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

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. Here, we examined neural correlates of imagining neck-specific movements designed to elicit pain-related distress in individuals with whiplash-associated disorders (n=63) as compared to gender-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 to 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 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 CWAD 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.

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 (i.e., the neural processing involved in the anticipation, fear and avoidance of pain).

Over the last decades, neuroimaging research has attempted to unravel the complexity of the pain experience and chronic pain.[35; 72; 80] To date, the vast majority of the 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 (e.g., pain-related fear, catastrophizing, and hypervigilance)[36] and emotional learning and memory (e.g., prior 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 imagining or even simply viewing feared movements can trigger pain and related fear similar to that observed during or prior to 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 (e.g., 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, catastrophizing and/or anxiety.[43; 63; 70] To date, research on 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 to 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 to neutral movements. Additionally, 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 sub-study 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 prior to enrolment. CWAD participants were included if they were 18-65 years old and had neck pain due to a whiplash injury ≥ 3 months ago, with moderate/severe pain-related disability (i.e., ≥ 15/50 on the Neck Disability Index [NDI][76]). Pain-free controls were recruited for the sub-study specifically, were age- and gender-matched and were included if they had no history of neck pain. Further details on the eligibility criteria can be found in **Table S1**.

The sub-study 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 prior to 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 short form-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 in 3 subscales: magnification, helplessness and rumination.[15] Pain-related fear and anxiety was 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 in 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 in 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 (i.e., specific directions of neck movement, arms 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 fear (PASS-20), catastrophizing (PCS) and disability (NDI).[34; 74] For the current fMRI paradigm, 15 PFActS-C pictures were selected across 3 categories (i.e., 5 pictures per category) in order to elicit different degrees of pain-related fear among the CWAD participants (i.e., 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 (e.g., full flexo-extension 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 3s, followed by a cue to imagine the movement/activity for 3s, and 4-8s of fixation cross or inter-trial interval (ITI; **Fig. 1**). One of three pseudo-randomized versions of the task was presented, each of them with 90 trials (i.e., 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.) and were synchronized with MR data

acquisition. The total duration of the scanning sessions was approximately 50 min (data from other acquisitions will be described elsewhere).

Prior to 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 (i.e., 4 pictures were shown, and these practice pictures were not included in the experimental task).

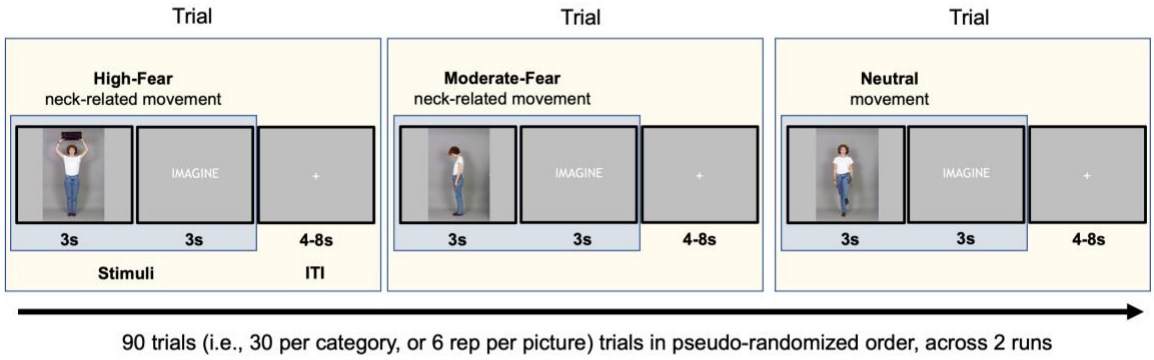

Figure 1: Experimental paradigm. One example trial from each of the three picture categories is presented (high-fear, moderate-fear and neutral pictures), including the timing. ITI = intertrial interval

2.5. Experimental paradigm ratings

After the scanning session, participants were requested to view and rate each picture from 0-10 in terms of **expected pain** (i.e., "*How painful would it be to perform the activity shown in the picture?*"), **worry** (i.e., *"How worried would you be to perform the activity shown in the picture?"*), **fear/anxiety** (i.e., "*How fearful/anxious would you be to perform the activity shown in the picture?"*) and **avoidance** tendency (i.e., *"To what extent would you want to avoid performing the activity shown in the picture?"*). Additionally, participants were asked how **easy** it was **to imagine** each picture within the scanner. Pictures and ratings were presented in random order on a laptop using Presentation Software and were self-paced.

2.6. MRI and physiological data acquisition

MRI data were collected using a 3T MRI scanner (Siemens MAGNETOM Prisma) using 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, SMS factor = 4. In total, 1040 volumes were collected across the two runs.

Structural images were acquired using an MPRAGE T1 protocol 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 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, 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 Acknowledge, Biopac Systems, USA). Data was continuously recorded at 2000 samples/s with a photoplethysmograph (PPG; TSD200-MRI) placed on the index finger of the non-dominant hand and a pneumatic respiratory belt (BN-RESP-XDCR) strapped around the participant's thorax. MRI trigger pulses were recorded using Acknowledge 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 (i.e., expected pain, worry, fear, avoidance tendency), 2-way repeated measures analysis of variance (ANOVA) were performed to examine differences across groups (CWAD and pain-free controls), pictorial categories (High-Fear, Moderate-Fear and Neutral) and interactions between group and picture category. Pairwise comparisons with 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. MRI pre-processing

MRIqc[18] 0.16.1 was used to generate reports for visual inspection of potential artifacts (e.g., reconstruction errors, registration issues, and incorrect brain masks) and Image

Quality Metrics (IQMs) for quality control. Functional runs were excluded if there was absolute head motion > voxel size (2.5mm), ≥ 20% outlier volumes, outlying tSNR (if > 1.5 * interquartile range from first/third quartile) or if no activation was observed in the occipital area when contrasting the pictures to baseline (i.e., indicating they did not view the pictures, or may have fell asleep). In total, 3 CWAD participants had to be excluded from the final analysis as well as one of the two fMRI runs in 13 participants (see study flowchart in the **Fig. S1**).

Pre-processing of fMRI data was performed using *fMRIPrep*[19] version 20.2.1. In brief, pre-processing steps included slice time correction, realignment, co-registration, field-map distortion correction, segmentation of T1-weighted structural images and normalization to the MNI space (see [19] for further information about the pipeline and workflow). The pre-processed 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 3rd order cardiac model (6 regressors, sine/cosine), a 4th order respiratory model (8 regressors), and a 1st 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. MRI data analysis

First-level analyses. Pre-processed volumes and nuisance regressors for both runs were entered in the 1st level SPM General Linear Model for each participant. The 6s of stimuli presentations (3s picture + 3s imagine cue; similar to Timmers et al. [70]) were convolved with the canonical hemodynamic response function to obtain 3 regressors of interest (i.e., 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 (i.e., High-Fear vs baseline, Moderate-Fear vs baseline, 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.

Second-level analyses. The obtained parameter estimate images were then entered in a 2nd 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 2x3 full factorial

model with group as between-group factor (CWAD, pain-free) and picture category as within-group factor (High-Fear, Moderate-Fear, Neutral) was fitted to test for group differences in our main contrasts of interest via interactions: 'High-Fear vs Neutral', 'Moderate-Fear vs Neutral' and 'High-Fear vs Moderate-Fear'. Mean framewise displacement was greater in the CWAD group 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 (FDR $p < .05$) correction to control for false positive results.[13] We further corrected for multiple testing across the 3 contrasts of interest with Bonferroni correction. For plotting purposes, one sample t-tests were carried out for each contrast of interest per group (e.g., High-Fear > Neutral in CWAD) within the fitted full factorial model.

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 .25). 4 mm spheres were taken centered around coordinates from previous studies for PCC (MNI coordinates x = -4, y = -50, z = 32 and x = 6, y = -46, z = 32)[67], ACC (x = -8, y = 30, z = 22 and x = 12, y = 36, z = 16)[67], anterior insula (x = 33, y = -10, z = 10)[43], posterior insula (x = 33, y = -10, z = 10)[70] and vmPFC (x = 0, y = 41, z = -11)[70]. We extracted the beta coefficients from High-Fear vs baseline, Moderate-Fear vs baseline, Neutral vs baseline fitting the same 2x3 full factorial model using *marsbar*[10] for each pre-defined ROI. We then performed an ANOVA in R, adding mean framewise displacement as a covariate, to test for group differences via 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]

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 (i.e., PASS-20, PCS, 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 can be found in **Table 1**.

Table 1. Participants' characteristics

	CWAD (N=63)	pain-free controls (N=32)	Between-group comparison
Gender			$\chi^2 = 0.012$, $p = 0.913$
Female	45 (71.4%)	22 (68.8%)	
Male	18 (28.6%)	10 (31.3%)	
Age (years)	42.60 (10.2)	41.0 (10.6)	$t = -0.598$, $p = 0.552$
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/week (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 is presented instead of mean and SD.

3.2. Experimental paradigm ratings

The picture ratings for each outcome are illustrated in **Fig. 2** (see further details on the scores per picture in **Table S2)**. A picture category by group interaction was found for all the examined outcomes: expected pain ($F[1,90] = 47.46$; $p < 0.001$, $\eta^2 = 0.35$), worry ($F[1,90] = 35.41$; $p < 0.001$, $\eta^2 = 0.29$), anxiety/fear ($F[1,90] = 26.04$; $p < 0.001$, $\eta^2 = 0.23$) and avoidance ($F[1,90] = 48.06$; $p < 0.001$, $\eta^2 = 0.35$). Overall, people with CWAD provided greater scores in High-Fear and Moderate-Fear compared to Neutral pictures as well as greater scores in High-

Fear compared to Moderate-Fear. No differences between picture categories were observed in pain-free controls. Full details on the results of the behavioral data can be found in **Table S3**. Also, participants rated pictures relatively high regardless of the category in terms of 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, η^2= 0.12) (**Table S2**).

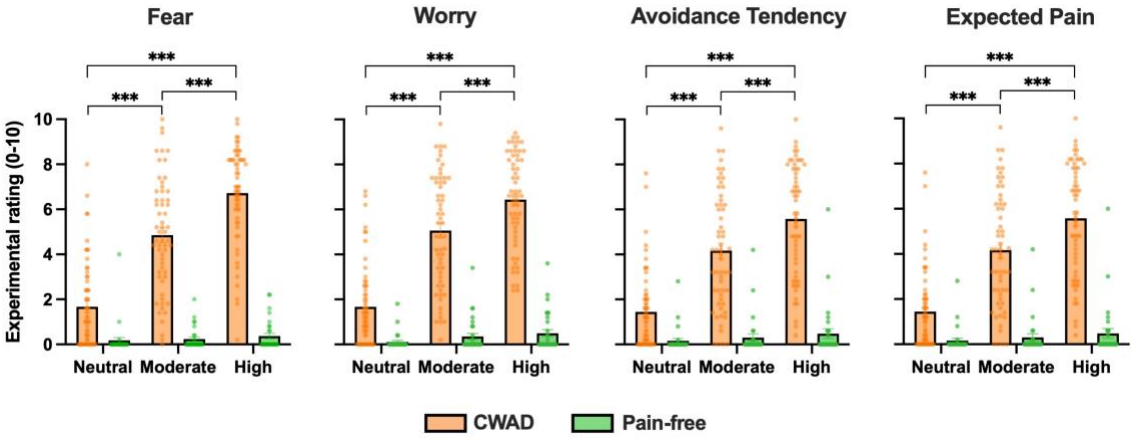

Figure 2: Within-group differences in experimental paradigm ratings. Presented are the averaged ratings across the five pictures in each category, for each rating (expected pain, worry, anxiety and avoidance), and separately per group.

3.3. Differences in BOLD activation between individuals with CWAD and pain-free controls

High-Fear vs Neutral pictures. **Fig. 3.A** shows the activation maps for the High-Fear vs Neutral contrast per group (see clusters and coordinates in **Table S4**). Overall, people with CWAD showed greater activation to High-Fear compared to Neutral pictures, including in regions such as post/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 during Neutral compared to High-Fear pictures was observed in superior parietal lobule and precentral gyrus. The controls, on the other hand, exhibited overall greater activation in Neutral pictures compared to the High-Fear pictures, in 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. 3.B, Table 2**), where individuals with CWAD showed greater difference in BOLD activation

in the contrast High-Fear > Neutral pictures compared to pain-free controls. These clusters included 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). There were no clusters in which pain-free controls showed a greater difference across the conditions. The pre-defined ROI analyses revealed a between-group difference for this contrast in left and right PCC and left ACC (**Table S5**), partly supporting the results from the whole-brain analysis.

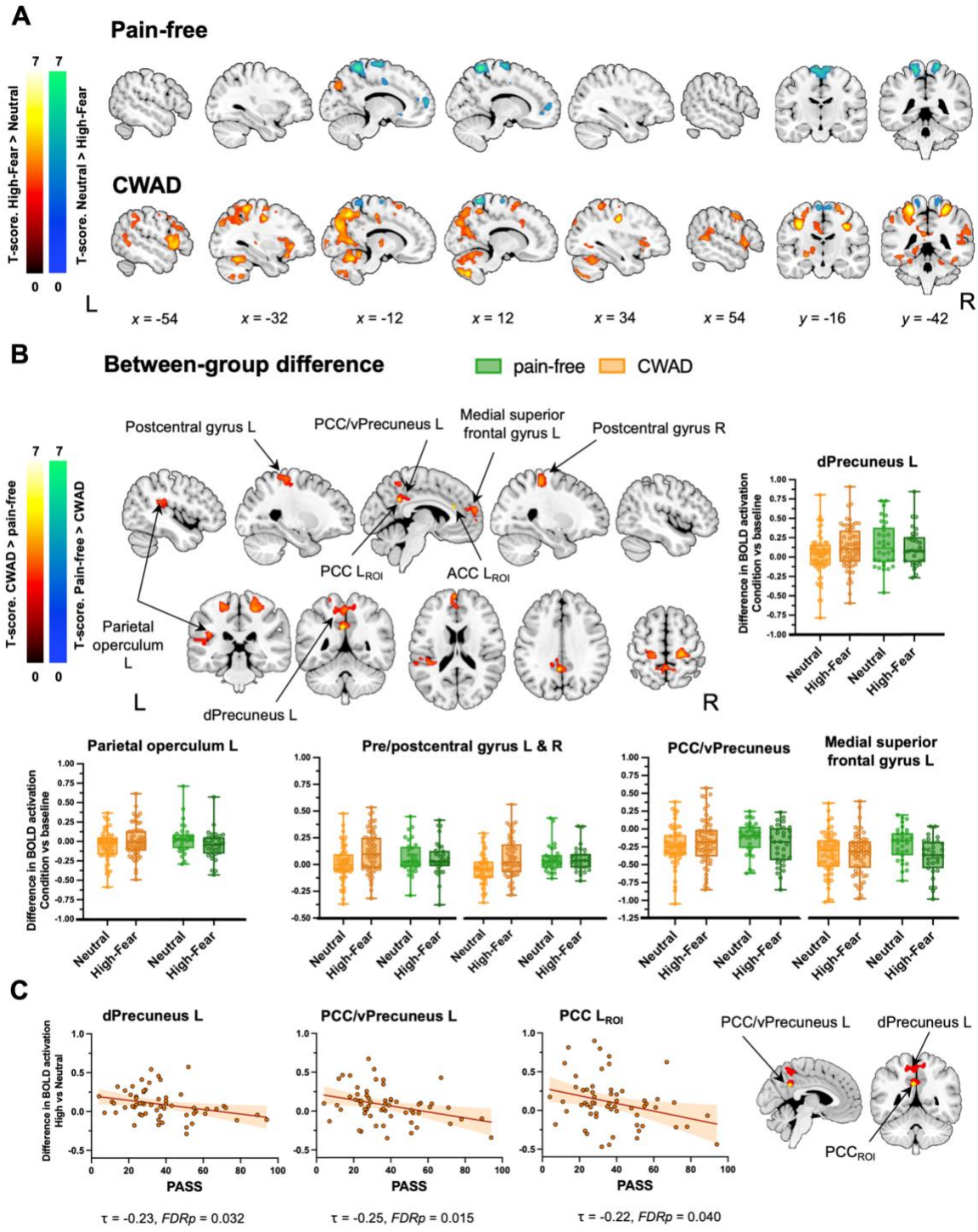

Figure 3. **(A)** Maps showing the contrast High-Fear vs Neutral, separately per group (one sample t-test). **(B)** Significant clusters and ROIs in the between-group comparison of the High-Fear vs Neutral contrast. Extracted beta coefficients for each of the significant clusters are presented in the 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).

Table 2. Cluster information on the group differences in contrasts High-Fear vs Neutral, and Moderate-Fear vs Neutral pictures. Information on local maxima is included as well, where applicable. Anatomical locations are derived from Harvard Oxford atlases

	cluster		peak	MNI coordinates				
	p(FDRc)	k	T_{max}	x	y	z	Anatomical location[1]	
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								

k = cluster size.
Notes: † denotes clusters not surviving the Bonferroni correction for multiple contrast testing ($p < 0.016$).

Moderate-Fear vs Neutral pictures. Overall, the Moderate-Fear > Neutral contrast yielded activation in a similar network than the contrast High-Fear > Neutral in individuals with CWAD, while greater bilateral activation was observed in cuneal cortex and lingual gyrus in pain-free controls (**Fig. 4.A**; **Table S6**). Again, increased bilateral activation in Neutral compared to Moderate-Fear pictures was observed in 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 (**Fig. 4.B**): in right and left posterolateral cerebellum for people with CWAD compared to pain-free controls (**Table 2**). The ROI analyses did not reveal any additional between-group differences for this contrast (**Table S5**).

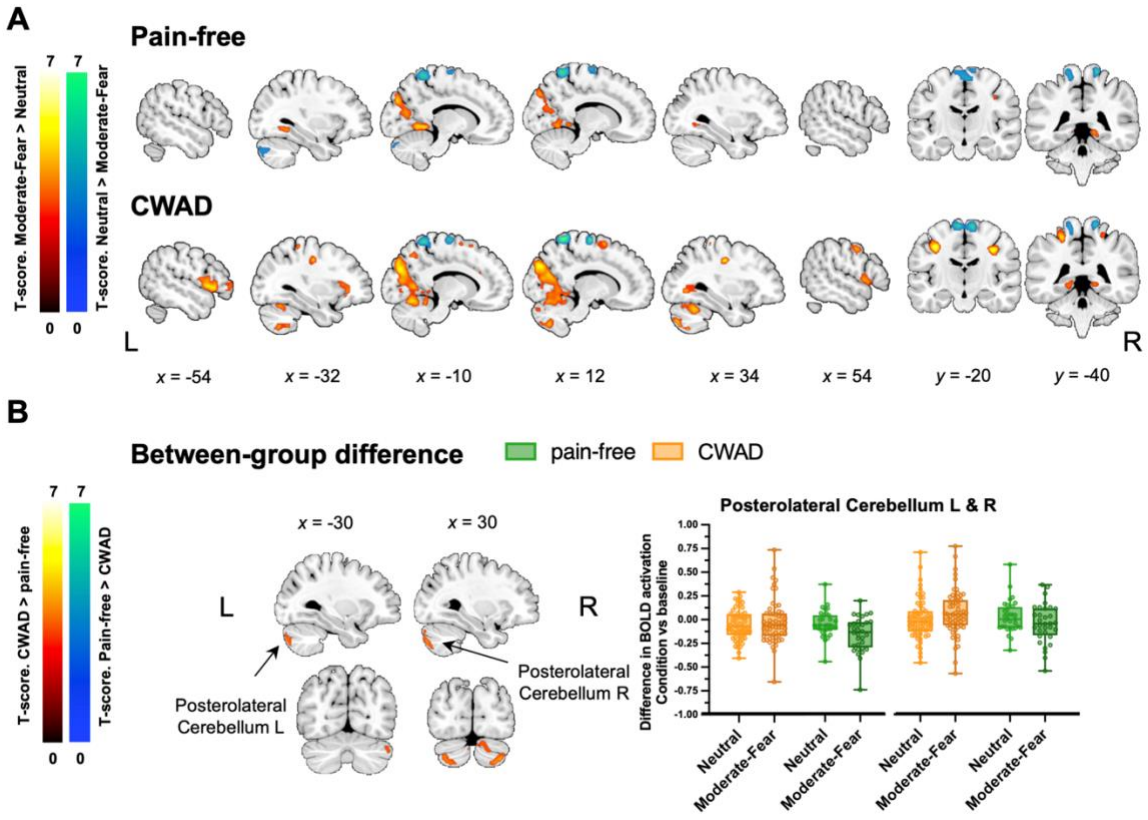

Figure 4. (A) Maps showing the contrast Moderate-Fear vs Neutral, separately per group (one sample t-test) **(B)** Significant clusters and ROIs in the between-group comparison of the Moderate-Fear vs Neutral contrast. Extracted beta coefficients for each of the significant clusters are presented in the boxplots.

High-Fear vs Moderate-Fear pictures. People with CWAD exhibited a greater activation in High-Fear compared to Moderate-Fear category in right lateral occipital cortex, supramarginal gyrus and middle/inferior frontal gyrus. Pain-free controls also showed greater activation in High-Fear compared to Moderate-Fear category in left and right supramarginal gyrus and angular cortex. Additionally, pain-free controls exhibited greater activation in the opposite contrast (Moderate-Fear compared to High-Fear) in left medial superior frontal gyrus, ACC and lingual gyrus and paracingulate gyrus and pre/postcentral gyrus (**Table S7 and Fig. S2**). 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**).

3.4.Associations with pain-related outcomes in CWAD

For the clusters showing a group difference in High-Fear vs Neutral, a small negative association was observed between pain-related fear (PASS-20) and the PCC/ventral precuneus cluster (cluster VI: τ = -0.250, *pFDR* = 0.015), the dorsal precuneus cluster (cluster IV: τ = -

0.228, *pFDR* = 0.032) and the predefined ROI for left PCC (τ = -0.217, *pFDR* = 0.040) (**Fig. 3C, Table S8**). These associations show that the smaller the difference in BOLD activation between High-Fear vs Neutral, the higher the level of pain-related fear. No other correlations were observed for the other clusters, nor for the contrasts Moderate-Fear vs Neutral (**Table S8**).

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 as compared to 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 sensorimotor regions of the primary (S1) and secondary (S2) somatosensory cortex (e.g., postcentral gyrus and parietal operculum) as well as in regions implicated in cognitive/affective aspects of pain (e.g., mPFC, ACC, PCC and precuneus). Overall, this altered activation 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 and Neutral, which showed a small negatively correlation with pain-related fear. The current 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, catastrophizing and avoidance behavior contribute to restricted neck movement and related disability in people with CWAD more than pain itself.[3; 30; 48; 74] Our behavioral data show that the experimental stimuli tap into these constructs, as CWAD participants provided higher ratings of pain-related fear, worry, tendency to avoid, and expected pain for the pictures of neck-specific movements (High- and Moderate-Fear) which is in line with the PFActS-C validation results.[74] Interestingly, 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, CWAD participants provided higher ratings than pain-free controls across all examined outcomes, including the neutral pictures.

In the current study, individuals with CWAD, relative to pain-free controls, showed increased activation to viewing neck-related movements compared 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 (e.g., 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 (i.e., sensations associated with executing a particular action).[24; 33] The increased S1 activation observed in our study was, in fact, somatotopically-specific to neck and upper limb. This suggests that the mere imagination of neck-related movements may have led CWAD participants 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 (e.g., 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 appears to be of additional importance in 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 (e.g., self-regulation of pain or threat via 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 (i.e., High-Fear, Moderate-Fear and Neutral) while this was only observed during the High-Fear pictures in pain-free controls. This finding may therefore reflect that all conditions were cognitively demanding for CWAD participants, potentially associated with 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[70] in people with chronic low back pain could point toward altered inhibitory control; particularly a reduced cognitive self-regulation and ability to modulate pain.[52; 83] On the other hand, PCC remained active or was less deactivated in CWAD participants during High- and Moderate-Fear compared to 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] 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 the current study, PCC (de)activation was correlated to a small degree with pain-related fear (i.e., CWAD participants with higher levels of pain-related fear showed lower deactivation in PCC during 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 (i.e., 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 duration of the paradigm under investigation. It is also possible that 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 relative to Neutral pictures (i.e., neck and upper limb-related) and vice versa (i.e., 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 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 and so, could have not fully served as neutral control condition in some CWAD participants and may have concealed further between-group differences in other important regions of pain processing. This could have been the case of 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 to baseline in previous similar studies.[68; 70] This could also partially explain why only one cluster's activation pattern correlated with the pain-related questionnaires in CWAD participants. Along the same lines, the behavioral scores illustrate that there was some within-category variability (i.e., 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 due to the fact that, like previous studies, pictures were pre-selected rather than individually tailored. In order to overcome this limitation, we plan to examine the inter-picture relationships via mediation analysis 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 to 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.

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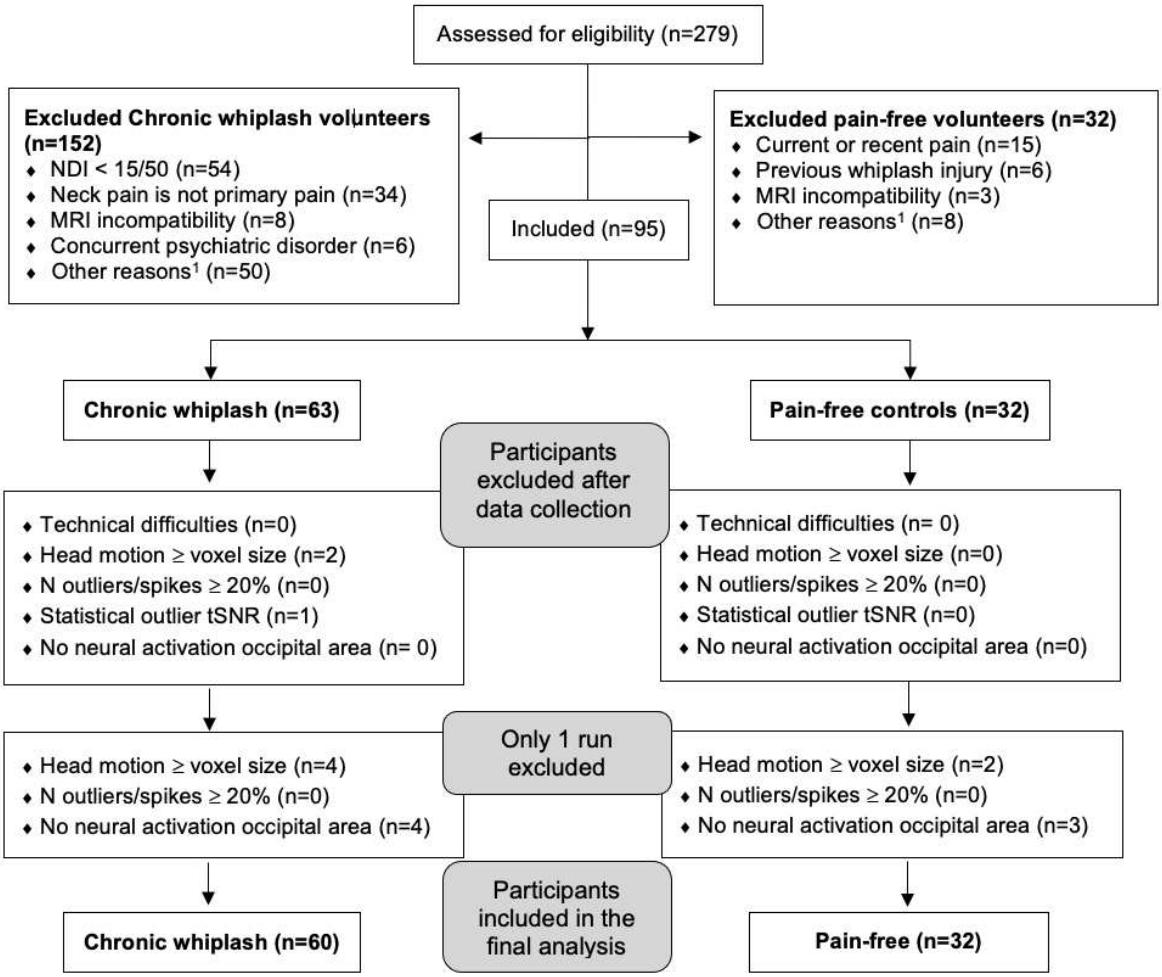
Supplementary Materials

Table S1. Eligibility criteria.

Inclusion criteria	Exclusion criteria
- Agreed to participate in the ongoing RCT. - Chronic neck pain due to a whiplash injury (≥ 3 months of duration) with frequency of at least 3 days/week. - Whiplash grade II to III as defined by the Quebec TaskForce scale. - Moderate/severe pain-related disability (≥15/50 on the Neck Disability Index) - Women or men aged between 18 and 65 years-old - Being a native Dutch speaker - Not starting new treatments or medication and continuing their usual care 6 weeks prior to and during study participation	- Severe cardiovascular, respiratory or endocrine disorder. - Neurological or rheumatoid disorder - Psychiatric disorder - History of neck or shoulder surgery in the past 3 years - Loss of consciousness after the whiplash trauma for > 1min - Being pregnant or having given birth in the preceding year - Neuropathic pain with diagnosis of nerve injury - Chronic widespread pain syndromes (e.g., fibromyalgia, chronic fatigue syndrome…) - Neuroscientific based therapy in patient history, andconcomitant therapies - Neck pain is not the primary pain-related complaint. **MRI-related** - Claustrophobia - non-MRI compatible (pacemaker, metal implant,..)

Figure S1 Flowchart



[1] "Other reasons" include fracture, surgery, non-Dutch speaking, age, (severe) cardiovascular, respiratory, neurological, rheumatic or endocrine disorder, head trauma, idiopathic neck pain…

Table S2. Experimental paradigm scores per picture (Mean and SD).

PFActS-C category		CWAD					Pain-free controls				
		Expected pain	Worry	Anxiety	Avoidance	Imagine	Expected pain	Worry	Anxiety	Avoidance	Imagine
High-Fear	Pic 1	6.57±2.24	5.34±2.70	4.87±2.91	7.03±2.46	6.73±2.31	0.46±0.97	0.43±1.38	0.33±0.84	0.53±1.71	8.00±1.66
	Pic 2	7.11±2.50	6.36±2.90	5.06±3.41	7.33±2.72	7.09±2.45	0.66±1.18	0.70±1.55	0.30±0.75	0.86±1.92	7.96±1.71
	Pic 3	4.82±2.53	4.22±2.72	3.60±2.89	4.92±2.74	7.14±2.15	0.26±0.64	0.16±0.53	0.10±0.40	0.16±0.46	8.30±1.46
	Pic 4	7.44±2.34	6.50±2.90	5.33±3.29	7.60±2.41	7.06±2.42	0.70±1.14	0.66±1.49	0.36±0.85	0.86±1.92	8.03±1.67
	Pic 5	5.63±2.61	4.84±2.74	3.81±2.96	5.84±2.70	6.90±2.20	0.43±0.81	0.40±1.38	0.30±0.70	0.56±1.85	7.90±1.70
Moderate-Fear	Pic 6	3.81±2.74	3.23±2.81	2.57±2.67	3.69±3.01	7.59±1.71	0.23±0.62	0.20±0.66	0.20±0.66	0.33±1.32	8.50±1.59
	Pic 7	5.12±2.91	4.27±2.90	3.41±3.05	5.06±3.05	7.04±2.17	0.36±0.76	0.20±0.76	0.16±0.59	0.40±1.47	8.10±1.53
	Pic 8	5.06±3.02	4.02±3.13	3.17±3.01	4.79±3.08	7.37±2.24	0.30±0.70	0.33±1.26	0.23±0.67	0.33±1.32	8.50±1.45
	Pic 9	4.74±2.92	3.95±2.91	3.12±2.94	4.54±3.11	7.31±2.14	0.30±0.70	0.26±1.11	0.20±0.61	0.40±1.47	8.60±1.65
	Pic 10	5.81±2.85	5.36±2.90	4.07±3.07	5.98±2.96	7.47±2.22	0.50±1.16	0.36±0.85	0.30±0.65	0.53±1.77	8.56±1.50
Neutral	Pic 11	1.85±2.22	1.69±2.21	1.22±2.02	1.88±2.43	7.49±1.96	0.10±0.40	0.16±0.53	0.06±0.25	0.16±0.74	8.23±1.71
	Pic 12	1.76±1.88	1.49±1.84	1.12±1.54	1.81±2.41	7.67±2.17	0.10±0.30	0.20±0.76	0.10±0.30	0.20±0.92	8.86±1.27
	Pic 13	1.12±1.57	1.03±1.79	0.84±1.35	1.15±1.90	7.09±2.27	0.06±0.25	0.06±0.36	0.03±0.18	0.13±0.57	8.70±1.44
	Pic 14	1.77±2.01	1.71±2.23	1.22±1.7	2.12±2.51	7.44±1.84	0.16±0.46	0.23±0.67	0.10±0.30	0.20±0.76	8.50±1.43
	Pic 15	1.92±2.15	1.79±2.23	1.33±1.79	1.93±2.48	7.50±1.80	0.16±0.59	0.16±0.59	0.16±0.53	0.16±0.74	8.60±1.38

High-Fear (weight bearing) pictures **(Pic1)** arms at shoulders – L neck lateral bending, **(Pic2)**, arms overhead - neutral neck, **(Pic3)** arms at side - neutral neck, **(Pic4)** arms at overhead - neck extension, **(Pic5)** arms at shoulders - neutral neck

Moderate-Fear (non-weight bearing) pictures **(Pic6)** arms at side – L neck lateral bending, **(Pic7)** arms at shoulders – L neck lateral bending, **(Pic8)** arms at side – R neck rotation, **(Pic9)** arms at side - neck flexion, **(Pic10)** arms at side - neck extension

Neutral control pictures **(Pic11)** arms at side – L leg extended backward at 90°, **(Pic12)** arms at side – rising up at toes 45°, **(Pic13)** arms at side – L split side-to-side at 60°, **(Pic14)** arms at side – L leg flexed forward at 90°, **(Pic15)** arms at side – L leg extended forward at 90°

Table S3. Results for the experimental paradigm scores (Mean, SD and 95% CIs).

Behavioral outcome	CWAD	Pain-free	Between-group Difference
Expected pain (0-10)			
Neutral	1.67±1.79	0.12±0.37	1.55 (0.90, 2.20)
Moderate-Fear	5.06±2.52	0.35±0.74	4.70 (3.78, 5.62)
Moderate-Fear – Neutral difference	3.39 (2.69, 4.09)	0.23 (-0.72, 1.20)	
High-Fear	6.44±2.07	0.49±0.87	5.94 (5.17, 6.72)
High-Fear - Neutral difference	4.77 (4.15, 5.38)	0.38 (-0.46, 1.22)	
High-Fear – Moderate-Fear difference	1.38 (0.74, 2.02)	0.14 (-0.73, 1.02)	
Worry (0-10)			
Neutral	1.44±1.72	0.16±0.55	1.28 (0.65, 1.91)
Moderate-Fear	4.17±2.58	0.30±0.82	3.86 (2.91, 4.82)
Moderate-Fear – Neutral difference	2.72 (2.02, 3.42)	0.14 (-0.82, 1.10)	
High-Fear	5.58±2.48	0.48±1.21	5.09 (4.15, 6.04)
High-Fear - Neutral difference	4.13 (3.54, 4.72)	0.31 (-0.50, 1.13)	
High-Fear – Moderate-Fear difference	1.40 (0.76, 2.05)	0.17 (-0.71, 1.06)	
Fear/anxiety (0-10)			
Neutral	1.16±1.51	0.09±0.28	1.07 (0.52, 1.62)
Moderate-Fear	3.31±2.68	0.22±0.55	3.10 (2.13, 4.06)
Moderate-Fear – Neutral difference	2.15 (1.51, 2.79)	0.13 (-0.76, 1.02)	
High-Fear	4.53± 2.87	0.27± 0.65	4.26 (3.22, 5.30)
High-Fear - Neutral difference	3.37 (2.70, 4.04)	0.18 (-0.74, 1.10)	
High-Fear – Moderate-Fear difference	1.21 (0.66, 1.77)	0.05 (-0.72, 0.82)	
Avoidance (0-10)			
Neutral	1.67±1.91	0.17±0.73	1.50 (0.80, 2.22)
Moderate-Fear	4.85±2.51	0.23±0.48	4.63 (3.72, 5.53)
Moderate-Fear – Neutral difference	3.18 (2.40, 3.96)	0.06 (-1.01, 1.13)	
High-Fear	6.72±2.13	0.36±0.66	6.36 (5.57, 7.14)
High-Fear - Neutral difference	5.04 (4.38, 5.71)	0.19 (-0.72, 1.11)	
High-Fear – Moderate-Fear difference	1.87 (1.20, 2.53)	0.13 (-0.78, 1.05)	
Easy to imagine (0-10)			
Neutral	7.41±1.65	8.60±1.36	-1.18 (-0.50, -1.87)
Moderate-Fear	7.33 ±1.80	8.47±1.43	-1.14 (-0.40, -1.88)
Moderate-Fear – Neutral difference	-0.08 (-0.50, 0.34)	-0.12 (-0.71, 0.45)	
High-Fear	6.95±2.05	8.07±1.55	-1.12 (-0.29, 1.96)
High-Fear - Neutral difference	-0.46 (-0.97, 0.04)	-0.52 (-1.22, 0.18)	
High-Fear – Moderate-Fear difference	-0.38 (-0.82, 0.06)	-0.39 (-1.01, 0.23)	

Table S4. Coordinates for contrast High-Fear vs Neutral per group

Presented are anatomical locations, corresponding MNI coordinates, cluster size *k* and max (peak) statistic of the clusters (T_{max}). The clusters coincide with those visually presented in **Figure 3.A** in the main text. Clusters are extracted using cluster defining threshold $p < .001$ and subsequent cluster-extent FDR-correction. Anatomical locations are derived from Harvard Oxford atlases. *FDRc* = cluster size threshold of *FDR-p* < .05.

cluster		peak	MNI coordinates				
p(FDRc)	k	T_{max}	x	y	z	Anatomical location	
CWAD High-Fear > Neutral; FDRc: k> 184							
<0.001	17902	7.60	-24	-34	58	Pre/postcentral gyrus (B); extending bilaterally into superior parietal, dorsal precuneus (B), supramarginal and angular gyrus, cuneal cortex, and posterolateral cerebellum as well as left middle and inferior frontal gyrus, left operculum cortex and left anterior insula	B
<0.001	1603	5.87	34	-14	40	Precentral gyrus	R
<0.001	1357	4.87	2	4	62	Supplementary motor cortex, paracingulate gyrus and anterior cingulate cortex	B
<0.001	750	4.81	44	-52	14	Supramarginal, middle temporal and angular gyrus	R
0.016	184	4.70	2	-36	20	Posterior cingulate gyrus	B
0.014	203	4.56	-26	-16	-6	Thalamus, putamen, pallidum	L
0.014	199	4.42	-10	-20	48	Posterior cingulate gyrus	L
CWAD Neutral > High-Fear; FDRc: k> 172							
0.008	281	6.94	14	-50	72	Superior parietal lobule	R
0.025	172	5.55	-16	-46	70	Superior parietal lobule	L
0.025	181	5.28	10	-14	70	Precentral gyrus	R
		4.90	-6	-16	70	Precentral gyrus	L
Pain-free controls High-Fear > Neutral; FDRc: k>238							
0.021	238	4.35	-10	-76	38	Dorsal precuneus	L
Pain-free controls Neutral > High-Fear; FDRc: k>168							
<0.001	732	7.85	-16	-48	68	Superior parietal lobule	L
<0.001	539	7.63	14	-50	68	Superior parietal lobule	R
<0.001	668	6.00	10	-12	74	Precentral gyrus (M1)	B
<0.001	1654	5.47	-4	60	18	Medial superior frontal gyrus	L
		4.77	12	54	4	Paracingulate gyrus	R
0.045	168	4.51	4	-8	44	Anterior cingulate cortex	B

Table S5. Between-group comparison (CWAD vs pain-free) in regions of interest for the 3 contrasts of interest

Region of interest	Contrast	Test statistic	Uncorrected p-value	FDRc p-value	95% CIs
vmPFC	**High vs Neutral**	1.387	0.167	0.310	-0.028, 0.161
	Moderate vs Neutral	-0.401	0.689	0.830	-0.113, 0.075
	High vs Moderate	1.787	0.075	0.399	-0.009, 0.180
Amygdala R	**High vs Neutral**	0.966	0.335	0.395	-0.030, 0.089
	Moderate vs Neutral	0.379	0.705	0.830	-0.048, 0.071
	High vs Moderate	0.586	0.558	0.679	-0.042, 0.077
Amygdala L	**High vs Neutral**	1.256	0.211	0.343	-0.022, 0.101
	Moderate vs Neutral	-0.834	0.405	0.712	-0.087, 0.036
	High vs Moderate	2.091	0.038	0.399	0.004, 0.127
Hippocampus R	**High vs Neutral**	0.862	0.390	0.423	-0.031, 0.079
	Moderate vs Neutral	-0.686	0.493	0.712	-0.074, 0.036
	High vs Moderate	1.548	0.123	0.399	-0.012, 0.098
Hippocampus L	**High vs Neutral**	1.892	0.060	0.172	-0.002, 0.110
	Moderate vs Neutral	0.254	0.800	0.830	-0.049, 0.064
	High vs Moderate	1.624	0.106	0.399	-0.010, 0.103
Anterior insula R	**High vs Neutral**	1.845	0.066	0.172	-0.006, 0.171
	Moderate vs Neutral	1.407	0.161	0.523	-0.025, 0.152
	High vs Moderate	0.438	0.661	0.716	-0.069, 0.108
Anterior insula L	**High vs Neutral**	1.079	0.282	0.366	-0.042, 0.142
	Moderate vs Neutral	1.281	0.202	0.523	-0.032, 0.151
	High vs Moderate	-0.201	0.841	0.841	-0.101, 0.082
Posterior insula R	**High vs Neutral**	0.387	0.699	0.699	-0.043, 0.064
	Moderate vs Neutral	-0.698	0.486	0.712	-0.073, 0.035
	High vs Moderate	1.085	0.279	0.518	-0.024, 0.084
Posterior insula L	**High vs Neutral**	1.446	0.150	0.310	-0.015, 0.097
	Moderate vs Neutral	0.885	0.377	0.712	-0.031, 0.081
	High vs Moderate	0.561	0.575	0.679	-0.010, 0.072
ACC R	**High vs Neutral**	1.115	0.266	0.366	-0.018, 0.068
	Moderate vs Neutral	-0.214	0.830	0.830	-0.048, 0.039
	High vs Moderate	1.329	0.186	0.483	-0.014, 0.072
ACC L	**High vs Neutral**	**2.525**	**0.011**	**0.047**	**0.017, 0.137**
	Moderate vs Neutral	1.417	0.158	0.523	-0.017, 0.104
	High vs Moderate	1.108	0.269	0.518	-0.027, 0.094
PCC R	**High vs Neutral**	**2.608**	**0.010**	**0.047**	**0.033, 0.239**
	Moderate vs Neutral	1.824	0.070	0.455	-0.008, 0.197
	High vs Moderate	0.784	0.434	0.626	-0.062, 0.143
PCC L	**High vs Neutral**	**3.412**	**0.001**	**0.010**	**0.088, 0.329**
	Moderate vs Neutral	2.425	0.016	0.208	0.027, 0.269
	High vs Moderate	0.987	0.325	0.528	-0.060, 0.181

vmPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex

Table S6. Coordinates for contrast Moderate-Fear vs Neutral per group

Presented are anatomical locations, corresponding MNI coordinates, cluster size *k* and max (peak) statistic of the clusters (T_{max}). The clusters coincide with those visually presented in **Figure 4.A** in the main text. Clusters are extracted using cluster defining threshold $p < .001$ and subsequent cluster-extent FDR-correction. Anatomical locations are derived from Harvard Oxford atlases. *FDRc* = cluster size threshold of *FDR-p* < .05.

cluster		peak	MNI coordinates				
p(FDRc)	k	T_{max}	x	y	z	Anatomical location	
CWAD Moderate-Fear > Neutral; FDRc: k>282							
<0.001	506	6.49	-36	-14	42	Precentral gyrus and middle frontal gyrus	L
<0.001	565	6.34	24	-22	64	Pre/postcentral gyrus	R
<0.001	547	6.14	38	-10	42	Precentral gyrus	R
<0.001	8209	6.10	-26	-36	60	Pre/postcentral gyrus (L), dPrecuneus (L); extending bilaterally (B) into lateral occipital cortex, cuneal cortex, lingual gyrus and cerebellum	B
		5.97	20	-72	-52	Posterolateral cerebellum	R
<0.001	1511	5.81	-56	10	4	Central/frontal operculum, inferior frontal gyrus, anterior insula	L
<0.001	1124	5.14	8	8	64	Supplementary motor area (B) and paracingulate gyrus (L)	B
0.002	282	4.86	-20	-64	-54	Cerebellum	L
<0.001	761	4.81	36	-56	-30	Cerebellum	R
<0.001	403	4.73	50	14	-2	Central/frontal operculum and inferior frontal gyrus,	R
CWAD Neutral > Moderate-Fear; FDRc: k>336							
0.001	411	8.18	16	-50	72	Superior parietal lobule	R
0.001	336	7.15	-16	-46	70	Superior parietal lobule	L
0.001	397	6.81	12	-12	70	Precentral gyrus	R
		5.59	-8	-14	72	Precentral gyrus	L
Pain-free controls Moderate-Fear > Neutral; FDRc: k>170							
<0.001	3164	5.24	-30	-56	-4	Cuneal cortex and lingual gyrus	B
0.033	170	4.54	44	-6	52	Precentral gyrus	R
pain-free controls Neutral > Moderate-Fear; FDRc: > 271							
<0.001	482	6.22	-16	-50	68	Superior parietal lobule	L
<0.001	451	5.99	16	-48	70	Superior parietal lobule	R
0.002	333	4.61	12	-12	74	Precentral gyrus	R
		3.83	-8	-12	74	Precentral gyrus	L
0.004	271	4.03	-16	-90	-32	Posterolateral cerebellum	L

Table S7. Coordinates for contrast High-Fear vs Moderate-Fear per group

Presented are anatomical locations, corresponding MNI coordinates, cluster size *k* and max (peak) statistic of the clusters (T_{max}). The clusters coincide with those visually presented in **Figure S2** of the supplementary (below). Clusters are extracted using cluster defining threshold $p < .001$ and subsequent cluster-extent FDR-correction. Anatomical locations are derived from Harvard Oxford atlases. *FDRc* = cluster size threshold of *FDR-p* < .05.

cluster		peak	MNI coordinates				
p(FDRc)	k	T_{max}	x	y	z	Anatomical location	
CWAD High-Fear>Moderate-Fear; FDRc: k>330							
<0.001	1295	5.15	36	-62	48	Lateral occipital cortex and supramarginal gyrus	R
0.005	330	4.40	50	26	24	Middle and inferior frontal gyrus	R
CWAD High-Fear>Moderate-Fear							
No significant clusters							
Pain-free controls High-Fear > Moderate-Fear; FDRc: k>200							
0.019	209	4.28	-48	-48	50	Supramarginal and angular gyrus	L
0.019	200	3.91	38	-54	38	Supramarginal and angular gyrus	R
Pain-free controls Moderate-Fear > High-Fear; FDRc: k>193							
0.019	242	5.61	-8	58	18	Medial superior frontal gyrus	L
0.003	394	5.18	12	46	-6	Paracingulate gyrus	R
		4.74	-6	38	-2	Anterior cingulate gyrus	L
0.027	193	4.38	50	-10	52	Precentral gyrus (more lateral)	R
0.019	225	3.99	-28	-60	-2	Lingual gyrus	L

Figure S2. Significant clusters for contrast High-Fear > Moderate-Fear per group

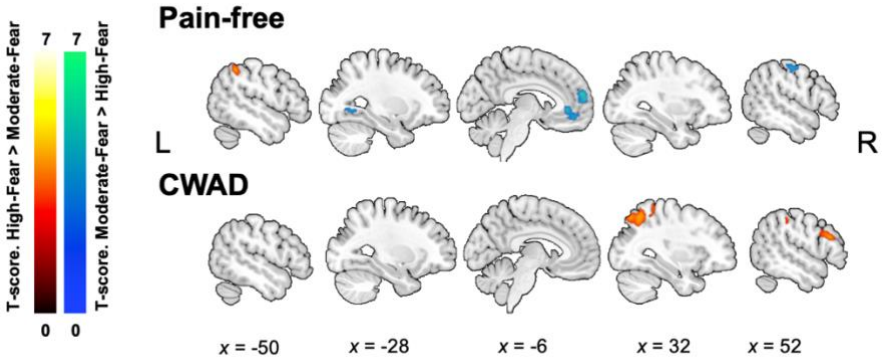


Table S8. Kendall correlations between the pain questionnaires and the significant clusters/regions of interest in the between-group comparison for the main contrast of interest.

Cluster/ROI		PCS	PASS-20	PVAQ
CWAD > pain-free. High-Fear > Neutral				
Postcentral gyrus R (Cluster I)	τ	-0.178	**-0.149**	**-0.137**
	pFDR	0.128	0.128	0.128
Postcentral gyrus L (Cluster II)	τ	-0.162	**-0.170**	-0.174
	pFDR	0.071	0.071	0.071
Parietal operculum L (Cluster III)	τ	-0.185	-0.159	0.026
	pFDR	0.118	0.152	0.779
Dorsal Precuneus (Cluster IV)	τ	-0.176	**-0.229**	-0.142
	pFDR	0.100	**0.032**	0.116
Medial superior frontal gyrus/ACC (Cluster V)	τ	-0.102	-0.143	-0.044
	pFDR	0.516	0.331	0.627
PCC/vPrecuneus (Cluster VI)	τ	-0.104	**-0.250**	-0.108
	pFDR	0.247	**0.015**	0.247
PCC R ROI	τ	-0.119	-0.206	-0.129
	pFDR	0.186	0.064	0.186
PCC L ROI	τ	-0.104	**-0.217**	-0.058
	pFDR	0.496	**0.040**	0.523
CWAD > pain-free. Moderate-Fear > Neutral				
Posterior cerebellum R (Cluster VII)	τ	0.021	-0.034	-0.015
	pFDR	0.868	0.868	0.868
Posterior cerebellum L (Cluster VII)	τ	-0.058	-0.121	-0.039
	pFDR	0.664	0.528	0.664

PCS, Pain Catastrophizing Scale; PASS-20, Pain Anxiety Symptoms Scale; PVAQ, Pain Vigilance and Awareness Questionnaire; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.