Neural processing of pain-related distress to neck-specific movements in people with chronic whiplash-associated disorders

Research Paper

PAIN 164 (2023) 1954–1964

PAIN®

Neural processing of pain-related distress to neck-specific movements in people with chronic whiplash-associated disorders

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Abstract

Pain-related distress contributes to long-term disability in chronic whiplash-associated disorders. Recently, neuroimaging studies have revealed altered neural responses to viewing pictures of movements associated with back pain in key regions for threat and affective processing. In this study, we examined neural correlates of imagining neck-specific movements designed to elicit pain-related distress in individuals with whiplash-associated disorders (n = 63) when compared with that in sex-matched pain-free controls (n = 32). In the scanner, participants were presented with neck-specific movement-related pictures divided into 3 categories (high fear, moderate-fear, and neutral control pictures) and asked to imagine how they would feel if they were performing the movement. Whole-brain analyses revealed greater differential activation (high-fear vs neutral) in individuals with whiplash-associated disorders when compared with that in pain-free controls in 6 clusters including right and left postcentral gyri, left parietal operculum, dorsal precuneus, left superior frontal gyrus/anterior cingulate cortex, and posterior cingulate cortex/ventral precuneus. For the contrast moderate-fear vs neutral, patients showed greater differential activation than controls in the right and left posterolateral cerebellum. Activation patterns in the precuneus and posterior cingulate cortex were negatively associated with pain-related fear, but no other correlations were observed. Together, the findings suggest that when conceptualizing neck-specific movements associated with pain, people with chronic whiplash-associated disorders may predict—and potentially amplify—their sensory and affective consequences and therewith trigger dysfunctional affective and/or behavioral responses. Herewith, we provide new insights into the neural mechanisms underlying chronic pain in people with whiplash-associated disorders, pointing towards a complex interplay between cognitive/affective and sensorimotor circuitry.

Keywords: Chronic whiplash, Pain-related distress, Functional magnetic resonance imaging, Fear of movement

1. Introduction

Half of the people who have a whiplash injury develop chronic pain (also known as chronic whiplash-associated disorder [CWAD]).[31,62] The mechanisms underlying the development and maintenance of CWAD are not fully understood yet, but growing evidence supports a prominent role for maladaptive pain cognitions, fears, and avoidance behaviors over other prognostic factors.[30,48,62] However, less is known about their neural correlates to date (ie, the neural processing involved in the anticipation, fear, and avoidance of pain).

Over the past decades, neuroimaging research has attempted to unravel the complexity of the pain experience and chronic pain.[35,72,80] To date, most studies have focused on nociceptive processing and the neural responses to evoked pain, yielding only subtle differences between individuals with and without chronic pain.[66,84] In addition, brain regions activated by noxious stimuli only partially overlap with those attributed to spontaneous (chronic) pain.[4,50] Neural activation related to pain experiences undergoes a large reorganization in people who develop chronic pain, shifting away from sensory brain regions associated with nociceptive/sensory towards cognitive/affective and motivational networks.[6,26,86] This shift illustrates that, especially in the chronic phase, pain is a highly complex individual experience influenced by psychological factors (eg, pain-related fear, catastrophizing cognition, and hypervigilance)[36] and emotional learning and memory (eg, previous pain experiences).[2]

The anticipation of pain associated with certain movements or activities is suggested to drive pain-related fear and its associated avoidance behavior more than the actual pain experience.[39,44,54] Anticipation of pain furthermore elicits neural activation in similar brain regions that are activated by an actual pain perception, in addition to other regions.[49] Research has demonstrated that

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

http://dx.doi.org/10.1097/j.pain.0000000000002890

imagining or even simply viewing feared movements can trigger pain and related fear similar to that observed during or before the actual performance of such movement and thus could activate the memory representation of the fear trace.[7,45,46] Under that premise, several functional magnetic resonance imaging (fMRI) studies have explored the neural responses to viewing pictures of movements and revealed altered neural activation in critical regions for pain cognition, affect, fear, and memory processing (eg, cingulate, somatosensory cortex, or insula).[8,17,43,63,68,70,79] In addition, some of these altered neural activation patterns have been found to be correlated with measures of pain-related distress such as fear of movement, pain catastrophizing, and/or anxiety.[43,63,70] To date, research in this vein has been focused on people with chronic low back pain almost exclusively, and studies on CWAD are still lacking.

The main aim of this fMRI study was therefore to investigate the neural circuitry involved in pain-related distress in people with CWAD compared with that in pain-free controls. We used a paradigm designed to evoke anticipatory responses to feared neck-specific movements. We evaluated group differences in evoked brain activation by contrasting pictures of feared neck-specific movements with neutral movements. In addition, we aimed to explore whether group differences in neural correlates of pain-related fear were associated with pain-related distress outcomes.

2. Methods

2.1. Study design

This case–control study presents the baseline cross-sectional patient data of a substudy of an ongoing multicenter randomized controlled trial (NCT04077619).[14] Research methods and reporting are in accordance with the STROBE statement[75] for case–control studies and the reporting guidelines for fMRI studies.[56]

2.2. Participants

Ninety-five participants (63 CWAD and 32 pain-free) were recruited from Flanders (Belgium) through poster/flyer advertisement and online media between September 2019 and January 2021. Participants were screened for potential eligibility before enrollment. Participants with CWAD were included if they were aged 18 to 65 years and had neck pain due to a whiplash injury ≥3 months ago, with moderate/severe pain-related disability (ie, ≥15/50 on the Neck Disability Index [NDI][76]). Pain-free controls were recruited for the substudy specifically, age matched and sex matched, and included if they had no history of neck pain. Further details on the eligibility criteria are summarized in Table S1, available as supplemental digital content at http://links.lww.com/PAIN/B797.

The substudy was approved by the Ethical Committee at the Ghent University hospital (UZGent), Belgium (reference number 2019/1144), and all procedures were performed in accordance with the Declaration of Helsinki. Data collection took place at Ghent Institute for Functional and Metabolic Imaging (GIfMI). All participants provided written informed consent before participation.

2.3. Assessment of pain-related outcomes: questionnaires

Pain frequency and intensity were collected. The participants rated the average and maximum pain intensity they had experienced in the previous week on a numeric pain rating scale (NPRS) from 0 (no pain) to 10 (worst imaginable pain). Neck pain–related disability and health-related quality of life were assessed with the NDI and 36-Item Short Form Health Survey (SF-36), respectively.[42]

Catastrophizing cognitions were assessed using the Pain Catastrophizing Scale (PCS). The PCS has shown excellent internal consistency and consists of 13 items (scored 0-4) divided into 3 subscales: magnification, helplessness, and rumination.[15] Pain-related fear and anxiety were assessed with the short form version of the Pain Anxiety Symptoms Scale (PASS-20). The PASS-20 has shown excellent internal consistency and consists of 20 items (0-5) divided into 4 subscales: cognitive, escape/avoidance, fear, and physiological anxiety.[15,59] Attention to pain and hypervigilance was assessed with the Pain Vigilance and Awareness Questionnaire (PVAQ). The PVAQ has shown good internal consistency and consists of 16 items (0-5) divided into 2 subscales: attention to pain and attention to changes in pain.[60]

2.4. Stimulus material and experimental protocol

In the scanner, the participants were presented with pictures of neck-related movements taken from the Pictorial Fear of Activity Scale-Cervical (PFActS-C).[74] The PFActS-C permits to evaluate pain-related fear and avoidance beliefs of different movements and activities (ie, specific directions of neck movements, arm positions, and weight-bearing activities).[51,74] The PFActS-C is a valid 77-item questionnaire and has shown to be moderately to largely correlated with measures of pain-related fear and anxiety (PASS-20), catastrophizing cognitions (PCS), and disability (NDI).[34,74] For the current fMRI paradigm, 15 PFActS-C pictures were selected across 3 categories (ie, 5 pictures per category) to elicit different degrees of pain-related fear among participants with CWAD (ie, high-fear, moderate-fear, and neutral pictures; see **Fig. 1**), based on the validation results for the PFActS-C in individuals with WAD (see Turk et al.[74] for further details). The pictures included in the high-fear category depicted weight-bearing activities, while the pictures in the moderate-fear category illustrate different neck movements (eg, full flexoextension and rotation). The 5 neutral pictures from the original PFActS-C questionnaire were included in the neutral category.

The experimental paradigm used a jittered event-related fMRI design, in which pictures were presented for 3 seconds, followed by a cue to imagine the movement/activity for 3 seconds and 4 to 8 seconds of fixation cross or intertrial interval (ITI; **Fig. 1**). One of 3 pseudorandomized versions of the task was presented, each of them with 90 trials (ie, 30 per category, or 6 repetitions per picture) divided across 2 runs of approximately 9 minutes each. Stimuli were presented using Presentation software (Neurobehavioral Systems, Inc, Berkeley, CA) and were synchronized with MR data acquisition. The total duration of the scanning sessions was approximately 50 minutes (data from other acquisitions will be described elsewhere).

Before the scanning session, the participants received task instructions. They were instructed to view each picture carefully and to imagine how they would feel if they had to perform the movement or activity shown in the picture. Then, participants were allowed to practice the task briefly (ie, 4 pictures were shown, and these practice pictures were not included in the experimental task).

2.5. Experimental paradigm ratings

After the scanning session, participants were requested to view and rate each picture from 0 to 10 for expected pain (ie, "How painful would it be to perform the activity shown in the picture?"), worry (ie,

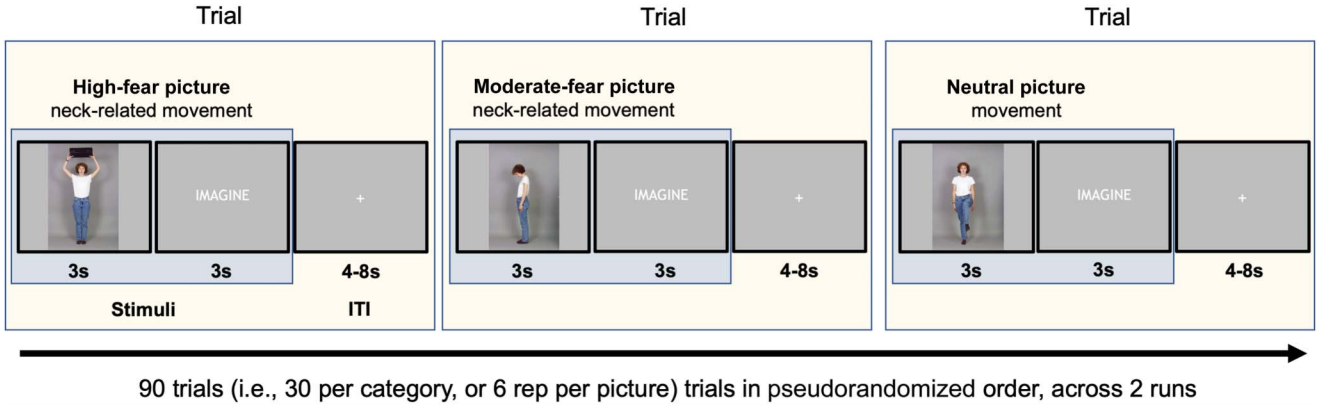

Figure 1. Experimental paradigm. One example trial from each of the 3 picture categories is presented (high-fear, moderate-fear, and neutral pictures), including the timing. ITI, intertrial interval.

"How worried would you be to perform the activity shown in the picture?"), fear/anxiety (ie, "How fearful/anxious would you be to perform the activity shown in the picture?"), and avoidance tendency (ie, "To what extent would you want to avoid performing the activity shown in the picture?"). In addition, participants were asked how easy it was to imagine each picture within the scanner. Pictures and ratings were presented in a random order on a laptop using Presentation software and were self-paced.

2.6. Magnetic resonance imaging and physiological data acquisition

Magnetic resonance imaging data were collected using a 3T MRI scanner (Siemens MAGNETOM Prisma) with a 64-channel head coil. For the functional images, a T2*-weighted standard echoplanar imaging (EPI) sequence was used to acquire 56 axial slices (2.5 mm isotropic) covering the entire cortical volume, using the following parameters: repetition time (TR) = 1000 ms, echo time (TE) = 27 ms, flip angle = 52°, FoV = 210 mm × 210 mm, and SMS factor = 4. In total, 1040 volumes were collected across the 2 runs.

Structural images were acquired using an MPRAGE T1-weighted sequence with 1 mm isotropic resolution, TR = 2250 ms, TE = 4.18 ms, TI = 900 ms, flip angle = 9°, FoV = 256 mm × 256 mm, GRAPPA acceleration factor 2. Field maps were acquired for the correction of geometric distortion[28] using a double-echo gradient echo (GRE) field map sequence, TR = 458 ms, TE1 = 4.92 ms, TE2 = 7.38 ms, flip angle = 60°, and FoV = 204 mm × 204 mm.

Cardiac and respiration cycle were simultaneously recorded during the fMRI acquisitions for offline physiological noise correction using the MR-compatible computer-based data acquisition system (MP150 and AcqKnowledge, Biopac Systems, Goleta, CA). Data were continuously recorded at 2000 samples/s with a photoplethysmograph (PPG; TSD200-MRI) placed on the index finger of the nondominant hand and a pneumatic respiratory belt (BN-RESP-XDCR) strapped around the participant's thorax. Magnetic resonance imaging trigger pulses were recorded using AcqKnowledge as well for offline synchronization of the physiological and MRI data.

2.7. Data analysis

2.7.1. Analysis of behavioral rating data

For the experimental paradigm ratings (ie, expected pain, worry, fear, and avoidance tendency), 2-way repeated measures analysis of variance (ANOVA) were performed to examine differences across groups (participants with CWAD and pain-free controls), pictorial categories (high-fear, moderate-fear, and neutral), and interactions between group and picture category. Pairwise comparisons with the Bonferroni adjustment were used to determine significant differences. The mean value across the 5 pictures in each category was taken for the analysis.

2.7.2. Magnetic resonance imaging preprocessing

MRIqc[18] 0.16.1 was used to generate reports for visual inspection of potential artifacts (eg, reconstruction errors, registration issues, and incorrect brain masks) and Image Quality Metrics for quality control. Functional runs were excluded if there was absolute head motion > voxel size (2.5 mm), ≥ 20% outlier volumes, outlying tSNR (if > 1.5 * interquartile range from the first/third quartile) or if no activation was observed in the occipital area when contrasting the pictures with baseline (ie, suggesting they did not view the pictures or may have fallen asleep). In total, 3 participants with CWAD had to be excluded from the final analysis as well as 1 of the 2 fMRI runs in 13 participants (see study flowchart in the Fig. S1, available as supplemental digital content at http://links.lww.com/PAIN/B797).

Preprocessing of fMRI data was performed using *fMRIPrep*,[19] version 20.2.1. In brief, preprocessing steps included slice time correction, realignment, coregistration, field map distortion correction, segmentation of T1-weighted structural images, and normalization to the MNI space (see Ref. 19 for further information about the pipeline and workflow). The preprocessed blood-oxygen-level-dependent (BOLD) time series for each participant were spatially smoothed (6 mm full width at half maximum Gaussian kernel [FWHM]) using *SPM12*.[53]

For denoising, 12 motion parameters (6 motion parameters and their first temporal derivatives) and motion outlier volumes (modelled as stick predictors, if any) for each run, as calculated by *fMRIprep*, were used. In addition, RETROICOR[23] Fourier expansion was used to model physiological-related low-frequency noise and compute nuisance regressors, as implemented in Matlab PhysIO[32] toolbox using a third-order cardiac model (6 regressors, sine/cosine), a fourth-order respiratory model (8 regressors), and a first-order interaction model (4 terms).[25] For those participants without or with low-quality cardiac data (n = 23), the average signal within an anatomically derived eroded cerebrospinal fluid (CSF) mask[19] was included in addition to the respiratory regressors.

2.7.3. Magnetic resonance imaging data analysis

2.7.3.1. First-level analyses

Preprocessed volumes and nuisance regressors for both runs were entered in the first-level SPM General Linear Model for each participant. The 6 seconds of stimuli presentations (3 seconds picture + 3 seconds imagine cue; similar to that in the study conducted by Timmers et al.[70]) were convolved with the canonical hemodynamic response function to obtain 3 regressors of interest (ie, high-fear, moderate-fear, and neutral). A high-pass filter was applied using a cutoff of 128 seconds. We contrasted each picture category with baseline (ie, high-fear vs baseline, moderate-fear vs baseline, and neutral vs baseline). A contrast of all picture categories together vs baseline was inspected visually to confirm the expected vision-related activation in the occipital cortex.

2.7.3.2. Second-level analyses

The obtained parameter estimate images were then entered in a second-level whole-brain analysis within a mask that excluded the white matter and CSF, based on the Harvard-Oxford atlases (probability threshold 0.25, dilated).[16,21] A 2 × 3 full factorial model with group as between-group factor (CWAD, pain-free) and picture category as within-group factor (high-fear, moderate-fear, and neutral) was fitted to test for group differences in our main contrasts of interest through interactions: "high-fear vs neutral," "moderate-fear vs neutral" and "high-fear vs moderate-fear." The mean framewise displacement was greater in participants with CWAD than in pain-free controls ($t = 2.56$, $P = 0.012$), so it was added as a covariate to control for potential remaining confounding effects of motion in all models.[85] For all maps, the primary cluster-defining threshold was set at $P < 0.001$, followed by a cluster-based false discovery rate (FDRc $P < 0.05$) correction to control for false-positive results.[13] We further corrected for multiple testing across the 3 contrasts of interest with the Bonferroni correction. For plotting purposes, 1-sample t tests were conducted for each contrast of interest per group (eg, high-fear > neutral in CWAD) within the fitted full factorial model.

2.7.3.3. Region of interest analyses

To further test our hypotheses in brain regions that have shown to play an important role in the affective, sensory, or cognitive aspects of chronic pain processing and their associations with pain-related fear according to previous research,[9,47,52,78] an a priori–specified ROI approach was performed in addition to the whole-brain analyses.[55] ROIs for key subcortical regions (bilateral amygdala and hippocampus) were obtained based on the Harvard-Oxford subcortical atlas (probability threshold 0.25). Four-millimeter spheres were taken centered around coordinates from previous studies for posterior cingulate cortex (PCC; MNI coordinates x = −4, y = −50, and z = 32; x = 6, y = −46, and z = 32),[67] anterior cingulate cortex (ACC; x = −8, y = 30, and z = 22; x = 12, y = 36, and z = 16),[67] anterior insula (x = 33, y = −10, and z = 10),[43] posterior insula (x = 33, y = −10, and z = 10),[70] and vmPFC (x = 0, y = 41, and z = −11).[70] We extracted the beta coefficients from high-fear vs baseline, moderate-fear vs baseline, and neutral vs baseline fitting the same 2 x 3 full factorial model using *marsbar*[10] for each predefined ROI. We then performed an ANOVA in R, adding mean framewise displacement as a covariate, to test for group differences through interactions in our main contrasts of interest: "high-fear vs neutral," "moderate-fear vs neutral" and "high-fear vs moderate-fear." The ROI analysis was adjusted for multiple comparisons using an FDR correction.[57]

2.7.3.4. Correlation analyses

To provide a better understanding of the identified effects, we also examined correlations between the activation patterns (beta coefficients) in the clusters and/or ROIs showing significant group-related effects in the main contrast of interest and the pain-related questionnaires (ie, PASS-20, PCS, and PVAQ). Kendall rank correlation coefficients were computed and adjusted for multiple comparisons across ratings/questionnaires with FDR correction.

3. Results

3.1. Participants and descriptive data

The final sample consisted of 60 participants with CWAD (age M = 42.6 ± 10.2 years, 44 women) and 32 pain-free controls (age M = 41.0 ± 10.6 years, 22 women). Participants' descriptive data per group are summarized in **Table 1**.

3.2. Experimental paradigm ratings

The picture ratings for each outcome are illustrated in **Figure 2** (further details on the scores per picture are listed in Table S2, available as supplemental digital content at http://links.lww.com/PAIN/B797). A picture category by group interaction was found for all the examined outcomes: expected pain ($F[1,90] = 47.46$; $P < 0.001$, and $\eta^2 = 0.35$), worry ($F[1,90] = 35.41$; $P < 0.001$, and $\eta^2 = 0.29$), anxiety/fear ($F[1,90] = 26.04$; $P < 0.001$, and $\eta^2 = 0.23$), and avoidance ($F[1,90] = 48.06$; $P < 0.001$, and $\eta^2 = 0.35$). Overall, people with CWAD provided greater scores in high-fear and moderate-fear pictures compared with neutral pictures as well as greater scores in high-fear compared with moderate-fear. No differences between picture categories were observed in pain-free controls. Full details on the results of the behavioral data are summarized in Table S3, available as supplemental digital content at http://links.lww.com/PAIN/B797. In addition, participants rated pictures relatively high regardless of the category for imagination (no main effect for picture: $F[1,90] = 2.07$; $P = 0.13$), though pain-free controls found the pictures slightly easier to imagine (main effect for Group: $F[1,90] = 12.18$; $P < 0.001$, $\eta^2 = 0.12$) (Table S2, available as supplemental digital content at http://links.lww.com/PAIN/B797).

3.3. Differences in BOLD activation between individuals with chronic whiplash-associated disorder and pain-free controls

3.3.1. High-fear pictures vs neutral pictures

Figure 3A shows the activation maps for the high-fear vs neutral contrast per group (clusters and coordinates are listed in Table S4, available as supplemental digital content at http://links.lww.com/PAIN/B797). Overall, people with CWAD showed greater activation to high-fear pictures compared with that to neutral pictures, including in regions such as postcentral/precentral gyrus, precuneus, supplementary motor cortex, inferior frontal gyrus, frontal operculum cortex, anterior insula, posterior cerebellum, posterior and middle cingulate cortex, among others. By contrast, increased bilateral activation to neutral pictures compared with that to high-fear pictures was observed in the superior parietal lobule and precentral gyrus. The controls, on the contrary, exhibited overall greater activation to

Table 1

Participants' characteristics.

	CWAD (N = 63)	Pain-free controls (N = 32)	Between-group comparison
Sex			$\chi^2 = 0.012$, $P = 0.913$
Female	45 (71.4%)	22 (68.8%)	
Male	18 (28.6%)	10 (31.3%)	
Age (y)	42.60 (10.2)	41.0 (10.6)	$t = -0.598$, $P = 0.552$
Health-related quality of life SF-36 (0-100)	49.00 (15.3)	89.3 (8.12)	$t = 16.3$, $P < 0.001$
Physical summary	44.40 (15.6)	92.1 (4.11)	
Mental summary*	54.30 [14.3, 90.7]	91.4 [28.7, 98.6]	
Current pain NPRS (0-10)	4.00 [3.00, 5.00]	0.12 (0.33)	
Average pain previous week NPRS (0-10)*	5.50 [1.00, 8.00]		
Worst pain previous week NPRS (0-10)*	7.00 [3.00, 9.00]		
Days with pain/wk (0-7)	6.03 (1.41)		
Neck-related disability NDI (0-50)*	18.00 [11.0, 35.0]		
Pain catastrophizing PCS (0-52)*	24.00 [5.00, 49.0]		
Pain-related fear PASS-20 (0-100)*	36.00 [4.00, 94.0]		
Pain hypervigilance PVAQ (0-80)*	37.00 [15.0, 64.0]		

* Median and IQR are presented instead of mean and SD.

CWAD, chronic whiplash-associated disorder; NDI, neck disability index; NPRS, Numeric Pain Rating Scale; PASS, Pain Anxiety Symptoms Scale; PCS, Pain Catastrophizing Scale; PVAQ, Pain Vigilance and Awareness Questionnaire SF-36, 36-Item Short Form Health Survey.

neutral pictures compared with that to the high-fear pictures, particularly bilaterally in superior parietal lobule, precentral gyrus, and in the medial superior frontal gyrus. The between-group contrast supported this observation, showing a significant between-group difference in 6 clusters (**Fig. 3B**, **Table 2**), where individuals with CWAD showed greater difference in BOLD activation in the contrast high-fear > neutral pictures compared with pain-free controls. These clusters included the right and left postcentral gyrus (clusters I and II), left parietal operculum (cluster III), dorsal precuneus (cluster IV), left superior frontal gyrus/ACC (cluster V), and PCC/ventral precuneus (cluster VI). No between-group differences were observed for the opposite contrast (neutral > high-fear pictures). There were no clusters in which pain-free controls showed a greater difference across the conditions. The predefined ROI analyses revealed a between-group difference for this contrast in the left and right PCC and left ACC (Table S5, available as supplemental digital content at http://links.lww.com/PAIN/B797), partly supporting the results from the whole-brain analysis.

3.3.2. Moderate-fear pictures vs neutral pictures

Overall, the moderate-fear > neutral pictures contrast yielded activation in a similar network than the contrast high-fear > neutral pictures in individuals with CWAD, while greater bilateral activation was observed in the cuneal cortex and lingual gyrus in

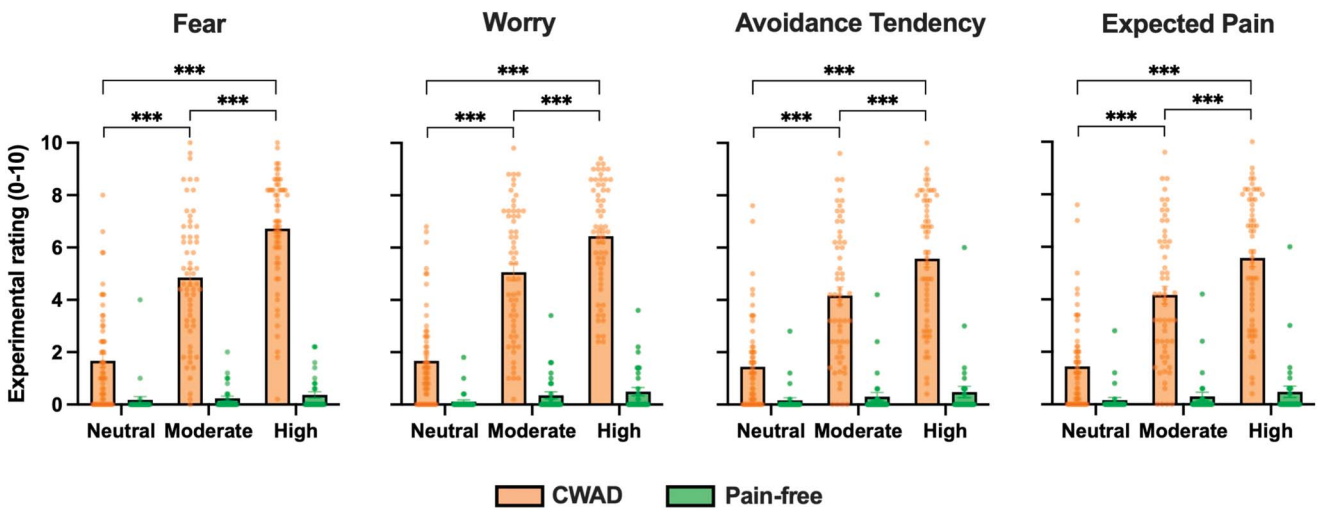

Figure 2. Within-group differences in experimental paradigm ratings. Presented are the averaged ratings across the 5 pictures in each category, for each rating (expected pain, worry, anxiety, and avoidance) and separately per group. CWAD, chronic whiplash-associated disorder.

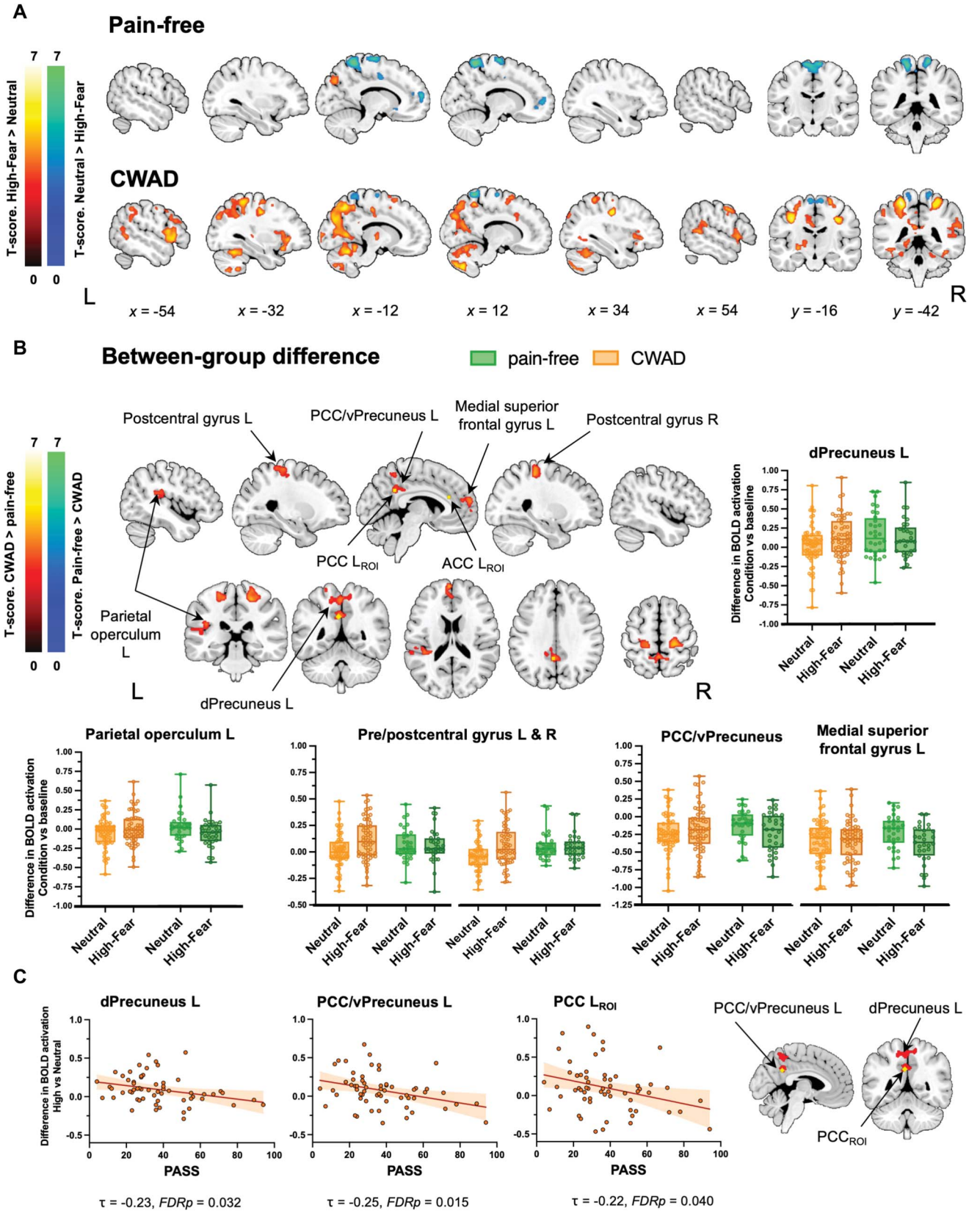

Figure 3. (A) Maps showing the contrast high-fear vs neutral, separately per group (1-sample *t* test). (B) Significant clusters and ROIs in the between-group comparison of the high-fear vs neutral contrast. Extracted beta coefficients for each of the significant clusters are presented in the boxplots. (C) Significant correlations between the cluster/ROI and pain-related questionnaires for the CWAD group. The insert presents the anatomical location of the cluster peak (red) and the ROI (yellow). ACC, anterior cingulate cortex; BOLD, blood-oxygen-level-dependent; CWAD, chronic whiplash-associated disorder; FDR, false discovery rate; PCC, posterior cingulate cortex; ROI, region of interest.

Table 2

Cluster information on the group differences in contrasts high-fear vs neutral and moderate-fear vs neutral pictures.

	Cluster p(FDRc)	k	Peak T_{max}	MNI coordinates x	y	z	Anatomical location	
CWAD > pain-free. High-fear > neutral (FDRc k > 204)								
I	0.002	421	5.00	22	−30	56	Postcentral gyrus	R
			3.38	18	−20	74	Precentral gyrus	R
II	0.004	349	4.54	−30	−18	52	Precentral gyrus	L
			4.43	−18	−32	58	Postcentral gyrus	L
III	0.006	304	4.19	−40	−34	22	Parietal operculum	L
IV	0.010	261	4.49	0	−48	56	Precuneus (dorsal)	L/R
V	0.015	204	4.47	−4	60	18	Superior frontal gyrus (medial)	L
			3.48	0	44	20	Anterior cingulate cortex	L
VI	0.012	243	4.22	−14	−42	32	Posterior cingulate cortex	L
			3.89	0	−48	36	Precuneus (ventral)	L
CWAD > pain-free. Neutral > high-fear								
No significant clusters were identified								
CWAD > pain-free. Moderate-fear > neutral (FDRc: k > 179)								
VIII	0.000	465	4.48	36	−82	−42	Posterolateral cerebellum	R
IX	0.037*	179	4.06	−30	−82	−46	Posterolateral cerebellum	L
CWAD > pain-free. Neutral > moderate-fear								
No significant clusters were identified								

Information on local maxima is included as well, where applicable. Anatomical locations are derived from Harvard-Oxford atlases.

* Clusters not surviving the Bonferroni correction for multiple contrast testing ($P < 0.016$).

CWAD, chronic whiplash-associated disorder; FDRc, cluster-based false discovery rate; k, cluster size MNI, Montreal Neurological Institute.

pain-free controls (**Fig. 4A**; Table S6, available as supplemental digital content at http://links.lww.com/PAIN/B797). Again, increased bilateral activation to neutral pictures compared with that to moderate-fear pictures was observed in the superior parietal lobule and precentral gyrus for both groups. The between-group comparison revealed a greater difference in BOLD activation between moderate-fear and neutral pictures in 2 clusters in the right and left posterolateral cerebellum for people with CWAD compared with pain-free controls (**Fig. 4B**, **Table 2**). The ROI analyses did not reveal any additional between-group differences for this contrast (Table S5, available as supplemental digital content at http://links.lww.com/PAIN/B797).

3.3.3. High-fear pictures vs moderate-fear pictures

People with CWAD exhibited greater activation in high-fear category compared with that in moderate-fear category in the right lateral occipital cortex, supramarginal gyrus, and middle/inferior frontal gyrus. Pain-free controls also showed greater activation in high-fear category compared with that in moderate-fear category in the left and right supramarginal gyrus and angular cortex. In addition, pain-free controls exhibited greater activation in the opposite contrast (moderate-fear category compared with high-fear category) in the left medial superior frontal gyrus, ACC and lingual gyrus, and paracingulate gyrus and precentral/postcentral gyrus (Fig. S2, Table S7, available as supplemental digital content at http://links.lww.com/PAIN/B797). No between-group differences were observed in this contrast. The ROI analyses did not reveal any between-group differences for this contrast either (Table S5, available as supplemental digital content at http://links.lww.com/PAIN/B797).

3.4. Associations with pain-related outcomes in chronic whiplash-associated disorder

For the clusters showing a group difference in high-fear vs neutral category, a small negative association was observed between pain-related fear (PASS-20) and the PCC/ventral precuneus cluster (cluster VI: $\tau = -0.250$, $pFDR = 0.015$), the dorsal precuneus cluster (cluster IV: $\tau = -0.228$, $pFDR = 0.032$), and the predefined ROI for left PCC ($\tau = -0.217$, $pFDR = 0.040$) (**Fig. 3C**, Table S8, available as supplemental digital content at http://links.lww.com/PAIN/B797). These associations show that the smaller the difference in BOLD activation between the high-fear and neutral, the higher the level of pain-related fear. No other correlations were observed for the other clusters nor for the contrasts moderate-fear pictures vs neutral pictures (Table S8, available as supplemental digital content at http://links.lww.com/PAIN/B797).

4. Discussion

This study investigated the neural circuitry involved in pain-related distress in people with CWAD for the first time, by examining group differences in evoked brain activation to viewing feared neck-specific movements when compared with pain-free controls. Our findings indicate that people with CWAD exhibit altered neural activation to the viewing of fear-evoking neck-specific movements when controlling for neutral movements in the primary (S1) and secondary (S2) somatosensory cortex (ie, postcentral gyrus and parietal operculum) as well as in regions implicated in cognitive/affective aspects of pain (eg, mPFC, ACC, PCC, and precuneus). Overall, these altered activation patterns did not correlate with pain-related distress questionnaires; with the exception of the differential activations in the ventral precuneus/PCC and the dorsal precuneus for the contrast between high-fear pictures and neutral pictures, which showed a small negative correlation with pain-related fear. This study therewith provides new insights into the neural mechanisms contributing to pain-related distress in people with CWAD, pointing towards a complex interplay between cognitive/affective and sensorimotor circuitry.

Pain-related fear, pain catastrophizing, and avoidance behavior contribute to restricted neck movement and related disability

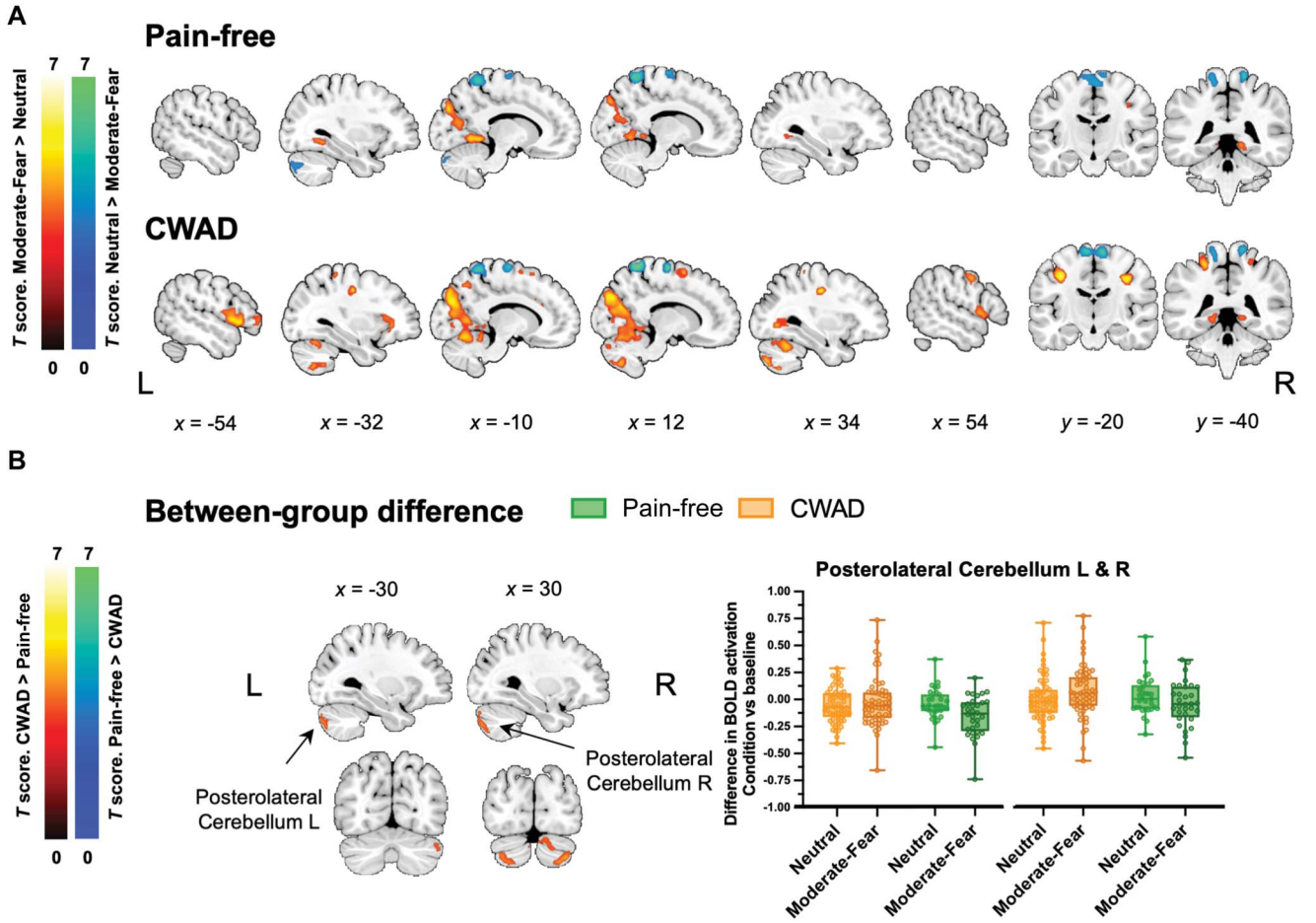

Figure 4. (A) Maps showing the contrast moderate-fear vs neutral, separately per group (1-sample *t* test) (B) Significant clusters and ROIs in the between-group comparison of the moderate-fear vs neutral contrast. Extracted beta coefficients for each of the significant clusters are presented in the boxplots. CWAD, chronic whiplash-associated disorder. BOLD, blood-oxygen-level-dependent; ROI, region of interest.

in people with CWAD more than pain itself.[3,30,48,74] Our behavioral data show that the experimental stimuli tap into these constructs because participants with CWAD provided higher ratings of pain-related fear, worry, tendency to avoid, and expected pain for the pictures of neck-specific movements (high-fear and moderate-fear categories), which is in line with the PFActS-C validation results.[74] Of interest, the different ratings show similar patterns across conditions, and hence it is difficult to pinpoint effects to pain-related fear specifically, and hence, we will refer to pain-related distress more generally. As expected, participants with CWAD provided higher ratings than pain-free controls across all examined outcomes, but this was also the case for the neutral pictures, which was not anticipated.

In this study, individuals with CWAD, relative to pain-free controls, showed an increased activation to viewing neck-related movements compared with that to neutral movements in S1 and S2. This is in line with previous studies investigating neural anticipatory responses to feared movements in people with chronic pain.[27,63,68] S1 and S2 are well known for encoding sensory information of pain (eg, pain perception and location).[77] Previous research has demonstrated that imagining oneself in painful situations can elicit patient's pain and triggers the activation of sensory areas of pain processing, which is likely driven by pain-related distress and prior painful experiences.[7,11,20,46] In paradigms involving motor observation/imagery, activation in these regions is coherent with kinesthetic aspects of the action observed (ie, sensations associated with executing a particular action).[24,33] The increased S1 activation observed in our study was, in fact, somatotopically specific to the neck and upper limb. This suggests that the mere imagination of neck-related movements may have led participants with CWAD to predicting their sensory consequences, including the pain experience.[11,20] Note, though, that we cannot infer whether the effect is induced by expected pain or by the more psychosocial constructs (eg, fear, worry) that may amplify the sensory experience.

Our findings of increased activation in dorsal precuneus and posterolateral cerebellum when viewing feared movements are in line with previous similar research in people with chronic low back pain and now thus extend to neck pain.[8,17,63,68,79] Both regions are functionally connected with the sensorimotor network and have been implicated in motor imagery, pain anticipation, and episodic memory.[12,24,69] In particular, the dorsal precuneus is involved in motor planning and vividness of memory retrieval during imagery (potentially mediating the relationship between egocentric perspective and vivid recall of prior experiences).[12,22] Likewise, the posterolateral cerebellum seems to be of additional importance in the emotional processing of pain and fear associative learning.[37,69] Pain anticipation, when confronted with feared movements, drives pain-related fear through previous experiences and classical conditioning processes.[39,44,54] Although speculative, the pattern of findings may reflect compensatory (vigilance–avoidance) mechanisms in people with CWAD characterized by greater attentional monitoring of feared neck-

specific movements, possibly evoked by memory retrieval of prior painful experiences.

Group differences were also observed in mPFC and PCC, which are important hubs of the default mode network in which they are characterized by deactivation when performing externally oriented attention tasks.[1,58] Broadly, the mPFC is involved in higher-order cognitive functions such as attention, emotion-based risk, and decision-making, as well as emotion regulation (eg, self-regulation of pain or threat through inhibitory control).[52] Within the default mode network specifically, mPFC deactivation has been associated with task-related demands on cognitive processing.[41,61] In our study, individuals with CWAD exhibited a marked task-induced deactivation in the mPFC across all the conditions (ie, high-fear, moderate-fear, and neutral categories), while this was observed only during the presentation of high-fear pictures in pain-free controls. This finding may therefore reflect that all conditions were cognitively demanding for participants with CWAD, potentially associated with an increased threat regulation, while this was not the case for controls.[71,81] Thus, the increased mPFC deactivation observed in this and previous similar studies in people with chronic low back pain[70] could point toward altered inhibitory control; particularly a reduced cognitive self-regulation and ability to modulate pain.[52,83] On the contrary, the PCC remained active or was less deactivated in participants with CWAD for high-fear and moderate-fear pictures compared with that for neutral pictures. Impaired PCC task-induced deactivation has been repeatedly observed in people with chronic pain when performing distinct cognitive and emotional tasks (including viewing feared movements).[5,63,68,81] The PCC has been associated with emotional value of potentially threatening stimuli contextualization and self-relevance; and it is suggested to mediate interactions of emotional and memory-related processing.[47,78] In this study, PCC (de)activation was correlated to a small degree with pain-related fear (ie, participants with CWAD with higher levels of pain-related fear showed lower deactivation in the PCC for both high-fear and neutral pictures). This, therefore, could reflect the underlying neural response to closely monitoring and evaluating the potential threat value of specific movements by people with CWAD and higher pain-related fear, although this remains speculative.[65]

As in previous studies,[8,17,70] no between-group differences were found in amygdala despite this is considered a key region within the fear circuitry and so in pain-related fear and avoidance learning.[64,82] Previous research has demonstrated that amygdala is associated with early and short-lasting BOLD responses to emotional/phobia-related threats (ie, initiating an arousal response to the presentation of fearful stimuli) that is followed by reductions in activation.[38,40] Thus, one reason for this finding could be related to the long duration of the paradigm under investigation. It is also possible that the amygdala's functional connectivity rather than task-related neural activation distinguishes people with chronic pain from pain-free controls.[5,29]

This study has several strengths. The first is our relatively large sample. Second, both groups reported that pictures were generally easy to imagine, supporting the idea that our paradigm was feasible. Likewise, the somatotopically specific cortical activation in motor cortices observed in each group when viewing moderate-fear and high-fear pictures relative to neutral pictures (ie, neck and upper limb–related) and vice versa (ie, lower limb–related) supports that the task, which involves motor imagery/observation, was well performed and strengthens the validity of the results.[24] In addition, in contrast to previous studies where the examined contrast compares the feared movement condition to baseline,[43,63,68,70,79] the inclusion of the neutral category helped to prevent from confounding effects related to the task instructions, visual effects, or attentional effects. Our findings, however, need to be interpreted in light of some considerations. Neutral pictures, which involved some standing balance actions,[73] still elicited some degree of distress, so they could have not fully served as neutral control condition in some participants with CWAD and may have concealed further between-group differences in other important regions of pain processing. This could have been the case for the insula, which is an important hub of the salient network and whose activation has been found to be increased in people with chronic pain when viewing feared movements compared with that at baseline in previous similar studies.[68,70] This could also partially explain why only 1 cluster's activation pattern correlated with the pain-related questionnaires in participants with CWAD. Along the same lines, the behavioral scores illustrate that there was some within-category variability (ie, some pictures elicited greater distress than others within the same category, potentially also resulting in greater activation patterns) that could have concealed further correlations. This is because, similar to previous studies, pictures were preselected rather than individually tailored. To overcome this limitation, we plan to examine the interpicture relationships through mediation analyses in future work.[83]

In conclusion, our findings demonstrate that viewing feared neck-specific movements is associated with increased pain-related distress and elicits altered neural activation in people with CWAD compared with controls. Overall, people with CWAD show more pronounced task-evoked activation in the somatosensory cortices and other brain areas implicated in motor imagery and pain anticipation, as well as impaired activation in areas implicated with cognitive and emotional appraisal of the feared movements. Taken together, this suggests that when conceptualizing forthcoming neck-specific movements associated with pain, people with CWAD may predict—and potentially amplify—their sensory and affective consequences and therewith trigger dysfunctional affective and behavioral responses.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

The authors thank Prof Dennis C. Turk for making the pictorial stimuli from the -PFActS-C *available*. The authors further thank Eveline Van Looveren, Elise Cnockaert, Thiemen De Smaele, Sarah De Schepper, and Sofie De Mulder for supporting data collection. Finally, the authors thank all volunteers who participated in the study.

This research was funded by Fonds Wetenschappelijk Onderzoek-FWO (G001419N). The funding body was not involved in the design of the study; collection, analysis, and interpretation of data; and in writing the manuscript.

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B797.

Article history:
Received 29 August 2022
Received in revised form 3 January 2023
Accepted 23 January 2023
Available online 22 March 2023

References

[1] Andrews-Hanna JR. The brain's default network and its adaptive role in internal mentation. Neuroscientist 2012;18:251–70.
[2] Apkarian AV. Pain perception in relation to emotional learning. Curr Opin Neurobiol 2008;18:464–8.
[3] Bahat H, Weiss PLT, Sprecher E, Krasovsky A, Laufer Y. Do neck kinematics correlate with pain intensity, neck disability or with fear of motion? Man Ther 2014;19:252–8.
[4] Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006;26:12165–73.
[5] Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008;28:1398–403.
[6] Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15:1117–9.
[7] Bandeira PM, Reis FJJ, Muniz FDN, Chaves ACS, Fernandes O Jr, Arruda-Sanchez T. Heart rate variability and pain sensitivity in chronic low back pain patients exposed to passive viewing of photographs of daily activities. Clin J Pain 2021;37:591–7.
[8] Barke A, Baudewig J, Schmidt-Samoa C, Dechent P, Kröner-Herwig B. Neural correlates of fear of movement in high and low fear-avoidant chronic low back pain patients: an event-related fMRI study. PAIN 2012; 153:540–52.
[9] Biggs EE, Timmers I, Meulders A, Vlaeyen JW, Goebel R, Kaas AL. The neural correlates of pain-related fear: a meta-analysis comparing fear conditioning studies using painful and non-painful stimuli. Neurosci Biobehav Rev 2020;119:52–65.
[10] Brett M, Anton J-L, Valabregue R, Poline J-B. Region of interest analysis using an SPM toolbox. Proceedings of the 8th international conference on functional mapping of the human brain, Vol. 16: Sendai, 2002. p. 497.
[11] Case LK, Pineda J, Ramachandran VS. Common coding and dynamic interactions between observed, imagined, and experienced motor and somatosensory activity. Neuropsychologia 2015;79:233–45.
[12] Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006;129:564–83.
[13] Chumbley J, Friston K. False discovery rate revisited: FDR and topological inference using Gaussian random fields. Neuroimage 2009;44:62–70.
[14] Coppieters I, Willaert W, Lenoir D, Meeus M, Cagnie B, Ickmans K, Malfliet A, Danneels L, De Petter B, Nijs J. A contemporary neuroscience approach compared to biomedically focused education combined with symptom-contingent exercise therapy in people with chronic whiplash associated disorders: a randomized controlled trial protocol. Braz J Phys Ther 2021;25:356–66.
[15] Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. PAIN 1999;80:329–39.
[16] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31: 968–80.
[17] Ellingsen DM, Napadow V, Protsenko E, Mawla I, Kowalski MH, Swensen D, O'Dwyer-Swensen D, Edwards RR, Kettner N, Loggia ML. Brain mechanisms of anticipated painful movements and their modulation by manual therapy in chronic low back pain. J Pain 2018; 19:1352–65.
[18] Esteban O, Birman D, Schaer M, Koyejo OO, Poldrack RA, Gorgolewski KJ. MRIQC: advancing the automatic prediction of image quality in MRI from unseen sites. PLoS One 2017;12:e0184661.
[19] Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, Kent JD, Goncalves M, DuPre E, Snyder M, Oya H, Ghosh SS, Wright J, Durnez J, Poldrack RA, Gorgolewski KJ. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods 2019;16:111–6.
[20] Fitzgibbon BM, Enticott PG, Rich AN, Giummarra MJ, Georgiou-Karistianis N, Bradshaw JL. Mirror-sensory synaesthesia: exploring 'shared' sensory experiences as synaesthesia. Neurosci Biobehav Rev 2012;36:645–57.
[21] Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR, Bent EK, Koneru VK, Dieterich ME, Hodge SM, Rauch SL, Grant PE, Cohen BM, Seidman LJ, Caviness VS, Biederman J. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 2005;162:1256–65.
[22] Gardini S, Cornoldi C, De Beni R, Venneri A. Left mediotemporal structures mediate the retrieval of episodic autobiographical mental images. Neuroimage 2006;30:645–55.
[23] Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magn Reson Med 2000;44:162–7.
[24] Hardwick RM, Caspers S, Eickhoff SB, Swinnen SP. Neural correlates of action: comparing meta-analyses of imagery, observation, and execution. Neurosci Biobehav Rev 2018;94:31–44.
[25] Harvey AK, Pattinson KT, Brooks JC, Mayhew SD, Jenkinson M, Wise RG. Brainstem functional magnetic resonance imaging: disentangling signal from physiological noise. J Magn Reson Imaging 2008;28: 1337–44.
[26] Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 2013;136:2751–68.
[27] Hotta J, Saari J, Koskinen M, Hlushchuk Y, Forss N, Hari R. Abnormal brain responses to action observation in complex regional pain syndrome. J Pain 2017;18:255–65.
[28] Jezzard P, Balaban RS. Correction for geometric distortion in echo planar images from B0 field variations. Magn Reson Med 1995;34:65–73.
[29] Jiang Y, Oathes D, Hush J, Darnall B, Charvat M, Mackey S, Etkin A. Perturbed connectivity of the amygdala and its subregions with the central executive and default mode networks in chronic pain. PAIN 2016; 157:1970–8.
[30] Kamper SJ, Maher CG, Menezes Costa LdC, McAuley JH, Hush JM, Sterling M. Does fear of movement mediate the relationship between pain intensity and disability in patients following whiplash injury? A prospective longitudinal study. PAIN 2012;153:113–9.
[31] Kamper SJ, Rebbeck TJ, Maher CG, McAuley JH, Sterling M. Course and prognostic factors of whiplash: a systematic review and meta-analysis. PAIN 2008;138:617–29.
[32] Kasper L, Bollmann S, Diaconescu AO, Hutton C, Heinzle J, Iglesias S, Hauser TU, Sebold M, Manjaly ZM, Pruessmann KP, Stephan KE. The PhysIO toolbox for modeling physiological noise in fMRI data. J Neurosci Methods 2017;276:56–72.
[33] Kilteni K, Andersson BJ, Houborg C, Ehrsson HH. Motor imagery involves predicting the sensory consequences of the imagined movement. Nat Commun 2018;9:1617.
[34] Kragting M, Voogt L, Neijenhuijs KI, Pool-Goudzwaard AL, Coppieters MW. Cross-cultural adaptation and validation of the Dutch language version of the pictorial fear of activity scale–cervical. BMC Musculoskelet Disord 2020;21:708.
[35] Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci 2015;38:86–95.
[36] Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. J Neurosci 2014;34:3969–75.
[37] Lange I, Kasanova Z, Goossens L, Leibold N, De Zeeuw CI, van Amelsvoort T, Schruers K. The anatomy of fear learning in the cerebellum: a systematic meta-analysis. Neurosci Biobehav Rev 2015;59:83–91.
[38] Larson CL, Schaefer HS, Siegle GJ, Jackson CA, Anderle MJ, Davidson RJ. Fear is fast in phobic individuals: amygdala activation in response to fear-relevant stimuli. Biol Psychiatry 2006;60:410–7.
[39] Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med 2007;30:77–94.
[40] Lueken U, Kruschwitz JD, Muehlhan M, Siegert J, Hoyer J, Wittchen HU. How specific is specific phobia? Different neural response patterns in two subtypes of specific phobia. Neuroimage 2011;56:363–72.
[41] Mayer JS, Roebroeck A, Maurer K, Linden DEJ. Specialization in the default mode: task-induced brain deactivations dissociate between visual working memory and attention. Hum Brain Mapp 2010;31:126–39.
[42] McCarthy MJH, Grevitt MP, Silcocks P, Hobbs G. The reliability of the Vernon and Mior neck disability index, and its validity compared with the short form-36 health survey questionnaire. Eur Spine J 2007;16:2111–7.
[43] Meier ML, Stämpfli P, Vrana A, Humphreys BK, Seifritz E, Hotz-Boendermaker S. Neural correlates of fear of movement in patients with

chronic low back pain vs. pain-free individuals. Front Hum Neurosci 2016; 10:386.
[44] Meulders A, Vansteenwegen D, Vlaeyen JW. The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. PAIN 2011;152:2460–9.
[45] Meulders A, Vlaeyen JW. Mere intention to perform painful movements elicits fear of movement-related pain: an experimental study on fear acquisition beyond actual movements. J Pain 2013;14:412–23.
[46] Moseley GL, Zalucki N, Birklein F, Marinus J, van Hilten JJ, Luomajoki H. Thinking about movement hurts: the effect of motor imagery on pain and swelling in people with chronic arm pain. Arthritis Rheum 2008;59: 623–31.
[47] Nielsen FÅ, Balslev D, Hansen LK. Mining the posterior cingulate: segregation between memory and pain components. Neuroimage 2005; 27:520–32.
[48] Nieto R, Miró J, Huguet A. The fear-avoidance model in whiplash injuries. Eur J Pain 2009;13:518–23.
[49] Palermo S, Benedetti F, Costa T, Amanzio M. Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies. Hum Brain Mapp 2015;36:1648–61.
[50] Parks EL, Geha PY, Baliki MN, Katz J, Schnitzer TJ, Apkarian AV. Brain activity for chronic knee osteoarthritis: dissociating evoked pain from spontaneous pain. Eur J Pain 2011;15:843.e1–e14.
[51] Pedler A, Sterling M. Assessing fear-avoidance beliefs in patients with whiplash-associated disorders: a comparison of 2 measures. Clin J Pain 2011;27:502–7.
[52] Peng K, Steele SC, Becerra L, Borsook D. Brodmann area 10: collating, integrating and high level processing of nociception and pain. Prog Neurobiol 2018;161:1–22.
[53] Penny WD, Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE. Statistical parametric mapping: the analysis of functional brain images. London, United Kingdom: Elsevier, 2011.
[54] Pfingsten M, Leibing E, Harter W, Kröner-Herwig B, Hempel D, Kronshage U, Hildebrandt J. Fear-avoidance behavior and anticipation of pain in patients with chronic low back pain: a randomized controlled study. Pain Med 2001;2:259–66.
[55] Poldrack RA. Region of interest analysis for fMRI. Soc Cogn Affect Neurosci 2007;2:67–70.
[56] Poldrack RA, Fletcher PC, Henson RN, Worsley KJ, Brett M, Nichols TE. Guidelines for reporting an fMRI study. Neuroimage 2008;40:409–14.
[57] Poldrack RA, Mumford JA. Independence in ROI analysis: where is the voodoo? Soc Cogn Affect Neurosci 2009;4:208–13.
[58] Raichle ME. The brain's default mode network. Annu Rev Neurosci 2015; 38:433–47.
[59] Roelofs J, McCracken L, Peters ML, Crombez G, van Breukelen G, Vlaeyen JWS. Psychometric evaluation of the pain anxiety symptoms scale (PASS) in chronic pain patients. J Behav Med 2004;27:167–83.
[60] Roelofs J, Peters ML, McCracken L, Vlaeyen JW. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. PAIN 2003;101: 299–306.
[61] Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. J Neurophysiol 2007;97:3651–9.
[62] Shearer HM, Carroll LJ, Côté P, Randhawa K, Southerst D, Varatharajan S, Wong JJ, Yu H, Sutton D, van der Velde G, Nordin M, Gross DP, Mior S, Stupar M, Jacobs C, Taylor-Vaisey A. The course and factors associated with recovery of whiplash-associated disorders: an updated systematic review by the Ontario protocol for traffic injury management (OPTIMa) collaboration. Eur J Physiother 2020;23:279–94.
[63] Shimo K, Ueno T, Younger J, Nishihara M, Inoue S, Ikemoto T, Taniguchi S, Ushida T. Visualization of painful experiences believed to trigger the activation of affective and emotional brain regions in subjects with low back pain. PLoS One 2011;6:e26681.
[64] Simons LE, Moulton EA, Linnman C, Carpino E, Becerra L, Borsook D. The human amygdala and pain: evidence from neuroimaging. Hum Brain Mapp 2014;35:527–38.
[65] Sterling M, Chadwick BJ. Psychologic processes in daily life with chronic whiplash: relations of posttraumatic stress symptoms and fear-of-pain to hourly pain and uptime. Clin J Pain 2010;26:573–82.
[66] Tanasescu R, Cottam WJ, Condon L, Tench CR, Auer DP. Functional reorganisation in chronic pain and neural correlates of pain sensitisation: a coordinate based meta-analysis of 266 cutaneous pain fMRI studies. Neurosci Biobehav Rev 2016;68:120–33.
[67] Taylor A, Harris A, Buck R, Varnava A, Hughes O, Wilkes AR, Hall J, Wise R. Imaging neural responses to affective and pain-related stimuli in chronic non-malignant pain patients vs healthy controls. Br J Anaesth 2011;107:830P–1P.
[68] Taylor AM, Harris AD, Varnava A, Phillips R, Taylor JO, Hughes O, Wilkes AR, Hall JE, Wise RG. A functional magnetic resonance imaging study to investigate the utility of a picture imagination task in investigating neural responses in patients with chronic musculoskeletal pain to daily physical activity photographs. PLoS One 2015;10:e0141133.
[69] Timmann D, Drepper J, Frings M, Maschke M, Richter S, Gerwig M, Kolb FP. The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. Cortex 2010;46:845–57.
[70] Timmers I, de Jong JR, Goossens M, Verbunt JA, Smeets RJ, Kaas AL. Exposure in vivo induced changes in neural circuitry for pain-related fear: a longitudinal fMRI study in chronic low back pain. Front Neurosci 2019; 13:970.
[71] Timmers I, Quaedflieg CWEM, Hsu C, Heathcote LC, Rovnaghi CR, Simons LE. The interaction between stress and chronic pain through the lens of threat learning. Neurosci Biobehav Rev 2019;107:641–55.
[72] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–91.
[73] Treleaven J. Dizziness, unsteadiness, visual disturbances, and sensorimotor control in traumatic neck pain. J Orthop Sports Phys Ther 2017;47:492–502.
[74] Turk DC, Robinson JP, Sherman JJ, Burwinkle T, Swanson K. Assessing fear in patients with cervical pain: development and validation of the Pictorial Fear of Activity Scale-Cervical (PFActS-C). PAIN 2008;139: 55–62.
[75] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative S. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4:e297.
[76] Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther 1991;14:409–15.
[77] Vierck CJ, Whitsel BL, Favorov OV, Brown AW, Tommerdahl M. Role of primary somatosensory cortex in the coding of pain. PAIN 2013;154: 334–44.
[78] Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 2005;6:533–44.
[79] Vrana A, Hotz-Boendermaker S, Stämpfli P, Hänggi J, Seifritz E, Humphreys BK, Meier ML. Differential neural processing during motor imagery of daily activities in chronic low back pain patients. PLoS One 2015;10:e0142391.
[80] Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368: 1388–97.
[81] Weissman-Fogel I, Moayedi M, Tenenbaum HC, Goldberg MB, Freeman BV, Davis KD. Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks. PAIN 2011;152:384–96.
[82] Wiech K, Tracey I. Pain, decisions, and actions: a motivational perspective. Front Neurosci 2013;7:46.
[83] Woo CW, Roy M, Buhle JT, Wager TD. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. PLoS Biol 2015; 13:e1002036.
[84] Xu A, Larsen B, Henn A, Baller EB, Scott JC, Sharma V, Adebimpe A, Basbaum AI, Corder G, Dworkin RH, Edwards RR, Woolf CJ, Eickhoff SB, Eickhoff CR, Satterthwaite TD. Brain responses to noxious stimuli in patients with chronic pain: a systematic review and meta-analysis. JAMA Netw Open 2021;4:e2032236.
[85] Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, Li Q, Zuo XN, Castellanos FX, Milham MP. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage 2013;76:183–201.
[86] Youssef AM, Azqueta-Gavaldon M, Silva KE, Barakat N, Lopez N, Mahmud F, Lebel A, Sethna NF, Zurakowski D, Simons LE, Kraft E, Borsook D. Shifting brain circuits in pain chronicity. Hum Brain Mapp 2019;40:4381–96.