Research Paper

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Cognitive behavioral training reverses the effect of pain exposure on brain network activity

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Abstract

Repeated sensory exposures shape the brain's function and its responses to environmental stimuli. An important clinical and scientific question is how exposure to pain affects brain network activity and whether that activity is modifiable with training. We sought to determine whether repeated pain exposure would impact brain network activity and whether these effects can be reversed by cognitive behavioral therapy (CBT)-based training. Healthy subjects underwent 8 experimental sessions on separate days on which they received painful thermal stimuli. They were randomly assigned to groups receiving either CBT-based training (regulate group, n = 17) or a non–pain-focused treatment (control group, n = 13). Before and after these sessions, participants underwent functional magnetic resonance imaging (fMRI) during painful stimulation and at rest. The effect of repeated pain over time in the control group was a decrease in the neurotypical pain-evoked default mode network (DMN) deactivation. The regulate group did not show these DMN effects but rather had decreased deactivation of the right ventrolateral prefrontal cortex (R vlPFC) of the executive control network. In the regulate group, reduced pain-evoked DMN deactivation was associated with greater individual reduction in pain intensity and unpleasantness over time. Finally, the regulate group showed enhanced resting functional connectivity between areas of the DMN and executive control network over time, compared with the control group. Our study demonstrates that trainable cognitive states can alter the effect of repeated sensory exposure on the brain. The findings point to the potential utility of cognitive training to prevent changes in brain network connectivity that occur with repeated experience of pain.

Keywords: Pain, CBT, fMRI, Default mode network, Functional connectivity, Cognitive training

1. Introduction

Repeated sensory exposure shapes the brain's function and its responses to exogenous stimuli. For example, repeated exposure to pain can alter the neural response to subsequent pain, potentially contributing to development of chronic pain.[6,19] However, pain and its neural representation are strongly influenced by cognitive context,[15,26,54] raising the possibility that cognitive training could alter the deleterious effects of repeated pain exposure on the brain. The effects of such training on brain activity, however, are poorly understood.

Examination of how pain reshapes brain networks has traditionally focused on sensory and antinociceptive brain systems. However, recent neuroimaging evidence suggests a more widespread system at play, referred to as the "pain connectome," a spatiotemporal signature comprising a broader set of interacting networks, including key roles of cognitive networks in association cortices.[26] For example, the default mode (DMN), salience, and frontoparietal/executive control networks underpin dynamic pain–cognition interactions. Functional organization of networks within the pain connectome is reshaped with repeated exposure to acute pain, clinical improvement in chronic pain, and transition from subacute to chronic pain.[6,19,34,38] This suggests that a treatment that alters the cognitive context in which pain occurs might alter maladaptive network changes occurring in response to repeated pain.

Cognitive behavioral therapy (CBT) is a structured psychotherapeutic intervention that targets maladaptive cognitive factors to reduce negative affect.[7] Although CBT was originally developed to treat depression, CBT has been successfully adapted to treat pain.[48,49,55] Therefore, CBT is well suited to investigate experience-dependent dynamics of pain perception and processing in the brain.

Longitudinal neuroimaging studies provide insight into the roles of structural and functional brain regions and networks in CBT for chronic pain.[22,43,45] However, a challenge in chronic pain studies is controlling for individual variability in the frequency and intensity of pain over the course of CBT treatment. Furthermore, these studies recruit patients after pain has already become chronic. Studying the effects of repeated pain exposure on brain network activity could provide insight into processes that contribute to chronification and how these changes might be reversed with early intervention.

Here, using a unique, controlled experimental paradigm in healthy subjects, involving repeated exposure to pain over many sessions,[40] we assessed the effects of CBT-based training on both pain-evoked brain activity and intrinsic network organization with

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functional magnetic resonance imaging (fMRI). We hypothesized that repeated pain exposure would alter brain network activity during pain and that those altered activities could be reversed by CBT-based training. Using an identical level of subjectively reported pain before and after training, we aimed to uncover functional plasticity in the neural processing of pain after pain exposure and cognitive training. Additionally, given that evoked brain network response patterns show strong similarities with the functional architecture of spontaneous activity,[17,46] we also expected that CBT-based training would change intrinsic organization of similar cognitive networks assessed with resting-state fMRI.

2. Methods

2.1. Subjects

The experimental manipulation has been described in detail elsewhere.[40] In brief, 34 healthy, pain-free, right-handed individuals (age range 21-38) each randomly assigned to either a CBT-based training or control group underwent 10 experimental sessions over 21 days that consisted of 8 test sessions and an initial and final session of fMRI during evoked pain and resting-state, and 8 test sessions (see below) (**Fig. 1**). All subjects provided informed consent to procedures approved by the University Health Network research ethics board. Behavioral, but not neuroimaging data, from this data set were previously reported.[40] At baseline, the 2 groups did not differ in pain-related attitudes, coping strategies, personality factors, or psychological factors such as depression and anxiety (see Ref. 40 for details). Four individuals in the control group (see below) were excluded from the present analyses because of excessive and/or stimulus-correlated motion in one or more scans (2 subjects) or because of lack of completion of all pain provocation scans at the final session (2 subjects). One subject completed the pain provocation but not resting-state scan at the final session. Therefore, 13 control and 17 regulator subjects were included in pain-evoked fMRI analyses, whereas 12 control and 17 regulator subjects were included in resting-state analyses.

2.2. Thermal detection and pain thresholds

Thermal stimuli were delivered to the left volar forearm with a 30- × 30-mm Peltier thermode (TSA-II, Medoc Ltd, Israel).

2.2.1. Determination of intensity of experimental stimuli

We used an iterative procedure based on each participant's pain threshold to determine individualized pain levels. Pain thresholds were determined using a ramp procedure (baseline 32°C, ramp rate 1°C/s, 30-second interstimulus interval). The threshold was calculated as the average of the final 3 of 4 total trials. Participants were asked to rate 8-second stimuli beginning at pain threshold + 1°C. If that temperature was rated ≥6/10 (numerical rating scale: 0 = "no pain," 10 = "worst pain imaginable") on 6 consecutive trials, it was used for further testing. If not, the temperature was raised by 0.5°C until that threshold was met (maximum temperature ≤50°C). The temperature determined during this calibration phase was then used throughout the training. In each of the subsequent 1-hour test sessions, participants received 45 eight-second noxious heat stimuli (30-second inter-stimulus interval [ISI]). Participants rated the stimulus intensity and unpleasantness every 15 trials (0–10 numerical rating scale; 0 = "no pain," 10 = "most intense pain imaginable"; 0 = "not unpleasant," 10 = "extremely unpleasant"). Between-session changes were analyzed by averaging within-session ratings.

The calibration procedure was repeated before the final scan session to adjust for habituation and other sources of variation occurring over the course of training, so that the stimulus used in the second scan run was perceptually matched to the one used in the first scan. Matching pain intensity across scanning sessions allowed us to investigate how the neural processing of an identical pain percept may change over time and how CBT-based training may affect the change in neural processing.

2.3. Cognitive behavioral training protocol

After the first scan, but before the beginning of training, participants were randomized into 1 of 2 conditions. Participants in the regulate group (n = 17, 8 females) were given a brief (~5 minute) session of pain-focused cognitive behavioral training based on an existing treatment manual[48] before administration of the thermal stimuli. The aim of this training was to reduce their response to the painful stimuli by identifying negative thoughts, reappraising their situation, and focusing on benefits of the training (eg, financial compensation, development of pain-coping skills). Participants in this group were educated on the relationship between different aspects of pain (cognitive, emotional, and sensory; eg, "Pain is a major stressor. It can and does produce biological, emotional, and cognitive stress responses") and engaged in interactive discussion about their responses to the experimental stimulus and how they might modulate these responses (eg, "How did your strategy work? Were there any barriers to your being able to successfully suppress the pain?"). Participants in the control group (n = 13, 5 females) were trained in interpersonal effectiveness.[30] The aim of this training was to improve interpersonal assertiveness and communications with others. Like training in the regulate group, this training involved

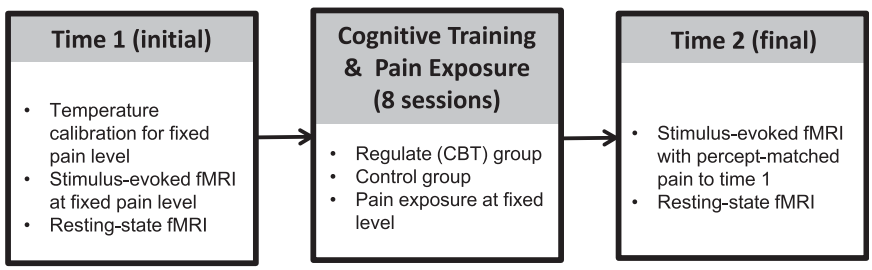

Figure 1. An overview of the study paradigm. Subjects underwent preintervention neuroimaging, including functional magnetic resonance imaging (fMRI) with painful stimulation and at rest, and were then either assigned to a regulate (cognitive behavioral training) group or (active) control group. Over 8 sessions on different days, subjects in each group received cognitive training and were exposed to pain. After training, subjects returned for a second neuroimaging session, including fMRI with painful stimulation percept-matched to the initial session and at rest.

both a psychoeducational component ("Just as it is difficult to balance priorities and demands in our lives, it can be difficult to balance 'wants' and 'shoulds'") and interactive discussion of how to implement the material in daily life (eg, "How effective is the balance between 'wants' and 'shoulds' in your life? What are some factors that prevent the balance from being more effective?"). Although participants in both groups received equivalent training (both in terms of the amount of time and the format), the regulate group was encouraged to apply their training during the painful stimuli, but the control group was not. Text describing these interventions is provided as supplemental material in our previously published study.[40]

2.4. Neuroimaging

Neuroimaging data were acquired with a 3-Tesla GE system equipped with an 8-channel phased-array head coil. Pain-evoked and resting-state fMRI scans were acquired using an echo-planar pulse imaging sequence (repetition time = 2000 milliseconds, echo time = 25 milliseconds, axial slice thickness = 4 mm, field of view = 20 × 20 cm, 64 × 64 matrix, voxel size of 3.125 × 3.125 × 4 mm^3). We collected 150 volumes (ie, 5 minutes) in each run. Functional runs were registered to T1 weighted scans (TR = 7.8 milliseconds, TI = 300, flip angle = 20°, matrix = 134, field of view = 20, bandwidth = 15.6, slice thickness = 1.5 mm, slices = 108).

At both sessions, subjects were given 6 painful 8-second thermal stimuli at the predetermined level (see above) delivered to their left volar forearm. There was a 30-second ISI, and subjects rated the pain intensity and unpleasantness after each stimulus (VAS, same anchors as above). The break between pain offset and rating scale onset was jittered between 8 and 14 seconds (mean = 11 seconds). Previous studies indicate that intersession test–retest reliability in fMRI activation can be high in several cortical regions for as few as five 15-second evoked heat painful stimuli (eg, intraclass correlations ranging from 0.5 to 0.859 across 2 sessions),[50] and that similarly few trials are needed to detect pain-evoked deactivations.[24] Therefore, we believe that we likely had sufficient trials to detect reliable effects (however, see Discussion).

2.5. Pain-evoked brain activity: functional magnetic resonance imaging preprocessing and analysis

Using FEAT in FSL v5.0,[21] whole-brain voxel-wise activation/deactivation analyses were conducted on the fMRI scans of painful stimulation that were percept-matched between pre- and post-training scans. Individual runs were preprocessed with the following procedures: first 5 volumes deleted, motion correction (MCFLIRT), brain extraction, spatial smoothing (6-mm full-width at half maximum kernel), and high-pass temporal filtering (0.01-Hz cutoff). Linear registration (FLIRT) was performed among T1, fMRI, and MNI152 2 × 2 × 2 mm standard space.

First-level (within-run) general linear model analyses in native fMRI space were conducted with FILM prewhitening and with 2 separate regressors (pain stimulation period and pain rating period), each convolved with a gamma hemodynamic response function and with temporal filtering applied. A first-level contrast was set up to create voxel-wise contrast of parameter estimate maps of pain-evoked activation. These maps were passed on as inputs to a second-level (within-subject) analysis of the 2 time points. The maps were converted to MNI152 space, and fixed effects analyses were performed with 4 contrasts to identify pain-evoked activation: time 1 alone, time 2 alone, time 1 > time 2, and time 2 > time 1. The resulting maps for each contrast were then entered into a third-level (group-level) FLAME2 mixed-effects analysis (threshold: cluster based $P < 0.05$; family-wise-error-corrected $Z > 2.3$), with 8 contrasts: time 1 activation, time 1 deactivation, time 2 activation, time 2 deactivation, time 2 > time 1 (each group separately), time 1 > time 2 (each group separately), time 2 > time 1 (control > regulate group), and time 1 > time 2 (regulate group > control group). Thus, the main analyses assessing the effect of group on brain activation changes over time were repeated measures (time 1, time 2) analysis of variance (ANOVA) with groups (control, regulate) as factors.

We next sought to determine whether significant group differences in pain-evoked activation over time were behaviorally relevant at the level of individual differences in changes in pain. We thus tested relationships between neural activation and behavior by extracting each individual's mean Z score values for the appropriate contrast from core regions DMN regions that showed significant group differences in pain-evoked activation from time 1 to time 2 (6-mm-diameter spheres drawn around peak coordinates in the medial prefrontal cortex [mPFC] [MNI xyz = −2, 52, 14] and posterior cingulate cortex [PCC]/precuneus [PCu] [MNI xyz = 4, −54, 18]). We calculated Pearson correlations between changes in activation in these regions and changes in secondary hyperalgesia (which demonstrated a significant group × time interaction in our previous analysis[40]), pain intensity, and pain unpleasantness over the course of training. We also performed these analyses for a right ventrolateral prefrontal cortex (R vlPFC) region that showed significant group differences in pain-evoked activation from time 1 to 2 (6-mm-diameter sphere drawn around peak coordinates [MNI xyz = 50, 42, 6]). The correlation analyses were thresholded at $P < 0.05$. Given previously identified associations between the DMN and pain-related cognition assessed with the pain catastrophizing scale (PCS),[20,28,47] we also correlated DMN activity changes with the PCS at time 2 compared with time 1 in both groups (although 1 control subject had missing PCS scores and was not included).

2.6. Resting-state functional magnetic resonance imaging: preprocessing and analysis

Longitudinal analyses of resting-state fMRI data were performed to test hypotheses that were based on between-group differences that were identified from the pain-evoked activation analyses. In line with the notion that stimulus-/task-evoked activity patterns show strong similarities with the functional architecture of spontaneous activity,[17] we expected that key regions showing group differences in pain-evoked activation due to CBT-based training would also show related effects on resting-state connectivity. Thus, seed regions for resting-state fMRI analysis (described below) were defined based on pain activation differences between groups.

Resting-state data were preprocessed as done previously,[25,28,29] using a combination of FSL, MATLAB v.7.12.0 (MathWorks), and fMRISTAT.[57] First, using FSL's FEAT, the following was done: deletion of the first 4 volumes, motion correction (MCFLIRT), brain extraction, and linear registration among fMRI, T1, and standard MNI152 2 × 2 × 2 mm space. The T1 scans were segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF) using FSL's FAST. The WM and CSF partial volume maps were then registered to fMRI space and were thresholded to retain the peak voxels constituting volumes of 198 cm^3 for WM and 20 cm^3 for CSF.[13] Following aCompCor procedures for removal of physiological and scanner-related noise,[8] principal components analysis was performed on the

fMRI data within the WM and CSF masks separately. The top 5 WM components, top 5 CSF components, and 6 motion parameters that were obtained with MCFLIRT were then regressed from the fMRI data. Finally, spatial smoothing (6-mm full-width at half-maximum kernel) and bandpass temporal filtering (0.005-0.05 Hz) were performed.

A first-level seed-based functional connectivity analysis was conducted with each run, using FEAT. Seed regions were chosen based on the significant group difference map showing effects of CBT-related training on pain-evoked activation. This map contained regions mainly within the DMN but also a lateral prefrontal region (R vlPFC) that had different directionality in group-related activation effects than the DMN regions.

Thus, 1 seed was defined as a 6-mm-diameter sphere surrounding peak coordinates in a location within R vlPFC (MNI xyz = 50, 42, 6) where the regulate group showed a greater decrease in pain-evoked activation from time 1 to time 2 than did the control group. The seed was registered from MNI to fMRI space, and the mean time course within seed voxels was extracted. This time course was entered as a regressor in a first-level general linear model for each run to create voxel-wise contrast of parameter estimate maps of functional connectivity. Second-level (within-subject) and third-level (group-level) analyses were conducted following the same procedures and statistical thresholds as in the pain-evoked activation analyses. An identical analysis was repeated for a seed in the PCC/PCu region (6-mm diameter around peak coordinates: MNI xyz = 4, −54, 18) that showed significant group differences in pain-evoked activation from time 1 to time 2 (greater decrease in deactivation over time in the control compared with the regulate group). We chose the PCC/PCu as the seed, as opposed to other regions within the DMN that showed similar pain activation effects because the PCC/PCu is considered a hub within the DMN.[1]

3. Results

3.1. Stimulus intensity and pain ratings

The temperatures (mean [SD]) used to evoke the "perceptually matched ratings" of pain within groups at both time points are listed in **Table 1**. There was no time-by-group interaction ($F = 0.26$, $P = 0.61$), and the groups did not differ significantly at either time point (time 1 $F = 1.25$, $P = 0.27$; time 2 $F = 2.68$, $P = 0.11$).

As previously reported,[40] during training sessions, there was a significant group-by-time interaction for pain unpleasantness, but not intensity, such that there was a significantly greater reduction in pain unpleasantness in the regulate group than in the control group. No such interaction was observed for pain intensity. It should be noted that unlike the stimuli used during the scan session, these stimuli were not delivered at a set perceptual level but, rather, at the level of stimulation used at the initial session.

Table 1

Mean (SD) temperature used and mean ratings for painful stimuli that were perceptually matched between groups and between time points.

	Temperature	Pain intensity rating	Pain unpleasantness rating
Control group			
Time 1	47.7 (1.82)	6.0 (0.94)	5.6 (0.71)
Time 2	48.7 (1.82)	7.0 (1.79)	6.8 (1.71)
Regulate group			
Time 1	48.3 (1.17)	6.7 (1.52)	6.3 (1.71)
Time 2	49.5 (0.7)	6.8 (2.01)	6.5 (2.20)

For pain ratings collected during the scan sessions, we intended to match the groups on pain ratings (see Introduction/Methods) and so we statistically tested whether this was successfully achieved. Mean (SD) pain intensity and unpleasantness ratings at both time points within each group are listed in **Table 1**. Pain intensity ratings at time 2 were not significantly different from those at time 1 for either group (repeated-measures ANOVA $F_{1,12} = 3.37$, $P = 0.09$ control, $F_{1,15} = 0.03$, $P = 0.86$ regulate), and the time-by-group interaction was not significant ($F = 1.4$, $P = 0.25$), confirming that stimuli were percept-matched between sessions. There were no significant group differences in pain intensity at time 1 ($F = 2.12$, $P = 0.16$) or at time 2 ($F = 0.11$, $P = 0.74$).

Pain unpleasantness ratings at time 2 were not significantly different from those at time 1 for either group (repeated-measures ANOVA $F_{1,12} = 4.39$, $P = 0.06$ control, $F_{1,15} = 0.06$, $P = 0.81$ regulate), and the time-by-group interaction was not significant ($F = 1.4$, $P = 0.24$). There were no significant group differences in pain unpleasantness at time 1 ($F = 1.94$ $P = 0.18$) or at time 2 ($F = 0.18$, $P = 0.68$).

3.2. Effect of cognitive behavioral training on pain-evoked brain activation

At time 1 (preintervention), both the regulate and control groups had pain-evoked activations located within regions of the somatosensory and salience networks including bilateral insula, mid-cingulate cortex (MCC), dorsolateral prefrontal cortex (dlPFC), secondary somatosensory cortex (S2), and caudate nucleus. There were also pain-evoked deactivations in regions of the default mode network (DMN) (bilateral PCC/PCu, mPFC, and lateral parietal cortex [LPC]) (**Fig. 2**). There were no significant group differences in pain-evoked activity at time 1 (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$). This demonstration, in each group, of pretraining whole-brain pain-related activation and deactivation patterns consistent with previous literature,[2,26,33] combined with the lack of significant group differences, served to validate our approach and suitability of the sample size (ie, we were powered enough to detect canonical pain-related neural activity in 2 independent groups with no preexisting group differences).

Crucially, there were significant group differences in the changes of pain-evoked brain activations from time 1 to time 2 (ie, the time-by-group interaction was significant) in several regions (**Fig. 3A-C**). Follow-up within group analyses indicated that the significant time-by-group interaction observed in DMN regions (PCC/PCu, mPFC, and lateral parietal cortex [LPC]—**Fig. 3C**) was driven by changes in deactivation in the control subjects that was not observed in the regulate group. Specifically, there was deactivation within these DMN regions in both groups at time 1, but a significant decrease in deactivation at time 2 relative to time 1 (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$) was observed in the control group (see **Fig. 3A** and example plot for PCC/PCu in **Fig. 3C**).

A significant time-by-group interaction was also observed in a dorsolateral prefrontal region with peak coordinates in the right ventrolateral prefrontal cortex (R vlPFC), but follow-up analyses revealed that the pattern of change for this region differed from the DMN. There was no activation in either group at time 1 but significant increase in deactivation in the regulate group (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$) but not the control group at time 2 compared with time 1 (see **Fig. 3B** and plot for vlPFC in **Fig. 3C**).

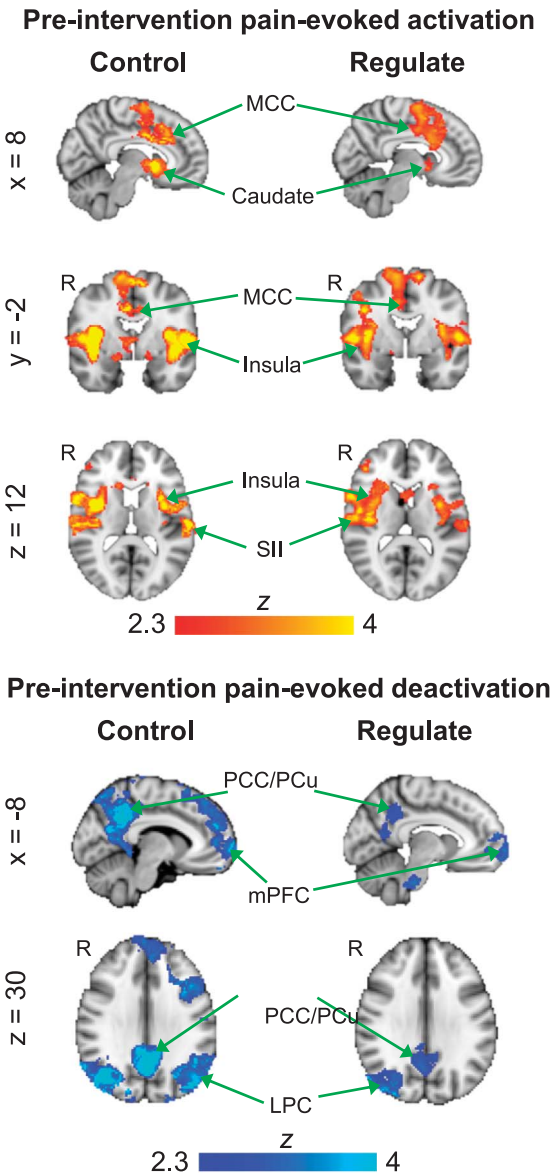

Figure 2. Preintervention brain activation and deactivation during painful stimulation in the control and regulate groups. Both groups show activation in salience- (eg, insula, MCC) and sensory-related (eg, SII) regions and deactivation in regions of the DMN (eg, mPFC, PCC) (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$). No significant group differences in brain activation/deactivation were found. LPC, lateral parietal cortex; MCC, mid-cingulate cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PCu, precuneus.

3.3. Brain activation changes over time correlate with individual pain ratings

Within the control group, changes in pain-evoked DMN core (PCC/PCu and mPFC) activity from the time 1 scan (pretraining) to the time 2 scan (posttraining) were not correlated with the pain intensity ($r = -0.09$, $P = 0.78$) or pain unpleasantness ($r = -0.12$, $P = 0.7$) changes from the first training session (behavioral session 1) to the last (behavioral session 8). However, in the regulate group, reduced pain-evoked DMN core deactivation from the time 1 scan (pretraining) to the time 2 scan (posttraining) was significantly correlated with the reduction in pain intensity ($r = 0.54$, $P = 0.025$) and pain unpleasantness ($r = 0.52$, $P = 0.033$) from the first training session (behavioral session 1) to the last (behavioral session 8) (**Fig. 4**). Correlations between the groups were compared using a Fisher r to z transform. For both intensity and unpleasantness, the correlations were not significantly different between groups at the 2-tailed level ($z = 1.68$, $P = 0.09$).

In the regulate group, the change in pain-evoked activation in the R vlPFC from scan time 1 to 2 correlated with pain intensity ($r = 0.48$, $P = 0.051$) and pain unpleasantness ($r = 0.5$, $P = 0.04$) changes from the first to last training session. There were no similar correlations in the control group ($r = 0.12$, $P = 0.71$ for intensity; $r = 0.02$, $P = 0.96$ for unpleasantness). However, for both intensity and unpleasantness, these R vlPFC activation correlations were not significantly different between groups ($z = 0.98$, $P = 0.16$ for intensity; $z = 1.29$, $P = 0.1$ for unpleasantness). There were no significant correlations between DMN activity changes and changes in PCS over time in the regulate group ($r = -0.02$, $P = 0.94$) or in the control group ($r = 0.47$, $P = 0.12$).

3.4. Effect of cognitive behavioral training–based training on resting-state functional connectivity

The R vlPFC region that demonstrated a significant group differences in response to CBT-based training in the pain-evoked analysis was used as a seed region to assess resting-state functional connectivity changes. This region showed increased pain-evoked deactivation over time in the regulate but not the control group, so we sought to investigate how its intrinsic network connectivity may have changed differentially between groups. At time 1 (pretraining), in both regulate and control groups, the R vlPFC exhibited resting-state functional connectivity with a fronto-temporal-parietal network including R TPJ and L dlPFC (**Fig. 5**), resembling the executive control network.[27,58] There were no significant group differences in R vlPFC functional connectivity at time 1 (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$).

As in the pain-activation analysis, there were significant group interactions with time for R vlPFC functional connectivity (**Fig. 6A-C**). The analysis of changes from time 1 to time 2 revealed that a region within mPFC exhibited a greater increase in functional connectivity with the R vlPFC in the regulate group compared with the control group (**Fig. 6C**) (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$). Within-group functional connectivity results reveal the changes over time that drove the group interaction with time (**Fig. 6A and B**). Within the control group, there was increased R vlPFC functional connectivity at time 2 compared with time 1 with the mid-cingulate cortex (MCC) and an anterior portion of the PCu (**Fig. 6A**), both of which are regions typically associated with the salience network.[58] In contrast, within the regulate group, there was increased R vlPFC functional connectivity at time 2 compared with time 1 with the mPFC and PCC/PCu, which are regions of the DMN (**Fig. 6B**) (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$).

The mPFC cluster that exhibited a group-by-time interaction effect in the resting-state analysis overlapped with mPFC regions that showed a greater increase in pain-evoked activation in the control compared with the regulate group at time 2 compared with time 1 (**Fig. 7**). No significant group differences in the change of resting-state functional connectivity over time were found when using the PCC/PCu as a seed region.

4. Discussion

We show that repeated exposure to pain alters pain-evoked brain activity, specifically by diminishing the normal pain-evoked deactivation of DMN. Importantly, this altered response was reversed

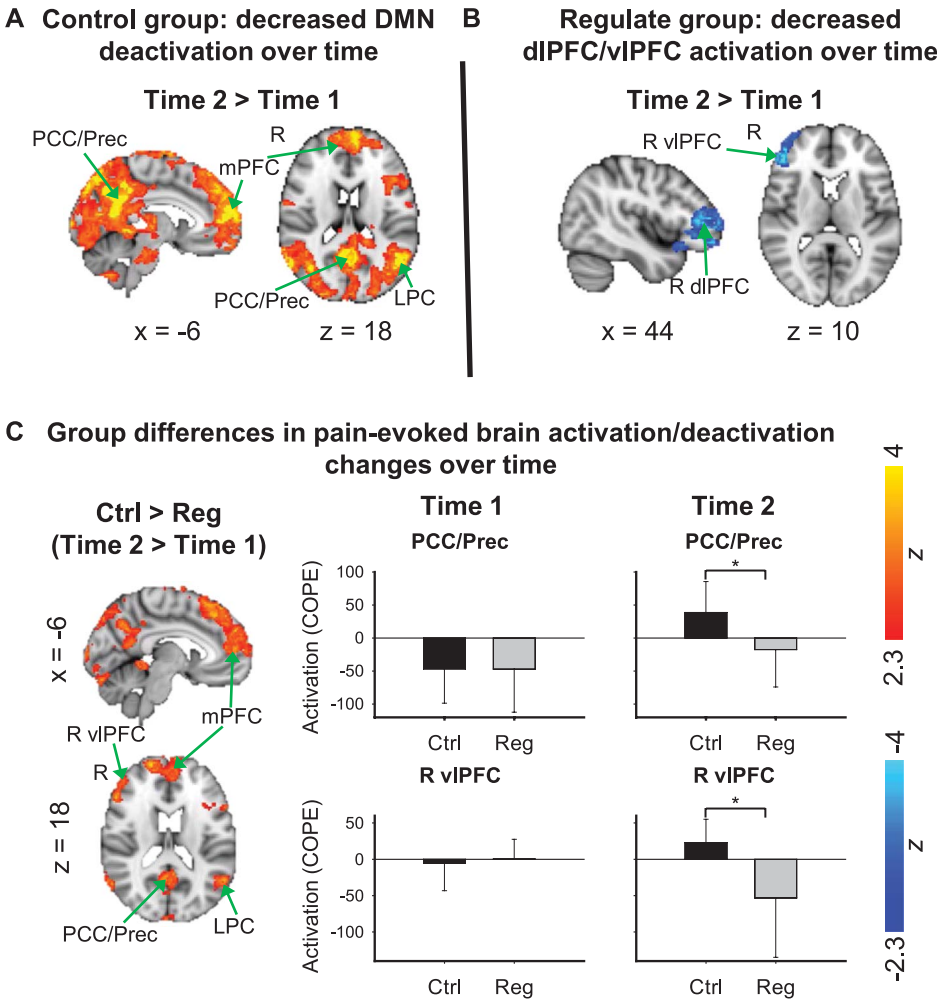

Figure 3. Changes in brain activation during painful stimulation after cognitive training compared with before training. (A) The control group largely showed decreases in deactivation of DMN areas over time; (B) The regulate group showed decreased activation of dorso-/ventro-lateral prefrontal cortical regions over time; (C) A group comparison revealed greater activation changes over time in the control group compared with the regulate group in default mode and lateral prefrontal regions (all maps displayed at FWE-corrected $Z > 2.3$; cluster-based $P < 0.05$). Ctrl, control; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; LPC, lateral parietal cortex; MCC, mid-cingulate cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; Prec, precuneus; Reg, regulate; vlPFC, ventrolateral prefrontal cortex.

by cognitive training. We show that 8 sessions of CBT-based training maintains normal patterns of pain-evoked DMN deactivation, and that the degree to which this DMN deactivation is reduced is associated with decreases in pain intensity and unpleasantness over time due to cognitive training. Additionally, cognitive training resulted in decreased R vlPFC activation during painful stimulation and increased spontaneous functional connectivity between the DMN and R vlPFC. This work highlights the dynamic nature of pain and its neural representation, emphasizing a role of cognitive brain networks in training effects on pain perception.

4.1. Default mode network (de)activation and pain

In healthy individuals, the DMN is typically deactivated during acute pain,[14,36,37,42] a result that was replicated in both groups in our preintervention findings. In our study, repeated pain exposure (in the control group) eradicated this DMN deactivation but cognitive training (in the regulate group) maintained it.

One interpretation is that control subjects, in the absence of cognitive training to cope with pain, gradually became "chronic pain-like" in their DMN responses. Previous studies showed changes in mPFC (of the DMN) activity and connectivity associated with chronic pain development.[6,19] Patients with chronic pain showed attenuated DMN deactivation during cognitive task performance.[4,11,44,52] Furthermore, patients with chronic pain showed a lack of DMN deactivation during painful stimulation, a response that was restored with successful analgesic treatment.[18] Also of relevance to our findings, prolonged exposure to uncontrollable (compared with controllable) pain was shown to elicit greater pain-evoked DMN activation.[41] It is thus possible that pain exposure (chronic or repeated instances of acute pain) results in attenuated pain-evoked DMN deactivation, but this attenuation can be prevented/reversed with CBT or analgesic treatment.

Another possible interpretation is that the observed group differences in brain activation are due to different pain-coping strategies. Attenuated DMN deactivation during painful stimulation has been linked to fluctuating attention to pain.[29] Together with our observation of an association between reduced pain-evoked DMN deactivation and reduced pain intensity and unpleasantness in the regulate group, this suggests that cognitive training might alter attentional focus on pain. Given the previously

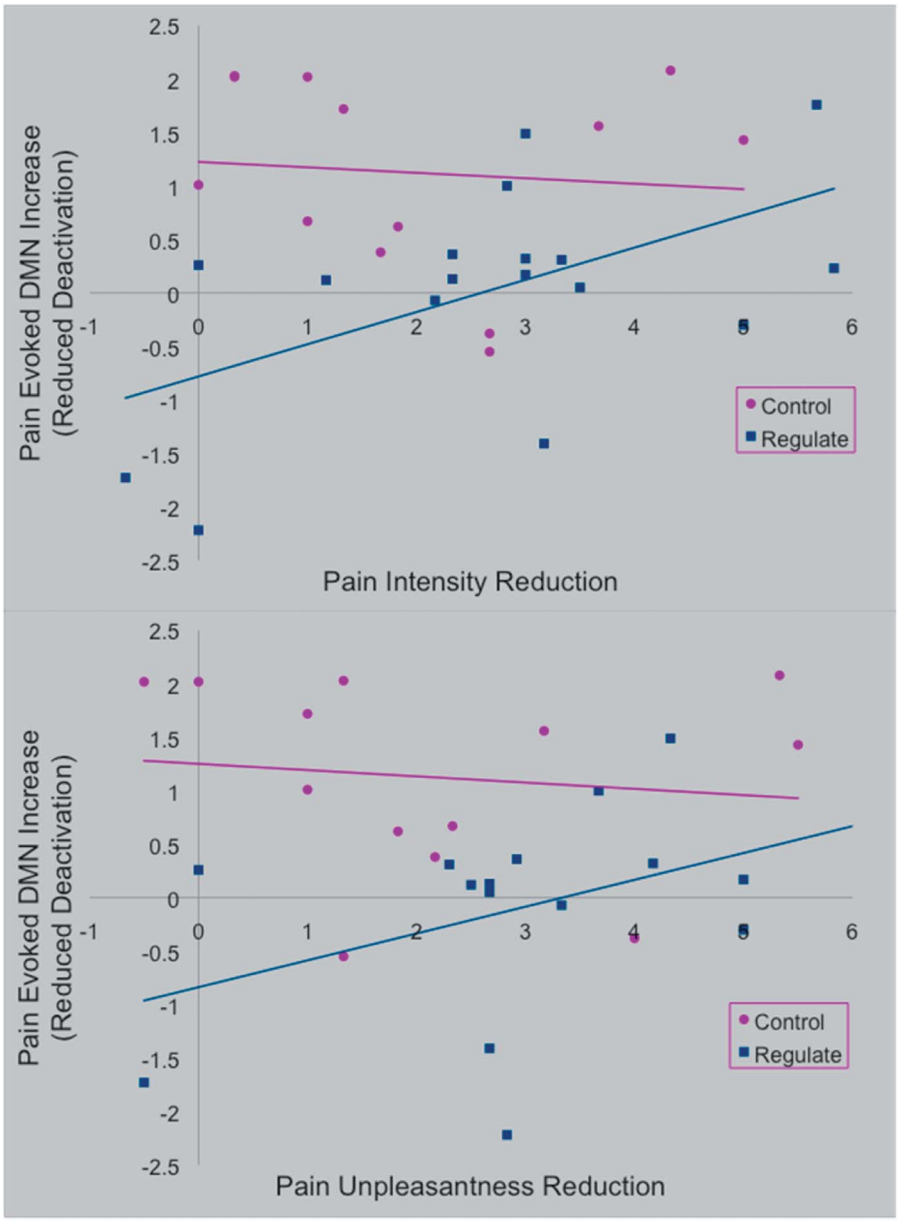

Figure 4. Relationships of reduced pain intensity and unpleasantness over time (measured in behavioral sessions) and pain-evoked default mode network (DMN) activity (measured during functional magnetic resonance imaging) in control and regulate groups. In the regulate group, there was a positive correlation of reduced pain-evoked DMN deactivation at the final compared with first scan with reduced pain intensity ($r = 0.48$, $P = 0.051$) and unpleasantness ($r = 0.5$, $P = 0.04$) at the last compared with first behavioral session. In the control group, there were no such correlations with pain intensity ($r = 0.12$, $P = 0.71$) or unpleasantness ($r = 0.02$, $P = 0.96$).

demonstrated link between vlPFC activation and reappraisal of pain,[39,41,53] it is possible that changes in pain-evoked activation of this region and resting-state connectivity between vlPFC and DMN are associated with a process whereby volitional appraisal alters subsequent attention to pain. Further studies with specific measures of reappraisal and attention to pain are needed to confirm these interpretations.

4.2. Cognitive–behavioral therapy for pain and the brain

Longitudinal studies have begun to uncover the effects of CBT on the brain in chronic pain. Jensen et al.[22] found enhanced pain-evoked vlPFC activation and functional connectivity with the thalamus due to CBT. Seminowicz et al.[43] showed increased gray matter volume after CBT in several regions spanning association (eg, prefrontal) and sensory (S1/S2) cortices. Shpaner et al.[45] revealed decreased spontaneous interactions between the DMN and antinociceptive regions, and increased connectivity between S2 and basal ganglia due to CBT.

This study is unique from previous studies in that we studied healthy subjects, exposed all subjects to equal amounts of pain, matched stimuli before and after treatment for pain intensity, and studied both pain-evoked and intrinsic brain activity in regulate and control groups. Our paradigm enabled us to specifically attribute effects to CBT-based training, with minimal impact of confounding factors.

We recently showed that this CBT training paradigm reduces secondary hyperalgesia (ie, a lack of enhanced pain sensitivity

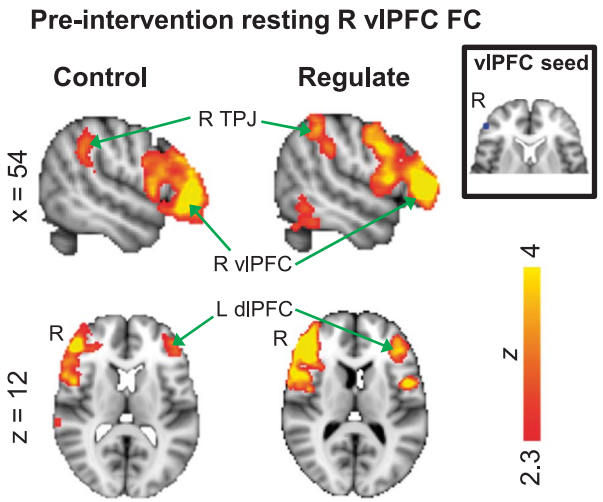

Figure 5. Preintervention resting-state functional connectivity of the right ventrolateral prefrontal cortex (R vlPFC) in the control and regulate groups. Both groups show functional connectivity with regions in the executive control network (eg, dlPFC, TPJ) (FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$). No significant group differences in resting R vlPFC functional connectivity were found. Ctrl, control; dlPFC, dorsolateral prefrontal cortex; FC, functional connectivity; Reg, regulate; TPJ, temporoparietal junction; vlPFC, ventrolateral prefrontal cortex.

beyond the site of stimulus-induced injury) in healthy individuals.[40] Neuroimaging results of the present study further delineate the biological mechanisms of CBT-based training for pain. Partly consistent with CBT studies of chronic pain,[45] our results emphasize a role of the DMN. Further studies with multimodal imaging approaches (such as those applied here) are needed to characterize pain-related and intrinsic activity in chronic pain. Interestingly, neuroimaging studies of CBT for depression have demonstrated effects on the DMN (particularly mPFC) and lateral prefrontal areas including vlPFC,[16,23,59] possibly indicating common mechanisms between CBT for mood and pain control.

Beyond CBT, neuroimaging studies of multiple, distinct cognitive regulation and reappraisal strategies for pain are revealing potentially specific brain mechanisms for different pain-coping strategies.[9] For example, recent studies of acute pain in healthy individuals point toward potentially unique brain mechanisms underlying self-regulation of pain[56] and mindfulness meditation.[60] Thus, an additional area requiring further inquiry pertains to how effects of CBT on the brain compare with effects of other cognitive strategies for pain coping.

4.3. Clinical implications

Accumulating evidence implicates abnormal DMN activation and connectivity in the pathophysiology of chronic pain. Patients with chronic pain show attenuated DMN deactivation during cognitive performance.[4,44,52] Resting-state fMRI studies reveal abnormal functional connectivity within the DMN and between the DMN and other networks in multiple chronic pain disorders.[3,5,12,28,31,32,35] Furthermore, DMN regions show altered interactions with cognitive-, pain- and antinociception-related networks as chronic pain improves over time with diverse

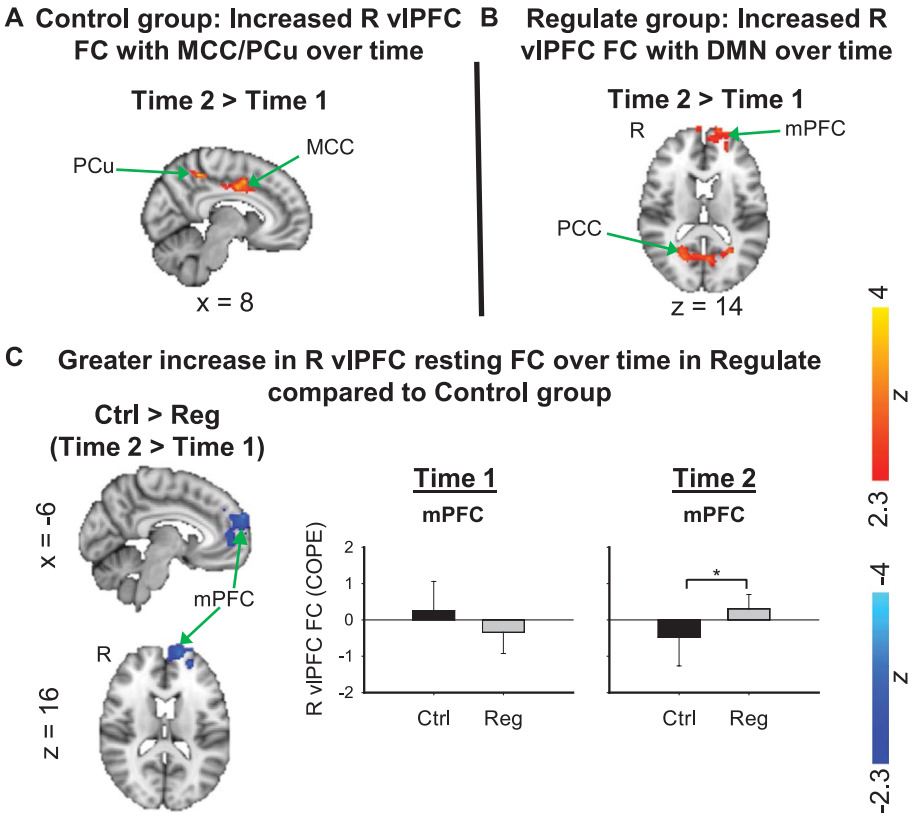

Figure 6. Changes in resting right ventrolateral prefrontal cortex (R vlPFC) functional connectivity after cognitive training compared with before training. (A) The control group showed increased functional connectivity with the MCC and PCu over time; (B) The Reg group showed increased functional connectivity with DMN areas (PCC, mPFC) over time; (C) A group comparison revealed a greater increase in functional connectivity with the mPFC in the Reg compared with the control group over time (all maps displayed at FWE-corrected $Z > 2.3$; cluster-based $P < 0.05$). Ctrl, control; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; FC, functional connectivity; MCC, mid-cingulate cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PCu, precuneus; Reg, regulate; vlPFC, ventrolateral prefrontal cortex.

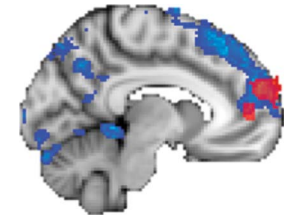

Figure 7. An overlay of regions showing control > regulate activation during painful stimulation over time (blue) and regions showing control > regulate resting-state functional connectivity of the right ventrolateral prefrontal cortex (R vlPFC) (red/yellow) over time. A common cluster within the medial prefrontal cortex was significant in both analyses (both maps displayed at FWE-corrected $Z > 2.3$, cluster-based $P < 0.05$). Ctrl, control; FC, functional connectivity; Reg, regulate; vlPFC, ventrolateral prefrontal cortex.

treatments.[6,12,34] Therefore, the DMN may be an important target whose aberrant activity and connectivity may be alleviated with CBT for chronic pain.

Cognitive behavioral training (and similar treatments) affects the pain experience by changing beliefs and expectations about pain. As such, we expect that some mechanistic overlap with effects, eg, placebo analgesia that work by manipulating pain-related beliefs.[51] A critical difference, from both a scientific and clinical standpoint, however, is that CBT brings these effects under an individual's volitional control. Further longitudinal study of the neural mechanisms through which CBT and other psychotherapeutic interventions work will facilitate enhancement of these effects through training, leading to more efficient and effective treatment for pain. Our paradigm detected changes in pain-evoked neural activation and reversal of these changes by CBT-based training. Although further study will be needed to test the applicability of the paradigm to chronic pain populations, it seems promising to better understand the transition from acute to chronic pain states and how cognitive training can alter neural processes that give rise to this transition.

4.4. Limitations

Our study should be considered preliminary and should ideally be reproduced and built upon in future work with higher sample sizes and greater numbers of trials for measuring pain-evoked brain activity.[10] There was a slight imbalance between the number of regulator (n = 17) and control (n = 13 for activation analyses, n = 12 for resting-state analyses) subjects, which could have introduced statistical power issues that could have partially undermined some of our findings. Our demonstration that the 2 groups showed canonical, and similar, pain-evoked brain activity and resting FC at the whole-brain level at baseline improves our confidence in our study as being sufficiently powerful, but we cannot be certain that longitudinal analyses were unaffected by issues with sample size and/or number of trials.

Although we speculate that subjects in the regulate group each adopted unique strategies based on their cognitive training to cope with pain, we did not include a measure to assess individual differences in strategies. Thus, future work is needed to link brain activity changes with specific pain-coping strategies. Furthermore, although our study design with healthy individuals was chosen to limit confounding factors that may be present with a clinical sample, understanding the relevance of our results to chronic pain states remains a challenge. It is possible that patients with chronic pain would develop different coping strategies in response to cognitive training than would healthy individuals coping with acute pain, and such strategies could be linked with different brain mechanisms than those investigated in this study.

5. Conclusion

Cognitive–behavioral training for pain regulation in healthy individuals changes the brain's typical response to repeated pain exposure. Consistent with findings in the chronic pain literature, we observed alterations in DMN responses with repeated exposure to pain. With CBT-based training, these alterations were ablated, in conjunction with increases in vlPFC responses to pain and increased intrinsic connectivity between vlPFC and DMN. Monitoring brain activity and connectivity before, during, and after CBT in clinical settings may facilitate development of effective personalized pain therapies.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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