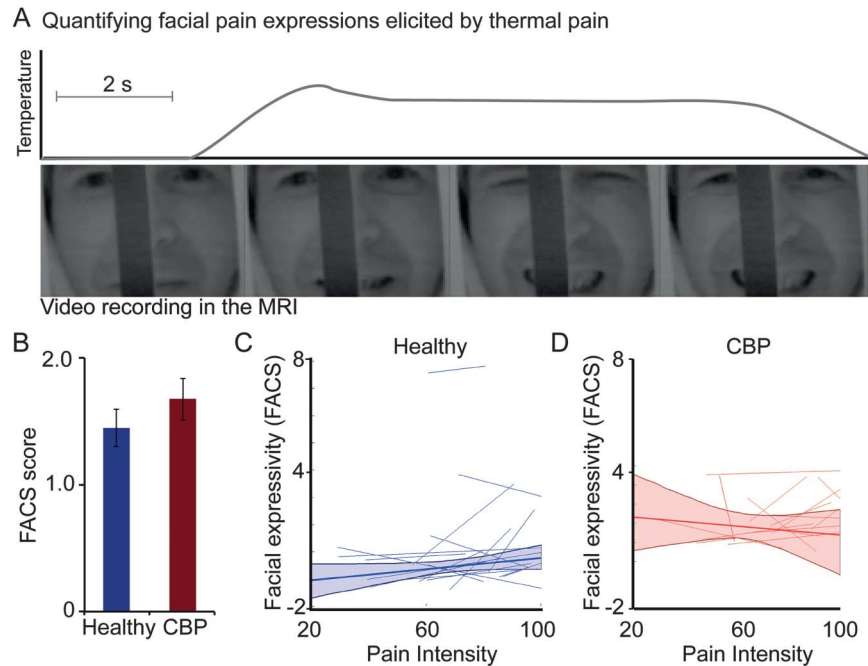
### 2.6.1. Whole-brain multilevel mediation

Mediation analysis is a widely used, simple procedure based on regression models. The procedure is based on a trial-by-trial approach.<sup>5,16</sup> Single-trial response was estimated with SPM8 using a GLM design matrix with separate regressors for each of the 16 pain trials. For each trial, the stimulus epoch was modeled using a boxcar function, based on the onset time and stimulus duration (9 s), convolved with the canonical hemodynamic response function, and entered as a regressor in the individual design matrix. This resulted in 16 different regressors representing each one of the painful thermal stimulations that were then used in the trial-by-trial mediation analyses. The 6 motion correction parameters and a constant were included as variables of no interest for each scanning session. The main effect of thermal pain examined by a linear contrast of all 16 regressors generated the expected brain pain-related brain activations presented in **Figure 1A**.

Mediation analysis allows for the assessment of both the shared and the unique variance associated with multiple predictors, as well as their interactions. The multilevel path modeling approach assesses relationships between brain activity (X) and pain responses such as facial expression (M) and pain intensity (Y) in the context of a single structural equation model. The structural model is formulated to test within-subjects relationships between X, M, and Y in a 2-level mixed-effects framework incorporating both first-level (within-subjects trial-by-trial variability) and second-level (between-subjects) effects. There are several advantages of using the structural model over a standard GLM approach. First, it can provide tests of mediation effects. Second, it estimates the contribution of each path using several GLM equations in the context of a single model, permitting the identification of regions showing significantly



**Figure 1.** Brain response to thermal pain and pain ratings were equivalent between the groups. (A) Brain activity associated with thermal pain stimulations across all participants. (B) A multivariate biomarker predicting thermal pain previously developed on independent data sets<sup>35</sup> was used a neurological pain signature (NPS). (C) Patients with chronic back pain (CBP) and healthy controls showed equivalent averaged amounts of pain intensity and equally expressed the NPS. Error bars on the graphs represent the SEM.



**Figure 2.** The relationship between pain intensity and facial expression was altered in chronic pain. (A) Facial pain expressions elicited by a thermal painful stimulation (gray line) in a representative participant. (B) Patients with chronic back pain (CBP) and healthy controls showed comparable averaged pain facial expressions (Facial Action Coding System [FACS] score) in response to noxious thermal pain stimulations. (C–D) Multilevel linear modeling performed on pain measurement fluctuations on a trial-by-trial basis revealed that pain reports were modestly but significantly associated with facial expressions in healthy controls but not in patients with CBP. The thin lines represent single-subject regressions, and the shade area represents the 95% confidence interval of the multilevel regression line. Error bars on the graphs represent the SEM.

stronger or specific effects related to one of the psychophysiological responses (eg, testing brain activity tracking pain report independently from facial expressions; or testing the mediating effect of facial expressions on the relationship between brain activity and pain report). Third, within-subject measurement error is taken into account when conducting group analyses, which is not the case in traditional GLM analyses.

On a trial by trial basis, we tracked the brain activity increasing as the facial expressions were most strongly displayed (X-M; *path a*) and as pain reports were higher (X-Y; *path c*). Importantly, the spontaneous fluctuations in these behavioural responses were observed even if the thermal stimulus was presented at the same temperature across painful trials. Using this model, we were further able to assess the mediating effect of facial pain expressions (*path ab*) on the relation between brain activation to thermal pain and the subjective pain report. Conceptually, this path tests the possible contribution of spontaneous pain expression during the noxious stimulus to the self-report of the pain experience obtained immediately after the stimulus. In addition, the model allowed the determination of specific

contribution of brain activation to pain reports after controlling for facial pain expression (*path c'*).

Multilevel path analyses were implemented in a voxel-wise analysis framework named “mediation effect parametric mapping” (MEPM)<sup>36,37</sup> using a custom Matlab toolbox (T.D.W.). Inferential statistics of MEPM were performed using a mixed-effects mediation analysis accounting for fixed and random effects (for details see <sup>5</sup>). Bootstrap significance testing was used to estimate distributions of subject-level path coefficients by randomly sampling, with replacement, 10,000 observations for each voxel. The moderating effect of chronic pain was examined using a mixed-effects model (<http://psych.colorado.edu/~tor/Software/mediation.html>), entering the individual strength of each path as a fixed effect and the group as a random effect. All mediation results were thresholded at a false discovery rate (FDR) of  $q < 0.05$  accounting for all voxels in the brain, 2-tailed. Clusters of activation were considered significant if more than 10 adjacent voxels survived the  $q < 0.05$ .

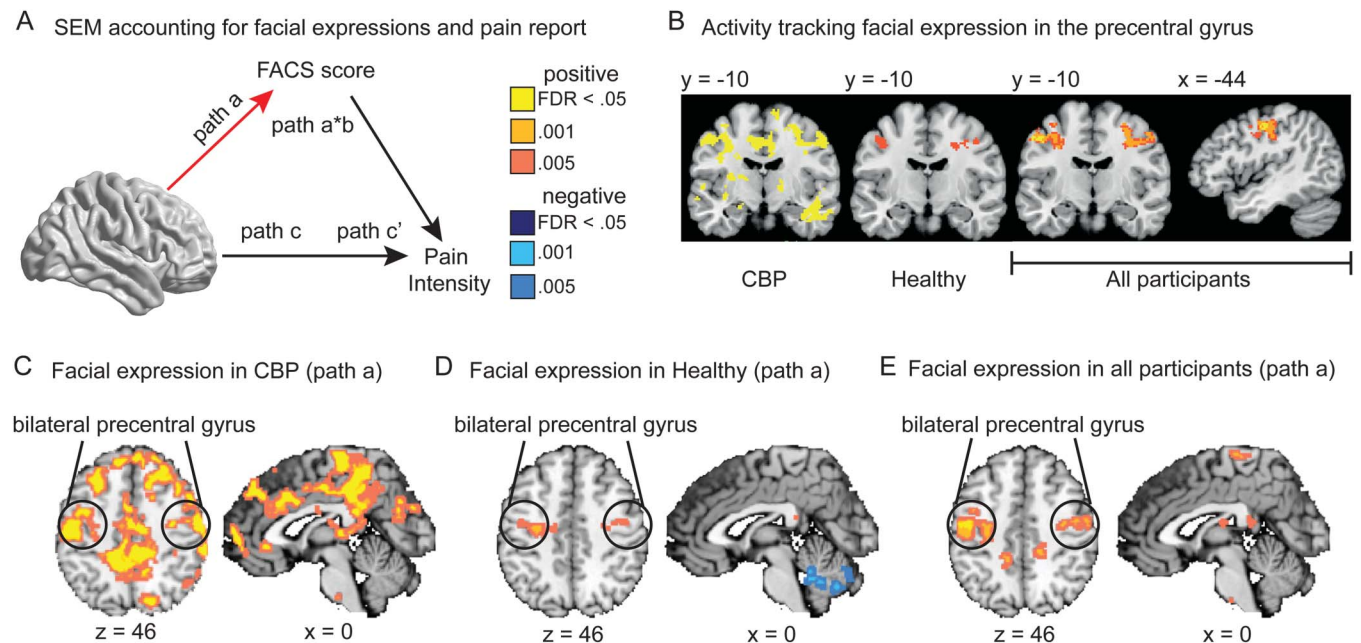
Regions showing interaction between facial expressions and chronic pain were further examined to understand the direction of

**Table 1**  
**Average frequency and intensity (0–4 scale) of facial expression in response to the 16 thermal pain stimulations in each group.**

Action unit	Description	Frequency healthy	Frequency CBP	Intensity healthy	Intensity CBP	Score healthy	Score CBP	P
AU4	Brown lower	6.0 ± 1.1	3.9 ± 0.9	2.1 ± 0.3	2.0 ± 0.3	9.9 ± 2.9	14.9 ± 3.7	0.29
AU6/7	Orbit tightening	11.6 ± 2.2	12.1 ± 2.1	2.5 ± 0.2	2.8 ± 0.2	33.6 ± 10.0	35.0 ± 6.4	0.91
AU9/10	Levator contraction	5.4 ± 2.7	6.9 ± 2.8	1.1 ± 0.4	1.7 ± 0.3	17.6 ± 11.0	18.3 ± 7.8	0.96
AU43	Eye closing	1.3 ± 0.52	1.0 ± 0.34	—	—	1.3 ± 0.52	1.0 ± 0.34	0.62

The comparison of frequency and intensity also yielded nonsignificant *P* values (not shown; all  $P > 0.12$ ), which suggests that patients with chronic back pain (CBP) displayed equivalent facial pain expressiveness even when decomposing the expression per action unit.





**Figure 3.** Brain activity tracking facial pain expressions on a trial-by-trial basis. (A) The structural equation model was used to identify brain activity accounting for spontaneous fluctuations in facial pain expression, brain activity accounting for pain intensity, and the mediation effect of facial expressions on the relationship between brain activity and pain intensity elicited by thermal stimulation administered at a constant temperature. In this mediation model, *path a* (red) represents the brain activity elicited by noxious thermal stimulations associated with facial expression, and *path c* (green) represents the brain activity elicited by noxious thermal stimulations associated with pain reports. *Path a\*b* represents the possible mediation by facial expressions of the relationship between brain activity elicited by noxious thermal stimulations and reports of pain intensity (eg, the variance in pain reports reflecting facial expression). *Path c'* represents the direct effect of brain activity on pain intensity when controlling for the effect of facial expression. (B) Brain activation associated with facial pain expressions (*path a*) was found in the putative face area of the precentral gyrus in both groups (also see C–E). (C–E) Whole-brain activity varying on a trial-by-trial basis with pain facial expressions (*path a*) was observed across several nonmotor area in patients with chronic back pain (CBP) (C), but was confined to the precentral gyrus in healthy controls (D), and when pooling all participants (E).

the interaction. Trials were classified using a within-subject median split on trials in which facial expressions were displayed. The low trials included the trials with no facial expressions and FACS scores lower than the median, and high trials included the trials in which the FACS score was above the median. Beta values were then extracted in each participant in a volume of interest of 27 voxels ( $3 \times 3 \times 3$  voxels) at the peak of the interaction term for visual display.

### 2.6.2. Pattern expression

Pattern expression was used to guide the functional interpretation of the results. The similarity between the maps was assessed by computing the dot product of the brain activity for each voxel in the whole brain or within a mask. The Neurological Pain Signature (NPS) was used as a multivariate pain signature mask. The NPS is a distributed pattern of fMRI activity that is highly sensitive and specific to acute thermal pain. The NPS was developed across four fMRI studies, in which the strength of the NPS response discriminated somatic pain from nonpainful warmth, pain anticipation, distressing images related to social rejection, and pain recall (for more details see 35).

### 2.7. Head motion during thermal pain and facial expressions

Submillimeter head motion correlating to the task can lead to substantial confounds and intersubject variability. This methodological issue is especially important when studying facial pain expressions elicited by thermal pain. Potential confounds due to head displacement were tested in our current data set in 3 different ways. We first compared the six head movement

parameters during the thermal pain task with the remaining volumes of the run. On average, the sum of absolute instantaneous (frame-wise) displacement from the 6 motion parameters was lower during the pain stimulus (mean = 0.89 mm; SD = 0.54) than during the rest of the run (mean = 0.98 mm; SD = 0.62;  $t(29) = 5.09$ ;  $P < 0.001$ ). Importantly, no significant differences were observed during the pain stimulus between the healthy (mean = 1.0 mm; SD = 0.73) and CBP participants (mean = 0.73 mm; SD = 0.42;  $t(28) = 1.57$ ;  $P = 0.14$ ). This replicates previously published observations that head movement slightly decrease during thermal pain rather than increasing.<sup>35</sup>

Second, we computed the sum of the absolute derivative of head displacement of the 6 parameters of movement during painful stimulations to fully examine microhead movements. During the painful condition, the mean sum of the absolute derivative of frame-wise displacement during pain was 0.14 mm (SD 0.07) in patients with CBP and 0.24 mm (SD 0.18) in healthy participants. During the remaining run, the mean sum of the absolute derivative of head displacement was 0.12 mm (SD 0.05) in patients with CBP and 0.19 mm (SD 0.13) in healthy participants. There were no significant group differences between micromovements during pain or within-subject differences between pain and the remaining of the run ( $ps > 0.07$ ). The patients with CBP had a tendency to be more still compared with healthy controls during both pain and the remaining of the run, which indicates that robust activations in patients with CBP during facial expressions were not the results of motion artifacts. The sum of absolute head movement displacement exceeded 0.5 mm in only 3.6% of volumes and exceeded 1 mm in only 0.6% of volumes during

**Table 2**

**Significant clusters of activation associated with facial pain expressivity (*path a*) in healthy controls, patients with chronic back pain (CBP), and when combining all participants after correcting for false discovery rate (FDR) ( $q < 0.05$ , 2-tailed).**

Path a	Hemisphere	x	y	z	Direction	Z values	No. voxels
Healthy							
Precentral gyrus*	L	−28	−16	46	Positive	6.50	27
CBP							
Insula	L	−36	−2	−6	Positive	Inf	1652
Temporal_Sup	R	44	−22	−2	Positive	Inf	2988
Hippocampus	L	−20	−10	−14	Positive	7.20	15
Frontal_Inf_Orb	L	−50	42	−10	Positive	7.48	39
Frontal_Sup_Medial	L	−2	54	4	Positive	Inf	551
Cingulum_Mid	R	6	−14	40	Positive	Inf	11,579
Precuneus	L	−18	−50	0	Positive	Inf	249
Cingulum_Ant	R	2	36	−4	Positive	7.06	75
Frontal_Inf_Tri	R	50	48	−2	Positive	Inf	19
Putamen	R	18	14	0	Positive	7.39	36
Temporal_Mid	L	−62	−46	6	Positive	6.16	30
Temporal_Sup	L	−54	−30	16	Positive	8.21	258
Cuneus	R	6	−74	28	Positive	Inf	1339
Occipital_Mid	L	−34	−88	22	Positive	7.11	117
Insula	R	34	18	12	Positive	Inf	51
Precentral gyrus	L	−50	2	18	Positive	5.86	30
Temporal_Sup	R	54	−32	22	Positive	5.91	21
Caudate	R	20	2	24	Positive	6.34	47
Frontal_Inf_Tri	L	−50	22	30	Positive	Inf	121
Occipital_Mid	R	36	−84	28	Positive	7.68	17
SupraMarginal	L	−60	−46	30	Positive	7.68	114
Postcentral	L	−38	−16	40	Positive	Inf	1341
SupraMarginal	R	66	−32	28	Positive	6.80	12
SupraMarginal	L	−44	−38	34	Positive	6.23	35
Parietal_Inf	R	52	−56	42	Positive	7.91	108
Occipital_Sup	L	−18	−86	36	Positive	6.21	18
Supp_Motor_Area	R	6	18	64	Positive	5.32	11
All_participants							
Precentral gyrus	L	−46	−10	48	Positive	7.76	30

The coordinates represent the center of the cluster, and the structure is identified using the anatomical automatic labeling (AAL) atlas.

\* Only significant with uncorrected  $P < 0.0001$ , 2-tailed.

L, left; R, right.

the pain task. In other words, pain elicited very little frame displacement.

Finally, we tested whether greater micromovements would occur specifically during trials in which high facial expressions were displayed. To address this issue, we contrasted the trials using a median split on the FACS score for each subject. A paired sample t-test indicated that the frame-wise sum of the absolute derivative during pain was not significantly higher during trials in which FACS scores were above the median (mean = 0.22 mm, SD = 0.21) compared with the one in which FACS scores were below the median (mean = 0.17 mm, SD = 0.13;  $t(28) = 1.42$ ;  $P = 0.17$ ).

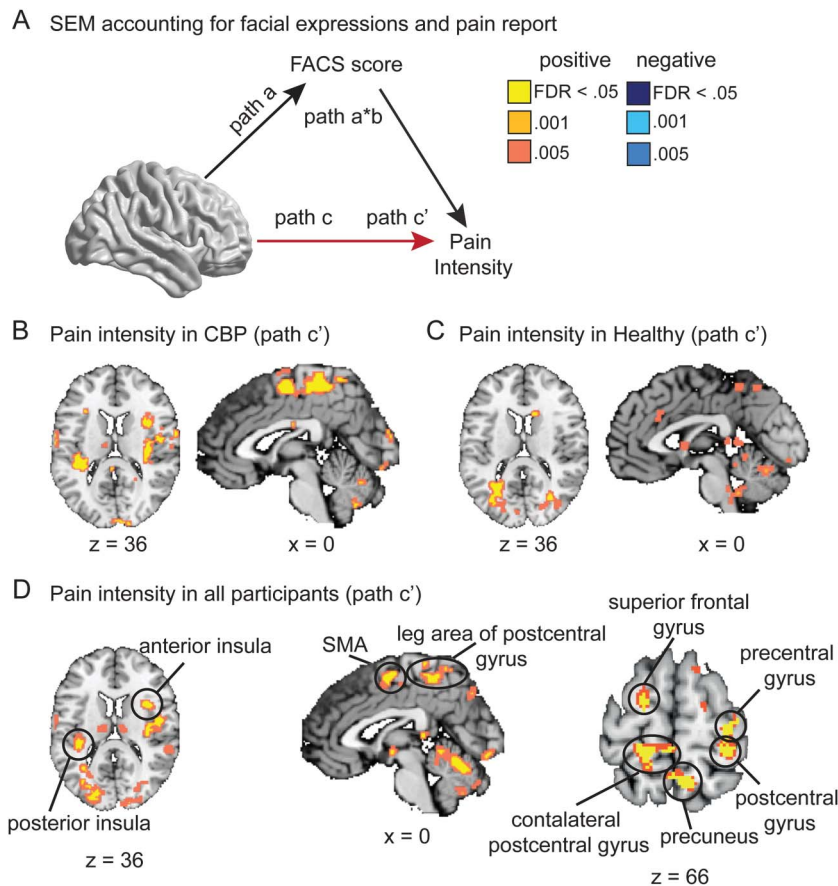
### 3. Results

#### 3.1. The relationship between pain report and facial expressions is altered in chronic back pain

The mean (SD) temperature of the noxious and innocuous stimulations was not different between the groups (noxious: healthy participants = 48.5°C [ $\pm 1.2$ ] and patients with CBP = 48.1°C [ $\pm 1.3$ ];  $P = 0.67$ ; innocuous: healthy participants = 43.2°C [ $\pm 1.8$ ] and patients with CBP = 43.5°C [ $\pm 1.3$ ];  $P = 0.64$ ). As expected, the thermal pain stimulations elicited very robust activation in pain-related brain areas (**Fig. 1A**).

Precisely, positive activity was found in the precentral and postcentral gyri, the supplementary motor area, the cingulate cortex, the insula, the lateral operculum, and the thalamus. Negative activity was further observed in the median prefrontal cortex, the precuneus, the median temporal lobe, and the occipital cortex. Whole-brain analyses of activity evoked by the thermal stimulation did not reveal any differences between healthy controls and patients with CBP, using either FDR correction or a low arbitrary threshold of  $P < 0.001$ . Importantly, the CBP and healthy participants reported comparable levels of pain intensity (**Fig. 1B**; healthy controls: 76.30, SD = 10.17; patients with CBP: 75.66, SD = 15.33;  $t(1,28) = 0.16$ ;  $P = 0.88$ ). The NPS (**Fig. 1B**), a multivariate biomarker predicting thermal pain, was also significantly expressed to a comparable level in both groups (**Fig. 1C**; healthy controls: 44.58, SD = 34.12; patients with CBP: 49.8, SD = 25.24;  $t(1,28) = 0.47$ ;  $P = 0.64$ ). This confirms that the distributed representation of acute pain in the spino-thalamo-cortical systems is preserved in chronic pain.

**Figure 2A** displays an example of facial pain expression elicited by the painful stimulations. The mean composite FACS score was not significantly different between patients with CBP and healthy controls (**Fig. 2B**; healthy controls: mean = 1.41, SD = 0.57, patients with CBP: mean = 1.63, SD = 0.60;  $t(1,28) = 1.04$ ;  $P = 0.31$ ). Deconstructing facial pain expressions



**Figure 4.** Brain activity tracking pain intensity on a trial-by-trial basis. (A) *Path c'* of the structural equation model represent brain activity varying on a trial-by-trial basis with pain intensity reports after controlling for variance in pain facial expressions. (B–D) Whole-brain activity tracking pain report in patients with chronic back pain (CBP) (B), healthy controls (C), and when pooling all participants together (D). In sharp contrast to facial pain expressions presented in Figure 3, brain activity varied with pain intensity in several regions of the “pain matrix” such as the posterior insula, the supplementary motor area (SMA), the contralateral postcentral gyrus matching with the putative representation of the leg, and the ipsilateral somatosensory cortex. Other non-pain-related regions such as the superior part of the precuneus and the superior frontal gyrus were also associated with pain intensity. Testing *path ab* however yielded no significant result, which indicates that facial expressions did not contribute to the brain activity varying with pain intensity.

revealed no group differences in the frequency or the intensity of each AU (**Table 1**). This implies that the genuine facial expression of acute pain was not altered by chronic pain in this study. Together, the metrics displayed in **Figures 1 and 2** revealed that pain ratings, facial pain expressions, and neural representation of noxious thermal pain were comparable between patients with CBP and healthy controls. Yet, the relationship between pain reports and facial expressions was significantly moderated by pain chronicity (**Figs. 2C–D**). Multilevel linear modeling performed on pain measurement fluctuations on a trial-by-trial basis revealed that patients with CBP and healthy participants differed in the strength of the relationship between pain intensity ratings and facial expressions ( $b = 0.06$ ;  $SD = 0.04$   $P = 0.05$ ), where a moderate but significant relationship was observed in the healthy participants ( $b = 0.03$ ,  $SD = 0.01$   $P = 0.006$ ) but not in patients with CBP ( $b = -0.03$ ,  $SD = 0.04$ ,  $P = 0.84$ ).

### 3.2. Independent brain mechanisms are encoding facial pain expressions and pain intensity

Brain imaging data were analyzed using the mediation model displayed in **Fig. 3A** (brain activity during painful thermal stimulation→facial expressions→pain ratings). This model allowed for the

dissociation of activity related to facial expressions (*path a*) from activity specifically associated with pain reports (*path c'*), as well as the identification of a potential contribution of facial expression to pain reports (mediation term *ab*).

Results showed that trial-by-trial fluctuations in facial expression (*path a*) were associated with bilateral motor-related brain activations within the face area of the precentral gyrus in both healthy individuals and patients with CBP (**Fig. 3B**, **Table 2**), indicating the presence of a common motor-related brain activation during facial expressions of pain. Facial expressions, however, also were associated with widespread activations outside the motor system in patients with CBP but not in healthy individuals (**Figs. 3C–E**). This suggests that pain expression in CBP involves spontaneous engagement of additional regulatory process possibly reflecting higher-order behavioral control or response monitoring.

Activity specifically related to trial-by-trial fluctuations in pain ratings (**Fig. 4A**; *path c'*) was found in a network of structures commonly activated by pain (**Figs. 4B–D**; anterior cingulate cortex, insula, and primary somatosensory cortex [s1]) and also in other motor regions (eg, premotor and SMA; **Fig. 4D**, **Table 3**). This raised the possibility that facial expression may have indirectly contributed to the pain intensity reported by the participant after the painful

**Table 3**

**Significant clusters of activation associated with pain intensity ratings after controlling for facial expressiveness (*path c'*) in healthy controls, patients with chronic back pain (CBP), and when combining all participants after correcting for false discovery rate (FDR) ( $q < 0.05$ , 2-tailed).**

Path <i>c'</i>	Hemisphere	x	y	z	Direction	Z values	No. voxels
<b>Healthy</b>							
Hippocampus	R	40	−12	−20	Positive	Inf	67
Lingual	L	−16	−86	−12	Positive	Inf	94
Occipital_Inf	R	36	−72	−8	Positive	Inf	122
Occipital_Sup	L	−18	−70	38	Positive	7.08	46
Precuneus	L	−14	−52	52	Positive	Inf	13
Frontal_Sup	R	24	32	50	Positive	7.07	23
Supp_Motor_Area	R	14	14	62	Positive	Inf	45
Frontal_Sup	L	−18	6	66	Positive	Inf	50
<b>CBP</b>							
Fusiform	L	−34	−30	−18	Positive	Inf	39
Calcarine	R	10	−96	4	Positive	Inf	150
Temporal_Pole_Sup	R	52	10	−14	Positive	6.55	13
Temporal_Inf	L	−50	−62	−10	Positive	6.54	15
Calcarine	L	−4	−86	−8	Positive	7.07	16
Lingual	L	−14	−54	−10	Positive	5.40	11
<b>All participants</b>							
Temporal_Mid	R	46	0	−30	Positive	6.90	10
Hippocampus	L	−36	−26	−14	Positive	8.21	63
Occipital_Inf	L	−38	−76	−10	Positive	7.82	98
Occipital_Inf	R	42	−68	−10	Positive	6.69	16
Temporal_Inf	R	46	−62	−6	Positive	6.78	16
Rolandic_Oper	L	−36	−32	16	Positive	6.75	79
Occipital_Mid	L	−22	−84	16	Positive	6.58	122
Occipital_Sup	R	14	−94	18	Positive	5.61	11
Cuneus	R	16	−72	38	Positive	6.58	152
Precentral	R	52	−10	42	Positive	Inf	311
Postcentral	L	−48	−14	44	Positive	Inf	186
Cingulum_Mid	R	14	10	42	Positive	5.77	16
Supp_Motor_Area	R	4	−4	52	Positive	7.60	87
Precuneus	L	−2	−74	46	Positive	5.90	11
Paracentralobule	L	−8	−36	60	Positive	Inf	465
Frontal_Sup	R	18	22	52	Positive	6.53	10
Postcentral	R	40	−40	58	Positive	6.28	19
Supp_Motor_Area	R	14	14	60	Positive	6.00	43
Postcentral	R	34	−28	66	Positive	7.91	159
Precuneus	R	6	−54	64	Positive	7.45	72
Frontal_Sup	L	−18	−6	68	Positive	5.99	34
Frontal_Sup	R	16	−14	74	Positive	Inf	70
Precentral	L	−22	−24	74	Positive	7.70	10

L, left; R, right.

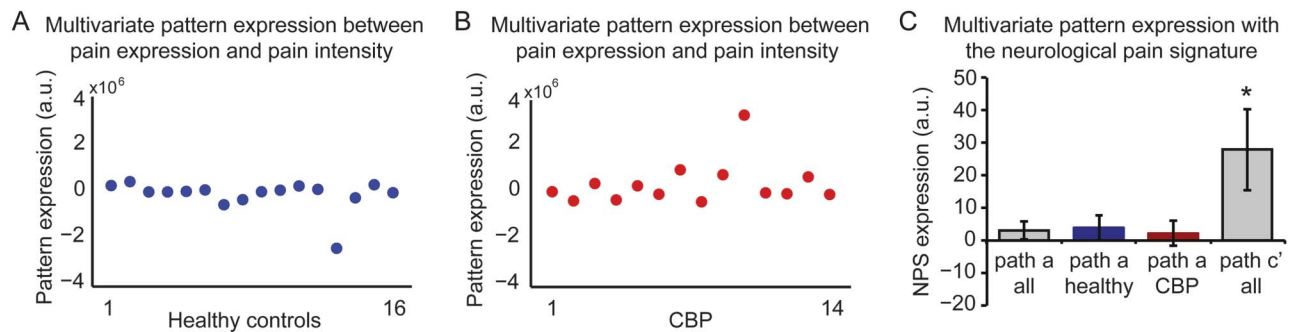
stimulation. The absence of a significant mediation effect of pain facial expressions on the relation between brain activity and pain report (mediation term *ab*) however indicated that the two processes are dissociable. To ensure that this apparent dissociation was not caused by a lack of statistical power on either *path a* or *path c*, we calculated the dot product of *path a* and *c* using unthresholded maps for healthy controls and patients with CBP. The resulting values were near 0 for the majority of healthy controls ( $t(15) = -0.84$ ;  $P = 0.41$ ; patients with CBP:  $t(13) = 1.63$ ;  $P = 0.13$ ) or when pooling all participants together ( $t(29) = 0.79$ ;  $P = 0.44$ ) (Figs. 5A–B), thus confirming that there was no resemblance between the two whole-brain patterns of activity. Individual mediation parametric maps of *path c'* significantly expressed the NPS ( $t(29) = 2.24$ ;  $P = 0.03$ ), confirming the signature's predictive value for subjective pain reports even when the stimulus intensity was held constant (ie, all thermal noxious stimuli were administered at the same temperature; Fig. 5C). By contrast,

the NPS was not significantly expressed by activity related to facial expressions, suggesting that it reflects a different process.

### 3.3. Additional brain mechanisms are recruited during facial expressions in chronic back pain

We finally tested the impact of chronic pain on the brain mediators of pain facial expressions and pain intensity ratings (Fig. 6A). Pain chronicity had a strong influence over activity associated with facial expressions (moderating effect of group on *path a*; Fig. 6B), as revealed by increased activations in the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (DLPFC), precuneus, bilateral extrastriate occipital cortex, and medial temporal lobes in patients with CBP (Table 4). The effects of pain chronicity on the brain activity related to facial expressions can also be appreciated by visual comparison (Fig. 6C), where activity in the DLPFC and vmPFC increased with high pain expression in the patients with CBP but not in controls.





**Figure 5.** Pain facial expressions and pain intensity ratings reflect different aspects of pain. (A) Computing the dot product (a similarity index) of mediation parametric maps of *path a* with *path c* indicates that the pattern observed during pain facial expressions was not expressed by pain intensity in healthy controls (A), in patients with chronic back pain (CBP) (B), or when pooling all participants together (not shown). (C) Individual mediation parametric maps of *path c'* significantly expressed the neurological pain signature, whereas individual parametric maps varying with pain facial expression (*path a*) did not. a.u., arbitrary units. Error bars display the SE.

By contrast, there were no effects of pain chronicity on brain activity related to pain reports (*path c*) or on the mediation effect of pain facial expressions on the relation between brain activity and pain report (mediation term *ab*). The robustness of the results strongly argues for dissociation between pain expression and report and suggests specific alterations of neural mechanisms regulating facial expression in chronic pain.

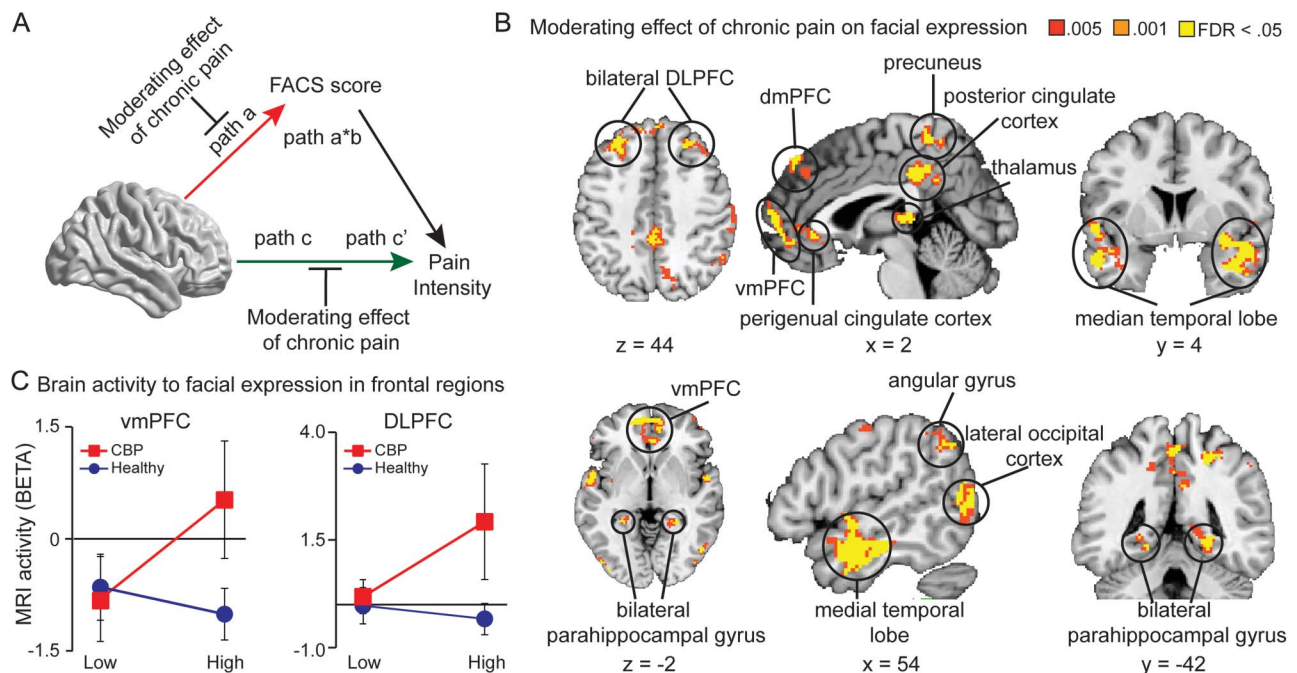
#### 4. Discussion

Facial expressions represent a fundamental behavioral output of pain through which pain is communicated to others. Yet, the neural systems underlying the generation of facial expressions of pain, as well as their relationship with the systems underlying pain

perception and subjective reports remain largely unexplored. Moreover, although several studies have shown that chronic pain disrupts the association between pain reports and nonverbal pain expressions, the effects of pain chronicity on the neural processes underlying the generation of facial expressions of pain has not been studied. In this study, we show that the neural systems underlying pain reports and facial expressions of pain are largely dissociable, and that chronic pain specifically affects the systems underlying facial expression, but not pain reports.

##### 4.1. Neural systems underlying facial expressions of pain

Previous studies have suggested that self-regulation of facial expression to painful shocks mediates autonomic responses and



**Figure 6.** Chronic pain moderated the relationship between brain activity with facial expressions but not pain reports. (A) The effects of chronic back pain (CBP) on *path a* and *path c* were tested by including the group (healthy controls vs patients with CBP) as 2nd-level moderators on all mediation path coefficients. (B) A widespread moderating effect of CBP on pain facial expressions (*path a*) was found in the vmPFC, dmPFC, DLPFC, precuneus, extrastriate cortex, and medial temporal lobe. No moderating effect of CBP was observed for *path c* or *path c'*. (C) Examining the beta values revealed that patients with CBP displaying stronger activity during high expressions mainly drove the moderation effect in frontal regions. Error bars display the SE. DLPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

**Table 4**

**Significant clusters of activation associated with the moderation of chronic pain on facial pain expressivity (*path a*) after correcting for false discovery rate (FDR) ( $q < 0.05$ , 2-tailed).**

Moderation of CBP on path a	Hemisphere	x	y	z	Direction	Z values	voxels
Temporal_Mid_L	L	−48	0	−16	Positive	7.21	609
Temporal_Mid_R	R	48	−4	−20	Positive	Inf	1283
ParaHippocampal_L	L	−26	−22	−20	Positive	6.39	18
ParaHippocampal_L	L	−22	−42	−6	Positive	6.20	13
ParaHippocampal_R	R	24	−44	−4	Positive	6.53	32
Frontal_Sup_Medial_L	L	0	54	0	Positive	7.42	358
Occipital_Mid_L	L	−44	−84	0	Positive	6.44	16
Temporal_Mid_R	R	50	−72	12	Positive	7.26	193
Cingulum_Ant_R	R	2	36	−2	Positive	5.98	21
Precuneus_L	L	−26	−62	4	Positive	7.20	67
Occipital_Mid_L	L	−30	−92	12	Positive	6.85	53
Frontal_Sup_R	R	26	64	12	Positive	7.26	21
Occipital_Sup_R	R	16	−92	28	Positive	6.54	22
Occipital_Mid_R	R	36	−82	28	Positive	6.48	10
Occipital_Sup_R	R	22	−80	34	Positive	6.36	15
Cingulum_Mid_R	R	6	−46	34	Positive	5.85	13
Cingulum_Mid_R	R	4	−36	40	Positive	6.35	125
Frontal_Mid_L	L	−28	36	42	Positive	8.21	295
Frontal_Sup_R	R	26	36	44	Positive	6.29	37
Parietal_Inf_R	R	54	−56	42	Positive	5.72	11
Frontal_Sup_Medial_L	R	2	44	48	Positive	7.07	145
Precuneus_R	R	16	−74	48	Positive	6.75	45
SupraMarginal_R	R	58	−32	50	Positive	6.53	24
Postcentral_R	R	26	−44	54	Positive	6.13	50
Precuneus_L	L	−6	−58	54	Positive	6.07	12
Precuneus_L	L	−2	−46	60	Positive	7.39	112
Precuneus_R	R	10	−54	62	Positive	7.64	64
Precuneus_L	L	−14	−54	68	Positive	7.02	10

L, left; R, right.

pain reports<sup>20</sup> and that facial expressions to acute heat pain are associated with stronger activation in pain-processing areas targeted by the spinothalamic pathways.<sup>17</sup> The present study directly compares the pattern of activity associated with facial expressions of pain with the activity supporting subjective pain reports. The absence of significant mediation, as well as the lack of any correlation between the two patterns of activity, strongly indicates that the neural processes underlying the generation of facial expressions of pain and pain ratings are largely dissociable in both healthy controls and patients with CBP. Although pain facial expressions mainly rely on activity in the precentral gyrus (M1), pain reports are associated with activity in a distributed network of structures that are predictive of the pain induced by thermal noxious stimulation.<sup>35</sup>

Additional structures associated with facial expressions of pain may constitute an independent network involved in another primary function of pain, one that is social/communicative in nature. Previous research focusing on pain reports as the sole output of pain-processing systems have so far largely ignored these processes as an important part of cerebral

representation of pain. The results of this study therefore contribute to the development of a more comprehensive multidimensional model of the neural processing of pain that gives more consideration to the various responses generated at multiple levels of the neuroaxis, such as autonomic and neuroendocrine responses,<sup>11,33,34</sup> behavioral decisions,<sup>26</sup> and facial expressions.<sup>17</sup> A better comprehension of the brain systems supporting these various dimensions of pain will help us understand the neurophysiology of chronic pain that may not necessarily be characterized by alterations in pain perceptual processing networks.

#### 4.2. Effects of chronic pain on facial expression

Our behavioral results first indicated that deconstructing facial pain expressions into AUs did not differentiate patients with CBP from healthy controls, which suggests that chronic pain does not modify pain expressions, at least to acute thermal pain. Our results, however, replicated the long-standing observation that chronic pain disrupts the correlation between

pain reports and facial expressions.<sup>19</sup> These findings are in agreement with operant theories of pain-related behavior, which propose that pain behaviors may become progressively dissociated from nociceptive processes and increasingly dependent on social reinforcements as the chronic pain condition progresses.<sup>13</sup> Our results even take operant theory a little further by showing that this dissociation holds *even if* the pain is induced experimentally *and* facial expression is spontaneously expressed, indicating that neural and behavioral changes instigated by chronic pain have become habits generalizing to other sources of pain. Remarkably, no other measure reliably differentiated patients with CBP from healthy controls; individualized levels of pain temperature, mean levels of pain intensity or facial expressions, pain-evoked brain activity, and NPS pattern expression were comparable between the groups.

Brain mediation results also support the operant theory of pain communication. Although a higher number of patients may have revealed an impact of chronic pain on acute thermal pain ratings, our finding that pain ratings were unaffected by pain chronicity is in line with the proposition that the function of the spinothalamic system in acute pain processing is preserved in patients with chronic pain.<sup>3,4</sup> In sharp contrast, chronic pain had a dramatic impact on the neural systems underlying facial expression. In addition to the precentral gyrus (putative face area), which was strongly associated with facial expression in all participants, chronic pain also recruited additional activity in many regions involved in reward processing and social cognition, such as the ventro- and dorso-medial prefrontal cortex (vmPFC, dmPFC<sup>2,26</sup>), precuneus,<sup>14</sup> medial temporal lobe,<sup>22</sup> and DLPFC.<sup>15</sup> The interaction observed between pain chronicity and facial expression in the vmPFC and the DLPFC was particularly interesting because these regions are believed to play an important role in emotional self-regulation,<sup>36</sup> secondary pain appraisals and affect,<sup>23</sup> pain chronicity,<sup>4</sup> and cognitive task performance impaired in CBP.<sup>9</sup>

Alternatively to the psychosocial model, higher activity during facial expressions in patients with chronic pain may also be attributed to other mechanisms going beyond communicative purposes. For instance, brain activity moderating facial expressiveness in these patients may be associated with mechanisms involving anxiety and depression,<sup>28</sup> motivation,<sup>7</sup> interoception,<sup>27</sup> memory of pain,<sup>1</sup> and cognitive control,<sup>22</sup> accounting for the dissociation between facial expressions and pain report. Furthermore, this study included both males and females but was not designed to compare them, so the present findings likely reflect what both groups have in common and may miss important sex-related effects on the brain and on pain behaviors.<sup>18</sup> These biopsychological processes may interact with pain experienced and expressed through alternative channel of communications.

Better understanding the mechanisms, function, and meanings of facial expression in chronic pain will contribute to viewing and treating pain as a multifaceted experience and might even improve pain management because clinicians strongly rely on pain behaviors.<sup>38</sup> In this study, we demonstrated that pain facial expressions and pain reports reflect different aspects of pain-evoked neural activity, which supports the conception that the pain experience is created through several processing channels that can be dissociated from one another. As predicted by the psychosocial model of chronic pain, our results also indicate that additional regulatory mechanisms are involved in facial expression in patients with chronic pain who may represent a socially driven adaptation in coping with the pathology.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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