

## Cognitive-Behavioral Therapy Increases Prefrontal Cortex Gray Matter in Patients With Chronic Pain

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**Abstract:** Several studies have reported reduced cerebral gray matter (GM) volume or density in chronic pain conditions, but there is limited research on the plasticity of the human cortex in response to psychological interventions. We investigated GM changes after cognitive-behavioral therapy (CBT) in patients with chronic pain. We used voxel-based morphometry to compare anatomic magnetic resonance imaging scans of 13 patients with mixed chronic pain types before and after an 11-week CBT treatment and to 13 healthy control participants. CBT led to significant improvements in clinical measures. Patients did not differ from healthy controls in GM anywhere in the brain. After treatment, patients had increased GM in the bilateral dorsolateral prefrontal, posterior parietal, subgenual anterior cingulate/orbitofrontal, and sensorimotor cortices, as well as hippocampus, and reduced GM in supplementary motor area. In most of these areas showing GM increases, GM became significantly higher than in controls. Decreased pain catastrophizing was associated with increased GM in the left dorsolateral prefrontal and ventrolateral prefrontal cortices, right posterior parietal cortex, somatosensory cortex, and pregenual anterior cingulate cortex. Although future studies with additional control groups will be needed to determine the specific roles of CBT on GM and brain function, we propose that increased GM in the prefrontal and posterior parietal cortices reflects greater top-down control over pain and cognitive reappraisal of pain, and that changes in somatosensory cortices reflect alterations in the perception of noxious signals.

**Perspective:** An 11-week CBT intervention for coping with chronic pain resulted in increased GM volume in prefrontal and somatosensory brain regions, as well as increased dorsolateral prefrontal volume associated with reduced pain catastrophizing. These results add to mounting evidence that CBT can be a valuable treatment option for chronic pain.

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**Key words:** Dorsolateral prefrontal cortex, neuroimaging, voxel-based morphometry, pain catastrophizing, CBT.

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**A**ccumulating evidence of structural brain changes in chronic pain patients indicates neuroplasticity in areas implicated in the experience and anticipation of pain.<sup>46</sup> Some studies reported a correlation between reduced gray matter ([GM] which could include changes in GM volume [GMV] or GM density [GMD]) in these regions and the duration or intensity of symptoms.<sup>1,37,39,64,65</sup> The degree to which these structural abnormalities are reversible with surgical treatment was the subject of several recent investigations. After hip replacement therapy, increases in GM were found in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), amygdala, brain stem, and

insular cortex.<sup>61</sup> Another study in the same patient population reported increased GMV in the thalamus after surgery.<sup>23</sup> Most recently, Seminowicz and colleagues<sup>68</sup> examined chronic low back pain patients before and after surgical intervention and reported a normalization of cortical thickness within the left DLPFC after effective treatment.

Building on previous research of structural brain changes following surgery for chronic pain and the documented structural changes following longer term (6 months to 2 years) cognitive interventions in clinical populations of chronic fatigue syndrome<sup>13</sup> and schizophrenia,<sup>14</sup> we aimed to examine cerebral GM changes in patients with chronic pain after an 11-week course of cognitive-behavioral therapy (CBT) (a typical clinical practice). CBT for chronic pain is designed to decrease maladaptive coping and improve self-regulatory skills and attention diversion abilities. Practicing these skills improves coping with pain and often reduces pain in clinical trials.<sup>4,5,35,36,47,51</sup>

We hypothesized that prefrontal brain regions involved in the experience and modulation of pain, which have documented structural abnormalities in chronic pain patients, will normalize following CBT and that the changes in these prefrontal regions will correlate with clinical improvement. Because CBT is likely to reduce the anticipatory fear and the emotional impact of pain, we hypothesized that regions implicated in the cognitive regulation of pain and emotion (particularly, the DLPFC, the ventrolateral prefrontal cortex [VLPFC] and the ACC) will be affected the most. Additionally, we tested how the clinical aspects of chronic pain showing post-CBT improvement were related to the measures of structural neuroplasticity.

## Methods

### Participants and Study Design

The study sample included in the analyses consisted of 13 patients with chronic pain (3 male, mean age = 51.4, standard deviation [SD] = 11.8, range = 30–70) and 13 healthy age-matched controls (3 male, mean age = 51.6, SD = 11.9, range = 31–68). Patients were scanned before and after 11 weeks of CBT (mean time elapsed = 3.58 months, SD = 1.06). Controls were scanned only once. An additional 10 healthy controls (4 male, mean age = 36.0, SD = 9.73, range = 22–54) from another study<sup>68</sup> who were scanned at 2 time points separated by 6 months were also included to show that GM levels are stable over time, as described below. 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 6 months of chronic pain; a subjective pain rating of at least 4 out of 10 on a 0 to 10 pain scale for the last month; ability to perform usual self-care; and ongoing care by a physician. Exclusion criteria included malignancy; pending pain-related surgery; involvement in pain-related litigation;

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 tions; psychosis; uncontrolled Axis I disorder or a severe personality disorder interfering with participation in group therapy; and typical magnetic resonance imaging (MRI) contraindications. Of the 24 patients originally recruited, 3 dropped out of treatment, and 6 were unwilling/unable to complete the second scan. The remaining 15 patients completed both scanning sessions and CBT group therapy; however, 2 patients were excluded because of late disclosure of exclusion criteria. The primary pain diagnoses in the patients included in this study were low back (n = 6), myofascial (n = 2), headache (n = 2), fibromyalgia, upper body, and pelvic floor. Self-reported duration of chronic pain ranged from 1 to 23 years (mean/SD = 9.15/7.16).

### Clinical Assessment Measures

The following measures of pain, function/disability, depression, and coping were used to assess patients with chronic pain. All the clinical measures have been validated by previous research. All were self-administered at each evaluation. More details about the clinical measures can be found in Naylor et al.<sup>54</sup>

#### Pain

Two measures were used to assess pain: 1) the Short Form McGill Pain Questionnaire (MPQ)<sup>49</sup> and 2) the Pain Symptoms subscale from the Treatment Outcomes in Pain Survey (TOPS).<sup>63</sup> In addition to the Short Form MPQ descriptors, 2 questions were added at the end of the questionnaire to assess typical (Pain Typical) and present (Pain Now) levels of pain on a 0 to 10 scale, with 0 labeled as no pain and 10 labeled as worst pain.

#### Function/Disability

The TOPS provides 3 measures of patients' functioning and disability: 1) the SF-36 Mental Health Composite, 2) the SF-36 Physical Health Composite, and 3) the TOPS Total Pain Experience scale.<sup>62,63,75</sup>

#### Depression

All participants completed the Beck Depression Inventory (BDI)<sup>6</sup> at all evaluations. BDI scores below 13 were interpreted as minimal depression, 14 to 19 as mild depression, 20 to 28 as moderate depression, and 29 to 63 as severe depression.

#### Pain Coping Strategies

Coping Strategies Questionnaire (CSQ) was used to measure the degree to which patients perceive themselves as able to use coping strategies to control and decrease pain and the degree of pain catastrophizing (Catastrophizing subscale).<sup>34,42</sup>

Control participants completed a demographics questionnaire and the BDI.

### CBT Intervention

CBT was delivered in eleven 90-minute weekly group sessions. Our CBT intervention for pain management was designed to 1) change cognitions and decrease maladaptive coping (pain catastrophizing), 2) enhance

patients' ability to use attention diversion to control pain, and 3) change activity patterns to better control pain. The curriculum was composed of 5 major components: self-regulatory skills, including relaxation techniques such as progressive relaxation training; cognitive coping strategies, such as cognitive restructuring and methods for reducing catastrophizing; attention diversion methods, including imagery; changing activity patterns, including activity pacing, pleasant activity scheduling, and regular exercise; and, last, methods for enhancing social support. An in-depth description of the program has been previously reported.<sup>53,54</sup>

## MRI

### Imaging Parameters

Anatomic MRI scanning was performed on a Philips Achieva 3-T system (Philips, Best, The Netherlands) with an 8-channel head coil. The scan sequence was a 3D T1-weighted turbo field echo, repetition time (TR) = 9.9 ms, echo time (TE) = 4.6 ms, flip angle = 8, field of view = 256 × 256, with 140 1-mm slices for a resolution of 1 × 1 × 1 mm. Five pre-CBT scans in the patient group and 2 scans in the control group took place on an identical scanner, using identical imaging parameters but in a different physical location. High reliability of structural neuroimaging methods has been established in several recent investigations,<sup>24,33</sup> provided identical hardware is used.<sup>17</sup> An axial T2-weighted gradient spin echo sequence was also obtained for radiologic reading to rule out neurologically significant abnormalities.

### Image Processing

We performed voxel-based morphometry (VBM) analysis on the anatomic MRI data. For VBM, data preprocessing was performed in VBM8 toolbox (version r435; <http://dbm.neuro.uni-jena.de/vbm/>) implemented through SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). All data underwent bias correction, segmentation, DARTEL normalization, modulation for nonlinear effects, and smoothing of 8-mm full width at half maximum. Because modulation accounts for total brain volume, no adjustments for total intracranial, brain, or ventricle volume were used in subsequent analyses. For patients, data additionally underwent longitudinal preprocessing, in which there was a realignment step prior to all other steps, where each patient's pre- and post-CBT scans were transformed midway to an average of the 2 scans, and no modulation was performed. In longitudinal analyses, it is expected that overall intracranial volume does not change in the short period between scans, and thus the images are not modulated by this volume adjustment (further details on longitudinal preprocessing can be found at <http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf>). When no modulation was performed, results are referred to as changes in GMD (all comparisons involving both pre-CBT and post-CBT scans), whereas GMV is used to refer to changes when the modulated data were used (patients vs controls, correlation between duration and GMV in patients pre-CBT).

Difference maps were created by subtracting each patient's pre-CBT scan from the post-CBT scan. VBM results are reported as increased or decreased GMV/GMD. For all whole-brain analyses, we used an initial threshold of  $P < .001$  to identify clusters. To correct for effects of nonstationary smoothing (NS),<sup>27</sup> we used the NS toolbox (<http://fmri.wfubmc.edu/cms/software#NS>) implemented in SPM5. Results reported in the tables are corrected for family-wise error (FWE) and NS at  $P < .05$ .

### Whole-Brain Analyses

Statistical analyses were performed in SPM8. We conducted separate t-tests comparing GMV in patients pre-CBT and controls and in patients post-CBT and controls, removing the effects of age. Additionally, a paired t-test was performed for GMD in patients pre- versus post-CBT. We performed further analyses to test the relationship between changes in pain, depression, pain catastrophizing, and quality of life measures with changes in GMD by subtracting each patient's pre-CBT GMD from the post-CBT GMD, then running a separate 1-sample t-test with the composite scores of each of the clinical measures as a covariate. We deemed a total of 6 measures highly relevant to this investigation and tested them as covariates. The physical health and mental health composites of SF-36 and the total pain experience composite were included from the TOPS questionnaire. The ability to control pain item and the pain catastrophizing subscale were included from CSQ. Ability to control pain consistently improved with this type of CBT in the past,<sup>53,54</sup> whereas catastrophizing modulates brain activity during acute pain and is proportional to structural changes in chronic pain.<sup>8,9,21,66</sup> We also examined the effects of pain duration on GMV in patients pre-CBT.

Because of the high comorbidity of chronic pain with depressive symptoms,<sup>29,67</sup> we included additional analyses to rule out the potential dependence of GMD changes on depression. We compared whole-brain 1-sample t-test results with and without the BDI composite score as a covariate and compared t-values in the peak coordinates identified in the repeated measures analysis. Furthermore, for regions that were identified as having an association with change in clinical outcome, we performed partial correlations controlling for BDI to rule out the dependence on depression scores.

### Region of Interest (ROI) Analyses and Plots

In order to perform comparisons across all the conditions (controls, pre-CBT, post-CBT), we performed separate analyses on the clusters that showed significant differences in the above whole-brain analyses. Thus, each significant cluster became an ROI. For each ROI detected in the whole-brain analyses, we extracted the GMD or GMV values for each participant and performed separate t-tests (pre-CBT vs post-CBT and pre-CBT vs controls) for each ROI and controlling for age. Because our sample did not show any whole-brain differences between patients and controls, only values for significant clusters from the whole-brain pre-CBT versus post-CBT analysis were extracted and submitted to the analysis

described above. Plots and data analysis on the ROI data were performed in SPSS version 19 (IBM SPSS Statistics, Armonk, NY). ROI data were extracted using MarsBar (<http://marsbar.sourceforge.net/>). We also qualitatively examined effects of pain type and individual differences on the ROI data, and we examined the effect of duration on these ROIs. The purpose of these ROI analyses was to test for subtler differences in the regions identified in whole-brain analyses, rather than using ROIs defined a priori based on the literature. Because only a few longitudinal studies on chronic pain interventions have been published and the types of chronic pain and interventions vary across studies, we find there is currently insufficient evidence for the latter approach.

## Pain Type

The patients in the current study had varying primary pain diagnoses. Because of our low sample size, we pooled patients into a single group. Our primary interest was on the effects of CBT on brain GM in patients with chronic pain, regardless of type. Nonetheless, we ran all the above whole-brain and ROI analyses again with pain type included as a covariate. We included 6 categories for pain type: low back ( $n = 6$ ), myofascial ( $n = 2$ ), headache ( $n = 2$ ), fibromyalgia ( $n = 1$ ), upper body ( $n = 1$ ), pelvic floor ( $n = 1$ ).

## Longitudinal Effects in Healthy Participants

Although the healthy control participants in the current study were only scanned at 1 time point, we were able to examine longitudinal changes in a separate sample of healthy control participants from a previously reported study.<sup>68</sup> We used MRI scans (3T Siemens Tim Trio scanner, 8 channel head coil resolution  $1 \times 1 \times 1$  mm; Eynsham, Oxfordshire, UK) from 10 healthy controls (4 male, mean age = 36.0, SD = 9.73, range = 22–54), each scanned at 2 time points separated by 6 months. Data were pre-processed the exact same way as described above (non-modulated). We used a 2 (group)  $\times$  2 (time point) repeated measures analysis of variance on the ROIs that showed significant changes in patients to determine whether effects could be related to natural time-dependent changes in the brain structure. Age was included as a covariate. Although the use of data sets acquired on different scanners and at different time points is not ideal, the within-group design nevertheless

allows us to compare changes over time between the 2 groups.

## Results

### Clinical Characteristics

Patients rated their pre-CBT typical pain as 6.3, SD = 1.7, on a scale of 0 to 10, with the mean length of pain of 9.7, SD = 7.5, years. Patients pre-CBT had significantly higher BDI scores than controls (patients: 19.85, SD = 10.07; controls: 2.5, SD = 2.91;  $t = 5.74$ ,  $P < .001$ ). After CBT, patients showed significant improvements in 6 out of 9 clinical measures. A summary of all clinical change scores are given in Table 1.

### Gray Matter VBM

#### Patients Versus Controls

Patients pre-CBT and controls had no significant differences in GM. Even at a very liberal initial height threshold of  $P < .05$  uncorrected, there were no clusters where controls had greater or less GM than patients.

#### Patients Pre- Versus Post-CBT

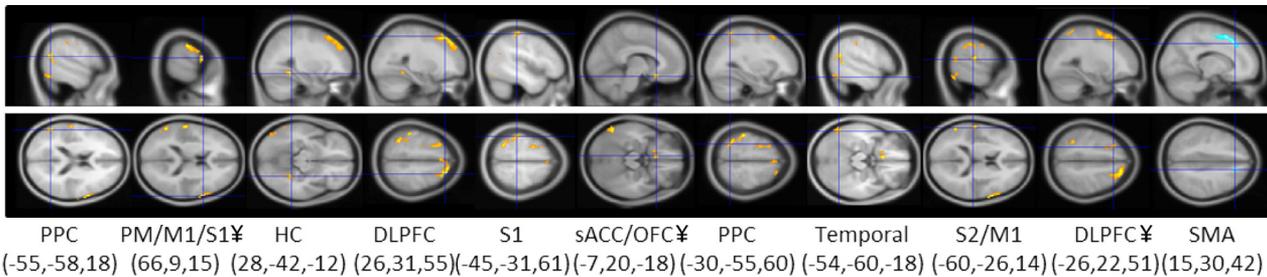
Ten clusters showed significantly increased GM post-CBT compared to pre-CBT. The clusters included left inferior posterior parietal cortex (PPC), right premotor/primary motor cortex/primary somatosensory cortex, right hippocampus (HC), right DLPFC, left primary somatosensory cortex, left subgenual ACC/orbitofrontal cortex (sACC/OFC), left superior PPC, left inferior temporal cortex, secondary somatosensory cortex/primary motor cortex, and right premotor/inferior frontal gyrus. Only 1 region, a right medial wall cluster that included supplementary motor area (SMA)/pre-SMA (referred to as juxtapositional lobule cortex in the Harvard-Oxford cortical atlas), had decreased GM after CBT. Clusters are shown in Fig 1 and statistics for each cluster are shown in Table 2.

Data from each of the clusters were extracted and these ROI data were used for subsequent analyses. Three ROIs and their plotted GM values for each group are shown in Fig 2. We chose to show the right and left DLPFC based on previous findings in the literature, and the SMA/pre-SMA because it was the only region that

**Table 1. Clinical Measures (Post-CBT Minus Pre-CBT Change Scores)**

	MEAN PRE-CBT SCORE (SE)	MEAN POST-CBT SCORE (SE)	POST – PRE (SE)	T	P
CSQ catastrophizing	16.23 (2.59)	8 (1.61)	–8.24 (2.28)	–3.607	.004*
CSQ ability to control pain	2.46 (.33)	3.65 (.25)	1.19 (.34)	3.533	.004*
TOPS total pain experience	59.59 (3.61)	43.75 (3.48)	–15.2 (2.85)	–5.338	<.001*
SF-36 mental composite	38.83 (3.45)	51.48 (2.37)	12.65 (3.19)	3.97	.002*
SF-36 physical composite	29.10 (2.34)	32.42 (2.55)	3.32 (1.85)	1.792	ns
TOPS pain symptoms	68.17 (3.81)	56.23 (5.44)	–11.94 (4.95)	–2.412	.033
MPQ pain now	5.85 (.55)	4.62 (.95)	–.62 (.87)	–.71	ns
MPQ pain typical	6.31 (.47)	5.23 (.72)	–1.08 (.52)	–2.05	.063
BDI	19.85 (2.79)	10.77 (1.63)	–9.08 (1.95)	–4.656	.001*

\*Significant after Bonferroni correction for multiple comparisons ( $P = .0056$  is the threshold).



**Figure 1.** All significant clusters from post-CBT versus pre-CBT repeated measures analysis. The order (left to right) matches the order of clusters shown in Table 2. Note that the SMA cluster on the far right is pre-CBT > post-CBT. MNI coordinates (x, y, z) for each crosshair location are shown for each cluster. M1, primary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. <sup>‡</sup>Cluster is not significant when a covariate for pain type is included.

showed a decrease in GM. Fig 2 shows that for ROIs where GM increased, the GM level in patients after CBT was significantly greater than that of controls. This was true for 3 other clusters that are not shown, ventral and dorsal left PPC, and right HC. None of the changes in GM in the ROIs extracted from the post-pre analysis correlated with change scores for catastrophizing, BDI, pain control, or physical component summary of the SF-36.

### Clinical Measures and GM

In a whole-brain analysis, pain catastrophizing was significantly negatively correlated with increased GM following CBT in 4 clusters: a very large right PPC cluster that included parts of the second and primary somatosensory cortices, a very large left DLPFC cluster and a smaller inferior frontal gyrus or VLPFC cluster, and a cluster in the bilateral pregenual ACC/medial prefrontal cortex (pACC/MPFC) (Fig 3, Table 2). That is, as pain catastrophizing went down after CBT, GM in these regions increased. There were also 2 clusters that were positively correlated with pain catastrophizing—right HC and right DLPFC. Extracted data from the HC cluster were also negatively correlated with the change in perceived pain control as measured by the CSQ ( $r = -.619, P < .05$ ). All significant clusters are shown in Fig 3. Fig 4 shows the scatter plots for change in GM of 3 clusters against the change in catastrophizing score (larger negative numbers indicate greater improvement).

Pain control as measured by the CSQ was significantly correlated with increased GMD in the right motor cortex (Table 2). Extracted data from this ROI identified in the pain control analysis were also significantly negatively correlated with pain catastrophizing ( $r = -.627, P < .05$ ). Improvement on the physical component summary of the SF-36 correlated with increased GM in the right middle temporal gyrus. No other clinical measures tested, including BDI depression scores, mental component summary of the SF-36, and total pain experience, reached our significance criteria.

### Depression

To rule out the possibility that the treatment changes in GM were driven by changes in depression, we ran 2 models using 1-sample t-tests with the subtraction

maps (post-CBT – pre-CBT) with and without BDI scores as a covariate. We then extracted the t-values for each coordinate identified in the repeated measures analysis. The t-values for the model with BDI included as a covariate were higher in 27 of the 32 coordinates, and in the remaining 5 coordinates, t-values were no more than .12 higher in the model without the covariate compared to the model with the covariate. This finding suggests that depression did not influence GM changes in the identified areas.

We tested whether the correlation between change in pain catastrophizing and change in the GMD was influenced by change in depression by controlling for BDI in partial correlations. BDI did not decrease the r-value or significance in any of the ROIs that correlated with pain catastrophizing. Of note, pain catastrophizing and depression scores were significantly correlated pre-CBT ( $r = .734, P < .005$ ) but not post-CBT ( $r = .441, P = .131$ ), and there was also no significant correlation between pain catastrophizing and depression change scores ( $r = .523, P = .0668$ ). Thus, there was a clear dissociation between treatment-related changes in pain catastrophizing and depression, and GM changes associated with improvement in pain catastrophizing are independent of changes in depression.

### Duration

Duration of chronic pain ranged from 1 to 23 years (mean/SD = 9.15/7.16). There were no significant correlations between duration and any of the post-pre differences in the clinical measures or in the ROIs. Similarly, age also did not correlate with the change in any of the variables.

There were 2 significant GMV clusters that were negatively correlated with duration in pre-CBT patient scans (ie, the longer they have had pain, the less GMV in these areas): posterior midcingulate cortex (pmCC; peak 3, -6, 28,  $T = 9.41, P < .000001$ , cluster  $k = 959, P [FWE] < .01$ ) and left temporoparietal junction (TPJ; peak -58, -51, 6,  $T = 6.03, P < .00001$ , cluster  $k = 531, P [FWE] < .05$ ).

We also examined the relationship between pain duration and the average GMD of the ROIs from the pre-CBT versus post-CBT analysis. Duration negatively correlated with the left PPC ROI pre-CBT ( $r = -.777, P < .005$ ) and post-CBT ( $r = -.750, P < .005$ ), and with the left inferior

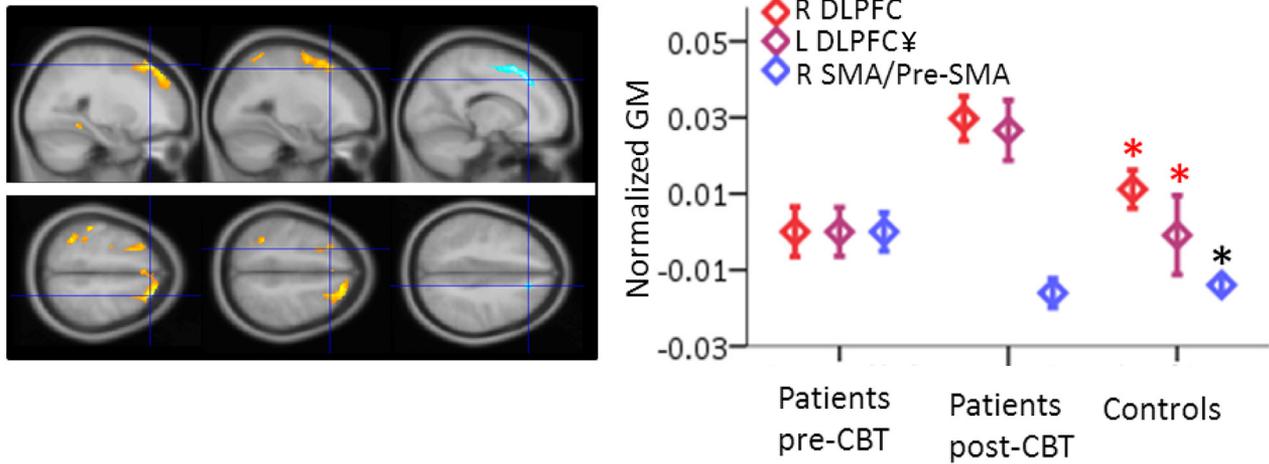
**Table 2. VBM Significant Results**

REGION	LEFT/RIGHT	P VALUE FOR CLUSTER*	VOLUME OF CLUSTER (MM <sup>3</sup> )	PEAK MNI COORDINATES			PEAK T VALUE
Patients post-CBT > patients pre-CBT							
PPC (inferior)	L	.008	1,195	-56	-58	18	8.50
				-54	-54	8	5.69
				-52	-68	15	4.65
Premotor/M1/S1†	R	.040	2,413	66	9	15	7.43
				69	-9	28	6.97
				68	-20	38	6.91
Hippocampus	R	.027	793	28	-42	-12	7.16
				33	-52	-3	5.17
				27	-52	-12	4.61
DLPFC	R	.001	8,414	26	32	56	7.10
				16	36	52	6.32
				21	45	44	6.25
S1	L	.013	1,225	-45	-32	62	7.05
				-39	-39	62	5.10
				-33	-40	56	4.17
sACC/OFC†	L	.016	996	-8	20	-18	6.92
				-15	14	-22	5.75
				-30	-56	60	6.35
PPC (superior)	L	.006	2,133	-34	-60	42	5.81
				-34	-51	52	5.68
				-54	-60	-18	6.17
Inferior temporal	L	.040	1,232	-46	-78	-12	4.65
				-60	-54	-12	4.61
				-60	-26	14	6.12
S2/M1	L	.009	2,400	-66	-20	33	5.79
				-60	-30	40	5.03
				-26	22	51	5.70
DLPFC†	L	.047	2,008	-27	-3	64	5.38
				-26	15	57	5.32
				Patients post-CBT < patients pre-CBT			
SMA/pre-SMA	R	.002	2,204	15	30	42	6.96
				16	14	54	6.72
				15	21	50	6.13
Decreased pain catastrophizing correlated with increased GMD							
S2/S1/PPC	R	.0001	12,477	54	-18	30	8.70
				62	-34	38	7.53
				46	-26	22	7.32
ACC	L	.0030	2,373	-4	52	0	6.45
				-3	50	22	6.41
				-6	48	10	5.81
DLPFC	L	.0005	5,755	-52	14	22	6.28
				-42	18	46	6.23
				-46	12	38	6.20
IFG	L	.0060	1,796	-56	6	4	5.77
				-54	22	-3	5.72
				-60	-8	6	5.65
Increased pain catastrophizing correlated with increased GMD							
Hippocampus†	R	.0040	1,438	24	-38	-3	9.12
				28	-42	-9	6.57
DLPFC†	R	.0200	824	38	40	16	7.57
				42	34	24	5.75
Increased ability to control pain correlated with increased GMD							
Motor cortex†	R	.0170	1,137	48	-8	48	7.14
				46	3	45	5.39
				52	-4	33	4.89
Decreased physical health (SF-36 subscale) correlated with increased GMD							
Middle temporal gyrus, inferior parietal†	R	.0040	824	39	-54	14	9.30
				40	-58	4	5.86
				34	-66	18	4.10

Abbreviations: M1, primary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex.

\*FWE corrected at cluster level, nonstationarity corrected.

†Cluster is not significant when a covariate for pain type is included.



**Figure 2.** VBM results showing 3 regions where GM increased (right and left DLPFC) or decreased (Pre-SMA/SMA) in patients post-CBT compared to pre-CBT. The plot to the right shows the means and standard errors for each region shown in the panels to the left. Data for all 3 groups (patients pre- and post-CBT and controls) are normalized to patients pre-CBT. See Table 2 for details on the SPM statistics. Red asterisks indicate ROIs where controls had significantly less GM than patients post-CBT, and the black asterisk indicates the ROI where controls had less GM than patients pre-CBT, as determined by t-tests on mean values of the ROIs. †Cluster is not significant when a covariate for pain type is included.

temporal gyrus ROI pre-CBT ( $r = -.582, P < .05$ ) but not post-CBT ( $r = -.422, P = .151$ ).

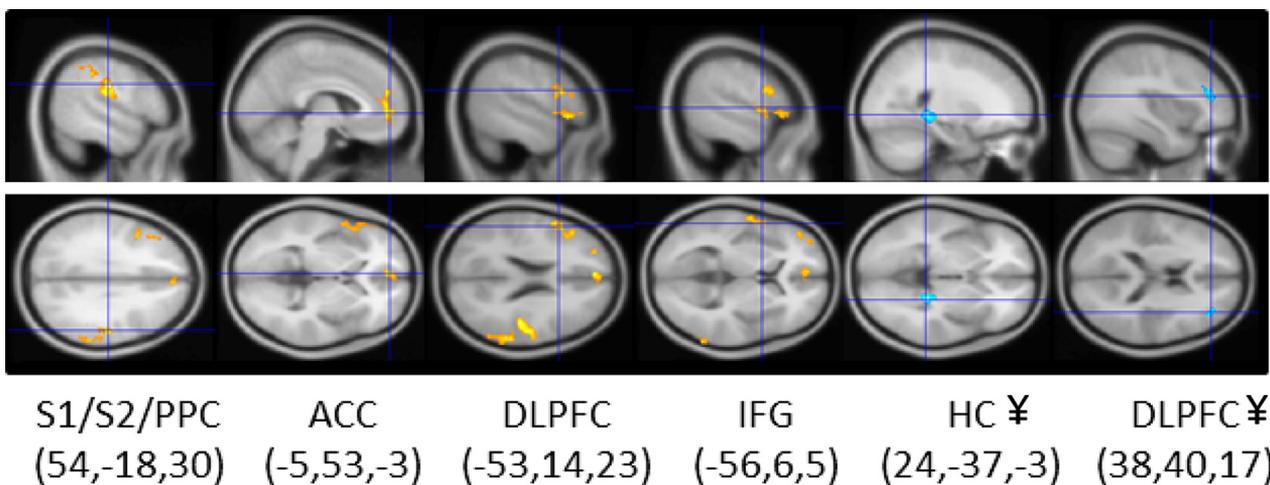
**Pain Type**

Upon examination of individual effects within the 11 ROIs that showed altered GMD post-CBT, 10 of the 13 patients always had an effect consistent with the overall group effect, and of the remaining 3 patients, 1 had low back pain and the other 2 headache. We reran the whole-brain and ROI analyses with pain type included as a covariate. The inclusion of pain type as a covariate had no effect on the ROI analyses: significant differences remained. For whole-brain analyses, inclusion of pain type had some effect, although most of the significant clusters reported in the 2 main analyses remained significant.

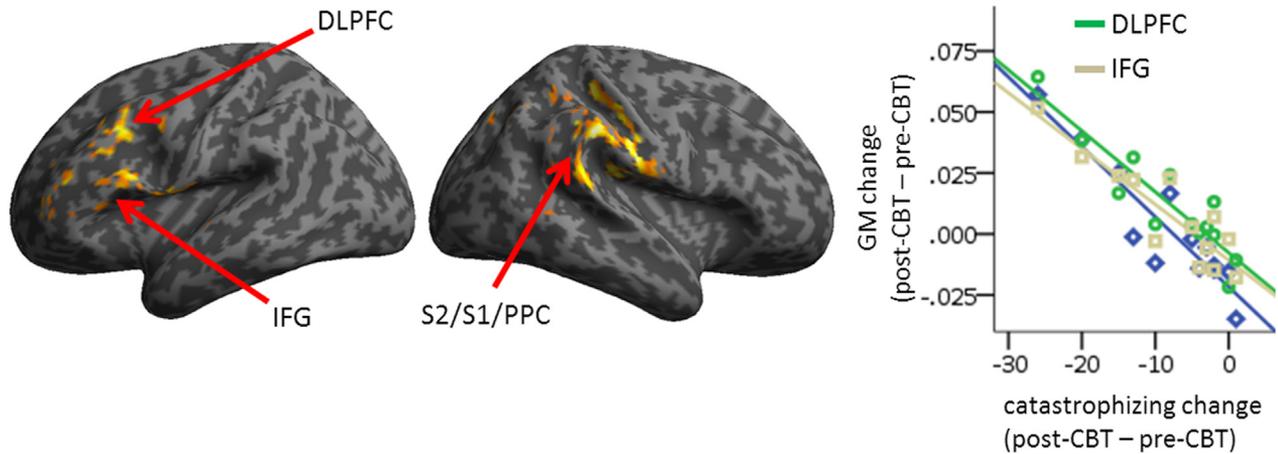
Clusters that were not significant after controlling for pain type are reported in Table 2 and Figs 1 to 3.

**Longitudinal Effects in Healthy Participants**

For the 11 ROIs showing altered GMD after CBT, we performed a 2 (group) × 2 (time) analysis of variance, with age as a covariate, comparing patients and a set of healthy controls from another study who were scanned at 2 time points separated by 6 months. For every ROI, there was a significant group-by-time interaction. There were very minimal and nonsignificant changes in GMD in these ROIs in the healthy control group, suggesting that GMD in these regions is stable over time in a pain-free group that has not undergone CBT.



**Figure 3.** All significant clusters from regression of change in catastrophizing and change in GM. The order (left to right) matches the order of clusters shown in Table 2. Note that the first 4 clusters from left to right were negative correlations between GM and catastrophizing, whereas the 2 right clusters (HC, DLPFC) were positive correlations. MNI coordinates (x, y, z) for each crosshair location are shown for each cluster. IFG, inferior frontal gyrus; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. †Cluster is not significant when a covariate for pain type is included.



**Figure 4.** Three of the 4 clusters where increased GMV after CBT correlated with decreased pain catastrophizing. The left DLPFC and IFG and the right S2/S1/PPC clusters are shown. Results are cluster corrected at  $P$  (FWE)  $< .05$ . See Table 2 for details. Scatterplot shows change in GM as a function of change in catastrophizing. IFG, inferior frontal gyrus; S1, primary somatosensory cortex; S2, secondary somatosensory cortex.

## Discussion

CBT resulted in increased GM in bilateral DLPFC and PPC and several other sensory, motor, and affective areas and decreased GM in the left SMA. Furthermore, pain catastrophizing negatively correlated with changes in left DLPFC, ACC, and right parietal cortical regions, and positively correlated with right DLPFC and hippocampus. The type of CBT implemented in this study provided training in several coping strategies, ranging from relaxation techniques and attention diversion away from pain to active engagement with and restructuring of the maladaptive cognitions leading to negative emotions associated with chronic pain. As predicted, CBT in this study was associated with GM increases in bilateral DLPFC. GM increases in the DLPFC are consistent with normalization of functional activity during performance of a cognitive task and concurrent cortical thickening in patients having undergone surgery or facet joint block for chronic low back pain.<sup>68</sup> We propose that changes in prefrontal regions reflect compensatory mechanisms to increase descending modulation of pain<sup>7,25,38,43,73,76-78</sup> or freeing of cognitive resources for cognitive or affective reappraisal of pain and pain-related challenges,<sup>28,48,55,56</sup> whereas changes in sensory and motor regions reflect adaptive responses to the repetitive input of noxious signals.

There have now been many studies reporting GM changes in chronic pain compared with healthy controls<sup>12</sup> and we therefore hypothesized that patients would have reduced regional GM compared to controls. Although the majority of these studies reported decreased GM in patients, some reported increased GM.<sup>50</sup> Furthermore, some studies reported relatively few regional differences in GM between patients and controls,<sup>12</sup> and at least 1 reported no differences at all.<sup>16</sup> In the current study, patients did not have significantly different GM than controls. This might not be surprising for a few reasons. First, it has been suggested that

different chronic pains might be associated with unique brain "signatures."<sup>3</sup> Second, the specific regions that have different GM in patients and controls vary across studies and patient groups.<sup>79</sup> Third, there have been suggestions that patient age might be an important factor in GM changes.<sup>50,65</sup> Importantly, in spite of the heterogeneous patient group in the current study and lack of difference from healthy controls, we still observed the expected regional changes in GM following CBT.

Although previous studies reported reversal of GM or cortical thickness changes in patients with effective treatment,<sup>23,61,68</sup> the GM changes reported in the current study are likely adaptive, rather than a return to normal levels. None of the regions that had increased GM in patients post-CBT compared to pre-CBT were significantly different from controls at the pre-CBT time point (based on t-tests for the average GM in the ROIs). However, after CBT, the GM in most of these regions increased beyond the GM level of controls. Thus, it is possible that these regions have gained function beyond normal levels to support pain coping mechanisms. Such a finding of increase in GM beyond the normal levels of healthy controls has been reported in recovery from addiction,<sup>11</sup> and a recent review of the literature suggests that the increase in PFC GM and functional activity reported in several studies is related to an increase in cognitive control required to maintain the new cognitive state.<sup>19</sup> It is also worth noting that the one area that had reduced GM after CBT treatment—the SMA/pre-SMA—was the only region that had significantly greater GM in patients pre-CBT compared to controls (Fig 1), and after CBT the GM level decreased to a level more similar to that in controls, making this region the only one that showed normalization. The SMA/pre-SMA plays a role in generation of voluntary movement<sup>30</sup> and has been implicated in motor dysfunction in chronic regional pain

syndrome.<sup>44</sup> In addition, SMA/pre-SMA is frequently activated in various pain and cognitive task paradigms<sup>18,58</sup>; it is activated by arthritic pain,<sup>40</sup> and its activity increases with increasing intensity of spontaneous chronic pain.<sup>2</sup> Thus, the normalization of GM in this region could be related to motor function or more directly to chronic pain. Disambiguating between these possibilities is an important avenue for future investigations.

In previous longitudinal studies on surgical treatment effects on GM in chronic pain, all of<sup>23,61</sup> or the majority of<sup>68</sup> patients had reduced pain after treatment. Here, in response to an 11-week cognitive-behavioral intervention, patients had relatively minor decreases in pain compared to the changes in coping and affect. In fact, of all the clinical measures, pain and physical health were the only ones that did not show significant reductions after treatment (after Bonferroni correction; see Table 1). However, improvement in pain beliefs, including control over pain, and catastrophizing were achieved, and these changes can predict later improvements in pain,<sup>32,72</sup> so it is possible that later (eg, 1-year post-CBT) patients would show reduced pain as well as pain-related GM changes. In fact, previous work showed that patients enrolled in a 4-month relapse prevention program after CBT had a significant decrease of pain and improved coping compared to immediately after CBT.<sup>54</sup>

Several studies have examined the effects of CBT for various conditions and have reported changes in PFC activity. For example, Jensen and colleagues reported increased pain-related activity in the left VLPFC in fibromyalgia patients after they underwent CBT.<sup>31</sup> The authors suggested that the increased VLPFC activity reflected reappraisal of the pain with resources freed up through cognitive coping. In schizophrenia, CBT led to increased DLPFC and frontopolar activation during a working memory task,<sup>26</sup> and bilateral DLPFC and ACC activation during a memory task predicted improvement of symptoms following CBT.<sup>41</sup> Generalized anxiety disorder patients also had increased VLPFC in response to threat stimuli after CBT.<sup>45</sup> Finally, in major depression, CBT led to increased activity in ventromedial PFC during an arousal task.<sup>60</sup> Therefore, one interpretation of the increased GM in prefrontal areas we report here is that they reflect increased activity related to changes in ongoing cognitive and affective appraisals.

Improvement in pain catastrophizing was the only clinical measure that significantly correlated with structural changes post-CBT in multiple regions (control of pain and physical ability each correlated with GM change in one region). Pain catastrophizing is known to be a particularly salient feature of chronic pain states,<sup>70,71</sup> and a significant portion of our current CBT program is devoted to developing skills to reduce catastrophizing and restructure patients' perception of pain. Functional neuroimaging studies of acute pain paradigms in healthy control participants and in chronic pain populations have reported catastrophizing-related activations primarily within networks engaged in anticipation of and attention to pain.<sup>21,66</sup> Furthermore, a

recent diffusion tensor imaging study revealed negative correlations between pain catastrophizing and fractional anisotropy (a measure of white matter tract integrity) in the cingulum in irritable bowel syndrome.<sup>9</sup> Similarly, in the present study, pain catastrophizing was associated with changes in pACC/MPFC, regions of the brain implicated in direct control of emotional circuits<sup>20</sup> as well as in placebo analgesia.<sup>57,73,74</sup> Consistent with the anticipation and attention to pain hypothesis of pain catastrophizing, GM also increased in the PPC after CBT. Interestingly, pain catastrophizing correlated negatively with GM change in the left DLPFC but positively correlated with the right DLPFC. In depression, high-frequency repetitive transcranial magnetic stimulation is generally more effective on the left side.<sup>22</sup> Likewise, previous work showed functional and structural changes primarily in the left DLPFC after peripheral interventions to relieve chronic low back pain.<sup>68</sup> Evidence of pain catastrophizing-related structural neuroplasticity presented here highlights the importance of teaching methods to reduce pain catastrophizing for effective control of chronic pain. In general, the structural changes in the prefrontal cortex were consistent with the theoretical models of CBT that generally implicate top-down mechanisms.<sup>10,15,59,69</sup>

Including depression scores as a covariate in the pre-CBT versus post-CBT analysis did not decrease significance levels in the great majority of significant peaks, and where it did decrease the significance it was by marginal amounts. Furthermore, although pain catastrophizing and depression scores were correlated before treatment, after CBT there was no significant correlation between the two. Controlling for depression has had large effects in other VBM studies in chronic pain populations,<sup>29,67</sup> but in the current study, the reported changes in GM appear to be independent of depression.

One final interesting finding involved the right hippocampus. This region had increased GM in patients post-CBT compared to pre-CBT, and GM in an almost identical cluster in the hippocampus was positively correlated with change in pain catastrophizing. The hippocampus was recently shown to have altered neurogenesis and short-term plasticity in a mouse model of neuropathic pain, and its volume was also decreased in chronic back pain and chronic regional pain syndrome patients.<sup>52</sup> Thus, the increased GM in this structure in the present study could indicate normalization of hippocampal function in learning, memory, and emotion. However, the inverse relationship between increased hippocampal GM and improvement in pain catastrophizing is unclear.

There are some limitations to our study. First, this is a nonrandomized study, with healthy participants serving as a control group. However, as our patients' average length of pain was 10 years, we do not think the structural brain changes could be attributed to the simple passage of time. Moreover, these changes correlated with clinical improvement. Furthermore, we compared the GMD in the ROIs that showed significant changes in patients pre- versus post-CBT to a set of healthy controls from another study who were scanned at 2 time

points, and the group  $\times$  time interaction was significant for every region, suggesting that the effect was specific to CBT, because brain GMD is stable in these areas in healthy individuals. It is also possible that the changes we report herein are an effect of participating in the CBT intervention and are not specific to the cognitive therapy itself. For these reasons, future studies should include scans at multiple time points for all participants to rule out nonspecific brain structural changes over time, and should include control groups such as an education session in which time spent in therapy is matched, to determine CBT-specific effects. Second, the pain diagnoses in our patients were heterogeneous. However, the goal of the current study was not to determine a treatment effect that is specific for 1 type of chronic pain (which has been shown in prior studies<sup>34-36</sup>) but rather to determine brain changes associated with CBT irrespective of chronic pain type. Despite a lack of GM differences between patients pre-CBT and controls, possibly owing to the mixed sample of pain diagnoses, we can assume that the brain changes we report in the short time frame of the study are related to the one

CBT Increases Prefrontal Gray Matter in Chronic Pain manipulation—that is, CBT intervention—that is common to all patients, rather than due to a change in the variability between chronic pain types. To clarify whether CBT is reversing abnormal GM in some subgroups while causing overcompensation in GM in others, a large study involving multiple chronic pain conditions would be required.

To conclude, we have shown that treating chronic pain with CBT leads to increased GM in several brain areas including prefrontal and parietal regions, and that decreased pain catastrophizing is associated with increased GM in prefrontal and parietal areas. Our data suggest that the GM changes following standard 11-week group CBT parallels clinical improvements in coping with pain and overall mental health.

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