Observational Studies

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Neural activity during cognitive reappraisal in chronic low back pain: a preliminary study

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Abstract

Objectives: Chronic pain patients often report higher levels of negative emotions, suggesting reduced ability to regulate emotions effectively, however, little is known of the underlying neural cognitive mechanisms. Therefore, the aim of this study was to explore brain activity and connectivity during cognitive reappraisal in chronic low back pain (CLBP).

Methods: This study recruited 24 female participants; 12 with CLBP and 12 healthy controls. Participants completed an emotion regulation task that involved cognitive reappraisal of negative images during functional magnetic resonance imaging. The negative affect following each image and perceived success of the task were reported. Region of interest and seed-to-voxel analyses were conducted using key regions involved in cognitive reappraisal (i.e., amygdalae and dorsomedial prefrontal cortex) as seed regions.

Results: During the task, there were no group differences in the behavioural measures and blood oxygen level-dependent (BOLD) brain activation in the seed regions. Functional connectivity analysis showed reduced coupling between the amygdalae and dorsolateral prefrontal cortex, orbitofrontal cortex and inferior parietal cortex in the CLBP group compared to controls. Connectivity between the amygdala and inferior parietal cortex positively correlated with the percent of reduced negative affect during reappraisal in the CLBP group.

Conclusions: These preliminary findings demonstrate that individuals with CLBP exhibit similar emotion regulation abilities to healthy controls at the behavioural and BOLD level. However, altered functional connectivity observed in the CLBP group may reduce effective cognitive reappraisal. These results provide evidence for the potential clinical impact of network changes in CLBP.

Keywords: chronic low back pain; cognitive reappraisal; emotion regulation; fMRI.

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Introduction

Current models of pain highlight that cognition and emotion are prominent domains that contribute to the development and maintenance of chronic pain [1–3]. Indeed, conditions such as chronic low back pain (CLBP) are often associated with elevated negative emotional states which are considered to be both a driver as well as a clinical consequence of the condition [4]. For example, studies have shown that depression not only increases the risk of developing CLBP [5, 6], it has been associated with higher levels of low back pain intensity [7, 8]; thus, demonstrating a complex, bidirectional relationship between chronic pain and emotion. It has been suggested that underlying cognitive processes

responsible for moderating negative emotional states, such as emotion regulation, are compromised in CLBP [9–12]. Emotion regulation refers to the ability to alter the magnitude or duration of an emotion [13], which may be important in alleviating pain-related symptoms and minimising the vulnerability to developing chronic pain [12]. Despite the potential clinical importance of emotion regulation in chronic pain, our understanding of its role and underlying neurobiology remains unclear.

Cognitive reappraisal, one such emotion regulation strategy, refers to the reinterpretation of a situation or stimulus to decrease its emotional significance [14]. It is not only believed to be more effective in reducing negative emotions compared to other strategies, such as suppression (i.e., the inhibition of current emotions) [15, 16], but it has also been found to modulate noxious pain and the related negative affect in healthy populations [17, 18]. More importantly, cognitive reappraisal appears to be involved in mediating psychological and emotional factors that influence chronic pain, suggesting it is a key secondary process that modulates risk factors [12]. However, the current literature has predominantly been based on self-report measures, and limited studies have examined emotion regulation capabilities at the behavioural and neural level in chronic pain populations.

Understanding the neural processes in cognitive reappraisal is important to identify the relevant brain regions and networks that can be used for the development of targeted therapies. Investigation of brain function in chronic pain has already demonstrated that brain activity and circuitry is disrupted in chronic pain [1, 19], potentially affecting processes such as cognitive reappraisal. In chronic low back pain (CLBP), for instance, decreased gray matter volume and altered functional connectivity has been identified in key regions associated with cognitive reappraisal, such as the amygdala [20, 21] and medial prefrontal cortex [22–24]. However, it remains unknown whether these brain alterations linked to chronic pain may affect cognitive reappraisal. Therefore, the primary aim of this pilot study was to investigate neural differences during cognitive reappraisal of negative emotion in a CLBP group compared to healthy controls using functional magnetic resonance imaging (fMRI). This study used region of interest (ROI) and seed-to-voxel analyses to compare blood oxygen level-dependent (BOLD) activity and functional connectivity during a cognitive reappraisal task. The bilateral amygdalae and the dorsomedial prefrontal cortex (DMPFC) were used as ROIs. These areas were selected as they were part of the network of brain regions that are involved in cognitive reappraisal [16, 25–27] and also shown to have extensive structural and functional changes [20, 21, 23, 24, 28], and is associated with spontaneous fluctuations of low back pain in CLBP populations [22, 29, 30]. The primary outcomes used for group comparisons include the BOLD activations and functional connectivity measures of the ROIs, as well as the negative affect reported by participants during the cognitive reappraisal task. Secondary analyses were conducted to explore whether aberrant functional connectivity in the CLBP group were related to behavioural task performance, including perceived success of cognitive reappraisal and ability to reduce negative affect during the task, as well as whether there was any relationship to depression. The outcomes used include perceived success of task (self-reported), the percent of reduced negative affect (calculated from negative affect reported during task) and depression measured by the Beck's Depression Inventory (BDI-II). We hypothesised the CLBP group would have a poorer performance and exhibit reduced functional connectivity within the brain regions during cognitive reappraisal compared to healthy controls.

Methods

Study population

This study recruited a total of 24 participants comprised of 12 healthy volunteers and 12 individuals with CLBP from the community. All potential participants were screened for eligibility through a phone screening. All participants were female, right-handed (Edinburgh Handedness Inventory [31], *M*, 83%) and did not have a current or history of psychiatric illness, excluding depression and anxiety following onset of CLBP (assessed by the Mini international Neuropsychiatry Interview (MINI) [32]). The inclusion of only females was to control for any potential gender differences during the reappraisal in the task [33, 34]. The participants in the CLBP group had experienced non-specific low back pain for more than three months, with moderate to severe low back pain (>21% on the Oswestry Disability Index [35]). The healthy participants were excluded if they reported current or a history of significant pain that persisted for more than three months. This study was approved by the Monash University and Alfred Health Human Research Ethics Committees.

Experimental paradigm and procedure

Eligible participants attended a 2-h session at the Monash Biomedical Imaging facility (MBI, Clayton, Victoria). During this session, participants completed the Beck's Depression Inventory II (BDI-II) [36], short-form McGill Pain Questionnaire (SF-MPQ) [37], and a training session for the experimental task. They also underwent an MRI scan where structural and functional data were acquired while completing the experimental task.

The BDI-II is a 21-item self-report measure of depression. Each item refers to different aspects of depression with four possible options (0–3) indicating the level of severity. Total scores range between 0 and 63, with scores between 0 and 13 indicating minimal range, 14–19 indicating mild depression, 20–28 indicating moderate depression and 29–63 indicating

severe depression [36]. BDI-II has been shown to have good reliability and validity in chronic pain [38] and healthy populations [39].

The SF-MPQ is a measure of pain that consists of three components. The first is the Pain Rating Index that comprises of 15 pain-related word descriptors (e.g., throbbing, aching, fearful pain) and rated on a scale from 0 to 3 (i.e., none, mild, moderate and severe). It has descriptors comprised of two subscales, the sensory (11 words) and affective subscales (4). The other two components consist of a 10 cm visual analogue scale (VAS) that measures average pain and the present pain intensity (PPI) item that indicates current level of pain [37]. In this study, as the healthy control group did not report any low back pain, only the CLBP group completed this questionnaire.

Emotion regulation task: All participants completed an emotion regulation task, adapted from Ochsner, Ray [40] and Erk, Mikschl [41], during an fMRI scan. In this task, participants were presented a series of negative and neutral images from the International Affective Picture System (IAPS) [42]. These images were selected based on their normative ratings in valence (1=unpleasant/negative, 5=neutral, 9=pleasant/positive) and arousal (1=calm, 9=excited). The negative images had a mean valence rating of 2.40 (SD=0.57) and arousal rating of 5.74 (0.75) while neutral images had a valence rating of 5.16 (0.39) and arousal rating of 3.41 (0.79). Independent *t*-tests comparing the negative and neutral images showed significant differences in valence ($t(70)=-24.08$, $p<0.001$) and arousal ($t(70)=12.81$, $p<0.001$) ratings.

Participants were asked to either view the images passively (i.e., *Look* condition), or reappraise any negative emotions induced by the images (*Decrease* condition). Specifically, participants were instructed to "simply look at the image and respond naturally" during the Look conditions or "to decrease your negative emotions, imagine the events of the image from a third person perspective" for the Decrease conditions. The task was designed to have 36 trials in each block. At the beginning of each trial, an instructional cue was shown for 2 s (i.e., *Look* or *Decrease*), followed by one of the selected negative or neutral images that was presented for 10 s. As a previous neuroimaging study showed that when presented with negative stimuli, other responses such as suppression may occur after 10 s, resulting in different neural responses [43], participants were only given 10 s to complete the cognitive reappraisal task instructions for each trial. Following each image, participants reported the strength of their negative affect. A rectangular bar appeared above a scale numbered 0–8 with larger numbers indicating higher negative affect. The bar started from the left at 0 and expanded to right towards the number 8 and participants pressed a button when the bar reached the number that represented their level of negative affect. A 4 s rest period was given before the next trial (Figure 1). Prior to the MRI scan, participants were provided full instructions of the task and completed a full practice block (i.e., 36 trials). They were given an opportunity to ask questions to ensure they understood the task. Once participants were familiar and proficient at the task, they completed two blocks of the task during an fMRI scan.

After the completion of the fMRI, participants reviewed all the negative images during decrease trials and rated their level of perceived success in reducing their negative affect on a scale of 0–10. The strength of negative affect reported after the Decrease-Negative and Look-Negative trials were used to calculate the percent of reduced negative affect due to cognitive reappraisal based on a formula from a previous study [44]: [(Mean rating during Decrease-Negative – Mean rating during Look-Negative)/Mean rating during Look-Negative] × –100, with higher percentages indicated greater reduction in negative affect due to cognitive reappraisal.

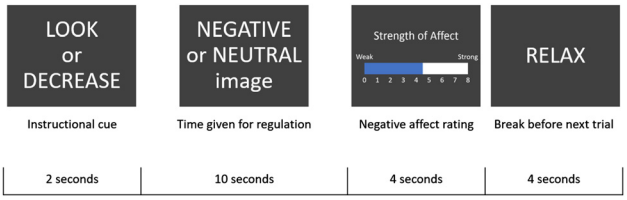

Figure 1: An example of a trial of the emotion regulation task.

MRI data acquisition

Structural and functional data were acquired on a Siemens Magnetom Skyra 3 Tesla MRI scanner with a 32 channel receive-only phased-array head coil (Siemens, Erlangen, Germany). High resolution magnetisation prepared rapid acquisition gradient echo (MPRAGE) T1-weighted structural data were acquired using the following parameters: repetition time (TR)=1540 ms, echo time (TE)=2.55 ms, flip angle=9°, acquisition matrix=256 × 256, FoV=256 mm, 1 mm isotropic voxels, yielding a total of 208 sagittal slices providing whole brain coverage. Whole-brain echo-planar images (EPIs) were acquired for the task-related functional data with a total of 46 contiguous transversal slices per volume. The following parameters were used: TR=2570 ms, TE=30 ms, flip angle=90°, acquisition matrix=64 × 64, FoV=192 mm, slice thickness=3.0 mm. The functional data were acquired in two runs, corresponding with two blocks of the task with a total of approximately 12 min each block, totalling 24 min for the entire task.

fMRI data preprocessing and analyses

All data were preprocessed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB R2017b (MathWorks, Sherborn, MA, USA). The anatomical image was segmented into white matter (WM), gray matter (GM) and cerebral spinal fluid (CSF). All functional images were slice time corrected and realigned to the mean image for motion correction. A motion threshold of 3 mm translation and 3° rotation was used. No participants exceeded this threshold and therefore were not excluded from analyses due to excessive motion. The mean images were co-registered to the respective anatomical image, which was then normalised to the Montreal Neurological Institute (MNI) T1 template (resampled to 2 × 2 × 2 mm voxels). These parameters were applied to the realigned EPIs and then smoothed using an 8 mm FWHM Gaussian kernel.

BOLD activation

The preprocessed images were entered into a first-level fixed effects analysis using the general linear model. The 10-s duration of when images were shown for each task condition (Decrease-Negative, Look-Negative, Decrease-Neutral and Look-Neutral) and the 4-s rest period were modelled as boxcar regressors. To control for participant movement during the fMRI scan, the six motion parameters obtained from the realignment step were regressed out as a covariate of no interest. All regressors were convolved with the canonical hemodynamic response function (HRF). A high pass filter set at 128 s was applied to remove low-frequency noise. These models were then used to create contrasts for cognitive reappraisal (Decrease-Negative>(Decrease-

Neutral and Look-Neutral) and emotional processing (Look-Negative>Decrease-Neutral and Look-Neutral) for each participant.

The first-level contrasts were entered into a second-level random effects analysis for group comparison using a full factorial 2 × 2 ANOVA design with the groups (CLBP and healthy controls) and task conditions (Cognitive reappraisal (Decrease-Negative>Decrease-Neutral and Look-Neutral) and emotional processing (Look-Negative>Decrease-Neutral and Look-Neutral) as factors in *a priori* regions of interest (ROI) analysis. Using the Marsbar toolbox (http://marsbar.source-forge.net), three 10 mm spheres were created for the left (−18, −3, −15) and right (30, −3, −15) amygdala as well as the DMPFC (9, 30, 39) using the coordinates from a meta-analysis in cognitive reappraisal [27]. The time series of the blood-oxygenated level dependent (BOLD) activity for each of the regions of interest were extracted and entered into SPSS for group comparisons. Significance was set at p<0.001 uncorrected at the peak level and p<0.05 family-wise error (FWE) corrected at the cluster level. Partial eta squared (η_p^2) was calculated to determine the effect sizes for group and task effects.

Functional connectivity: Functional connectivity was assessed using the generalized psychophysiological interaction (gPPI) method in the Conn toolbox [45] using MATLAB. The gPPI analyses have been found to be more sensitive and powerful in detecting functional connectivity differences than standard PPI [46, 47]. In addition to the preprocessing procedures described previously, the functional data were denoised according to the CompCor method [48] implemented within the Conn toolbox to remove physiological noise. This involved regressing out outliers identified during ART from head motion as well as signals from the WM and CSF.

The gPPI method is used to estimate the changes in functional connectivity between seed regions and the rest of the brain (physiological factor) during a specific task (psychological factor). The time course of BOLD activity in the bilateral amygdalae and DMPFC (defined above) were extracted as the physiological factor and the Decrease-Negative>Look-Negative contrast was defined as the psychological factor. The interaction term was calculated from the product of the ROI time course and the contrast between the conditions.

The gPPI analyses were conducted for each ROI and entered into a one-sample *t*-test to examine functional connectivity for each group separately and then into a two-sample *t*-test for group comparisons. The beta estimates from the gPPI were extracted for further correlational analyses with the behavioural measures using SPSS version 23. The significances threshold was set at p<0.001 uncorrected at the voxel level and p<0.05 FWE-corrected at the cluster level. All significant clusters were labelled using the Brodmann's Area (BA) and Automated Anatomical Labeling (AAL) atlases defined within MRIcro [49]. Cohen's *d* was calculated to establish the effect sizes of the group differences. The connectivity values of the CLBP group were extracted and used to examine whether it was related to perceived level of success during the Decrease-Negative (i.e., reappraisal) conditions, the percent of decreased negative affect as well as depression scores in correlational analyses.

Results

Behavioural data

The study sample did not have significant differences in age or years of education, although BDI scores were significantly higher in those with CLBP compared to healthy controls (Table 1). The average level of strength of affect reported during the emotion regulation task was calculated for the Decrease-Negative, Look-Negative, Decrease-Neutral and Look-Neutral conditions in each group. When comparing CLBP to healthy controls, there were no significant differences observed in each of the four conditions. However, within-group comparisons showed the negative affect during the Look-Negative conditions were significantly higher than the Decrease-Negative (CLBP: $t(11)=2.38$, p=0.037; Controls: $t(11)=4.87$, p<0.001), the Decrease-Neutral (CLBP: $t(11)=8.29$, p<0.001; Controls: $t(11)=8.64$, p<0.001), and Look-Neutral conditions (CLBP: $t(11)=8.00$, p<0.001; Controls: $t(11)=9.02$, p<0.001) in both the CLBP and healthy control group. Similarly, both groups reported a significantly higher strength of affect during the Decrease-Negative condition than the Decrease-Neutral (CLBP: $t(11)=7.13$, p<0.001; Controls: $t(11)=6.12$, p>0.001), and Look-Neutral conditions (CLBP: $t(11)=6.36$, p<0.001; Controls: $t(11)=4.56$, p=0.001). There was a significantly higher strength of affect during the Look-Neutral condition compared to the Decrease-Neutral in the healthy control group ($t(11)=3.06$, p=0.011) but this was not observed in the CLBP group ($t(11)=1.63$, p=0.131). Bonferroni adjustments were performed to correct for multiple comparisons of the strength of negative affect scores; therefore p-value of <0.008 was considered statistically significant. All comparisons remained significant except between the Look-Negative and Decrease-Negative in the CLBP group and between the Look-Neutral and Decrease-Neutral conditions in the healthy control group (Figure 2A). Additionally, there were no significant group differences in the percent of reduced negative affect (M ± SE: CLBP=14.7 ± 5.86 vs. healthy controls=28.4 ± 5.43) and the perceived level of success (M ± SE: CLBP=5.72 ± 2.18 vs. healthy controls=6.97 ± 1.39) during cognitive reappraisal (Figure 2B, C).

Region of interest – BOLD activation

There were no significant main group effects observed in the left amygdala ($F(1, 22)=0.098$, p=0.757, $\eta_p^2=0.004$), right amygdala ($F(1, 22)=1.28$, p=0.27, $\eta_p^2=0.055$) or the DMPFC ($F(1, 22)=0.57$, p=0.46, $\eta_p^2=0.025$). No significant task effects were observed in the left amygdala ($F(1, 22)=1.76$, p=0.20, $\eta_p^2=0.074$) or DMPFC ($F(1, 22)=0.009$, p=0.93, $\eta_p^2<0.001$). There were significant main tasks effects in the right amygdala ($F(1, 22)=4.36$, p=0.049, η_p^2, 0.165). Post-hoc tests using Bonferroni correction showed there were decreased activation during cognitive reappraisal (Decrease-Negative > Decrease-Neutral and Look-Neutral) compared to emotional processing (Look-Negative > Decrease-Neutral

Table 1: Demographic of chronic low back pain and healthy control groups.

Characteristics	Chronic low back pain	Healthy controls	p-Value
Mean age, years	36.5 (10.59)	30.25 (5.22)	0.085
Education, years	16.45 (2.71)	18.27 (2.73)	0.142
BDI-II	13.00 (9.05)	3.18 (2.64)	0.003
ODI	45.17 (12.58)	–	–
SF-MPQ pain rating	17.08 (6.01)	–	–
SF-MPQ VAS	54.29 (19.43)	–	–
SF-MPQ PPI	2.50 (0.52)	–	–

BDI-II, Beck's Depression Index II; ODI, Oswestry Disability Index; SF-MPQ, short-form McGill Pain Questionnaire; VAS, Visual analogue scale PPI, Present Pain Index.

and Look-Neutral). Additionally, no significant group × condition interaction effects were observed in any of the seed regions (left amygdala: $F(1, 22)=0.77$, p=0.39, $\eta_p^2=0.034$; right amygdala: $F(1, 22)=1.26$, p=0.27, η_p^2, 0.054); DMPFC: $F(1, 22)=0.05$, p=0.83, $\eta_p^2=0.002$) (see Figure 3).

Functional connectivity

Within-group comparisons showed that in the healthy control group, the gPPI analysis showed significant coupling between the left amygdala and right orbitofrontal cortex and left inferior frontal gyrus (pars orbitalis) as well as between the DMPFC and the right posterior cingulate gyrus (Table 2). No significant relationships were observed with the right amygdala in the healthy control group. In the CLBP group, no significant relationships were observed in any of the three seed regions and the rest of the brain.

Between-group comparisons showed the healthy control group had stronger functional coupling between

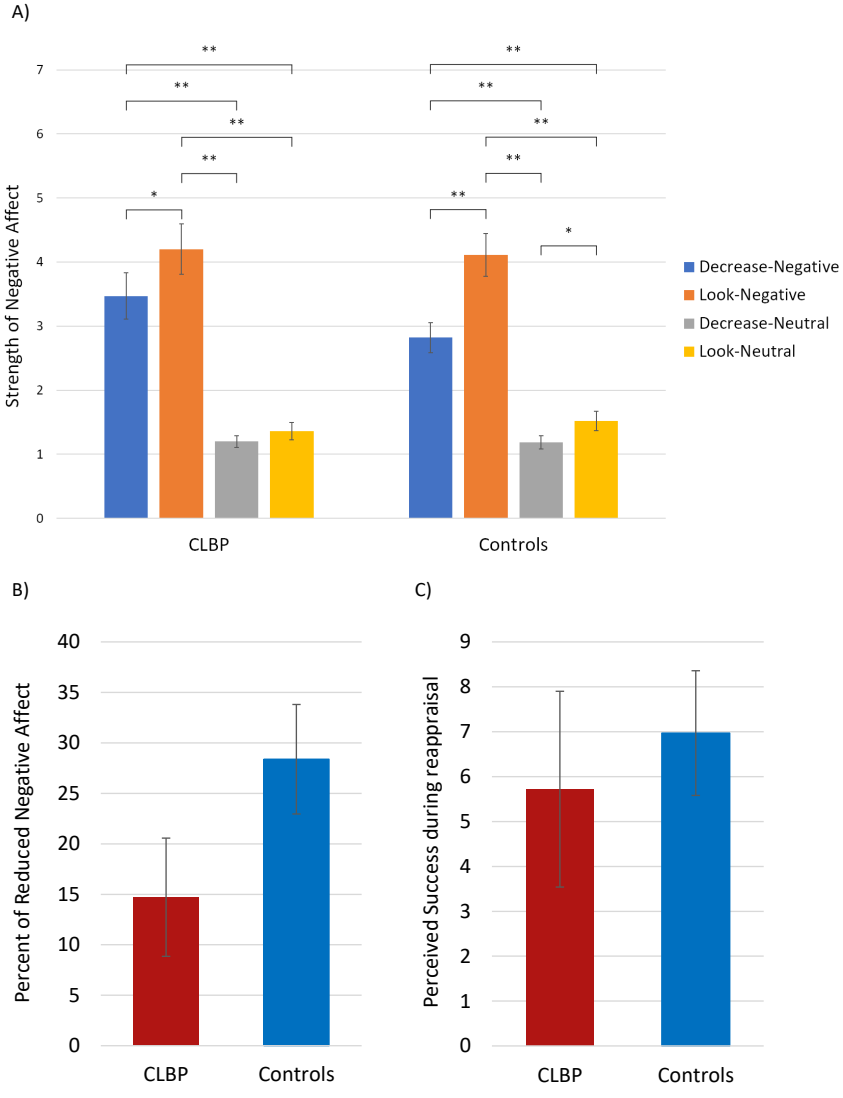

Figure 2: (A) Average strength of negative affect (M ± SE) for the Decrease-Negative, Look-Negative, Decrease-Neutral and Look-Neutral trials in the chronic low back pain (CLBP) and healthy control groups (*p<0.05 [unadjusted], **p<0.008 after Bonferroni adjustment), (B) Percent of reduced negative affect (M ± SE) during cognitive reappraisal, (C) Overall perceived success of cognitive reappraisal (M ± SE) during Decrease-Negative trials.

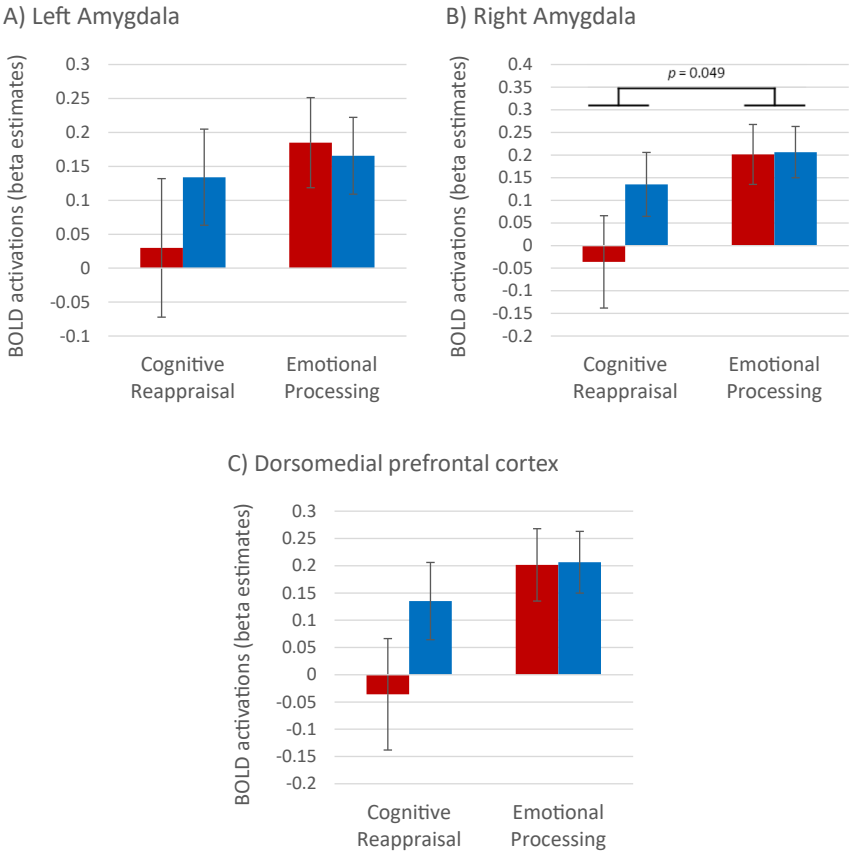

Figure 3: BOLD activations (M ± SE) observed during the Decrease-Negative, Look-Negative, Decrease-Neutral and Look-Neutral conditions during the emotion regulation task in the regions of interest: (A) Left amygdala (–18, –3, –15), (B) Right amygdala (30, –3, –15), and (C) Dorsomedial Prefrontal Cortex (DMPFC) (9, 30, 39). Red, CLBP, Blue, Healthy controls.

Table 2: Functional connectivity analyses during cognitive reappraisal (Decrease-Negative>Look-Negative) in the healthy control group.

Seed	Region	Cluster	Peak, *t*	MNI coordinates		
				x	*y*	*z*
L amygdala	R orbitofrontal cortex (BA 11)	85	6.09	22	62	–10
	L inferior frontal gyrus (pars orbitalis) (BA 47)	78	7.29	–48	42	–8
DMFPC	R posterior cingulate gyrus (BA 23)	51	6.14	2	–12	40

DMPFC, dorsomedial prefrontal cortex; MNI, Montreal Neurological Institute. p<0.001 uncorrected at voxel level, p<0.05 FWE-corrected at cluster level.

the right amygdala and the right dorsolateral prefrontal cortex (DLPFC) as well as between the left amygdala and the right orbitofrontal cortex (OFC) and left inferior parietal cortex (IPL) during reappraisal (Decrease-Negative>Look-Negative, see Table 3 and Figure 4).

In the CLBP group, Spearman's rho correlation analysis showed that the connectivity values between the left amygdala and IPL was positively related with the percent of reduced negative affect (r=0.81, p=0.001, see Figure 5). No other significant correlations were observed in the CLBP group, including with depression scores.

Table 3: Functional connectivity analyses showed significant differences during cognitive reappraisal (Decrease-Negative>Look-Negative) between groups (healthy controls>CLBP).

Seed	Region	Cluster	Peak, *t*	MNI coordinates			*d*
				x	*y*	*z*	
R amygdala	R dorsolateral prefrontal cortex (BA 46)	127	6.49	30	22	38	2.65
L amygdala	R orbitofrontal cortex (BA 11)	113	5.41	24	58	–12	2.21
	L inferior parietal cortex (BA 40)	65	4.64	–48	–44	58	1.89

CLBP, chronic low back pain; *d*, Cohen's *d*; MNI, Montreal Neurological Institute. p<0.001 uncorrected at voxel level, p<0.05 FWE-corrected at cluster level.

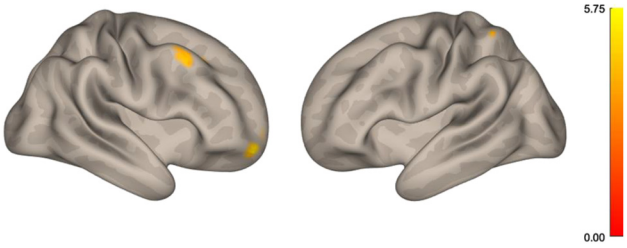

Figure 4: Functional connectivity analyses showed significant differences between right amygdala and dorsolateral prefrontal cortex, as well as between the left amygdala and right orbitofrontal cortex, and left inferior parietal cortex during cognitive reappraisal (Decrease-Negative>Look-Negative) between groups (healthy controls>CLBP).

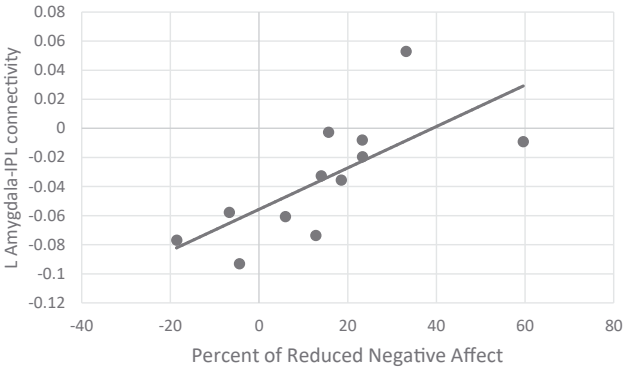

Figure 5: Spearman's rho of functional connectivity of the left amygdala and inferior parietal cortex with percent of reduced negative affect in the chronic low back pain group. IPL, Inferior Parietal cortex.

Discussion

This preliminary study investigated behavioural and neural properties associated with cognitive reappraisal in the CLBP group compared with healthy controls. There were no significant differences in behavioural measures including the level of negative affect reported after each trial across the four task conditions, as well as percent of reduced negative affect and the perceived level of success during cognitive reappraisal between the CLBP and healthy control groups. The BOLD analysis showed significant deactivation in the right amygdala and a trend in the left amygdala during reappraisal across both groups, however, no significant group differences were observed. In the functional connectivity analysis, the CLBP group had reduced coactivation between the right amygdala and dorsolateral prefrontal cortex (DLPFC) as well as between the left amygdala and orbitofrontal cortex (OFC) and the inferior parietal cortex (IPL) than the healthy control group. Finally, there was a significant positive correlation between the connectivity between the left amygdala and IPL and greater reduction of negative affect during cognitive reappraisal in the CLBP group.

Behavioural results

When comparing the CLBP participants with healthy controls, similar levels of negative affect were reported in each of the four different task conditions. Within-group comparisons indicated higher levels of negative affect during the Negative conditions compared to the Neutral conditions. More importantly, the negative affect during the Decrease-Negative conditions were significantly lower than the Look-Negative conditions in both groups, suggesting a degree of effective cognitive reappraisal during the task. Interestingly, the healthy control group also reported a higher strength of affect during the Decrease-Neutral compared to the Look-Neutral condition. While the Decrease-Neutral condition primarily served as a control condition, these findings may suggest that healthy controls have the ability to reduce negative affect in neutral stimuli while the CLBP group may not. However, this interpretation must be considered with caution given our small sample size, it may not be translatable to the general population. There is also the possibility that these results are due to participant bias. As the instructions given for the Decrease conditions would result in reduced negative affect, participants may tend to report lower levels of negative affect even to neutral images. The percent of reduced negative affect and perceived success during the cognitive reappraisal task did not differ between groups. These findings might suggest that the CLBP and healthy control groups were equally successful in down-regulating their emotional response to negative stimuli at the behavioural level.

BOLD analysis

The BOLD analysis showed no group differences across the three seed regions with only small to moderate effect. Significant task effects where decreased activity during cognitive reappraisal when compared to emotional processing across the overall sample were observed in the right amygdala. This was consistent with previous studies reflecting reduction in negative emotional response during reappraisal [26, 27, 50–54].

Taken together with the behavioural results, these findings may demonstrate that individuals with CLBP have the capacity to engage in effective cognitive reappraisal. However, this only reflects behaviour within a control setting where participants were specifically instructed on the type of

emotion regulation strategy used and thus, does not consider the *type* of emotion regulation strategies that are used spontaneously or habitually. For example, previous studies found that individuals with mood conditions demonstrated similar levels of performance in reappraisal to healthy controls when provided with specific instructions. Instead, during spontaneous emotion regulation (i.e., when no instructions were given), they reported greater use of maladaptive strategies, such as suppression or rumination, which was also related to sustained negative emotions [55, 56]. Furthermore, different strategies are employed depending on the context [57]. Therefore, it is possible that emotion regulation strategies are domain specific and individuals with CLBP may have adopted ineffective strategies in response to pain-related events, although may not necessarily translate to other aspects of their lives.

Functional connectivity

While group differences in BOLD activity were not observed in our sample, reduced functional connectivity between the amygdalae and prefrontal regions, including the DLPFC and OFC as well as with the IPL were apparent in the CLBP group when compared with controls. As these prefrontal and parietal cortical regions are commonly active during cognitive reappraisal [41, 51, 58], our findings may reflect disruption in brain regions involved in emotional regulation in CLBP. Our results are consistent with another fMRI studies where altered connectivity in the amygdala was observed in CLBP [21]. Although this occurred during resting-state, it may suggest the brain changes in CLBP may affect multiple networks and processes.

Furthermore, as the behavioural data (i.e., reported negative affect and perceived success of task) did not show significant group differences, the results of the functional connectivity analysis may suggest that the differences observed in the brain could possibly be due to other processes that were not examined in this study. For example, there is evidence that has demonstrated that the amygdala is involved in processing negative emotional stimuli at the unconscious level [59]. This could explain why the self-report behavioural data does not reflect the functional connectivity results. Additionally, another potential confounding variable may be age. While our sample did not report a significant difference in age, the groups were not age-matched and had a 6-year mean difference between the CLBP and control group. As there are age-related differences in brain circuitry during emotion regulation [60] it may account for some of the group differences. Additionally, the CLBP group reported higher levels of depression than the healthy controls. While no significant correlations between functional connectivity and depression scores were observed, depression may be associated with altered brain circuitry [61]. Even in cases of mild depression, changes in brain regions involved in emotional processing have been observed [62]. Interestingly, there were no significant group differences observed with the DMPFC seed, suggesting not all regions involved in reappraisal are affected in CLBP.

Furthermore, only the connectivity between the left amygdala and IPL significantly correlated with the percent of reduced negative affect. Previous studies have demonstrated an association of the IPL with perspective taking [63, 64]. Therefore, this might reflect reduced ability to engage in effective cognitive reappraisal, such as distancing, where changing perspective is required in the CLBP group. Despite this, it is possible that the functional connectivity differences observed with the DLPFC and OFC may reflect other cognitive processes involved in reappraisal that was not measured in this study. For instance, the DLPFC has been shown to be active during different types of emotion regulation strategies, as well as negative and neutral stimuli, and therefore, has broadly been associated with cognitive load in response to the attentional demands of the task [51, 65].

Future directions and implications

The overall findings contribute to the growing body of evidence that has observed cortical reorganisation in CLBP populations. The differences observed in this study were within regions of the network linked to cognitive reappraisal, which could potentially serve as targets for intervention in normalising reappraisal of negative emotions and thus, minimising secondary factors that exacerbate pain, such as depression. Non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) has demonstrated that targeting brain regions such as the DLPFC may promote self-regulation in both emotional and pain processes [66, 67]. For example, a previous study found that stimulating the DLPFC using tDCS can modulate reappraisal processes [68]. Another study reported that using cognitive-behavioural therapy to change pain-related cognition in a chronic pain group was effective in increasing GM volume in areas including the DLPFC, which was associated with reduced pain catastrophizing [69]. Hence, these studies demonstrate there are different types of interventions that could potentially be used to reverse maladaptive neuroplastic changes that may have occurred during the development of persistent pain. It could also

improve the behavioural aspect of cognitive reappraisal, whereby individuals may be taught to use adaptive emotion regulation strategies in response to pain-related negative affect and thus, reducing their vulnerability to persisting pain.

It is important to note that the generalizability of the findings may be limited to CLBP. Indeed, there is evidence to show that changes in brain regions associated with cognitive reappraisal have been observed in other chronic pain conditions. For example, differences in functional connectivity in the amygdala have been observed in chronic migraine [70] and fibromyalgia patients [71] while increased functional connectivity in the medial prefrontal cortex in temporomandibular disorder [72]. While these studies investigated functional connectivity during resting-state, it is possible that these disruptions may affect emotional processes such as cognitive reappraisal. However, further investigations are required.

While this was a preliminary study, the study utilised a small sample size and therefore interpretation of the findings are limited. For instance, only female participants were included and the CLBP and healthy control group were not age matched. Future studies should recruit a larger sample to increase statistical power and explore co-variates such as age and sex as well as secondary psychological factors such as depressed mood. Despite significant differences in depressed mood (measured by BDI-II) in the sample of this study, the mean scores of the CLBP were still with the minimal range, indicating low levels of depressed mood. Furthermore, we could not control for depressed mood in our statistical analysis as our study design violates the assumptions for an analysis of covariance (ANCOVA). However, future studies could investigate whether depression may also impact cognitive reappraisal in CLBP. Additionally, this study examined cognitive reappraisal in a female sample, although, the information related to the phase of menstrual cycle was not collected or controlled for and thus, should be considered in future studies. As this is a cross-sectional study, causality cannot be determined. Longitudinal studies will be needed to determine if underlying deficits in the emotion regulation brain networks contribute to the development of CLBP, while exploring effective connectivity in emotion regulation could contribute to a more comprehensive understanding of the networks involved. It is also important to note that gPPI analyses measure relative connectivity values between regions where direction of connectivity cannot be determined, hence, advanced connectivity analyses may allow a more comprehensive understanding of the networks involved and affected during reappraisal in CLBP. This study only explored cognitive reappraisal for emotion regulation. As individuals with chronic pain often report using maladaptive regulation processes such as catastrophizing or rumination (Koechlin et al., 2018), it may impact the ability to successfully reappraise negative emotions. Comparing the different adaptive and maladaptive types of emotion regulation and the habitual coping strategies, particularly those in response to events related to the pain events, would be valuable in establishing the role of emotion regulation in CLBP.

Conclusion

Overall, this preliminary study demonstrated that individuals with CLBP reported effective emotion regulation at the behavioural level compared to healthy pain-free controls. While there were no group differences in the BOLD activity within the amygdala, the CLBP group exhibited altered functional connectivity during cognitive reappraisal. Specifically, the CLBP group showed reduced coupling between the amygdalae and the DLPFC, OFC and IPL compared to controls. Moreover, greater connectivity between the amygdala and IPL positively correlated with the percent of reduced negative affect during reappraisal in the CLBP group. These findings suggest that the underlying brain changes observed in CLBP may affect cognitive processes such as emotion regulation which has the potential to be used as treatment targets in future studies.

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