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Functional brain mapping in patients with chronic back pain shows age-related differences

Timothy M. Baran[a,b], Feng V. Lin[c,d], Paul Geha[e,f,g,*]

Abstract

Low back pain is the most common pain condition and cause for disability in older adults. Older adults suffering from low back pain are more disabled than their healthy peers, are more predisposed to frailty, and tend to be undertreated. The cause of increased prevalence and severity of this chronic pain condition in older adults is unknown. Here, we draw on accumulating data demonstrating a critical role for brain limbic and sensory circuitries in the emergence and experience of chronic low back pain (CLBP) and the availability of resting-state brain activity data collected at different sites to study how brain activity patterns predictive of CLBP differ between age groups. We apply a data-driven multivariate searchlight analysis to amplitude of low-frequency fluctuation brain maps to classify patients with CLBP with >70% accuracy. We observe that the brain activity pattern including the paracingulate gyrus, insula/secondary somatosensory area, inferior frontal, temporal, and fusiform gyrus predicted CLBP. When separated by age groups, brain patterns predictive of older patients with CLBP showed extensive involvement of limbic brain areas including the ventromedial prefrontal cortex, the nucleus accumbens, and hippocampus, whereas only anterior insula paracingulate and fusiform gyrus predicted CLBP in the younger patients. In addition, we validated the relationships between back pain intensity ratings and CLBP brain activity patterns in an independent data set not included in our initial patterns' identification. Our results are the first to directly address how aging affects the neural signature of CLBP and point to an increased role of limbic brain areas in older patients with CLBP.

Keywords: Chronic low back pain, Aging, fMRI, Multivariate searchlight

1. Introduction

The prevalence of chronic pain increases with aging.[34,45,65] Studies have suggested that the prevalence of musculoskeletal pain in older adults is more than 60%,[34] with 36% to 70% of them suffering from low back pain (LBP).[31,78] Low back pain in older adults is associated with significantly increased disability,[21,25,42,81] LBP severity,[87] and psychological distress.[9,18,79] The mechanism of increased prevalence and severity of LBP in the older population is unknown, with the majority having no definite pathology.[58,101] While radiologic signs of spine degeneration increase with age, they are unlikely to explain the pain source because they are also present to a large extent in asymptomatic older adults.[15,101]

Low back pain is associated with significant neuroadaptation in somatosensory, limbic, and frontal brain areas.[2,4–7,35,39,50,57,63,82,83,91,104,106] Specifically, patients with chronic LBP (CLBP) exhibit compromised structure of primary somatosensory cortex,[35,50] dorsolateral prefrontal cortex,[2,83] and major limbic areas such as the nucleus accumbens (NAc),[8,59] amygdala,[63] and hippocampus[70] and altered functional connectivity between, and activity in, NAc[7,8,59] and medial prefrontal cortex.[5–7,43,91,106] Independently, normal aging is associated with "neural dedifferentiation" accompanied by structural and functional decline in sensory, limbic, and frontal circuitries.[11,13,29,71,80,89] Elderly patients with CLBP may therefore have increased vulnerability to severe disabling pain whereby afferent nociceptive input to brain circuits already compromised by aging leads to more severe experience of pain and disability.

Despite evidence for neuroadaptation in chronic pain conditions,[19,64] few functional magnetic resonance imaging (fMRI) studies have directly addressed how aging and chronic pain interact in the brain. Meanwhile, anatomical studies showing decreased gray matter thickness or density[2,38,53,83] have been interpreted as accelerated aging; however, 2 recent studies directly tested this hypothesis in community-dwelling older adults with conflicting results.[28,86]

Here, we study how resting activity patterns predictive of CLBP differ between age groups. We apply multivariate searchlight analysis, used broadly in fMRI,[32] to the amplitude of low-frequency fluctuation (ALFF) values derived from the resting-

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[a] *Department of Imaging Sciences, University of Rochester, Rochester, NY, United States,* [b] *Department of Biomedical Engineering, University of Rochester, Rochester, NY, United States,* [c] *Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, United States,* [e] *Department of Neuroscience, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States,* [f] *Department of Neurology, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States,* [d] *Department of Brain and Cognitive Sciences, University of Rochester, Rochester, NY, United States,* [g] *Department of Psychiatry, School of Medicine and Dentistry, University of Rochester, Rochester, NY, United States*

**Corresponding author. Address: Department of Psychiatry, School of Medicine and Dentistry, University of Rochester, 430 Elmwood Ave, Rochester, NY 14620. fax: (585)276-2094. Tel.: (585)-275-8675. E-mail address: paul_geha@urmc.rochester.edu (P. Geha).*

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state activity. Amplitude of low-frequency fluctuation describes the amplitude of oscillations of resting brain activity at different frequency bands.[16,102] This allows for differentiation of the frequency-specific changes identified for multiple neurological disorders.[41,56,103] Calculation of voxel-wise ALFF allows the application of multivariate pattern analysis, specifically searchlight analysis, which reveals whole-brain patterns of activation that would not be apparent using mass-univariate approaches.[32] Unlike other techniques, the searchlight method is applied at each location for a local neighborhood, which reveals voxel combinations that can discriminate between groups of individuals.[93] This avoids the utilization of a priori regions of interest. However, searchlight analysis is vulnerable to distortion by rare, highly informative voxels and may obscure broader, more weakly informative groups of voxels.[32] Accuracy is also dependent on the veracity of image registration between subjects. Here, we use a data-driven approach and pool resting-state brain activity data sets of patients with CLBP collected at different sites to identify patterns predictive of CLBP in 2 different age groups.

2. Materials and methods

2.1. Data sources and participants

Data used in the preparation of this work were acquired from 2 sources: (1) the OpenPain project (https://www.openpain.org) and (2) data previously collected by the authors, referred to here as the New Haven data set, which is also now available on OpenPain. The OpenPain Project (Principal Investigator: A. Vania Apkarian, Ph.D., at Northwestern University) is supported by the National Institute of Neurological Disorders and Stroke and National Institute of Drug Abuse. To be included in this study, data met the following requirements: (1) resting-state fMRI (rsfMRI) data available at baseline with repetition times (TR) less than or equal to 2.5 seconds, in-plane resolution of 3.5 mm or better, and slice thickness of 4 mm or better; (2) T1-weighted structural MRI data available at baseline with 1-mm isotropic voxels; (3) healthy controls (HCs) and CLBP subjects included; and (4) subjects available older than 55 years of age and younger than 45 years of age. Based on these criteria, the Chicago[4,61](CLBP_resting) and Cambridge-Osaka (BrainNetworkChange_Mano)[60] OPP data sets were useable, as well as the New Haven data set.[59] Data within the Cambridge-Osaka data set were collected at 2 sites with varying rsfMRI protocols, so these data were analyzed independently. Patients with chronic low back pain were recruited into the 3 studies if they had low back pain for at least 6 months and no other chronic pain, neurologic, or psychiatric conditions. While the Chicago and New Haven studies set a minimum pain report of 40/100 and 30/100, respectively, defined back pain according to the International Association for the Study of Pain criteria,[72] and excluded patients with more than moderate depression defined as a score $>$ 19 on the Beck Depression Index, the Cambridge study did not impose these additional criteria. Differences in demographics, Beck Depression Index, pain intensity, and pain duration are reported in **Table 1** and plotted in **Figure 1**. Pain intensity was rated using a Visual Analog Scale (VAS) at the time of the rsfMRI scan. It should be noted that the Cambridge data include subjects labeled as healthy controls, but with reported values for pain intensity or duration. These subjects were excluded from the analyses described below.

As can be seen in **Table 1** and **Figure 1**, the Chicago data set had significantly greater pain intensity and duration than the other data sets. We therefore selected this data set for training of the classifiers described below, whereas the other data sets were used for external validation of the training results. Throughout, "training data" are used to refer to the Chicago data set, which was additionally used for the internal validation described in section 2.6. The other data sets collectively (Cambridge-Osaka and New Haven) are referred to as "test data" and were used to perform the external validation described in section 2.7. All subjects studied by our group in New Haven gave written informed consent to participate in the study, which was approved by the Yale University Institutional Review Board. Brain images obtained from OpenPain.org was deidentified data used according to the repository use license.

2.2. Data acquisition and preprocessing

As described above, all data sets were required to include T1-weighted and rsfMRI sequences to be included in this study. All T1-weighted images had 1-mm isotropic resolution. For rsfMRI, imaging parameters varied across data set and are summarized in **Table 2**. For each individual, the first 10 volumes of the rsfMRI data were removed to avoid errors related to scanner equilibrium and participant adaptation. The remaining volumes were then corrected for slice timing and head motion. Images were resampled at $3 \times 3 \times 3$ mm^3 resolution, registered to the corresponding T1-weighted images, normalized to Montreal Neurological Institute standard space, and smoothed spatially with a 4-mm FWHM Gaussian kernel. Linear detrending was then performed. All preprocessing was performed in MATLAB (MATLAB 2017a, MathWorks, Natick, MA) using the Data Processing Assistant for Resting-State fMRI toolbox.[23]

2.3. Amplitude of low-frequency fluctuation calculation

After preprocessing, Data Processing Assistant for Resting-State fMRI was used to calculate the ALFF at each voxel. This was performed by first converting each rsfMRI time series to the frequency domain using a fast Fourier transform. Amplitude of low-frequency fluctuation at each voxel was calculated as the average square root of the power spectrum over the 0.01 to 0.08 Hz frequency band. This is referred to as "ALFF (full)" throughout. We additionally calculated ALFF for the slow-4 (0.027-0.073 Hz) and slow-5 (0.01-0.027 Hz) frequency bands. These are referred to as "ALFF (slow-4)" and "ALFF (slow-5)," respectively. Our primary endpoint was ALFF over the entire 0.01 to 0.08 Hz frequency band, whereas slow-4 and slow-5 were areas of secondary analysis.

2.4. Searchlight analysis

We applied searchlight analysis to whole-brain ALFF data from the Chicago data set ($n = 68$) to identify voxels that discriminate between CLBP and HC subjects. Searchlight analysis is a multivariate pattern analysis method that performs multivariate analysis at each location in the brain for a local neighborhood of voxels, as opposed to investigating specific regions of interest or performing whole-brain mass-univariate analysis.[52] Rather than displaying results for individual voxels or brain regions, searchlight analysis reveals combinations of voxels that can discriminate between groups of individuals.[93] While searchlights are compared locally, this process results in a whole-brain map of classification accuracy that can then be used to interpret group differences in brain activation.[32]

We used a searchlight width of 3 voxels ($3 \times 3 \times 3$), which resulted in a searchlight neighborhood of 27 ALFF values for each voxel. These voxels were collapsed into a 27-dimensional

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Table 1

Subject demographics, separated by the study group and source data set.

	Group	Chicago (HC, n=34; CLBP, n=34)	Cambridge-1 (HC, n=35; CLBP, n=24)	Cambridge-2 (HC, n=11; CLBP, n=17)	New Haven (HC, n=26; CLBP, n=26)	*P* (by study)
Age (y)	HC	49.3 ± 9.13	37.9 ± 12.8	45.3 ± 14.2	30.1 ± 8.43	$<10^{-4}$
	CLBP	49.2 ± 8.6	46.2 ± 11.3	44 ± 11.4	30.5 ± 11.8	$<10^{-4}$
P Value (by group)		0.97	0.012	0.80	0.87	
Sex (% male)	HC	55.9%	62.9%	45.5%	53.80%	0.75
	CLBP	55.9%	50.0%	29.40%	42.30%	0.32
P Value (by group)		> 0.99	0.43	0.44	0.58	
BDI	HC	1.53 ± 2.63	4.85 ± 3.36	3.36 ± 5.35	2.27 ± 3.29	$<10^{-4}$
	CLBP	6.26 ± 5.81	15.2 ± 10.5	15.9 ± 11.5	6.6 ± 6.22	$<10^{-4}$
P Value (by group)		$<10^{-4}$	$<10^{-4}$	$<10^{-3}$	0.003	
Pain intensity (VAS)	HC	0	0	0	0	>0.99
	CLBP	6.66 ± 1.7	2.62 ± 2.44	4.82 ± 2.81	4.62 ± 1.9	$<10^{-4}$
P Value (by group)		$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	
Pain duration (y)	HC	0	0	0	0	>0.99
	CLBP	15.7 ± 11.3	12.2 ± 9.09	10.4 ±7.49	5.38 ± 4.73	$<10^{-3}$
P Value (by group)		$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	

Values are mean±standard deviation for continuous variables and percentage male for sex. *P* values comparing studies are results of ordinary one-way ANOVA for continuous variables and chi-square test for sex. *P* values comparing groups within a particular study are results of unpaired t tests for continuous variables and Fisher exact test for sex.
ANOVA, analysis of variance; BDI, Beck Depression Index; CLBP, chronic low back pain; HC, healthy control.

vector for each subject, yielding a 68 × 27 matrix of values for each voxel location. At each searchlight location, we then used a Gaussian Naïve Bayes classifier[69] with a leave-one-out cross-validation approach[77] to determine classification accuracy. This was repeated across the whole brain to generate a map of classification accuracy, referred to here as the searchlight map.

To determine statistical significance for each voxel, we used permutation tests.[73] We first randomly permutated subjects' group labels and repeated the above searchlight analysis. This was repeated 5000 times, which resulted in a distribution of permutation accuracy for each voxel. Based on knowledge of the true group labels, we then counted the number of permutations for which the accuracy of the classifier was greater for the permutated labels than the true labels. *P* values were then calculated as $\frac{n_{\text{permutations with accuracy} > \text{true labels}}}{n_{permtations}}$. The resulting *P* values were then corrected for the false discovery rate (FDR) using the method of Storey.[88] This process first applied the entire training data set to obtain an overall searchlight map for each frequency band (full, slow-4, and slow-5). Searchlight analysis was then performed separately for subjects who were younger than 45 years of age ("younger group"; n = 16) and those who were older than 55 years of age ("older group"; n = 17). This was performed to examine age-related differences in the relationship between ALFF and chronic back pain. The lower age threshold was derived from other early onset back pain studies.[95] The upper age threshold was chosen to provide a distinct older group, while capturing an adequate number of subjects for analysis.

2.5. Brain map identification

The searchlight analysis described above resulted in a whole-brain map of classification accuracy and FDR-corrected *P*-value for each brain voxel. To translate these results to a useful classifier, we further applied thresholds on accuracy, *P*-value, and voxel cluster size. All voxels were required to have an FDR-corrected *P* values < 0.05, and only clusters containing at least 20 voxels were included. We explored accuracy thresholds ranging from 65% to 80%, based on prior experience.[100] After applying these constraints, a final CLBP brain map was identified. As with the searchlight analysis, this was performed for the whole training data set and for the younger and older groups separately, across each frequency band (full, slow-4, and slow-5).

2.6. Internal validation

The goals of internal validation were to examine the classification accuracy of CLBP vs HC and the relationship between pain intensity and ALFF values within the predictive CLBP brain maps, using the Chicago data set which the searchlight maps were derived from. This was performed in 2 ways: 1) classifying CLBP vs HC using all voxels in the CLBP map and 2) correlating pain intensity with mean ALFF across the voxels in the predictive CLBP map. All analyses were performed for the whole training data sets (n = 68) and for the younger (n = 16) and older (n = 17) groups separately, across each frequency band (full interval, slow-4, and slow-5). To determine classification accuracy, we again used a Gaussian Naïve Bayes classifier with leave-one-out cross-validation. All ALFF values within the CLBP map were used as predictors, with CLBP vs HC as the outcome. Permutation tests were used as described above to determine statistical significance. For the approach using mean ALFF across all voxels in the CLBP map, we used partial correlation to examine the relationship between mean ALFF and pain intensity. In this case, mean ALFF was the predictor, VAS pain intensity was the outcome, and age and pain duration were covariates. Pearson partial correlation coefficients were calculated for each brain map and frequency band. Although both the New Haven[59] and Chicago[4] studies collected VAS ratings within the hour before scanning as a report of how much pain was the patient experiencing at that point, the time of the low back pain rating was not provided for the Cambridge data.[60]

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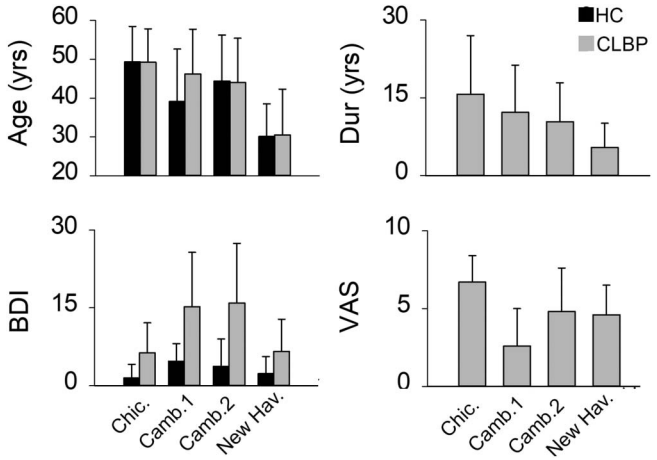

Figure 1. Age, pain duration, depression, and pain scores for each of the analyzed data sets (Chic: Chicago, Camb. 1: Cambridge-Osaka Site 1, Camb. 2: Cambridge-Osaka site 2, New Hav: New Haven). The Chicago data set was used to train the searchlight map and perform internal validation. The other data sets were used for external validation.

2.7. External validation

The goal of external validation was to examine prediction of pain intensity based on ALFF values in the identified CLBP brain maps for data sets that were not used in the identification of these brain maps (Cambridge-Osaka and New Haven). Here, we again performed linear regression, with the mean ALFF within the brain map as the predictor, pain intensity on the VAS as the outcome, and age and pain duration as covariates. Regression analysis was performed for the Cambridge-Osaka (S1: n = 59, S2: n = 28) and New Haven (n = 52) data sets independently, as well as for these data sets combined (n = 139). These external data sets were significantly younger than the Chicago data set used for training, so younger vs older subjects were not analyzed separately for external validation.

2.8. Statistical analysis

Values are reported throughout as mean ± SD. Differences in demographics and pain metrics were compared between data sets using ordinary one-way analysis of variance. The Tukey test was used to perform pairwise comparison. Healthy control and CLBP groups were compared within each study using unpaired t tests. Specific details on statistical analysis for each component of the study are described in the above subsections. All statistical analysis was performed in MATLAB and SPSS (IBM Corporation, Armonk, NY).

3. Results

3.1. Selection of accuracy threshold

Searchlight maps generated from the training data set consisted of a voxel-wise map of accuracy in discriminating HC vs CLBP subjects. To translate these accuracy maps to a binary mask, a threshold for accuracy needed to be established. To do this, we varied the accuracy threshold from 65% to 80% and looked at the number of voxels that surpassed the chosen threshold, while also having an FDR-adjusted P value < 0.05 and a cluster size of $>$ 20. As shown in **Figure 2**, the number of significant voxels declined dramatically with increasing accuracy threshold. We selected a threshold of 70% accuracy, as higher accuracy thresholds resulted in an insufficient number of voxels for analysis (75% accuracy: 23 voxels and 80% accuracy: 0 voxels).

3.2. Predictive brain maps using the full frequency range

Chronic low back pain brain maps were generated by applying the 70% accuracy threshold described above, as well as the requirements for FDR-corrected $P < 0.05$ and cluster size >20. The full low-frequency band (0.01-0.08 Hz) results are shown for the whole training data set in **Figure 3A**. The predictive map derived from the complete data set includes the left frontal operculum or orbitofrontal or insular cortex, the paracingulate or cingulate and supplementary motor area, the left posterior insula or secondary somatosensory area (SII) or opercular cortex, bilateral middle temporal gyri, and bilateral temporal occipital fusiform cortices. Predictive brain maps were additionally generated separately for subjects younger than 45 and older than 55 years of age. These are shown in **Figure 3B and 3C**. In the younger group, the most discriminative regions included the paracingulate and cingulate cortices, the right frontal operculum or orbitofrontal or insular cortex, and the right fusiform gyrus. In the older group, on the other hand, the predictive map was much more spatially extensive and included frontostriatal, limbic, and sensory brain areas. The map comprised the ventromedial prefrontal cortex (vmPFC), bilateral dorsal, and ventral striatum including the NAc, right inferior frontal gyrus, bilateral anterior insula, left dorsolateral prefrontal and somatosensory motor cortices, left frontal operculum or posterior insula or SII, posterior cingulate, precuneus, right superior parietal lobule, bilateral hippocampi, and midbrain.

3.3. Predictive brain maps using the slow-4 and slow-5 frequency bands

The same approach was repeated using the slow-4 (0.027-0.073 Hz) and slow-5 (0.01-0.027 Hz) frequency bands instead. Because these frequency bands were included in the full range shown above, many of the same regions were involved. For the slow-4 band, additional involved regions are shown in Supplementary Figure 1 (available at http://links.lww.com/PAIN/B533). Using the full training data set, areas discriminating between CLBP and HC subjects included the bilateral SII or insular cortex, bilateral middle temporal gyrus, the dorsal ACC, and bilateral lingual and fusiform and gyri (Supplementary Fig. 1A, available at http://links.lww.com/PAIN/B533). In the younger

Table 2

Resting-state functional magnetic resonance imaging parameters for each of the datasets included in the study.

	Chicago	Cambridge-1	Cambridge-2	New haven
TR (s)	2.5	2.5	2.0	1.0
In-plane resolution (mm)	3.4375 × 3.4375	3.3125 × 3.3125	3.0 × 3.0	2.0 × 2.0
Slice thickness (mm)	3.0	4.0	3.75	2.0
No. of volumes	255	224	285	360

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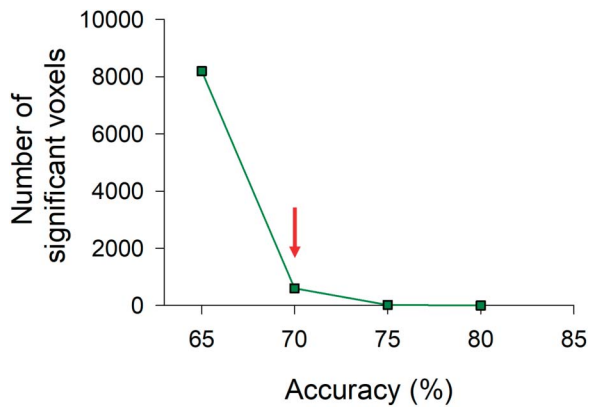

Figure 2. Number of voxels in the CLBP brain map for a range of accuracy thresholds. Voxels were required to surpass the desired accuracy threshold in discriminating HC vs CLBP, as well as have an FDR-corrected *P*-value < 0.05 for permutation tests and cluster size > 20 voxels. CLBP, chronic low back pain; HC, healthy control.

group, the right frontal pole, the supplementary motor area, the right anterior insula, right middle temporal gyrus, and cerebellum discriminated between patients and control (Supplementary Fig. 1B, available at http://links.lww.com/PAIN/B533). In the older group, the slow-4 band analysis showed extensive involvement of cortical and subcortical areas reminiscent of the results presented in **Figure 3**. Supplementary Figure 1C shows that vmPFC bilateral dorsal and ventral striatum, bilateral insula, left hippocampus, left somatosensory or motor cortices, bilateral lingual, and fusiform gyri discriminated between older patients and control. The slow-5 frequency band analysis showed additional involved regions presented in Supplementary Figure 2 (http://links.lww.com/PAIN/B533). In the full training data set, the discriminative regions included the left dorsal striatum (caudate), dorsal ACC, and bilateral SII or insula (Supplementary Fig. 2A, available at http://links.lww.com/PAIN/B533). For the younger group, the slow-5 frequency band analysis showed significant discrimination in the vmPFC, ACC, left anterior insula, and left fusiform gyrus (Supplementary Fig. 2B, available at http://links.lww.com/PAIN/B533). In the older group, activity in the midbrain, left striatum, left thalamus, left fusiform gyrus, right superior frontal, and supramarginal gyri discriminated between the groups (Supplementary Fig. 2C, available at http://links.lww.com/PAIN/B533).

3.4. Internal validation

All ALFF values within each CLBP brain map were first used to classify CLBP vs HC using a Gaussian Naïve Bayes classifier. Results are summarized in **Table 3** for all frequency bands. Amplitude of low-frequency fluctuation values were most predictive in the younger group, and least predictive in the older group, with the overall brain map showing intermediate accuracy. Prediction was comparable between frequency bands, with no clear trend between frequency and accuracy of prediction. The prediction of pain intensity using mean ALFF described in section 2.7 for external validation was also performed on the training data. These results are summarized in Supplementary Table 1 (available at http://links.lww.com/PAIN/B533) for all frequency bands, with mean ALFF being a significant predictor of pain intensity in all cases.

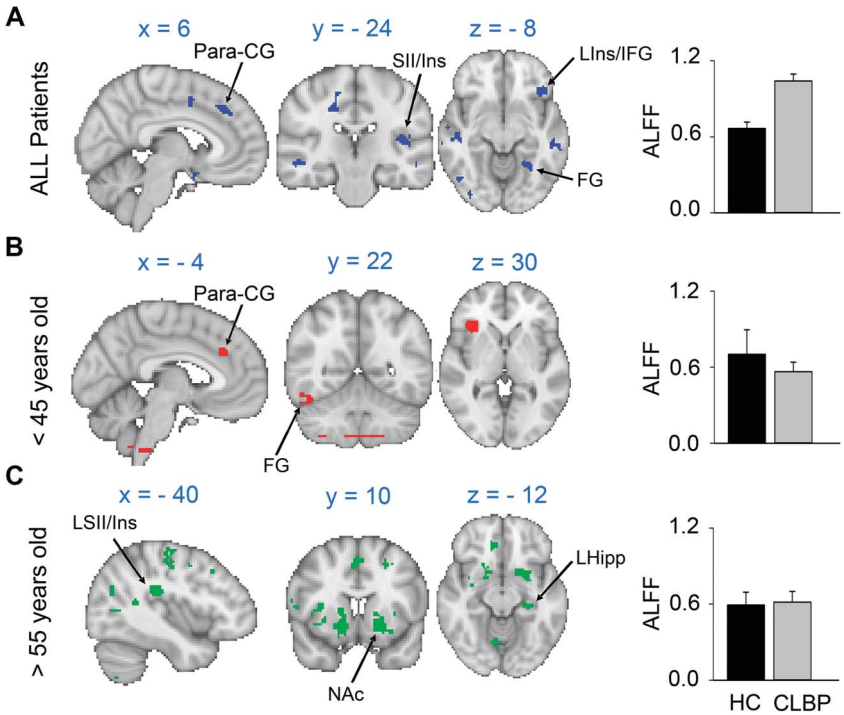

Figure 3. Brain maps predictive of CLBP resulting from searchlight analysis of the entire frequency range examined (0.01-0.08 Hz) for (A) the entire training data set (n = 68), (B) the younger group (age < 45 years, n = 16), and (C) the older group (age > 55, n = 17). Note that the sample in **A** included participants between the ages of 45 and 55 years. Histogram plots present average ± SEM of the ALFF values for each groups falling within the significant voxels. All depicted voxels were at least 70% accurate in discriminating HC vs CLBP, cluster size was at least 20 or larger, and $P < 0.05$ (permutation testing with 5000 permutations of group label, FDR-corrected). ALFF, amplitude of low-frequency fluctuation; CLBP, chronic low back pain; FDR, false discovery rate; FG, fusiform gyrus; HC, healthy control; Hipp, hippocampus; IFG,inferior frontal gyrus; Ins, insula; NAc, nucleus accumbens; Para-CG, paracingulate gyrus; SII, secondary somatosensory cortex.

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Table 3

Classification accuracy, sensitivity, and specificity of chronic low back pain vs healthy control, using all amplitude of low-frequency fluctuation values in the specified brain map as predictors and leave-one-out cross-validation.

CLBP brain map	Metric	Full low-frequency band (0.01-0.08 Hz)	Slow-4 frequency band (0.027-0.073 Hz)	Slow-5 frequency band (0.01-0.027 Hz)
Complete training data set (n=68)	Accuracy	77.6% ($P < 10^{-3}$)	77.6% ($P < 10^{-3}$)	77.6% ($P < 10^{-2}$)
	Sensitivity	79.2%	79.2%	79.2%
	Specificity	76.0%	76.0%	76.0%
< 45 years of age (n=16)	Accuracy	90.0% ($P < 10^{-3}$)	90.0% ($P < 10^{-3}$)	90.0% ($P < 10^{-3}$)
	Sensitivity	100%	100%	100%
	Specificity	83.3%	83.3%	83.3%
> 55 years of age (n=17)	Accuracy	76.9% ($P < 10^{-3}$)	61.5% ($P = 0.39$)	76.9% ($P < 10^{-3}$)
	Sensitivity	88.9%	88.9%	88.9%
	Specificity	50.0%	0%	50.0%
Complete external validation data set (n=139)	Accuracy	57.0% ($P = 0.049$)	58.5% ($P = 0.022$)	59.2% ($P = 0.017$)
	Sensitivity	67.6%	68.9%	66.2%
	Specificity	45.6%	47.1%	51.5%

3.5. External validation

To verify that the identified brain maps are not specific to a particular data set, we performed external validation using multiple data sets not used in the identification of predictive brain maps. To do this, we predicted pain intensity rated on the VAS using mean ALFF in the overall CLBP brain map depicted in **Figure 3A** (not separated by age), controlling for age and pain duration. Pain duration was included as a covariate because of its positive correlation with age in the test data set (partial correlation, $\rho = 0.32$, $P < 0.0001$) (See Also Supplementary Table 2, available at http://links.lww.com/PAIN/B533) The external validation was performed for each data set separately and then repeated using all of them combined. The results are shown in **Figure 4** for the full frequency band and summarized in **Table 4** for all examined frequency bands. For all but the Cambridge-Osaka_S1 data set, mean ALFF within the overall predictive CLBP brain map (**Fig. 3A**) was a significant predictor of pain intensity, with $R^2 = 0.31$ ($P < 10^{-3}$) for the New Haven data set and $R^2 = 0.56$ ($P < 10^{-3}$) for the Cambridge-Osaka_S2 data set. This prediction was preserved for the combination of all data sets ($R^2 = 0.25$, $P < 10^{-3}$), despite these data sets having been collected at different locations with different imaging protocols (as shown in **Table 2**). This was also true across frequency bands, with similar accuracy and significance for each. Any relationship between mean ALFF map and pain duration was ruled out (Supplementary Table 3, available at http://links.lww.com/PAIN/B533). The classification process described in section 2.6 was also performed for the whole external data set, with results summarized in **Table 3**. Although accuracy, sensitivity, and specificity tended to be lower than for the Chicago data set, permutation tests still showed statistically significant classification between CLBP and HC subjects.

4. Discussion

Using our own data set and publicly available data sets, we have shown that (1) the ALFF within prefrontal-limbic and sensory areas can accurately discriminate healthy control subjects from those with CLBP; (2) predictive brain regions vary between younger and older subjects, with older subjects showing greater discrimination in limbic brain areas such as the ventromedial prefrontal cortex, NAc, and hippocampus; (3) ALFF values within these brain maps can accurately predict low back pain intensity ratings, with prediction being more accurate in younger subjects; and (4) mean ALFF values within the brain map can accurately predict back pain intensity ratings in data sets that were not included in the model training (ie, unseen data) and were obtained using different data acquisition parameters.

A brain ALFF pattern comprising the anterior insula or inferior frontal gyrus, posterior insula or SII, paracingulate, fusiform, and midtemporal gyrus classified patients with CLBP with more than 70% accuracy irrespective of age. Many of these areas receive direct nociceptive input from the periphery such as the SII, insula, and paracingulate cortex[26,30] and have been part of brain activity patterns associated with acute pain in healthy subjects[1,98] and subacute low back pain.[43] While patients with CLBP younger than 45 years old showed a similar activity pattern comprising mainly the insula, paracingulate, and fusiform gyrus, patients older than 55 years showed more extensive cortical and subcortical involvement of prefrontal-limbic and somatosensory motor areas reminiscent of what we and others have observed in patients with CLBP in general, irrespective of age groups.[59,107] The vmPFC and NAc activity and connectivity in particular have been repeatedly shown to track back pain intensity[5,7,43,59,91] and predict the risk of transition from subacute to CLBP.[8,59] These limbic brain areas are rich in opioid receptors,[62,109] mediate value-based decision making,[40,55] and link motivation to action.[36] Hence, the increased involvement of these areas in the older patients' group suggest that aging increases the vulnerability of this circuitry in patients with CLBP enhancing the negative affective experience of back pain in the elderly. Indeed, older adults suffering from LBP are more disabled than their healthy peers[48,68,81] and are more predisposed to frailty.[21,25] Age is also one of the important predictors of outcome in patients with LBP.[47,75,97] In a study of 166 patients with LBP, both suffering from disabling back pain in the past 4 to 12 weeks age and pain intensity predicted most of the outcomes at 12 months.[47] In a different study where patients with back pain were identified in a random sample of the general population and surveyed 3 times in a 10-year interval, older age was significantly associated with the persistence of LBP at 10 years.[96] Likewise, compared with working age adults, older adults aged 65 years and older are more likely to develop CLBP that lasts more than 3 months[42,90]. It is therefore plausible that the increased vulnerability of the elderly to a worse prognosis after an acute bout of back pain is mediated by brain circuitry made susceptible to reorganization by aging.[13,29]

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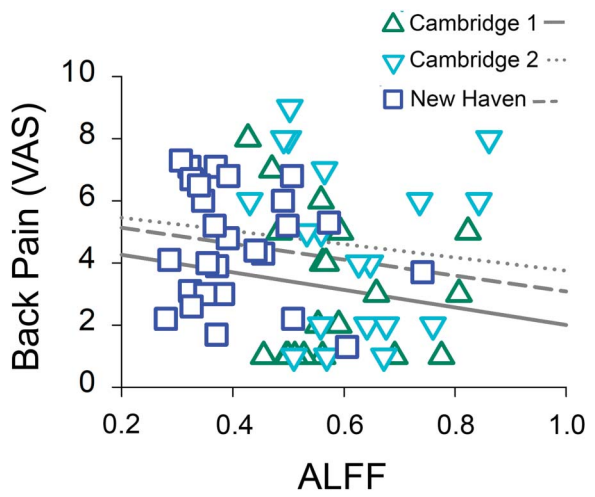

Figure 4. Mean ALFF within the CLBP brain map for each external data set, plotted against back pain intensity rated using the VAS. Lines represent correlation between mean ALFF and pain intensity for each data set independently. The correlation coefficients of the regression lines depicted were as follows: Cambridge-1, r = −0.22 (P = 0.08, n = 59); Cambridge-2, r = 0.04 (P = 0.82, n = 28), and New Haven, r = 0.08 (P = 0.56, n = 52). ALFF, amplitude of low-frequency fluctuation; CLBP, chronic low back pain.

Notably, the anterior insula or inferior frontal and fusiform gyri were the common areas seen in all ALFF patterns predictive of CLBP irrespective of age groups. The insula or inferior frontal gyrus are rich in μ-opioid receptors[10,99,108,109] and integrate input from nociceptive[66] and interoceptive afferents including pain.[20, 27] The insula is highly interconnected with other limbic structures such as the amygdala[3,67] and the NAc.[24] It is regularly activated in acute[1,46] and chronic pain including chronic low back pain[5, 22, 43, 104]. Interestingly, insula activity tracks subacute back pain intensity before back pain is chronic[43] and tracks periods of change in CLBP intensity,[5] suggesting its activity to be closely linked to early processing of afferent input. In addition, insula connectivity to the medial prefrontal cortex is consistently increased in patients with CLBP[4,49,91] and decreases after successful treatment.[49] The anatomical distribution of ALFF pattern predictive of CLBP suggest therefore an expansion of the limbic circuitry involved to include striatum, hippocampus, or ventromedial prefrontal cortex in the older group compared with the younger group as peripheral nociceptive input increasingly engages affective processing brain areas. There are scarce data studying the possible role of the fusiform gyrus in chronic pain. This brain area was recently reported to be part of a robust functional connectivity–based biomarker of pain intensity rated by healthy participants during experimental pain or by patients with CLBP reporting their spontaneous clinical pain.[54] One study[85] suggested also that the fusiform gyrus links the visualization of painful experiences, like carrying a load, for example, to affective processing occurring in the amygdala and hippocampus to which the fusiform gyrus is anatomically connected part of the ventral visual network.[51]

The classification performance (>70%-75%) of our searchlight analysis using ALFF maps is as good as or better than the published literature using functional imaging data as features to discriminate between patients with CLBP and controls.[17,33,54,59,60,76] While we reported lower classification accuracy in the external validation data set (57%-59%, see **Table 3**), this accuracy was in the range reported for studies using an independent testing cohort.[60,84,106] For example, Zhang et al. demonstrated accuracies ranging from 53% to 67% for classification of CLBP using multiple ALFF-based features in a second validation cohort.[106] Most of these studies used functional connectivity to derive classification patterns, except Callan et al.,[17] who used brain response to acute pain, and our previous study,[59] which used slow-5 frequency in a hypothesis-based approach within the NAc. The advantage of using ALFF maps with searchlight-based classification is the absence of an atlas or specific regions of interest and the interpretability of spatial patterns and directions of change (ie, increases or decreases in activity fluctuations). Unlike connectivity ALFF does not suffer from the transitivity problem,[105] the problem of anticorrelations,[37] and has a better reliability than connectivity.[12,14,44,74,92,110] Hence, ALFF-based classifiers can identify physiological hot spots (eg, **Fig. 3**) and directions of change that are easier to interpret and necessitate less assumptions than correlations. However, as described in the Introduction, searchlight analysis can be overly sensitive to small groups of voxels and miss broader trends that may be found with other methods. These findings point to potential synergy between the current technique and other methods, which may lead to improvements in future classification studies of patients with chronic pain.

In conclusion, to the best of our knowledge, we show the first brain activity pattern discriminating between patients with CLBP and healthy controls across younger and older age groups using a data-driven approach. Older patients with CLBP exhibit a more extensive pattern of altered ALFF discriminating them from healthy controls covering corticolimbic areas such as the vmPFC, NAc, and hippocampus whereas ALFF patterns in the insula significantly discriminated both older and younger patients with CLBP. This work accords with accumulating evidence supporting the critical role of corticolimbic circuitry in CLBP[106] and the vulnerability of these areas to aging. Further brain imaging research is highly needed in this field especially that the number of individuals aged older than 60 year is expected to triple by 2050.[94]

Table 4

Results of external validation for prediction of Visual Analog Scale pain intensity in the test data sets (Cambridge-Osaka and New Haven) using mean amplitude of low-frequency fluctuation within the overall chronic low back pain brain map as predictor, with age and pain duration as covariates.

Test dataset	Full low-frequency band (0.01-0.08 Hz)	Slow-4 frequency band (0.027-0.073 Hz)	Slow-5 frequency band (0.01-0.027 Hz)
Cambridge-Osaka_S1 (n = 59)	0.14 (P = 0.054)	0.15 (P = 0.057)	0.16 (P = 0.046)
Cambridge-Osaka_S2 (n = 28)	0.56 ($P < 10^{-3}$)	0.57 ($P < 10^{-3}$)	0.56 ($P < 10^{-3}$)
New Haven (n = 52)	0.31 ($P < 10^{-3}$)	0.31 ($P < 10^{-3}$)	0.31 ($P < 10^{-3}$)
All test data combined (n = 139)	0.25 ($P < 10^{-3}$)	0.25 ($P < 10^{-3}$)	0.26 ($P < 10^{-3}$)

Reported results are R^2 values returned by the model fit, with P values provided in parentheses.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B533.

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