Unlearning chronic pain: A randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy

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ABSTRACT

Chronic pain is a complex physiological and psychological phenomenon. Implicit learning mechanisms contribute to the development of chronic pain and to persistent changes in the central nervous system. We hypothesized that these central abnormalities can be remedied with Cognitive Behavioral Therapy (CBT). Specifically, since regions of the anterior Default Mode Network (DMN) are centrally involved in emotional regulation via connections with limbic regions, such as the amygdala, remediation of maladaptive behavioral and cognitive patterns as a result of CBT for chronic pain would manifest itself as a change in the intrinsic functional connectivity (iFC) between these prefrontal and limbic regions. Resting-state functional neuroimaging was performed in patients with chronic pain before and after 11-week CBT ($n = 19$), as well as a matched (ages 19–59, both sexes) active control group of patients who received educational materials ($n = 19$). Participants were randomized prior to the intervention. To investigate the differential impact of treatment on intrinsic functional connectivity (iFC), we compared pre–post differences in iFC between groups. In addition, we performed exploratory whole brain analyses of changes in fractional amplitude of low frequency fluctuations (fALFF). The course of CBT led to significant improvements in clinical measures of pain and self-efficacy for coping with chronic pain. Significant group differences in pre–post changes in both iFC and fALFF were correlated with clinical outcomes. Compared to control patients, iFC between the anterior DMN and the amygdala/periaqueductal gray decreased following CBT, whereas iFC between the basal ganglia network and the right secondary somatosensory cortex increased following CBT. CBT patients also had increased post-therapy fALFF in the bilateral posterior cingulate and the cerebellum. By delineating neuroplasticity associated with CBT-related improvements, these results add to mounting evidence that CBT is a valuable treatment option for chronic pain.

1. Introduction

Chronic pain is a complex physiological and psychological phenomenon. A variety of implicit learning mechanisms contribute to the development of chronic pain and to persistent changes in the central nervous system (Apkarian, 2011; Flor, 2012). Although chronic musculoskeletal pain was originally conceptualized as a purely bottom-up perceptual process, there is now mounting physiological evidence in support of the involvement of central mechanisms. This evidence includes documented functional (Apkarian et al., 2004; Baliki et al., 2011a; Baliki et al., 2008; Bingel and Tracey, 2008; Buffington et al., 2005; Cauda et al., 2010; Cauda et al., 2009; Geha et al., 2007; Giesecke et al., 2004; Gracely et al., 2002; Napadow et al., 2010; Otti et al., 2013; Parks et al., 2011; Weissman-Fogel et al., 2011) and structural (Baliki et al., 2011b; Buckalew et al., 2008; Ceko et al., 2013; May, 2011; Moayedi et al., 2011; Schweinhardt et al., 2008; Seminowicz et al., 2010; Seminowicz et al., 2011; Valet et al., 2009) abnormalities in chronic pain populations, relative to pain-free controls, and even points to specific brain predispositions that can lead to chronification of pain (Baliki et al., 2012; Mansour et al., 2013). It is thus not surprising that pain-related

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maladaptive perceptual and behavioral patterns can be mitigated by non-pharmacological interventions such as Cognitive Behavioral Therapy (CBT) (Bernardy et al., 2010; Veehof et al., 2011; Vickers et al., 2012; Williams et al., 2012), particularly in combination with relapse prevention programs (Naylor et al., 2002; Naylor et al., 2008). The neural mechanisms underlying non-pharmacological remediation of the maladaptive behavioral and cognitive patterns of chronic pain remain poorly understood.

Recently investigations of the neural underpinnings of chronic pain have adopted resting state functional magnetic resonance imaging (R-fMRI) and intrinsic (resting state) functional connectivity (iFC) methods, which are advantageous in that they permit the interrogation of multiple functional networks without the need for targeted tasks. Development of reliable R-fMRI biomarkers for chronic pain holds promise for diagnostic, prognostic, and outcome evaluation purposes because of the relative ease of implementation in clinical and research settings. At least two longitudinal studies of iFC in chronic pain exist (Baliki et al., 2012; Napadow et al., 2012); however, neither can inform our understanding of the mechanisms of recovery from maladaptive chronic pain states related to therapy. In the present study, we set out to bridge this gap in our understanding of recovery from chronic pain by conducting longitudinal neuroimaging before and after Cognitive Behavioral Therapy (CBT) for coping with chronic pain as compared to an active Educational Materials (EDU) control.

Studies of chronic pain populations often implicate changes within the Default Mode Network (DMN), including anterior portions of the DMN (Baliki et al., 2008; Loggia et al., 2013; Napadow et al., 2008; Napadow et al., 2012; Otti et al., 2013). For example, a recent investigation in patients with somatoform pain disorder (Otti et al., 2013) documented frequency shifts in R-fMRI oscillations in the anterior but not in the posterior DMN relative to those in healthy controls. Medial prefrontal cortex (mPFC) and perigenual anterior cingulate cortex (ACC) constitute the anterior DMN and are centrally involved in emotional regulation via connections with limbic regions, such as the amygdala (Etkin et al., 2011; Milad et al., 2007; Phelps et al., 2004). Alterations in the functional interactions between anterior DMN regions and limbic regions are thus likely candidates for the mediation of CBT-related changes in clinical symptoms.

In addition to changes in DMN iFC, prior studies of iFC in chronic pain also implicate the salience (Loggia et al., 2013; Malinen et al., 2010; Napadow et al., 2012; Napadow et al., 2010) and basal ganglia (BG) networks (Baliki et al., 2010; Baliki et al., 2012; Yuan et al., 2013). Napadow et al. (2012) investigated the relationship between chronic pain levels and iFC in fibromyalgia before and after verum or sham accupuncture and showed that pre–post decreases in iFC between the salience network and DMN were correlated with a reduction in pain, irrespective of treatment. Baliki et al. (2012) followed patients with subacute pain over the course of 1 year and compared patients who went on to develop chronic pain to those who recovered. Their data suggest that increased corticostriatal connectivity may contribute to the *development* of chronic pain.

Here, we sought to build on these findings, to gain a better understanding of treatment-related functional neuroplasticity, and to better define biomarkers of recovery from chronic pain. We thus compared pre- and post-intervention changes in the iFC of default, salience and BG networks between the CBT and EDU groups. Since emotional regulation has been associated with negative connectivity between anterior DMN and limbic regions across studies (Etkin et al., 2011), we hypothesized decreased iFC between anterior DMN and limbic regions following CBT. In addition, we expected altered iFC in the salience and BG networks in the CBT, relative to the EDU group. We also explored whether the remediation of maladaptive behavioral and cognitive patterns as a result of CBT (i.e., CBT-related changes in patient-reported clinical outcomes) would be related to CBT-related alterations in iFC. Finally, in order to capture other potential correlates of treatment-related change, we performed an exploratory whole-brain analysis examining changes in the fractional amplitude of low frequency fluctuations (fALFF).

2. Materials and methods

2.1. Participants

The study sample comprised 38 patients with chronic musculoskeletal pain, ages 18–60. The sample was mixed in terms of diagnoses and included patients with chronic back pain, osteoarthritis, post-trauma/post-surgical pain, temporomandibular disorder, and fibromyalgia. 21 participants had multiple sources of chronic pain (see Supplementary Table 1 for details), and an additional three participants endorsed headaches as secondary diagnosis. Scanning was rescheduled if any participant got a headache on the day of the experimental session. Demographic characteristics are summarized in Table 1. Participants were randomized, stratified by pain level (pain of 4, 6, and 7–10 on an 11-point scale) and sex, into CBT ($n = 19$) or Educational Materials (EDU, $n = 19$) interventions. MRI scanning and clinical evaluations were performed before and after each intervention. The University of Vermont Institutional Review Board approved the research protocol, and informed consent was obtained from each participant. All procedures were in compliance with the Declaration of Helsinki.

Inclusion criteria were defined as: at least 12 months of chronic pain and a minimal subjective pain rating of 4 out of 10 (with 0 "no pain" to 10 "worst pain") for the last month. Exclusion criteria included: malignancy, pending pain-related surgery, involvement in pain-related litigation, psychosis, Axis I disorder (other than controlled mild/moderate depression or anxiety) or a severe personality disorder interfering with participation in group therapy, and typical MRI contraindications. Initially, scans for 48 participants were available. Six of these participants were dropped due to excessive movement (fewer than 240 s of resting state data remaining after regression of motion outliers; see neuroimaging analyses, below) for either of the scans (Power et al., 2014). Four additional participants were dropped from analysis due to poor registration of their high resolution T1 image to the standard template.

2.2. Medication use

Detailed medication information, including PRNs, was compiled based on patient reports and medical records at both time points. All medications were converted to standard units for each class. Most participants relied on non-opioid analgesics for pain relief, however, several participants also took other medication classes (see Supplementary Table 2 for number of participants and average doses). Two participants (1 CBT and 1 EDU) reported daily "as needed" (PRN) opioid use prior to the intervention, and two additional participants (1 CBT and 1 EDU) reported daily PRN opioid use post-intervention. There was no significant difference in non-opioid analgesic use over time, no difference between groups and no interaction between time and group. Other medication classes had very few participants for a meaningful analysis but approximately the same number of participants had a change in medication dosage in the two groups over the course of the study.

Table 1
Sample demographic characteristics (n (CBT) = 19, n (EDU) = 19).

Mean (SD)	CBT	EDU	P value
Age (years)	43.6 (13.7)	39.2 (14.1)	0.333
Females/males	16/3	13/6	0.252
# days between scans	114.5 (35.3)	97.4 (19.9)	0.075
Depression from BDI	13.16 (7.6)	11.05 (9.7)	0.463
Pain duration (years)	8.8 (6.8)	5.2 (3.1)	0.046

2.3. CBT intervention

CBT was delivered in 11 90-minute weekly group sessions. Our CBT intervention for pain management was designed to: 1) change cognitions and decrease maladaptive coping (e.g., pain catastrophizing), 2) enhance patients' ability to use attention diversion strategies, and 3) change activity patterns to better control pain. The curriculum comprised five major components: self-regulatory skills, including relaxation techniques; cognitive coping strategies such as cognitive restructuring to reduce catastrophizing; attention diversion methods; changing activity patterns, including activity pacing and regular exercise; and enhancing social support. Participants received weekly homework assignments that included keeping a pain diary and documenting the use of coping strategies. Clinicians reviewed completed assignments and provided feedback. An in-depth description of the program has been previously reported (Naylor et al., 2002; Naylor et al., 2008).

2.4. Educational materials intervention

Educational materials included 11 weekly mailings on pain physiology, the "vicious cycle" of chronic pain, the importance of managing stress and depression, physical exercise, sleep hygiene and proper nutrition. All of the didactic information included in the mailings was also covered during CBT sessions. However, specific cognitive and behavioral coping strategies were not introduced in the mailings. Participants in the educational condition did not receive feedback or encouragement on their progress.

2.5. Clinical assessment measures

All clinical measures were self-administered at each evaluation. Participants were instructed to think of their musculoskeletal pain when responding to questionnaires. Several measures of pain and disability were assessed using subscales from Treatment Outcomes in Pain Survey (TOPS) (Rogers et al., 2000): Pain Symptoms, SF-36 Mental Health Composite, SF-36 Physical Health Composite, Perceived Family Disability and Total Pain Experience. Passive Coping subscale from TOPS was used to assess maladaptive coping strategies, such as social withdrawal and hoping for a miracle. Passive coping is associated with negative outcomes in chronic pain (Nicassio et al., 1995). All of these scales are composite scores from multiple items and range from 0 to 100.

Depression was assessed using the Beck Depression Inventory (BDI) (Beck et al., 1961). BDI scores below 13 were interpreted as minimal depression, 14–19 — mild depression, 20–28 — moderate depression, and 29–63 — severe depression. Participants were minimally depressed on average (see Table 1), and there were no baseline differences between groups.

The Chronic Pain Self-Efficacy Scale adapted from the Arthritis Self-Efficacy Scale (Anderson et al., 1995) measures patients' perceived ability to perform specific behaviors aimed at controlling persistent pain and disability (on a 10-point scale from 0, "very uncertain", to 10, "very certain"). It consists of three subscales: Self-Efficacy for Pain Management, Self-Efficacy for Physical Function, Self-Efficacy for Coping with Symptoms.

Pain Catastrophizing was assessed using either the Pain Catastrophizing Scale (PCatS, $n = 26$, Sullivan et al., 1995) or the Catastrophizing Subscale of the Coping Strategies Questionnaire (CSQ, $n = 12$, Lawson et al., 1990). A surrogate measure was derived from these questionnaires in order to make them comparable. Five questions (5 out of 6 in CSQ and 5 out of 13 in PCatS) in these questionnaires overlap and were used to derive a score on a common scale. Since the original scales are from 0 to 6 for CSQ and from 0 to 4 for PCatS, scores were transformed to a scale of 0–100 and expressed as an average rather than a total. The exact wording of the questions is provided in Appendix 1.

Clinical improvement was assessed using a 2 (pre, post) × 2 (groups) repeated-measures ANOVA with one within-subject factor (time) and one between-subject factor (group).

2.6. Neuroimaging measures

2.6.1. Imaging parameters

MRI scanning was performed on a Philips Achieva 3 T system (Best, Netherlands) with an 8-channel head coil. Resting state fMRI (R-fMRI) data were acquired while participants were instructed to keep their eyes closed and not to think about anything in particular. Two echo planar pulse sequences were used: 1)TR/TE/FOV = 2000 ms/35 ms/240 × 240, with 33 4 mm continuous slices for a resolution of 3 × 3 × 4 mm ($n = 26$) or 2) TR/TE/FOV = 2000 ms/35 ms/240 × 240, with 29 4 mm slices (1 mm gap), reconstructed to a resolution of 1.875 × 1.875 × 4 mm ($n = 12$, $n = 4$ in CBT and $n = 8$ in EDU). High-resolution anatomical sequences were acquired to facilitate spatial normalization to the MNI152 standard space. Two 3D T1-weighted TFE (turbo field echo) sequences were used: 1)TR/TE/FA/FOV = 9.9 ms/4.6 ms/8/256 × 256, with 140 1 mm slices for a resolution of 1 × 1 × 1 mm or 2) TR/TE/FA/FOV = 8.65 ms/4.01 ms/8/240 × 240, with 160 1 mm slices for a resolution of 1 × 1 × 1 mm. Participants were always scanned using the same R-fMRI and T1 sequences pre- and post-intervention. An axial T2-weighted gradient spin echo (GRASE) sequence was also obtained for radiological reading to rule out neurologically significant abnormalities. The uneven sequence distribution across groups presents a potential problem arising from possible differences in sensitivity of the different sequences to treatment effects (i.e., an interaction of sequence and group over time). We tested this triple interaction, controlling for age and gender, and observed no significant effects in networks of interest.

2.6.2. Image preprocessing

Functional connectivity analyses were completed with a modified version of the 1000 Functional Connectomes Project Scripts available at http://www.nitrc.org/projects/fcon_1000/, which use AFNI (Cox, 1996) and FSL (http://www.fmrib.ox.ac.uk). The first four volumes of each scan were discarded. Motion correction was conducted by aligning each volume to the mean volume using AFNI's 3dvolreg. To quantify motion and identify motion outliers (spikes), we computed root mean square framewise displacement (rmsFD; Jenkinson et al., 2002) as well as mean FD (Power et al., 2012). Average mean FD was 0.15 ± 0.05 for the baseline scan and 0.17 ± 0.07 for the follow-up scan. Although the slight increase in mean FD from pre- to post-intervention was significant ($P = 0.034$), there were no differences in mean FD between groups ($P = 0.15$) and no group × time interaction($P = 0.619$). Next, data were despiked (extreme time-series outliers were identified and reduced using the AFNI program 3dDespike) and grand-mean intensity-normalized, and linear and quadratic trends were removed.

2.6.3. Nuisance signal regression

To control for the effects of motion, physiological noise and other nuisance signals and artifacts, we regressed each patient's preprocessed volume on the following nuisance covariates: (1) the first five principal components obtained in a principal components analysis of white matter and cerebrospinal fluid signals using the component based noise correction (CompCor) procedure (Behzadi et al., 2007); (2) 18 motion parameters (six squares of motion parameters, six temporal differences of motion parameters, six squares of the difference values), to account for spin history effects and variation not otherwise accounted for by motion correction; and (3) regressors coding for motion "spikes," identified as time points with rmsFD > 0.25. Global signal regression was not performed (Gotts et al., 2013; Murphy et al., 2009; Saad et al., 2012). Finally, data were spatially smoothed using a 6-mm FWHM Gaussian filter and a temporal bandpass filter was applied (0.01–0.1 Hz). Note that

data were not filtered prior to computation of amplitude of low frequency fluctuations (ALFF).

2.6.4. Registration

Functional images were registered to standard space using: 1) FSL's linear Boundary-Based Registration tool to transform into the individuals' anatomical space (Greve and Fischl, 2009) and 2) nonlinear transformation (FNIRT) to the Montreal Neurological Institute's 152 brain template (MNI152).

2.6.5. Probabilistic independent component analysis (ICA)

Model-free ICA was performed in FSL MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) (Beckmann et al., 2005; Beckmann and Smith, 2004). Group-level components were determined by including data for all patients (CBT, EDU) and both time-points (pre, post). The ICA identified 22 components, three of which were disregarded as noise components. Next, we applied dual regression (Filippini et al., 2009), whereby two separate linear regressions were performed for each group-level ICA template: first, group ICA templates were regressed onto each participant's preprocessed 4D data, producing a set of regression weights across time for each scan (i.e., pre, post); next, these time courses were used as temporal regressors to generate a set of participant-specific spatial maps (separately for pre and post). The resulting pre-intervention parameter estimates were subtracted from post-intervention parameter estimates for group-level analyses.

2.6.6. Group analyses

Separate group-level regression analyses were performed on selected individual-level dual-regressed ICA maps using permutation testing in FSL RANDOMISE with 5000 permutations and threshold-free cluster enhancement (TFCE). Age and sex were modeled as covariates of no-interest (i.e., de-meaned age, 1 for males and −1 for females). De-meaned FD differences across time for each participant were also included as nuisance regressors to capture any residual motion-related signal (Power et al., 2012; Satterthwaite et al., 2013; Yan et al., 2013). All group-level analyses were performed using subtraction (post − pre) images; group analyses identified significant between-group differences in pre–post changes in iFC.

We explored brain–behavior relationships between significant group differences in pre–post intervention iFC and changes in clinical measures using bivariate Spearman correlations to accommodate the presence of non-normal distributions in the difference scores of 5 out of 10 clinical measures tested (as assessed with the Shapiro–Wilk test). Since the goal of these exploratory analyses was to generate hypotheses for future work, they were not corrected for multiple comparisons.

2.6.7. Amplitude of low frequency fluctuations (ALFF)

To explore intervention-related changes in regional/local intrinsic BOLD fluctuations, ALFF was computed by performing a Fourier decomposition of the preprocessed time series data and summing amplitudes in the 0.01–0.1 Hz frequency range. Fractional ALFF (fALFF) was computed as the ratio of the ALFF to the sum of frequency amplitudes across the entire frequency range (Zou et al., 2008; Zuo et al., 2010). fALFF was converted to Z-scores for group-level analysis.

2.6.8. Follow-up iFC analyses

To better understand significant pre–post changes in fALFF, we performed exploratory follow-up iFC analyses to probe whether these regions also exhibited changes in their iFC. Specifically, spherical regions of interest (ROIs; 5 mm radius) were created, centered on peak regions in the map of significant group differences in post–pre fALFF. A mean time course for each seed was extracted from each patient's preprocessed volume by averaging across voxels within the ROI. The correlation between this time series and that of each other

voxel in the brain was then determined using AFNI 3dfim+. The resultant individual-level correlation maps were transformed using Fisher's r-to-z transformation. Pre-intervention z-values were subtracted from post-intervention z-values for group-level analyses.

Exploratory whole brain group comparisons and brain–behavior analyses for fALFF and seed-based connectivity were performed using the more sensitive mixed-effects Ordinary Least Squares analyses in FSL. In addition to the group-level nuisance regressors listed above, individual global means for each metric were also included for seed-based connectivity analyses to correct for additive effects and to improve reliability (Yan et al., 2013). Cluster-level thresholding was set at $z = 2.3$ with 0.05 cluster probability threshold. All group-level analyses were performed using subtracted (post–pre) data. T-test contrasts were set up to explore between group differences across time.

3. Results

3.1. Clinical results

Groups were well-matched in terms of their baseline clinical characteristics with no significant differences in any of the measures tested with the exception of pain duration, where participants in the CBT group had on average longer pain duration (see Table 1). CBT patients improved on all ten clinical measures of interest (see Table 2), and on five of these measures (Mental Composite Score, Pain Symptoms, Self-Efficacy for Pain Management and Self-Efficacy for Coping with Symptoms and Passive Coping), they showed significant improvement over the EDU group. The most consistent results were observed in measures of Self-Efficacy, which has been established as a good predictor of pain management success (Denison et al., 2004).

3.2. Neuroimaging results

3.2.1. Probabilistic independent component analysis (ICA)

Probabilistic independent component analysis resulted in 22 independent components (ICs). Four of the components included regions of the DMN (Fig. 1A), two of the components were deemed to comprise the salience network (Fig. 1B), and a single component was identified as a BG component (Fig. 1C). All DMN components included the posterior cingulate cortex (PCC)/precuneus, the inferior parietal lobule and either the medial prefrontal or the perigenual anterior cingulate (ACC) regions—all "core regions" of the DMN (Buckner et al., 2008) (see Table 3 for details).

All regions were bilateral unless indicated otherwise. OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; IPL, inferior parietal lobule; SFS, superior frontal sulcus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; DCC, dorsal singulate cortex; AIC, anterior insula; PIC, posterior insula; BG, basal ganglia; aDMN, anterior Default Mode Network; IC, independent component.

Of the three networks of interest (DMN, BG, and salience), we observed significant CBT-related changes in whole-brain connectivities with the DMN, specifically aDMN, and BG networks. Relative to the EDU group, CBT participants exhibited weaker connectivity between aDMN and the amygdala, periaqueductal gray (PAG) and left lateral occipical cortex and stronger connectivity between BG and right S2 (Figs. 2 and 3, Table 4). To better understand these group differences, we performed exploratory analyses to examine brain–behavior relationships by correlating pre–post changes in iFC with clinical measures.

3.2.2. Decreased connectivity between DMN and the amygdala/dorsal periaqueductal gray

DMN connectivity in the two groups (CBT and EDU) was assessed before and after the interventions using dual regression independent component analysis. We observed significant reductions in iFC between the DMN and the amygdala, periaqueductal gray and left lateral occipital cortex after CBT, as compared to EDU, for the aDMN

Table 2
Clinical improvement over time (n (CBT) = 19, n (EDU) = 19). a

Clinical measure (SD)	CBT pre	CBT post	EDU pre	EDU post	Post–pre CBT	Post–pre EDU	Time × group F	Time × group P
Physical Composite Score (SF-36)	35.05 (8.77)	39.07 (8.38)	35.95 (8.26)	38.94 (9.86)	4.09 (4.22)	2.78 (5.39)	0.659	ns
Mental Composite Score (SF-36)	32.65 (13.32)	37.12 (12.83)	38.82 (11.41)	37.6 (9.13)	4.44 (5.23)	−1.32 (9.67)	4.911	0.033
Pain Symptoms (TOPS)	67.51 (17.74)	53.43 (20.50)	60.62 (14.0)	58.17 (15.60)	−16.09 (19.0)	−2.87 (12.02)	4.619	0.038
Perceived Family Disability (TOPS)	46.22 (22.32)	42.34 (21.99)	38.23 (19.76)	36.19 (18.35)	−5.55 (19.02)	−2.49 (14.71)	0.107	ns
Total Pain Experience (TOPS)	51.63 (19.07)	42.17 (17.32)	45.49 (15.04)	41.37 (15.56)	−10.87 (11.83)	−4.31 (8.56)	2.260	ns
Self-Efficacy for Pain Management (PSE)	5.16 (1.96)	7.23 (2.03)	4.76 (1.98)	5.11 (2.00)	2.09 (1.61)	1.18 (1.53)	11.851	0.001
Self-Efficacy for Physical Function (FSE)	7.32 (1.99)	8.14 (1.99)	8.19 (2.50)	8.50 (1.84)	0.88 (1.10)	0.37 (2.0)	1.006	ns
Self-Efficacy for Coping with Symptoms (CSE)	5.21 (1.99)	7.55 (1.48)	5.27 (1.81)	5.86 (1.93)	2.42 (1.54)	0.65 (1.41)	13.523	0.001
Passive Coping (TOPS)	39.58 (17.96)	30.21 (15.64)	36.84 (22.43)	37.17 (22.54)	−10.53 (12.41)	0.00 (19.65)	4.141	0.049
Catastrophizing	29.89 (18.48)	15.85 (17.98)	29.89 (21.53)	19.91 (18.66)	−14.16 (13.99)	−11.65 (19.75)	0.517	ns

[a] Clinical data from 2 participants were missing for the SF-36 scores and from 1 participant for the Passive Coping subscale.

component (IC7). Compared to other DMN components, this component had more prominent OFC, ACC, and medial prefrontal contributions, and the network's peak was located at MNI coordinates −4, 46, 8 (x, y, z), in pregenual ACC. DMN iFC with the left amygdala and the dorsal periaqueductal gray decreased at follow-up in the CBT group but not in the EDU group (Fig. 2A). Relaxing the statistical threshold to $P = 0.1$ also lead to the emergence of a cluster in the right amygdala. Brain–behavior analyses revealed a significant relationship between the pre–post change in DMN–amygdala iFC and the pre–post change in Self-Efficacy for Coping with Symptoms ($\rho = -0.329$, $P = 0.044$, Fig. 2B), such that the patients with the greatest pre–post reduction in DMN–amygdala iFC were those who exhibited the greatest pre–post increase in the Self-Efficacy for Coping with Symptoms scale. Brain–behavior analyses for the change in DMN–PAG iFC also revealed similar relationships with the pre–post change in Self-Efficacy for Pain Management ($\rho = -0.457$, $P = 0.004$) and in Self-Efficacy for Coping with Symptoms ($\rho = -0.514$, $P = 0.001$, Fig. 2C).

3.2.3. Increased connectivity between basal ganglia and secondary somatosensory cortex

Compared to the EDU group, the CBT group exhibited increased BG connectivity with the right S2 from pre to post (Fig. 3A). This pre–post increase in connectivity was correlated with a pre–post decrease in

Pain Symptoms (from TOPS) ($\rho = -0.343$, $P = 0.035$; Fig. 3B); a decrease in Passive Coping (from TOPS) ($\rho = -0.329$, $P = 0.047$), an increase in Self-Efficacy for Pain Management ($\rho = 0.574$, $P < 0.001$; Fig. 3C) and an increase in Self-Efficacy for Coping with Symptoms ($\rho = 0.399$, $P = 0.013$).

3.2.4. Increased fALFF in the cerebellum and the PCC

Whole brain analyses of intervention-related changes in fALFF revealed a significant effect of group assignment on pre–post differences in fALFF in the cerebellum (bilateral lobules IV and V) and the PCC (Fig. 4A). fALFF in these regions increased after CBT and decreased after EDU. The changes in the cerebellar region were correlated with pre–post changes in Total Pain Experience ($\rho = -0.396$, $P = 0.014$; Fig. 4C); Self-Efficacy for Pain Management ($\rho = 0.345$, $P = 0.034$; Fig. 4B); Perceived Family Disability ($\rho = -0.365$, $P = 0.024$); and Total Pain Symptoms ($\rho = -0.323$, $P = 0.048$) across the entire sample. fALFF changes in the PCC correlated with changes in Total Pain Symptoms ($\rho = -0.326$, $P = 0.046$) and Self-Efficacy for Pain Management ($\rho = 0.385$, $P = 0.017$). We performed follow-up iFC analyses to identify whether these regions also exhibited changes in their functional connectivity. Spherical seed ROIs were created centered on the peak of fALFF group differences across time (see Table 4 for coordinates). The CBT group exhibited a greater pre–post increase iFC between the
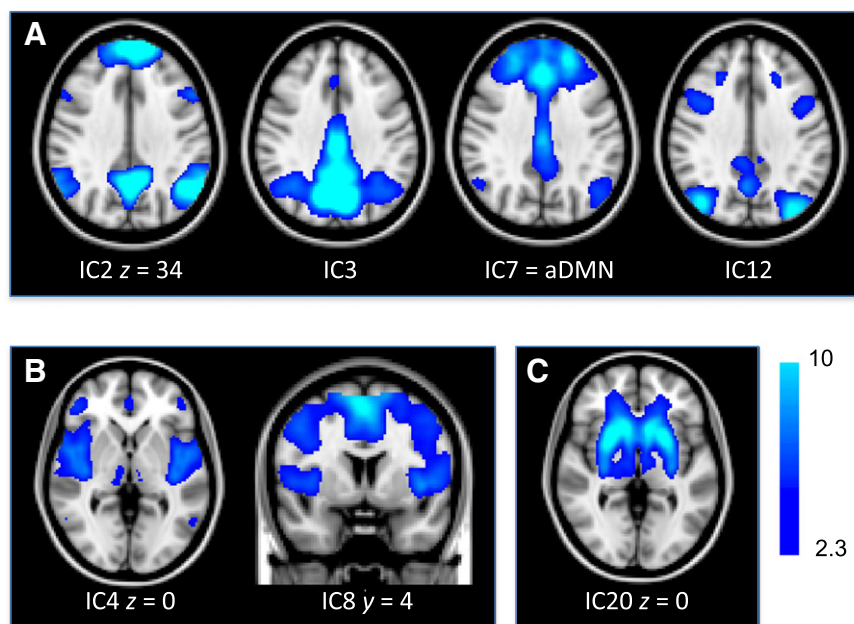

Fig. 1. Probabailistic independent component analysis. ICA of the entire dataset resulted in a) four Default Mode Networks (DMNs), including anterior DMN (IC7); all ICs are overlaid onto the MNI template at $z = 34$; b) two salience networks; and c) a single basal ganglia (BG) network. The blue color bar represents the z statistic thresholded at $P > 0.5$ following alternative hypothesis testing (indicating that the probability of being active exceeds the probability of being noise). All images are displayed in radiological coordinates with left on the right side.

Table 3
Regions of the brain grouped into each network of interest with probabilistic independent component analysis (ICA).

Brain region	IC2 DMN	IC3 DMN	IC7 aDMN	IC12 DMN	IC4 salience	IC8 salience	IC20 BG
OFC	*		*	*	*		
mPFC	*	*	*	*			
ACC			*	*	*	*	
PCC	*		*	*			
Precuneus	*	*	*	*		*	
IPL	*	*	*	*		*	
SFS			*	*			
IFG	*				*		
MFG						*	
DCC	*				*	*	
AIC			*			*	
PIC					*		
STS	*			*			
STG					*		
S1			*				
Premotor						*	
Fusiform				*			
Cuneus (V2)							*
Cerebellum			*			*	
Hippocampi			*	*			
Accumbens			*				*
Caudate	Left		*				*
Putamen							*
Globus pallidus							*
Thalamus		*					*

cerebellar seed and neighboring regions of the cerebellum as well as PCC/precuneus (a core node of the DMN) and thalamus than the EDU group. This region of the PCC was located posterior to the region of the PCC identified in the whole brain fALFF analysis. The PCC seed identified in whole brain fALFF analysis did not exhibit any significant group differences in intervention-related whole brain connectivity changes.

3.2.5. Examination of possible confounding effects of medication and menstrual cycle

One challenge of longitudinal projects is that it is sometimes difficult to control patients' behavior with respect to changes in medication. Most patients used non-opioid analgesics, 12 also used antidepressants and six used opioids (see Supplementary Table 2). There were no statistically significant changes in non-opioid analgesic use. Formal statistical analysis was not performed for other medication classes due to the very small sample size.

Although most participants were either male or post-menopausal ($n = 23$), a second possible confound is menstrual cycle phase. While efforts were made to schedule participants for the MRI session at the same phase of the menstrual cycle, this was not always possible. To evaluate possible confounding effects of menstrual cycle on emotional regulation and pain levels (LeResche et al., 2003; Ossewaarde et al., 2010; Protopopescu et al., 2005; Sherman and LeResche, 2006; Tousignant-Laflamme and Marchand, 2009), we examined changes in the neuroimaging as well as clinical measures over time in 12 participants whose phase was different at the time of the second scan. Data from these participants spanned the range of the entire sample, and, if anything, removing these participants' data reduced the brain–behavior correlations of interest.

4. Discussion

We showed that CBT, as compared to active educational control, is associated with significant changes in resting state functional connectivity in chronic pain patients. Specifically, we demonstrated that learning new pain management strategies in a CBT intervention results in measurable alterations in intrinsic functional connectivity (iFC) within and between networks previously implicated in chronic pain, including
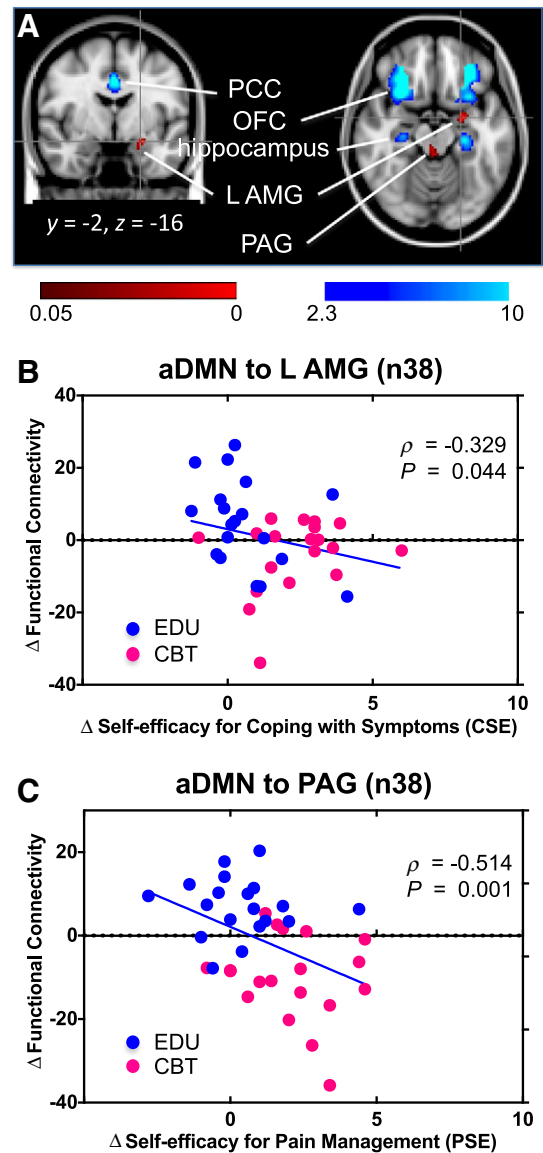

Fig. 2. Decreased connectivity between aDMN and left amygdala and periaqueductal gray after CBT. a) Dual regression of the aDMN network revealed lower connectivity to the left amygdala (L Amg) and periaqueductal gray (PAG) after CBT shown in red (the color bar represents the corrected P value following RANDOMISE and TFCE). Regions of the aDMN are in blue (posterior cingulate cortex, PCC; bilateral hippocampus; and bilateral orbitofrontal cortex, OFC); the blue color bar represents the z statistic thresholded at $P > 0.5$ for alternative hypothesis testing (indicating that the probability of being active exceeds the probability of being noise).b) The decreased connectivity between aDMN and L Amg correlated with increased Self-Efficacy for Coping with Symptoms; and c) decreased connectivity between aDMN and PAG correlated with increased Self-Efficacy for Pain Management. Panels b and c depict regression lines (blue) as well as individual data points; the CBT group is pink and the EDU group is blue. All images are displayed in radiological coordinates with left on the right side.

motor, perceptual, affective, default mode and striatal circuits. Notably, treatment-related changes in the iFC of nodes of the DMN emerged across several analyses. Further, CBT-related changes were observed in BG functional connectivity, as well as in the amplitude of intrinsic fluctuations in the cerebellum. Initial clues regarding the behavioral significance of these CBT-related alterations were provided by brain–behavior correlations demonstrating that patients showing the greatest treatment-related change in self-efficacy and pain symptoms exhibited the greatest treatment-related change in iFC. We discuss these findings in more detail below.
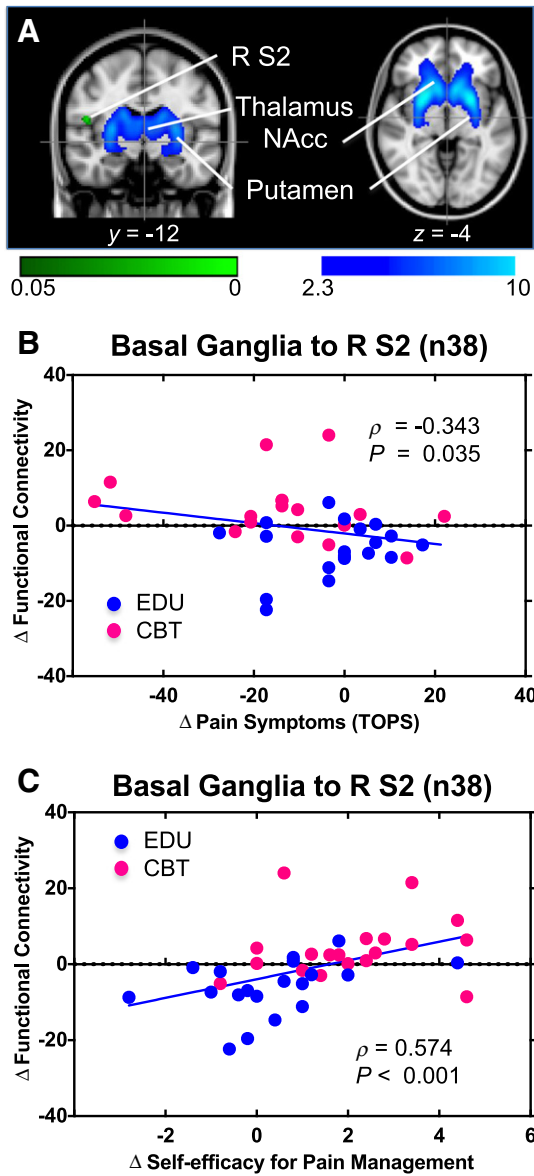
Fig. 3. Increased connectivity between basal ganglia and right secondary somatosensory cortex after CBT. a) Dual regression of the basal ganglia (BG) network revealed higher connectivity to the right secondary somatosensory cortex (R S2) after CBT in green (the color bar represents the corrected P value following RANDOMISE and TFCE). Regions of the BG are in blue (nucleus accumbens, NAcc, and putamen); b) the increased connectivity between BG and R S2 correlated with decreased Pain Symptoms; and c) the increased connectivity between BG and R S2 correlated with increased Self-Efficacy for Pain Management. Panels b and c depict regression lines (blue) as well as individual data points; the CBT group is pink and the EDU group is blue. All images are displayed in radiological coordinates with left on the right side.

Table 4
Changes in resting state connectivity across time (n (CBT) = 19, n (EDU) = 19). Peak MNI coordinates for significant clusters from ICA and fALFF analyses.

ICA–based	x	y	z	max T
BG to R S2	50	−12	16	6.41
aDMN to LAMG	−24	−2	−16	6.73
aDMN to PAG	2	−30	−14	6.93
aDMN to LLOC/IPL	−44	−68	34	5.30
fALFF	x	y	z	max Z
PCC	8	−44	22	3.18
Cerebellum	−8	−54	−18	3.87
Seeds based on fALFF above	x	y	z	max Z
Cerebellar seed to thalamus	14	−30	10	4.22
Cerebellar seed to cerebellum	−4	−58	−8	4.06
Cerebellar seed to PCC	−8	−58	22	3.74

BG, basal ganglia; aDMN, anterior Default Mode Network; LAMG, left amygdala; PAG, periaqueductal gray; LLOC/IPL, left lateral occipical cortex—inferior parietal lobule; PCC, posterior cingulate cortex.

terms of extinction of fearful responses to pain, which is also a core feature of exposure therapy and mindfulness training. Extinction of behaviors has been shown to engage different circuits than initial learning of behaviors (Rescorla, 2001). There is converging neurobiological evidence for the unique role of ventral medial prefrontal areas (pregenual ACC and mPFC), and connections between these areas and the amygdala, in extinction (Etkin et al., 2011; Milad et al., 2007; Phelps et al., 2004). The CBT program described here was associated with significantly reduced iFC between aDMN and the amygdala. Accordingly, we suggest that the post-CBT changes in connectivity between aDMN and the amygdala likely represent extinction mechanisms (see also Holzel et al., 2011).

In exploratory analyses examining brain–behavior relationships, we found that the CBT-related change in aDMN–amygdala iFC was correlated with CBT-related improvements in emotional regulation (e.g., better Mental Composite Scores). This brain–behavior link is consistent with an emerging literature implicating prefrontal–limbic functional connections with emotional regulation and dysregulation. For example, in a comprehensive review, Etkin et al. (2011) proposed that, during emotional regulation tasks (i.e., tasks that involve inhibition of the prepotent response and reappraisal, as opposed to emotional appraisal or expression tasks), connectivity between pregenual ACC/mPFC and the amygdala is primarily negative. Conversely, clinical studies point to increased iFC between medial prefrontal areas/ACC and the amygdala in populations with impaired emotional regulation (Brown et al., 2014; Hahn et al., 2011; Liao et al., 2010 although see; Prater et al., 2013 for opposite results), and iFC in corticolimbic circuits has been shown to decrease following 1-week of antidepressant treatment in healthy controls (McCabe and Mishor, 2011). Our findings suggest that a cognitive–behavioral treatment can also alter corticolimbic connectivity; coupled with behavioral improvements, these findings underscore the promise of such approaches for other conditions characterized by emotional dysregulation.

4.1. Decreased aDMN–amygdala connectivity and its putative role in extinction

One of the core elements of the course of CBT administered in this study is an emphasis on "active" as opposed to "passive" coping styles. Accordingly, post-treatment, the CBT group had significantly lower "passive" coping subscale scores. Active coping includes learning to recognize one's thoughts and emotions, particularly as they relate to fluctuations in chronic pain, and learning new behavioral and thought patterns to ameliorate suffering from chronic pain. In other words, one of the key skills developed through the training program is the ability to identify, attend to and fully experience the painful sensations. This conscious exposure to the troublesome stimuli can be conceptualized in

4.2. Decreased aDMN–PAG connectivity and its putative role in descending pain modulation and homeostatic regulation

While the role of mPFC–amygdala circuitry in fear extinction is fairly well-established, ventral and medial prefrontal areas may also play a more direct role in pain modulation. In addition to reduced iFC between aDMN and the amygdala, we also observed reduced iFC between the same aDMN and PAG. PAG has been implicated in a variety of animal and human behaviors, including descending pain modulation, emotion/panic and homeostatic regulation (Linnman et al., 2012). Interestingly, both anterior cingulotomy and deep brain stimulation of the PAG can be successful in relieving intractable pain (Bittar et al., 2005; Yen et al., 2005). The PAG cluster in our analyses was located in the more caudal sections of lateral/ventrolateral PAG. In addition to the projections
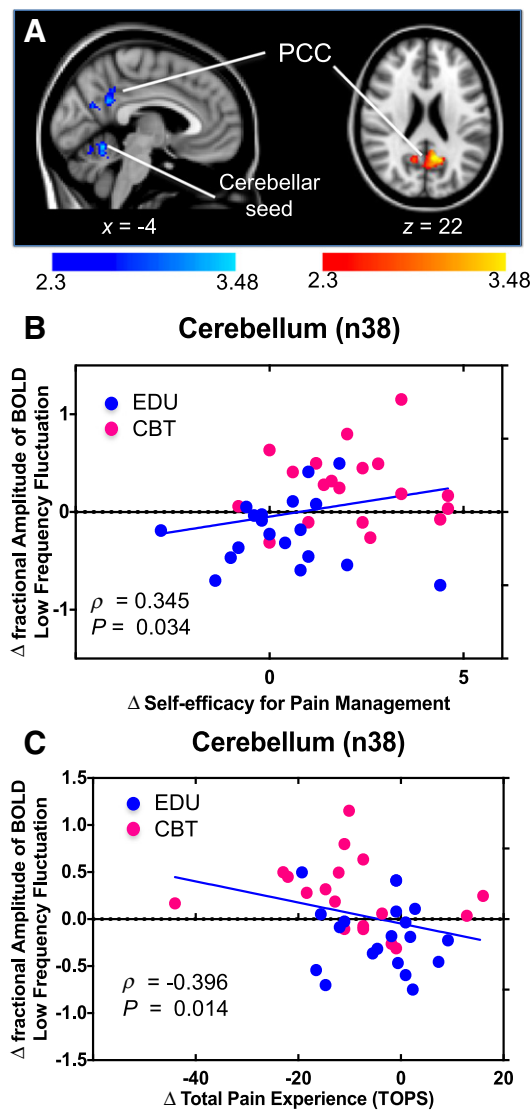
Fig. 4. Increased fALFF in the cerebellum and the posterior cingulate cortex as well as increased connectivity between the two regions following CBT. a) Whole brain analysis of changes in regional fALFF revealed increased fluctuations in the cerebellum and the posterior cingulate cortex (PCC) (see left panel in blue). When the peak of the cerebellar cluster was used as a seed for connectivity analysis, there was higher connectivity to the PCC after CBT (right panel in red-yellow). Maps are a result of exploratory OLS analysis, cluster corrected for multiple comparisons at $P < 0.05$. b) The increased fALFF in the cerebellum correlated with increased Self-Efficacy for Pain Management. c) The increased fALFF in the cerebellum also correlated with decreased Total Pain Experience. Panels b and c depict regression lines (blue) as well as individual data points; the CBT group is pink and the EDU group is blue. All images are displayed in radiological coordinates with left on the right side.

from the central nucleus of the amygdala, putatively as part of fear and emotion circuits (Fendt and Fanselow, 1999), lateral PAG receives direct projections from the mPFC and the ACC and ventrolateral PAG receives direct projections from the orbitofrontal cortex (An et al., 1998). These anatomical connections make corresponding functional connections at rest when PAG is used as a seed (Kong et al., 2010). While excitatory stimulation of the lateral sections of the PAGes mediate endogenous non-opioid analgesia and fight-or-flight sympathetic response, ventro-lateral PAG mediates opioid analgesia and parasympathetic responses in animals (Linnman et al., 2012). At the same time, ventral, but not dorsal, PAG stimulation in humans reduces sympathetic activity as well as chronic pain (Green et al., 2006). Since CBT can result in improvements of both cardiovascular (Gulliksson et al., 2011) and pain modulatory (Williams et al., 2012) functions, the decreased connectivity between

the aDMN and the PAG observed here may mediate either or both functions.

The finding of decreased iFC between aDMN and PAG following CBT stands in seeming contradiction to the majority of functional connectivity studies of placebo analgesia. Most studies point to a stronger coupling between the PAG and prefrontal regions during placebo analgesia as well as during distraction away from pain (Bingel et al., 2006; Eippert et al., 2009; Ellingsen et al., 2013; Kucyi et al., 2013; Sprenger et al., 2011; Wager et al., 2007), while elicitation of "panic" leads to lower functional connectivity between the same regions (Mobbs et al., 2009). The discrepancy between the literature and our findings may appear puzzling, however, the studies described above reported on *task-related* functional connectivity (i.e., psychophysiological interaction, which captures context-dependent functional connectivity), while here we analyzed intrinsic functional connectivity *at rest*. We should not expect that these two types of functional connectivity always match. Divergent results between these two methods have been previously documented in anxiety, where anxiety resulted in increased intrinsic amygdala–PFC connectivity and decreased task-related decoupling in the same regions in response to threat (Monk et al., 2008). Similarly, divergent iFC findings have been reported in a study of tonic pain (Kim et al., 2013). iFC between primary somatosensory regions and the entire sensory–motor network during rest was higher when directly compared to iFC during tonic pain.

4.3. CBT-related changes in the sensory-discriminative aspects of chronic pain as indexed by increased BG–S2 connectivity

The CBT-related increase in iFC between the BG network and S2 may not be surprising given the presence of distributed anatomical projections from S2 to the BG in animals, predominantly to the putamen (Alloway et al., 2006; Alloway et al., 2000; Haber, 2003), and given that somatosensory inputs can drive cellular learning mechanisms (long-term potentiation and depression) within the BG (Fino et al., 2005). As indicated in a meta-analysis of neuroimaging studies, BG co-activates with S2 during task performance (Postuma and Dagher, 2006). Several recent investigations reported abnormalities in BG iFC in chronic pain (Baliki et al., 2010; Baliki et al., 2012; Cifre et al., 2012; Yuan et al., 2013). However, only a single study (Cifre et al., 2012) reported pain-related significant abnormalities (increased connectivity) in BG–S2 iFC. If increased connectivity exists between BG and S2 in chronic pain, a further increase in the strength of this connection following an intervention for chronic pain could suggest the improvement of an existing coping mechanism. This suggestion is consistent with the brain–behavior correlation between the pre to post change in BG–S2 iFC and improvements in Self-Efficacy for Pain Management.

An alternative explanation is that increased iFC between the BG and S2 after CBT may reflect changes in the perceptual aspects of chronic pain. Although BG were originally implicated primarily in motor functions, research over the past several decades has emphasized their involvement in cognitive, emotional, reward and sensory processing (Arsalidou et al., 2013). At the same time, a recent investigation in patients with lesions in the putamen (Starr et al., 2011) highlighted its role in acute pain processing by documenting abnormal activations within the pain network, including reduced S2 activation as compared to healthy controls. Chronic pain patients often perceive their pain as constant and relentless. During CBT, patients learn to use pain diaries to track fluctuations in pain levels throughout the day. In combination with the cognitive training introduced during CBT, this leads to changes in patients' perception and experience of pain (as documented here in improved Pain Symptoms scores). S2 subserves sensory-discriminative aspects of pain, and some researchers consider it to be the primary nociceptive region of the brain (Apkarian et al., 2005). While the relationship between S2 activity and pain intensity is not clear (Ellingsen et al., 2013; Howard et al., 2012; Kucyi et al., 2013; Loggia et al., 2012), S2 has been shown to be engaged during pain modulation (see Apkarian et al.,

2005; Price et al., 2006 for reviews), and together with BG, may mediate improvements in Pain Symptoms seen here (Fig. 3B).

4.4. Exploratory analyses: fALFF changes in the cerebellum and the PCC

Exploratory whole-brain analyses of fALFF revealed CBT-related changes in the cerebellum and the PCC. The cerebellum is emerging as a major nexus of pain processing (Moulton et al., 2010). Through its pontine and olivary connections, it receives inputs from motor, sensory, cognitive and pain modulatory cortical and subcortical regions. As reviewed by Moulton and colleagues, animal studies provide unambiguous evidence for nociceptive activity in the cerebellum, and electrical or chemical stimulation of the cerebellum modulates pain experience. While motor-related withdrawal or anticipatory activity remains a possible explanation of nociceptive responses in the cerebellum, Moulton and colleagues argue for a more direct role of the cerebellum in the sensory and emotional processing of pain (see also Moulton et al., 2011). Since the experience of pain is itself multidimensional, the exact role of the cerebellum in pain processing in general and in chronic pain in particular remains a disputed issue.

As part of the DMN, the PCC has been most prominently implicated in self-referential processing (Molnar-Szakacs and Uddin, 2013). Its role in pain processing is not as clear-cut. In healthy controls, verum (true) as compared to sham accupuncture leads to a relative deactivation of the PCC to acute pain (Maeda et al., 2013), and at least one study also reported activations of the PCC in response to acute pain in a fibromyalgia sample (Gracely et al., 2004). In contrast, reducing painful sensations by attending away from pain can lead to a relative activation of the PCC (Kucyi et al., 2013). Structural changes to the PCC have been documented in chronic pain patients (e.g., Absinta et al., 2012; Ceko et al., 2013; Gerstner et al., 2011) with most studies reporting decreased PCC gray matter. Since the precise role of the PCC in chronic pain remains unclear, the preliminary fALFF effects observed in the present study may indicate either improved general emotional coping mechanisms following CBT or more specific pain-related changes. Future research is necessary to disambiguate between these possibilities.

4.5. Limitations

Our study is subject to several limitations inherent to the study of chronic pain and treatment effects: the mixed sample (including patients with a variety of chronic musculoskeletal pain diagnoses), changes in medication use across time, and the challenge of disentangling neurobiological measures of improved emotional regulation from those of improved pain coping. Nonetheless, the CBT-related changes across resting state networks observed here reflect the effects common across different diagnoses. Although patients in both interventions reported reduced consumption of analgesics at follow-up, recruitment of medication-free participants would be highly challenging, and changes to patient medication schedules are essentially uncontrollable in the context of a behavioral treatment program. Finally, depression, anxiety and pain are tightly interconnected in chronic pain, and the CBT intervention resulted in clinical improvements in both. This leads to difficulty in separating neuroplasticity specific to chronic pain and not to emotional regulation. That being said, our aim was to gain a better understanding of treatment-related functional neuroplasticity, and to better define biomarkers of recovery from chronic pain. Our success provides a basis for future large cohort studies aimed at identifying independent and interacting effects of CBT interventions on the neural bases of the emotional, cognitive and physiological aspects of chronic pain.

Appendix 1

Questions taken from Coping Strategies Questionnaire (0, never do that; 3 sometimes do that; 6 always do that).

1 I worry all the time about whether it will end.

2 I feel like I cannot go on.
3 It's terrible and I feel it's never going to get any better.
4 It's awful and I feel that it overwhelms me.
5 I feel I cannot stand it anymore.

Questions taken from Pain Catastrophizing Scale (0, Not at all; 1, To a slight degree; 2, To a moderate degree; 3, To a great degree; 4, All the time).

1 I worry all the time about whether it will end.

2 I feel like I cannot go on.
3 It's terrible and I feel it's never going to get any better.
4 It's awful and I feel that it overwhelms me.
5 I feel I cannot stand it anymore.

Supplementary material

Supplementary Table 1
Individual primary and secondary chronic pain diagnoses.

	ID#	Group	Primary DX					Secondary DX
			OA	FM	Back	TMJ	Post-trauma	
1	517	CBT			1			
2	523	CBT			1			
3	533	CBT			1			OA
4	536	CBT			1			
5	2603	CBT					1	FM
6	2612	CBT			1			FM
7	2617	CBT					1	Headaches
8	2618	CBT		1				
9	2619	CBT		1				
10	2625	CBT			1			FM
11	2626	CBT			1			FM
12	2628	CBT			1			OA
13	2629	CBT					1	Back
14	2630	CBT			1			OA
15	2631	CBT			1			
16	2634	CBT				1		Post-trauma
17	2636	CBT					1	OA
18	2639	CBT	1					Back
19	2641	CBT					1	Back
20	2701	EDU			1			FM
21	2702	EDU			1			FM
22	2707	EDU			1			FM
23	2709	EDU			1			

Supplementary Table 1 *(continued)*

	ID#	Group	OA	FM	Back	TMJ	Post-trauma	Secondary DX
			Primary DX					
24	2710	EDU			1			
25	2711	EDU					1	OA
26	2712	EDU	1					Back
27	2714	EDU	1					Post-trauma
28	2715	EDU			1			Headaches
29	2717	EDU			1			FM
30	2721	EDU			1			
31	913	EDU			1			OA
32	914	EDU			1			
33	915	EDU			1			
34	916	EDU			1			Headaches
35	918	EDU			1			OA
36	921	EDU			1			
37	924	EDU			1			
38	925	EDU			1			
		Totals	3	2	26	1	6	
		CBT %	5.26%	10.53%	52.63%	5.26%	26.32%	
		EDU %	10.53%	0.00%	84.21%	0.00%	5.26%	
		Overall %	7.89%	5.26%	68.42%	1.00%	15.79%	

DX, diagnosis; OA, osteoarthritis; TMJ, temporo-mandibular junction disorder; FM, fibromyalgia.

Supplementary Table 2
Number of participants (N) and average doses of medications taken before and after both interventions. Non-opioid analgesics are expressed as mg aspirin per day, opioid medications as mg of morphine per day, antidepressants as mg of fluoxetine per day, benzodiazepines as mg of valium per day, sleeping aids as mg of zolpidem per day.

Medication Class	N pre	N post	Mean (SD) dose pre (mg/day)	Mean (SD) dose post (mg/day)
Non-opioid analgesics	28	25	2027 (2351)	1545 (2020)
Opioids	5	6	18 (23)	25 (21)
Antidepressants	8	12	22 (26)	32 (28)
Benzodiazepines	6	6	5 (4)	7 (8)
Sleeping aids	4	0	5 (5)	0

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