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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 determinewhether 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 (23subacuteand 68chronic 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 wasobserved 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 inwhole-brain volume. Regionally, we detected less gray matter volume in 2 voxels in the middle frontal gyrusin 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 thatlow back pain does not affect brain volume.

Keywords: low back pain, chronic, subacute, neuroimaging, voxel-based morphometry, volumetric measurements, brain, structure.

Level of Evidence: 5

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 ofspine images and clinicalsymptoms(12, 13) makesproper diagnosis and understandingofLBP difficult.Regardless of its underlying cause, “pain”as a nociceptive experience is processedin certain regionsin the brain(14, 15). Brain imaging methods can be used to determine the relationship between pain and brain function and structure.

Pain is subjectiveand idiosyncratic. In general,the painexperience incorporatestwo 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.

Smallerbrain volumeshavebeen reported in such neurodegenerative diseases as multiple sclerosis(21-23), Alzheimer’s disease(24-26),and schizophrenia(27-29),andalso in chronic pain conditions like fibromyalgia(30-32), complex regional-pain syndrome(33, 34), and chronic LBP(35, 36).To date,only a fewstructural brain imaging studiesin people with chronic LBP(35-42) have been completed. Findings from these studies were inconsistent, with some reporting smallervolumes in participants with chronic LBP compared to healthy controls, and others reporting no differencesin brain volume. Importantly,the sample sizes in these studies were modest, and many that reported significance differences in brain volumedid 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 differencesin 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 wouldhavesmallerwhole-brain volumes as compared to subacute and healthy controls, andparticipants with subacute LBP would have smaller whole-brain volumes compared to healthy controls.Secondly,we hypothesized that we wouldfindsmallerbrain volumeswithin sensory and affective pain processingregions 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 participantswere: 1) male/female between 21 and 70 years, 2) having pain for less than 6 months (subacute group) and more than 6 moths (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 (includinghead 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 participantsprovided 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=256x256;208 slices; voxels=1.0 mm x 1 mm x 0.97 mm; TE=3.05 ms; and TR=2300 mson 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 (Welcome 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 intogray 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 ofpain-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 movementwasmeasured by the Fear Avoidance Belief Questionnaire (FABQ), which quantifiesthe 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 22.0software (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 aunivariate one-way ANOVA test using SPSSfor 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 eachclinical outcome measure in the subacute and chronic LBP groups separatelyusing SPSSsoftware, while controlling for age, sex, and scanner in each test.

Results:

The ANOVA test revealed a significant age difference between the groups ($F(2,127)=3.99$, $p=0.021$, $\eta^2=0.06$), withthe chronic groupbeingsignificantly older than the subacute group ($p=0.025$,$M_{difference}$=*-8.39, std. error=3.18*)and no difference between the healthy and subacute ($p=0.527$, $M_{difference}$*=3.74, std. error=3.46)* or healthy and chronic groups ($p=0.189$, $M_{difference}$*=-4.64, std. error=2.65*).The Chi-square test showed thatthe ratio of males/females was different across the groups($\chi^2(2)=7.67$, $p=0.022$) 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 ($\chi^2(2)=5.40$, $p=0.067$) 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 painlonger than the subacute LBP group ($t(86)=-5.63$, $p<0.001$) and showed greater levels of disability thansubacute 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 volumesfor 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 observedevidence 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 ofthe cortical affective mask indicated that the chronic LBP group have less GM volume in 2 voxels (6.75 mm^3) within the middle frontal gyrus (MNI-coordinates: -34/51/15) compared tohealthy controls (corrected $p<0.05$; Figure 2). Noother ROI comparisons showed any differences in GM volume.

- Correlation Analysis:

The clinical outcome measures were not correlated with the normalized whole-brain volumesin either subacute or chronic LBP groupsafter 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 isnot 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 differencesassociated with persistent LBPmust 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 measuresand brain volume(31, 56, 57),studies specifically examining LBP reported no correlations betweensuch outcomes and brain volume even in the presence ofbrain volume differences(36, 40).Such findings question the clinical relevance of the differences in brain volume reported inprevious 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 permutationtesting(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 brainvolume(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.

Severaltheoretical modelshave 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 paincondtions(60-64).Prolonged exposure to high levels of glutamate is neurotoxic, and this neurotoxicity could result in loss of neurons via neurodegeneration orneuronal 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 thesetheories.

Although we used alarge 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 withinour sample. This was also anticipated since chronic pain is more prevalent in females(69).Finally, although we collected data on twoscanners, 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 othermethods 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.

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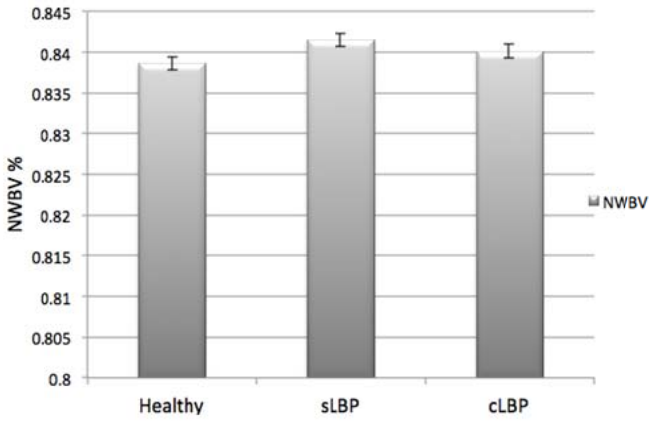
Figure Legends:

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 1: normalized whole-brain volumes for each group:

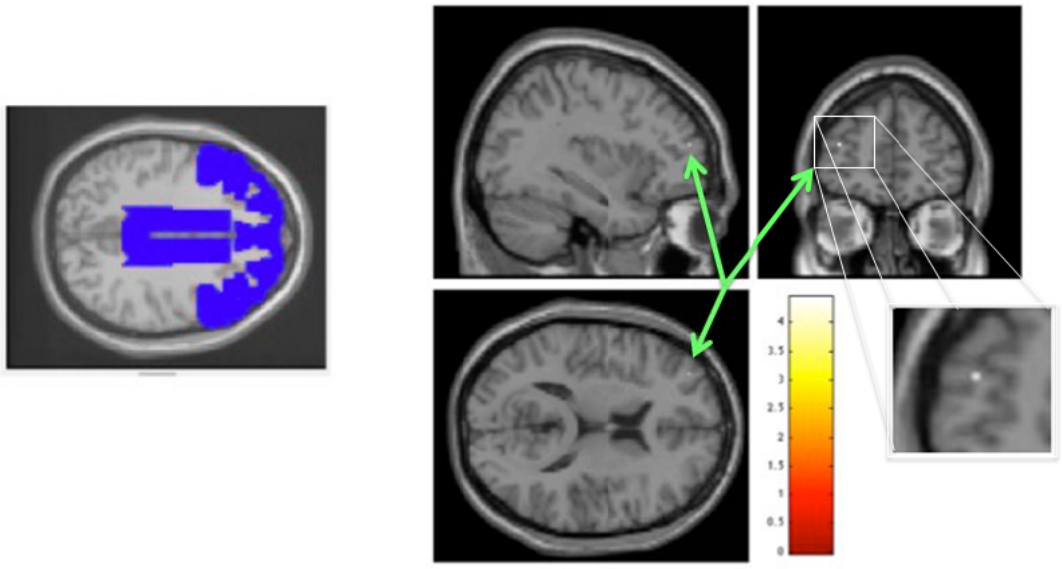


NWBV: normalized whole-brain volume, sLBP: subacute low back pain, cLBP: chronic low back pain. Error bars represent standard deviation.

Figure 2: Cortical affective mask and regions of gray matter volume loss within that mask in chronic LBP participants

Fig 2a 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; $p_{corrected} < 0.05$

Figure 2: Cortical affective mask and regions of gray matter volume loss within the mask in chronic LBP participants



2a 2b

Fig 2a 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; $p_{corrected} < 0.05$

Tables:

Table 1: Demographic and clinical outcome measures:

Characteristic	sLBP	cLBP	HC	Statistic	*p*
Sex (Female/Male)†	13/10	48/20	17/22	χ^2=7.67	0.022*
Age ‡	36±11	45±12	40±16	*F*=3.99	0.021*
Pain Duration §	3.16±2.17	98.58±81.18	-	*t=-5.63*	<0.001**
Pain Intensity §	4.18±2.19	4.28±1.89	-	*t=-0.21*	0.834
FABQ-w §	13.63±13.28	12.55±12.01	-	*t=0.36*	0.723
FABQ-p §	11.77±6.22	13.81±5.08	-	*t=-1.54*	0.127
ODI §	19±14.97%	29.88±18.79%	-	*t=-2.47*	0.016*
BDI §	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: Oswestery disability index, BDI: Beck depression inventory.

†Chi-square

‡One-way ANOVA

§ Independent 2-sample *t*-test

Table 2: Correlation of clinical outcome measures and normalized whole-brain volume:

Characteristic	**Statistic**	**NWBV**	***p***
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.

Table 1: non-significant trends ($p_{uncorrected}$< 0.001, 100 voxels)showing overall gray matter volume differences:

Contrast	Location	Size
Healthy>cLBP	Middle frontal gyrus	603
	Precuneus	352
	Fusiform	264
	Middle temporal gyrus	234
	Parahippocampalgyrus	208
	Postcentralgyrus	205
	Superior frontal gyrus	196
	Medial frontal gyrus	181
	Cerebellum	123
	Parahippocampalgyrus	122
	Lingual gyrus	101
	Superior frontal gyrus	100
cLBP>Healthy	Cerebellum	342
	Cerebellum	195
Healthy>sLBP	Middle temporal gyrus	1506
	Cingulate gyrus	530
	Inferior frontal gyrus	351
	Occipito-temporal gyrus	266
	Caudate	241
	Superior frontal gyrus	224
	Inferior frontal gyrus	182
	Precuneus	122
	Middle frontal gyrus	119

	Parahippocampalgyrus	110
	Middle temporal gyrus	106
sLBP>Healthy	*No differences*	-
sLBP>cLBP	Pons	123
cLBP>sLBP	Cingulate gyrus	123

cLBP: chronic LBP, sLBP: subacute low back pain. Size is in voxels. All the contrasts indicate more gray matter in the first group as compared to the second group.