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## Structural Brain Imaging in People with Low Back Pain

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### Abstract

**Study Design**—cross-sectional study

**Objective**—The aim of this study was to determine whether low back pain (subacute and chronic) is related to differences in brain volume.

**Summary of Background Data**—Inconsistent findings have been reported about the effect of chronic low back pain on brain volume, and the effect of subacute low back pain on brain volume has not been sufficiently investigated.

**Methods**—130 participants were included (23 subacute and 68 chronic low back pain; 39 healthy controls). The main outcome measure was whole and regional brain volume. Clinical outcome measures included pain duration, pain intensity, fear avoidance belief questionnaire, Oswestry disability index, and Beck's depression inventory.

**Results**—Decrease in brain volume in several regions was observed in chronic low back pain when compared to health subjects; however after correcting for multiple comparisons, no significant differences were detected between any of the 3 groups in whole-brain volume. Regionally, we detected less gray matter volume in 2 voxels in the middle frontal gyrus in chronic low back pain participants compared to healthy controls. None of the clinical outcome measures were correlated with brain volume measurements.

**Conclusion**—Low back pain (subacute or chronic) is not related to significant differences in brain volume after correction for multiple comparisons. The effect size was too small to detect possible subtle changes unless much larger sample sizes are examined, or it is possible that low back pain does not affect brain volume.

## Keywords

low back pain; chronic; subacute; neuroimaging; voxel-based morphometry; volumetric measurements; brain; structure

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## Introduction

Low back pain (LBP) is one of the most common pain conditions affecting millions of people worldwide(1, 2), and can be a major cause of disability(3, 4), depression (5–7), and loss of work(8, 9). Consequently, its economic impacts are tremendous with an annual cost in the US exceeding \$100 billion(10). Furthermore almost 85% of patients have no specific patho-anatomical diagnosis but rather have idiopathic or “nonspecific” LBP(11). The mismatch between radiographic findings of spine images and clinical symptoms(12, 13) makes proper diagnosis and understanding of LBP difficult. Regardless of its underlying cause, “pain” as a nociceptive experience is processed in certain regions in the brain(14, 15). Brain imaging methods can be used to determine the relationship between pain and brain function and structure.

Pain is subjective and idiosyncratic. In general, the pain experience incorporates two main components: sensory-discriminative and affective-emotional components. These components are processed in different brain regions, yet are integrated and influenced by each other(16). Although recent evidence suggests that people with LBP have altered brain neurochemistry(17, 18) and function(19, 20), similar structural brain differences have not been established.

Smaller brain volumes have been reported in such neurodegenerative diseases as multiple sclerosis(21–23), Alzheimer’s disease(24–26), and schizophrenia(27–29), and also in chronic pain conditions like fibromyalgia(30–32), complex regional-pain syndrome (33, 34), and chronic LBP(35, 36). To date, only a few structural brain imaging studies in people with chronic LBP(35–42) have been completed. Findings from these studies were inconsistent, with some reporting smaller volumes in participants with chronic LBP compared to healthy controls, and others reporting no differences in brain volume. Importantly, the sample sizes in these studies were modest, and many that reported significance differences in brain volume did not correct for multiple comparisons(37, 40, 41), drawing into question the significance of the observation. Moreover, only one study has addressed subacute LBP in terms of brain structure and whether such potential differences exist during earlier stages of the disease(43) is unclear. The clinical significance of possible volumetric differences in LBP is also unclear.

The main aims of this study were to determine whether there are: 1) whole-brain volumetric differences in participants with subacute and chronic LBP compared to healthy controls; 2) regional brain differences in participants with subacute and chronic LBP compared to healthy controls; and 3) relationships between clinical outcome measures and brain volumes in participants with subacute and chronic LBP. We hypothesized that participants with chronic LBP would have smaller whole-brain volumes as compared to subacute and healthy controls, and participants with subacute LBP would have smaller whole-brain volumes

compared to healthy controls. Secondly, we hypothesized that we would find smaller brain volumes within sensory and affective pain processing regions in participants with LBP. Finally, we hypothesized a negative correlation between normalized whole-brain volumes and clinical outcome measures such as pain intensity, pain duration, depression, or fear avoidance.

## Materials and Methods

A total of 130 participants were included in this study: subacute (<6 months) LBP (n=23, 57% female), chronic (>6 months) LBP (n=68, 71% female), and healthy controls (n=39 participants, 44% female). Inclusion criteria for the LBP participants were: 1) male/female between 21 and 70 years, 2) having pain for less than 6 months (subacute group) and more than 6 months (chronic group), and 3) being able to read and understand English. Exclusion criteria were: 1) spinal cord compression or spine surgery within the past year, 2) known injuries or arthritis to the hip, knee or ankle joints, 3) neurologic condition (including head trauma, stroke, or Alzheimer's disease), 4) psychiatric or cardiovascular disease, tumor, or infection, 5) use of drugs or alcohol abuse, 6) pregnancy, and 7) MRI exclusion criteria (such as metallic object implants not compatible with MRI, epilepsy, or claustrophobia). The healthy controls self-reported no history of LBP within the last year. Participants were recruited through broadcast e-mails to university staff and employees, and word-of-mouth. The study was approved by the Human Subjects Committee at the University of Kansas Medical Center, and all participants provided informed consent prior to taking part in the study.

High-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) brain images were collected at 3-Tesla (matrix=256×256; 208 slices; voxels=1.0 mm × 1 mm × 0.97 mm; TE=3.05 ms; and TR=2300 ms on Allegra and Skyra scanners, Siemens Medical Solutions, Germany). Standard preprocessing was performed for all images using VBM8 toolbox(44) through Statistical Parametric Mapping software SPM8 (Wellcome Department of Cognitive Neurology, London, UK) operating under MATLAB (Mathworks, Sherborn, MA, USA). Preprocessing included spatial normalization of all acquired images into the same stereotactic space, to account for head size differences between participants. DARTEL segmentation into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and Gaussian spatial smoothing (8 mm full-width at half-maximum) as determined by previous studies was performed. Image quality and sample homogeneity were verified through visual inspection using the voxel-based morphometry (VBM8) tools(44). We used volumetric outputs from VBM8 stream to calculate individual normalized whole-brain volume, which is the sum of GM volume and WM volume divided by total intracranial volume. Further, we used VBM analysis to generate smoothed, modulated, warped statistical brain maps of the probability of difference in brain volume between groups of participants(44).

For region-of-interest (ROI) analysis we used the Wake-Forest PickAtlas(45, 46) to create masks of pain-related brain regions(16). Four ROI masks were created; a sensory mask, which included the primary somatosensory cortex and the posterior insula; a cortical affective mask which included the cingulate, orbitofrontal, and medial prefrontal cortices

and the anterior insula; a subcortical affective mask which included nucleus accumbens, amygdala, caudate, and hippocampus; and a mask of the thalamus.

The clinical outcome measures were collected only from participants with LBP (subacute and chronic) and included pain duration, pain intensity, fear avoidance, disability, and depression. Average pain intensity for previous week was measured with the Numeric Rating Pain Scale (NRS)(47). The NRS is a 0–10 scale with 0=no pain and 10=worst pain imaginable. Fear of movement was measured by the Fear Avoidance Belief Questionnaire (FABQ), which quantifies the subjective impact of work and physical activity on pain(48). Disability was measured by the Oswestry Disability Index (ODI(49)), which quantifies individual disability due to LBP. ODI scores greater than 60% indicate severe disability(50–52). Finally, depression symptoms were measured using the Beck Depression Inventory (BDI–II), which has been validated in multiple studies(53).

To investigate difference in age between the groups, we conducted an analysis-of-variance (ANOVA) test, followed by Tukey’s post-hoc testing using SPSS 22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp). Then, we conducted Chi-square testing to investigate differences in sex and scanner between groups. Age, sex, and scanner were then used as covariates in each of the brain volume analyses listed below.

### Normalized Whole-Brain Volumes

To determine whether there were overall brain volume differences between the three groups, we conducted a univariate one-way ANOVA test using SPSS for the normalized whole-brain volumes as the dependent variable, and group (subacute, chronic, healthy) as the independent variable.

### Voxel-Based Analysis (whole-brain and ROI)

We examined GM volume differences between the groups using SPM8. We conducted two-sample *t*-tests between each pair of groups (healthy-subacute, healthy-chronic, subacute-chronic) over the whole brain and then within the four regional masks, correcting for multiple comparisons in each test.

### Correlation Analysis

We conducted partial correlations between the normalized whole-brain volumes and each clinical outcome measure in the subacute and chronic LBP groups separately using SPSS software, while controlling for age, sex, and scanner in each test.

## Results

The ANOVA test revealed a significant age difference between the groups ( $F(2,127)=3.99$ ,  $p=0.021$ ,  $\eta^2=0.06$ ), with the chronic group being significantly older than the subacute group ( $p=0.025$ ,  $M_{\text{difference}}=-8.39$ ,  $\text{std. error}=3.18$ ) and no difference between the healthy and subacute ( $p=0.527$ ,  $M_{\text{difference}}=3.74$ ,  $\text{std. error}=3.46$ ) or healthy and chronic groups ( $p=0.189$ ,  $M_{\text{difference}}=-4.64$ ,  $\text{std. error}=2.65$ ). The Chi-square test showed that the ratio of

males/females was different across the groups ( $F(2)=7.67, p=0.022$ ) with a greater proportion of females in the chronic LBP group. The ratio of participants scanned on the two scanners was not significantly different across groups ( $F(2)=5.40, p=0.067$ ) with more participants scanned on the Allegra scanner in all 3 groups (healthy 84.6%, subacute 60.8%, and chronic 66.2%). Therefore, throughout this study we included age, sex, and scanner as covariates in our analyses.

Demographic and clinical data are presented in Table 1. There was no statistical difference between both LBP groups in any of the outcome measures except for pain duration and disability scores. Participants in the chronic LBP group had experienced pain longer than the subacute LBP group ( $t(86)=-5.63, p<0.001$ ) and showed greater levels of disability than subacute LBP group ( $t(87)=-2.47, p=0.016$ ).

### Normalized Whole-Brain Volumes

There was no overall difference in normalized whole-brain volume between groups after controlling for age, sex, and scanner ( $F(2,124)=1.63, p=0.20, \eta^2=0.03$ ). Figure 1 presents the mean and standard deviation of the normalized whole-brain volumes for each group. Additionally we determined the effect size using G-Power software(54, 55). Through calculating the means and standard deviations of the normalized whole-brain volumes for each of our groups we detected an effect size of 0.07, which is considered a small effect size. The sample size required to detect such small effect size (0.07) at a power of 80% would require 1717 participants.

### Voxel-Based Analysis (whole-brain and ROI)

Following corrections for multiple comparisons (family-wise error corrected  $p<0.05$ ), we found no differences between any inter-group comparisons on the whole-brain level. All comparisons tested both contrasts of each set (for example, subacute>healthy and healthy>subacute). However, to verify whether previously reported trends were also observed in this large sample, we repeated the comparisons using uncorrected  $p<0.001$  and a threshold of 100 contiguous voxels. At this less stringent threshold we observed evidence of volume differences in regions of middle frontal gyrus, superior frontal gyrus, parahippocampal gyrus, and cerebellum (see Supplementary Table 1), presenting findings similar to previous studies.

The ROI analysis of the cortical affective mask indicated that the chronic LBP group have less GM volume in 2 voxels ( $6.75 \text{ mm}^3$ ) within the middle frontal gyrus (MNI-coordinates:  $-34/51/15$ ) compared to healthy controls (corrected  $p<0.05$ ; Figure 2). No other ROI comparisons showed any differences in GM volume.

### Correlation Analysis

The clinical outcome measures were not correlated with the normalized whole-brain volumes in either subacute or chronic LBP groups after controlling for age, sex, and scanner (all  $r<0.18$  Table 2).

## Discussion

Our results are consistent with previous reports that found no difference in whole-brain volumes in chronic LBP(37, 38, 41, 42), and suggest that chronic LBP is not associated with robust differences in brain structure and volume. Consistent with this theoretical argument, we also found no difference in brain volume in participants in the earlier (subacute) stages of the disease. Additionally, when examining sensory and affective pain-related ROIs we found evidence of lower middle frontal gyral (cortical affective mask) volume in 2 voxels in participants with chronic LBP compared to healthy controls. These results suggest that any structural brain differences associated with persistent LBP must be subtle and would require a large sample size (about 1700 subjects) to detect. This finding is consistent with Dolman et al. who reported needing 1616 participants(38).

We did not find any correlation between clinical measures and normalized whole-brain volume. Although the broader pain literature generally suggests a correlation between clinical outcome measures and brain volume(31, 56, 57), studies specifically examining LBP reported no correlations between such outcomes and brain volume even in the presence of brain volume differences(36, 40). Such findings question the clinical relevance of the differences in brain volume reported in previous studies.

Several considerations can explain our findings of no difference in brain volume. We employed rigorous methods to avoid type 1 errors to correct for multiple comparisons as recommended by the creators of VBM(44). Previous studies either did not correct for multiple comparisons(37, 40, 41) or used a different analysis method (such as permutation testing(35)). Another difference is related to the methodology and subject recruitment. We used two-sample *t*-tests, unlike some of the methodology used by other researchers.

The study by Dolman et al. concluded that controlling for the main covariates (such as age and pain levels) could reduce - or even potentially eliminate - the previously reported findings of differences in brain volume(38). It is well known that aging is associated with decreases in brain volume(58). This loss is not homogeneously distributed across the brain, with some regions demonstrating more decline in GM volume with aging than others, including pain regions(59). This might explain our failure to detect volume differences after controlling for age effects. Our finding of decrease in GM volume in 2 voxels in the middle frontal gyrus of chronic LBP group represents an average of <0.001% annual loss, which is clinically nonsignificant, as 0.05% annual GM loss is associated with normal aging. Finally, our cohort represents subjects with minimum to no fear of movement and depression. Subjects with greater fear avoidance behavior, depression, or disability may experience brain volume loss.

Several theoretical models have been proposed as mechanisms for brain volume changes in chronic LBP, however these models account for both theoretical decreases and increases in brain volume, making interpretation of brain volumes from MR images difficult. Increased levels of glutamate have been reported in chronic pain conditions(60–64). Prolonged exposure to high levels of glutamate is neurotoxic, and this neurotoxicity could result in loss of neurons via neurodegeneration or neuronal apoptosis(65). Conversely, some have argued

that increased glutamate might lead to tissue scarring and therefore increasing cortical thickness(38). In addition to neurochemical hypotheses, some researchers credit volumetric differences to changes in lifestyle, since chronic pain leads to decreased mobility and activity(66). Exercise has been shown to assist in increasing brain volume(67, 68), suggesting that less mobility might be related to decreased brain volume. More research is needed to confirm or refute these theories.

Although we used a large sample size and stringent data analysis methods available, we acknowledge some limitations. First, there was a significant difference in age between groups. This was anticipated since our LBP groups are defined by duration of their pain, and hence we expected the chronic group to have older participants than those in the subacute group. Second, there was a significant difference in sex proportion within our sample. This was also anticipated since chronic pain is more prevalent in females(69). Finally, although we collected data on two scanners, all acquisition parameters were identical. Since we are comparing calculated volumes that are based on careful scanner calibrations completed during routine quality assurance procedures, this is unlikely to contribute to false findings. Nonetheless, we added each of these factors as covariates in our analyses. Finally, we had no clinical data on our healthy controls (such as depression or disability scores).

Our results suggest that brain volume is not severely affected by LBP, with other factors (such as age) having a larger impact on brain volume. Nonetheless, the brain cyto-architecture might be affected by pain. Such differences require other methods of detection such as spectroscopy or fMRI (17, 19, 20, 70–72) (18, 73)) to detect changes in brain neurochemistry and function in people with chronic LBP.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The manuscript submitted does not contain information about medical device(s)/drug(s).

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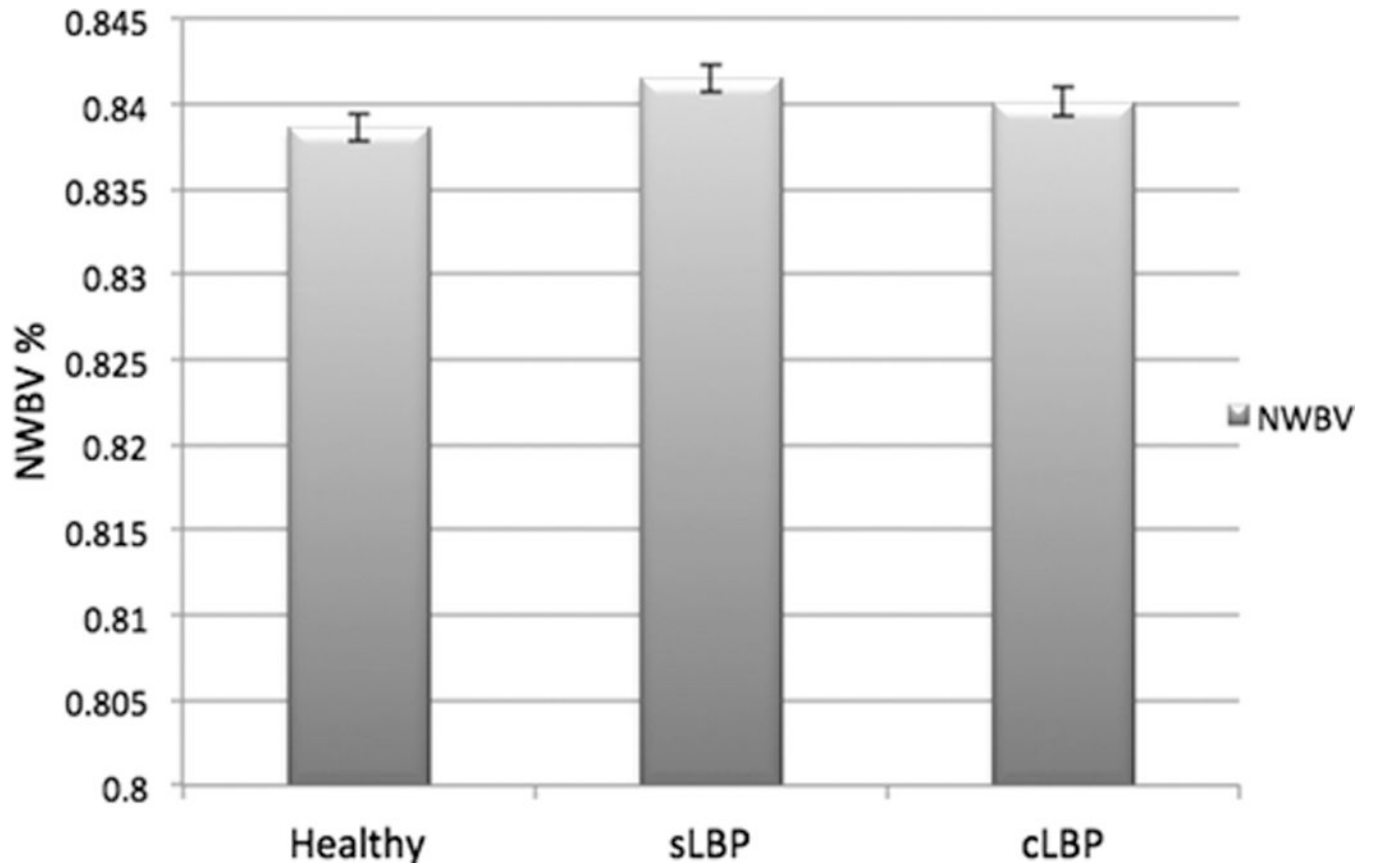
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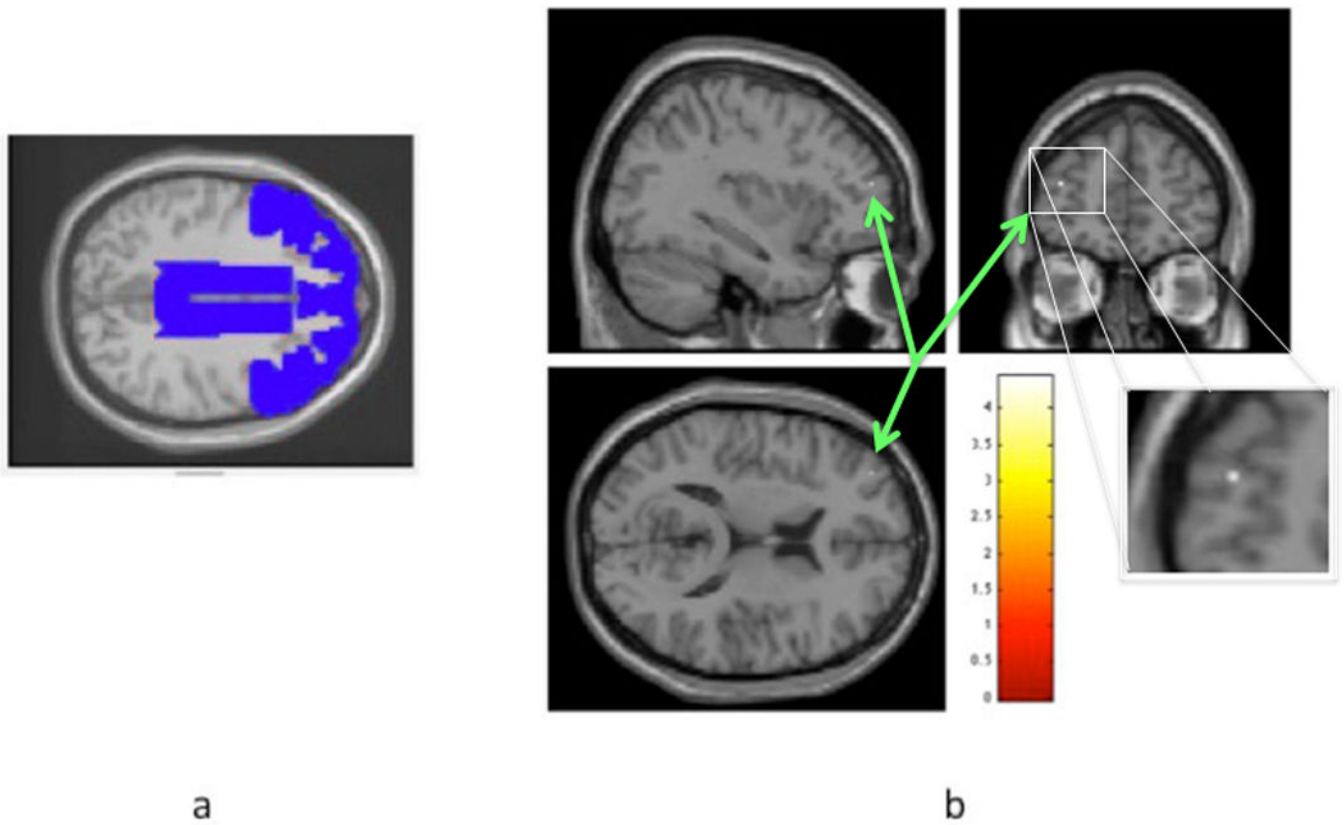
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**Figure 1. normalized whole-brain volumes for each group**  
HC: Healthy controls, sLBP: subacute low back pain group, cLBP: chronic low back pain group, NWBV: normalized whole-brain volume



**Figure 2. Cortical affective mask and regions of gray matter volume loss within that mask in chronic LBP participants**  
 a represents cortical affective mask with cingulate, orbitofrontal, and medial prefrontal cortices in blue drawing; Fig 2b is a statistical parametric map representing scale of t-scores for the contrast healthy >cLBP; arrows indicate voxels with less gray matter volume in the cLBP group compared to healthy controls;  $p_{corrected} < 0.05$

**Table 1**

Demographic and clinical outcome measures:

Characteristic	sLBP	cLBP	HC	Statistic	p
Sex (Female/Male) <sup>‡</sup>	13/10	48/20	17/22	$\chi^2=7.67$	0.022*
Age <sup>‡</sup>	36±11	45±12	40±16	$F=3.99$	0.021*
Pain Duration <sup>§</sup>	3.16±2.17	98.58±81.18	-	$t=-5.63$	<0.001***
Pain Intensity <sup>§</sup>	4.18±2.19	4.28±1.89	-	$t=-0.21$	0.834
FABQ-w <sup>§</sup>	13.63±13.28	12.55±12.01	-	$t=0.36$	0.723
FABQ-p <sup>§</sup>	11.77±6.22	13.81±5.08	-	$t=-1.54$	0.127
ODI <sup>§</sup>	19±14.97%	29.88±18.79%	-	$t=-2.47$	0.016*
BDI <sup>§</sup>	8.45±7.88	10.36±9.91	-	$t=-0.82$	0.414

Age is measured in years, pain duration is measured in months, pain intensity is measured using a 0–10 pain scale, FABQ-w: Fear-avoidance belief questionnaire – work component, FABQ-p: Fear-avoidance belief questionnaire – physical component, ODI: Oswestry disability index, BDI: Beck depression inventory.

<sup>‡</sup> Chi-square

<sup>‡</sup> One-way ANOVA

<sup>§</sup> Independent 2-sample t-test

**Table 2**

Correlation of clinical outcome measures and normalized whole-brain volume:

Characteristic	Statistic	NWBV	<i>p</i>
Pain Duration	Partial correlation	0.179	0.109
Pain Intensity	Partial correlation	0.098	0.382
FABQ-w	Partial correlation	0.068	0.546
FABQ-p	Partial correlation	0.167	0.136
ODI	Partial correlation	0.091	0.418
BDI	Partial correlation	-0.059	0.600

FABQ-w: Fear-avoidance belief questionnaire – work component, FABQ-p: Fear-avoidance belief questionnaire – physical component, ODI: Oswestery disability index, BDI: Beck depression inventory, NWBV: normalized whole-bran volume.

All correlations are partial correlations after controlling for age, sex, and scanner. The number of participants is 84 for all the outcome measures including participants from both the subacute and chronic LBP groups.