

Hippocampal Functional Radiomic Features for Identification of the Cognitively Impaired Patients from Low-Back-Related Pain: A Prospective Machine Learning Study

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Purpose: To investigate whether functional radiomic features in bilateral hippocampi can identify the cognitively impaired patients from low-back-related leg pain (LBLP).

Patients and Methods: For this retrospective study, a total of 95 clinically definite LBLP patients (40 cognitively impaired patients and 45 cognitively preserved patients) were included, and all patients underwent functional MRI and clinical assessments. After calculating the amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), voxel-mirrored homotopic connectivity (VMHC) and degree centrality (DC) imaging, the radiomic features ($n = 819$) of bilateral hippocampi were extracted from these images, respectively. After feature selection, machine learning models were trained. Finally, we further analyzed the relationship between the hippocampal functional radiomic features and clinical measures, to explore the clinical significance of these features.

Results: The combined radiomic features model logistic regression algorithm superior performance in distinguishing cognitively impaired patients from LBLP (AUC = 0.970, accuracy = 92.3%, sensitivity = 92.3%, specificity = 92.3%) compared to the other models. Additionally, radiomic wavelet features were correlated with Montreal Cognitive Assessment (MoCA) and Hamilton Anxiety Scale, present pain intensity scores in cognitively impaired LBLP patients ($P < 0.05$, with Bonferroni correction).

Conclusion: Hippocampal functional radiomic features are valuable for diagnosing cognitively impaired patients from LBLP.

Keywords: cognitive impairment, resting-state functional MRI, low-back-related leg pain, radiomic, logistic regression algorithm

Introduction

Low-back-related leg pain (LBLP) is one of the most common *variations* of low back pain. Individuals commonly experience pain that radiates to the leg, and it is believed to be associated with the severity of disease, increased disability, prolonged recovery, and higher health-related costs. Several studies have shown that chronic pain is associated with cognitive impairment.^{1,2} This decline in cognitive function has also been observed in patients with LBLP and has a negative impact on their quality of life and ability to maintain employment.³⁻⁵

Chronic pain patients with cognitive impairment may exhibit executive function deficits, particularly on working memory and emotional control subscales.⁶ A recent study has suggested that abnormalities of the mesolimbic dopamine system and the noradrenergic system in the locus coeruleus and microglial dysfunction in hippocampus play a crucial role

in the cognitive impairment process.^{7,8} The Hippocampus is an important brain structure for cognitive decline. Studies of humans and animals both shown abnormalities in the hippocampus, including reduced volume, neurogenesis, and synaptic plasticity, reflecting certain functional abnormalities in cognitively impaired chronic pain patients.^{9,10} Recent resting-state functional magnetic resonance imaging (rs-fMRI) approaches have focused on the hippocampus, targeting altered intrinsic connectivity measures. Decreased hippocampal functional connectivity is related to anxiety, while increased connectivity involved in emotion regulation has been observed in chronic pain patients.¹¹ The alterations of regional homogeneity (ReHo) in the hippocampus may be the result of chronic pain and then affect the cognitive function of patients.¹² These findings indicate that hippocampus may play a specific role in the pathological process of the cognitively impaired LBLP (CI-LBLP).

Radiomics has traditionally been utilized as a method for morphological imaging analysis, which can use advanced imaging features to objectively and quantitatively describe phenotypic information for classification.¹³ Radiomic features include first-order features, textural features and wavelet features. Currently, studies have shown that there are significant abnormalities in hippocampal radiomic features, which served as a neuroimaging biomarker to distinguish between mild cognitive impairment (MCI) and Alzheimer's disease (AD),¹⁴ as well as between cognitively impaired and cognitively preserved multiple sclerosis patients.¹⁵ In addition to the structural radiomic features of the hippocampus, the texture features of the hippocampus extracted from rs-fMRI have also been employed for the identification of cognitive impairment types.¹⁶ Moreover, previous study has found that the functional radiomic information contained in the hippocampus can better reflect the cognitive status of patients.¹⁶ It may assist in developing more appropriate and effective treatment plans for the cognitively impaired patients from those with LBLP in clinical settings, such as therapeutic exercise mentioned in certain studies.¹⁷

In this study, we hypothesize that hippocampal functional radiomic features would be disrupted and that these alterations might be employed in the classification of CI-LBLP patients from cognitively preserved LBLP (CP-LBLP) patients. In addition, correlation analysis between hippocampal functional radiomic features and clinical scores was performed in the patients to confirm that these radiomic features play an important role in the clinical symptoms of LBLP patients. This study aims to investigate the value of hippocampal functional radiomic features in distinguishing the cognitively impaired patients from those with LBLP and to provide valuable information for clinical practice.

Materials and Methods

Participants

This prospective recruitment study involved a total of 85 clinically diagnosed LBLP patients who were recruited from October 2021 to October 2023 at the First Affiliated Hospital of Jiangxi Medical College, Nanchang University. Inclusion criteria were as follow: (1) 20–65 years old; (2) radiological and clinical diagnosis, including reports of discogenic compression with at least 1 ruptured annulus fibrosus on lumbar computed tomography (CT) and/or magnetic resonance imaging (MRI); (3) visual analog scale (VAS) score ≥ 3 ; (4) getting ineffective prior conservative treatment, including medications without opioids and physical therapy (eg, non-steroidal anti-inflammatory drugs). Exclusion criteria were as follow: (1) any other non-discogenic causes of low-back-related leg pain (eg, spinal protrusion, lateral recess stenosis, spinal stenosis, piriformis syndrome, sciatica); (2) a history of major intracranial and spinal cord diseases or surgery and any contraindications; (3) image artifacts or incomplete clinical information. All participants were given written informed consent. A flowchart detailing exclusion by each criteria is presented in [Figure 1](#). We used the G*Power tool to estimate the required sample size, and the number of patients included in both groups exceeded the estimated requirement. All subjects provided informed written consent for the procedures approved by the Medical Research Ethics Committee of the First Affiliated Hospital of Jiangxi Medical College, Nanchang University, in accordance with the Declaration of Helsinki, under the ethical number of (2022) CDYFYLYK(08–009).

Clinical Assessment and Cognitive Groups

On the day of scanning, all participants underwent a series assessment, including (1) the present pain intensity (PPI) and visual analogue scale (VAS) used to evaluate both the intensity and quality of pain, see reference^{18,20,21} for their normal range and the

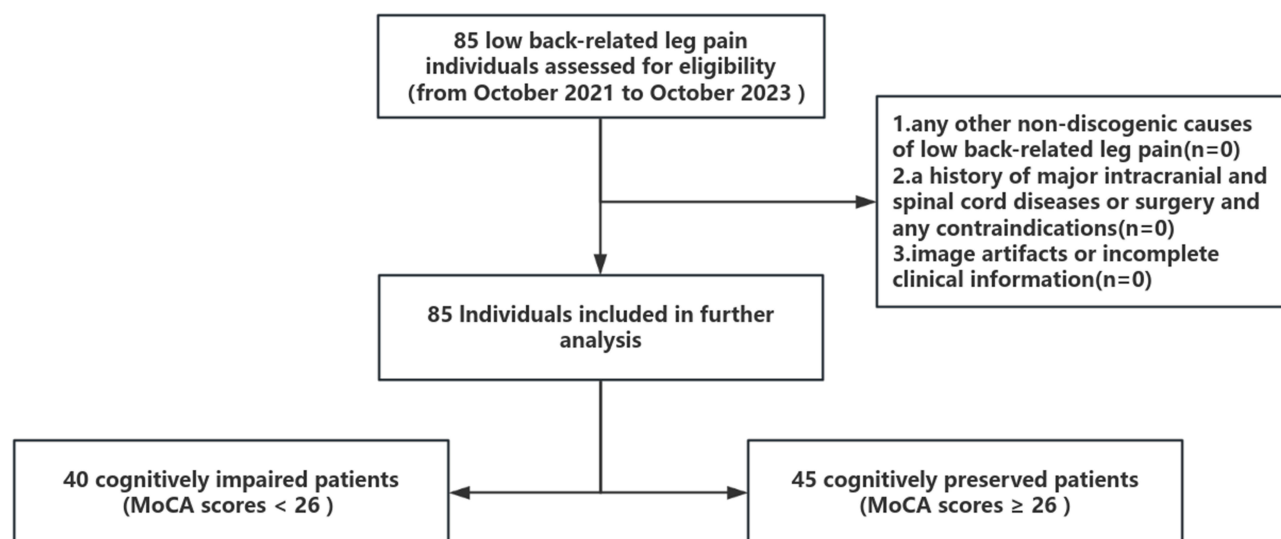


Figure 1 A flowchart detailing exclusion by each criteria.
Abbreviation: MoCA, Montreal Cognitive Assessment.

significance of abnormal values; (2) the central sensitization inventory (CSI) used to help identify patients with central sensitivity syndrome; (3) the Montreal Cognitive Assessment (MoCA) (from 0 to 30) used to evaluate neuropsychological test for detecting cognitive decline or dementia; (4) the Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD) used to evaluate anxiety symptoms and depressive symptoms, respectively; (5) the Brief Pain Inventory (BPI-17) questionnaire used to evaluate the severity and interference of pain with daily functioning.

After MoCA score adjusted for education, the total score of those with less than 12 years of education is added to one point.²¹ Patients with LBLP were categorized into cognitively impaired (CI, score less than 26) and cognitively preserved (CP, score of 26–30) subgroups.

MRI Data Acquisition

All MRI data were collected on a 3.0T MRI (Signa Pioneer, GE Healthcare, Milwaukee, CA, USA) with a 32-channel head/neck coil at our hospital. The whole-brain 3D T1-weighted acquisition parameters were as follows: 176 sagittal slices, repetition time (TR) = 8.0 ms, echo time (TE) = 3.0 ms, flip angle (FA) = 12°, slice thickness/gap = 1.0/0 mm, field of view (FOV) = 256 × 256 mm², matrix = 256 × 256. Rs-fMRI was acquired using a gradient echo-planar imaging pulse sequence with the following parameters: 40 axial slices, TR = 2000 ms, TE = 25 ms, FA = 90°, slice thickness/gap = 3.5/0.7 mm, FOV = 190 × 190 mm², matrix = 64 × 64, and 240 volumes. All subjects were asked to keep their eyes closed during scanning, avoid systematic thinking and refrain from falling asleep. Noise and head-motion were controlled by foam padding and earplugs. Additionally, the conventional T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences are acquired to exclude subjects with anatomical brain abnormalities. Lumbar spine evaluation on CT/MRI was consistent with that previously reported.²²

Data Preprocessing and rs-fMRI Derivatives/Connectivity Measures

All fMRI data were processed and analyzed using the toolbox for Data Processing & Analysis of Brain Imaging (DPABI v5.2; <http://rfmri.org/dpabi>) and Statistical Parametric Mapping (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>). The main steps include the following: (1) Dicom to Nifti format, (2) delete initial 10 volumes (image) for data stabilization, (3) slice timing for signal corrected, (4) realignment for movements correction, in which head motion exceeded 3 mm translation or 3° rotation according to the criteria of Van Dijk et al,²³ (5) co-registered 3D T1-weighted imaging to mean functional image, (6) segmented the transformed structural images into gray matter, white matter and cerebrospinal fluid with Dartel tool,²⁴ (7) covariates such as linear drift, white matter signal, and cerebrospinal fluid were removed without global signal

regression, (8) spatial normalization, resampling the image to 3 mm isotropic voxels and smoothing (FWHM kernel: 6 mm) except for ReHo and degree centrality calculation, (9) temporal filtering (0.01–0.1 Hz) for further rs-fMRI-based indices calculations. Standardized fMRI data preprocessing steps are referenced.²⁴ The amplitude of low frequency fluctuations (ALFF), regional homogeneity (ReHo), voxel-mirrored homotopic connectivity (VMHC) and degree centrality (DC) values were calculated based on previous studies using DPABI (detail information see [Table S1](#)).

Hippocampal Radiomic Feature Extraction and Selection

Python3.7.12 Pandas was used for data encapsulation, and then PyRadiomics was employed to extract the hippocampal radiomic features from amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), voxel-mirrored homotopic connectivity (VMHC) and degree centrality (DC) images, as previously reported. The radiomic features encompassed three categories: (1) 18 first-order features to evaluate the signal level, (2) 73 textural features to describe the spatial distribution information, and (3) 728 wavelet features to combine the spatial and frequency characteristics (for detailed information, please refer to [Table S2](#)). In total, 819 hippocampal radiomic features were extracted from ReHo, ALFF, VMHC, and DC images, respectively.

To identify the optimal features, all features are first preprocessed by Z-score normalization prior to feature screening, and each dimension feature is linearly stretched between [0–1]. Subsequently, the Spearman rank correlation test was employed to evaluate the linear correlation between individual features for redundancy elimination. Once two features have a stronger correlation, they will have a higher absolute value of the correlation coefficient. We selected one of the features for subsequent analysis when a Spearman correlation coefficient >0.9 between each feature. Finally, the least absolute shrinkage and selection operator (LASSO) regression was utilized for feature selection with non-zero coefficients serving as valuable predictors.

Hippocampal Functional Radiomic Model

Following the selection of hippocampal functional radiomic features, this study assessed the discriminative capability of various feature types in distinguishing between patients with CI-LBLP and CP-LBLP. Each radiomic feature of derivatives/connectivity measures captures different aspects of the information carried by rs-fMRI and may play different roles in the identification of CI-LBLP and CP-LBLP. Thus, a total of 15 combinations were created in this study, including (1) hippocampal radiomic features derived from single imaging metrics such as ReHo, ALFF, DC, and VMHC; (2) hippocampal radiomic features derived from two imaging metrics like ReHo + ALFF, ReHo + DC, ReHo + VMHC, ALFF + DC, ALFF + VMHC, and DC + VMHC; (3) hippocampal radiomic features derived from three imaging metrics including ReHo + ALFF + DC, ReHo + ALFF + VMHC, ReHo + DC + VMHC, and ALFF + DC + VMHC; and (4) hippocampal radiomic features derived from all four imaging metrics: ReHo + ALFF + DC + VMHC.

Two groups of LBLP patients were randomly divided into training set and test set at a ratio of 7:3. Then, machine learning classification models were developed using Python Scikit-learn (<https://scikit-learn.org/stable/install.html>) to differentiate patients between the CI and CP groups. The chosen features served as input vectors for support vector machine (SVM), logistic regression (LR), multilayer perceptron (MLP), NaiveBayes and k-nearest neighbors (KNN) to train the classification model. The diagnostic performance of the hippocampal functional radiomic models was evaluated by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, with quantitative indicators such as accuracy, sensitivity, and specificity. To estimate the clinical usefulness of the prediction models, decision curve analysis (DCA) was performed to assess the net benefit of the models in the test cohorts.

Statistical Analysis

IBM SPSS Statistics (Version 21.0, SPSS Inc., Chicago, Illinois, USA) was utilized for analyzing the clinical variables. Chi-square tests were used to compare categorical variables, while t-tests or the Mann–Whitney *U*-test were used for comparing quantitative variables to assess differences in clinical characteristics among patients ($P < 0.05$). To investigate the clinical correlations, a partial correlation analysis was conducted between the final selected hippocampal functional radiomic features and clinical information in both the CI group and CP group ($P \times n < 0.05$, Bonferroni correction).

Results

Demographic and Clinical Data Analysis

Forty CI-LBLP patients and forty-five CP-LBLP patients were entered into the final analysis. The demographic and clinical information is shown in [Table 1](#). In this study, the age of CI-LBLP patients was significantly older than that of CP-LBLP patients ($P < 0.001$), the proportion of female patients in the former group was higher ($P = 0.021$), and the interference of pain on daily activities was more obvious in CI-LBLP patients ($P = 0.046$).

Hippocampal Functional Radiomic Features Selection and Model

(1) Hippocampal functional radiomic features selection

Following dimensionality reduction through Spearman rank correlation test and LASSO regression, a total of 31 hippocampal functional radiomic features were identified. These features consisted of 10 from DC, 5 from ALFF, 11 from ReHo, and 5 from VMHC ([Figure 2](#) and [Table S3](#)).

(2) Hippocampal functional radiomic features models

Fifteen models were established based on the optimal features of the hippocampal radiomic features based on each machine learning algorithms. The combined radiomic features (DC + ReHo + VMHC) models based LR algorithm exhibited the highest accuracy (AUC = 0.970) in the validation set. [Table 2](#) and [Figure 3](#) show the ROC curves and the sensitivity, specificity, and accuracy of the training set and test set of hippocampal functional radiomic models developed by LR algorithms. The results of hippocampal functional radiomic models developed by other machine learning algorithms are shown in [Table S4](#).

Correlation Analysis

In the CI-LBLP group, partial correlation analysis revealed found that a positive correlation between wavelet features (wavelet-HHH_ngtdm_Coarseness) from DC and MoCA score ($r = -0.598$, $P = 0.001 \times 8 < 0.05$, with Bonferroni correction), as well as and a negative correlation between wavelet features (wavelet-HLL_firstorder_TotalEnergy) from DC and HAMA score ($r = -0.517$, $P = 0.001 \times 8 < 0.05$, with Bonferroni correction). Additionally, a negative correlation was observed between the wavelet features (wavelet-LLL_glszm_ZoneVariance) from ALFF and the PPI score ($r = 0.568$, $P = 0.001 \times 8 < 0.05$, with Bonferroni correction) ([Figure 4](#)). For the CP-LBLP patients, the ReHo wavelet features (wavelet-HLL_firstorder_Skewness) show a positive correlation with HAMD score ($r = 0.45$, $P = 0.002 \times 8 < 0.05$, with

Table 1 Demographic and Clinical Characteristics of CI-LBLP and CP-LBLP Patients

	CI-LBLP (N=40)	CP-LBLP (N=45)	T/ χ^2 /Z value	P value
Age	54.13±9.29	44.67±11.87	-4.112 ^a	<0.001***
Sex (male / female)	19/21	33/12	5.950 ^b	0.021*
Duration, months (median (IQR))	2.115(17.00)	3.00(8.00)	-0.716 ^c	0.474
Neuropsychological assessment				
MoCA (mean ± SD)	23.55±1.70	27.22±1.20	11.252 ^a	<0.001***
HAMD (mean ± SD)	3.15±2.70	3.38±2.76	0.384 ^a	0.702
HAMA (mean ± SD)	1.83±1.84	1.78±2.25	-0.105 ^a	0.916
Pain assessment				
VAS (mean ± SD)	5.60±0.93	5.29±1.06	-1.433 ^a	0.156
PPI (mean ± SD)	2.90±1.30	2.69±1.23	-0.767 ^a	0.445
BPI (mean ± SD)	37.10±10.98	32.38±10.54	-2.021 ^a	0.046 *
CSI (mean ± SD)	11.08±7.11	8.67±4.77	-1.817 ^a	0.073

Note: ^a, two-sample t test; ^b, chi-square test; ^c, Mann-Whitney U-test; * $P < 0.05$, *** $P < 0.001$.

Abbreviations: CI, cognitively impaired; CP, cognitively preserved; SD, standard deviation; IQR, inter-quartile range. MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale. VAS, visual analog scale; PPI, present pain intensity; BPI, Brief Pain Inventory; CSI, central sensitization inventory.

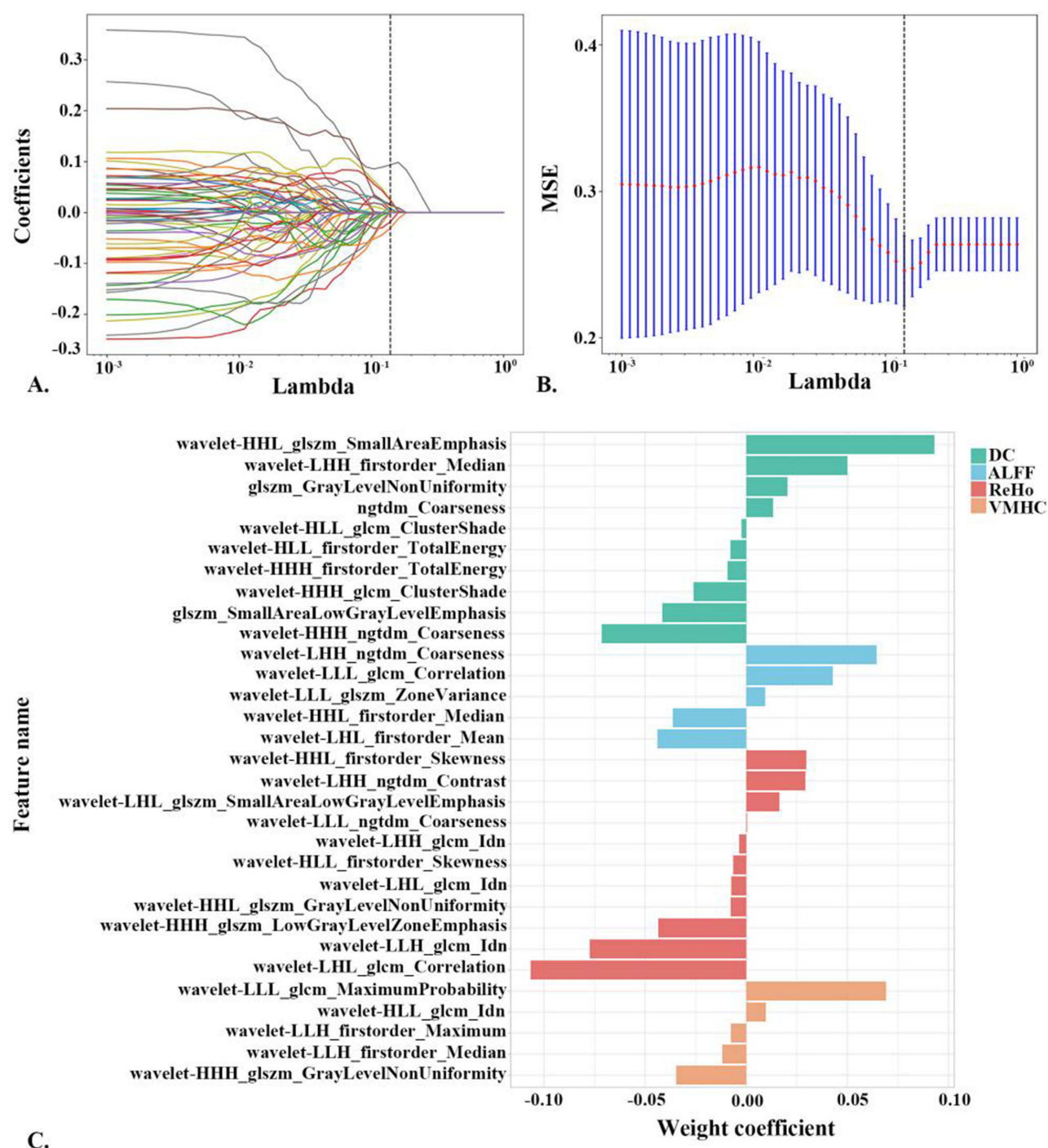


Figure 2 Hippocampal functional radiomic features dimension reduction. **(A)** The LASSO coefficient profiles of these features are displayed, with different colored lines representing the corresponding coefficients of each feature. **(B)** The selection of tuning parameter (λ) in the LASSO model is illustrated. **(C)** The weight coefficients of the selected features are shown.

Abbreviations: ALFF, amplitude of low-frequency fluctuations; ReHo, regional homogeneity; VMHC, voxel-mirrored homotopic connectivity; DC, degree centrality.

Bonferroni correction), while ReHo wavelet features (wavelet-LHH_glm_Idn) were negatively correlated with CSI score ($r = -0.456$, $P = 0.002 \times 8 < 0.05$, with Bonferroni correction) (Figure 4).

Table 2 The Classification Results of Hippocampal Functional radiomic Models Developed by LR Algorithms Between CI-LBLP and CP-LBLP Patients

Imaging Metric	Data Set	Logistic Regression Model			
		AUC (95% CI)	ACC	SN	SP
Modeling of hippocampal radiomic features derived from single imaging metric					
DC	Train	0.830(0.727–0.933)	0.763	0.625	0.926
	Test	0.781(0.5582–0.980)	0.808	0.846	0.833
ALFF	Train	0.796(0.729–0.863)	0.732	0.683	0.754
	Test	0.700(0.532–0.868)	0.574	0.867	0.437
ReHo	Train	0.858(0.758–0.957)	0.814	0.875	0.741
	Test	0.811(0.6443–0.977)	0.769	0.615	0.923
VMHC	Train	0.768(0.697–0.840)	0.709	0.700	0.713
	Test	0.786(0.637–0.935)	0.812	0.533	0.939
Modeling of hippocampal radiomic features derived from two imaging metrics					
ALFF + DC	Train	0.852(0.757–0.947)	0.797	0.750	0.852
	Test	0.740(0.533–0.946)	0.731	0.769	0.750
ALFF + ReHo	Train	0.895(0.802–0.987)	0.881	0.969	0.778
	Test	0.828(0.657–1.000)	0.808	0.615	1.000
ALFF + VMHC	Train	0.837(0.729–0.945)	0.831	0.897	0.767
	Test	0.800(0.612–0.988)	0.837	0.938	0.700
DC + ReHo	Train	0.976(0.944–1.000)	0.932	1.000	0.852
	Test	0.917(0.807–1.000)	0.885	0.923	0.846
DC + VMHC	Train	0.889(0.802–0.976)	0.881	0.906	0.852
	Test	0.846(0.688–1.000)	0.808	0.923	0.692
ReHo + VMHC	Train	0.874(0.786–0.962)	0.814	0.938	0.667
	Test	0.917(0.802–1.000)	0.885	0.846	0.923
Modeling of hippocampal radiomic features derived from three imaging metrics					
ALFF + DC + ReHo	Train	0.968(0.931–1.000)	0.915	0.906	0.926
	Test	0.870(0.730–1.000)	0.808	0.692	0.923
ALFF + DC + VMHC	Train	0.904(0.820–0.989)	0.881	0.875	0.889
	Test	0.763(0.571–0.955)	0.731	0.769	0.692
ALFF + ReHo+ VMHC	Train	0.927(0.860–0.994)	0.864	0.875	0.852
	Test	0.917(0.812–1.000)	0.846	0.769	0.923
DC + ReHo + VMHC	Train	0.972(0.934–1.000)	0.932	0.938	0.926
	Test	0.970 (0.916–1.000)	0.923	0.923	0.923
Modeling of hippocampal radiomic features derived from four imaging metrics					
ALFF + DC + ReHo + VMHC	Train	0.987(0.969–1.0000)	0.949	0.906	1.000
	Test	0.893(0.767–1.000)	0.846	0.923	0.769

Note: Bold font: The highest accuracy of hippocampal functional radiomic models developed by LR algorithms in the validation set.

Abbreviations: AUC, Area Under Curve; CI, Confidence interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value. ALFF, amplitude of low frequency fluctuations; ReHo, regional homogeneity; VMHC, voxel-mirrored homotopic connectivity; DC, degree centrality.

Discussion

In this study, we successfully developed a machine learning algorithm model based on multilevel functional radiomic features of the hippocampus. This model is capable of distinguishing cognitively impaired patients from those with

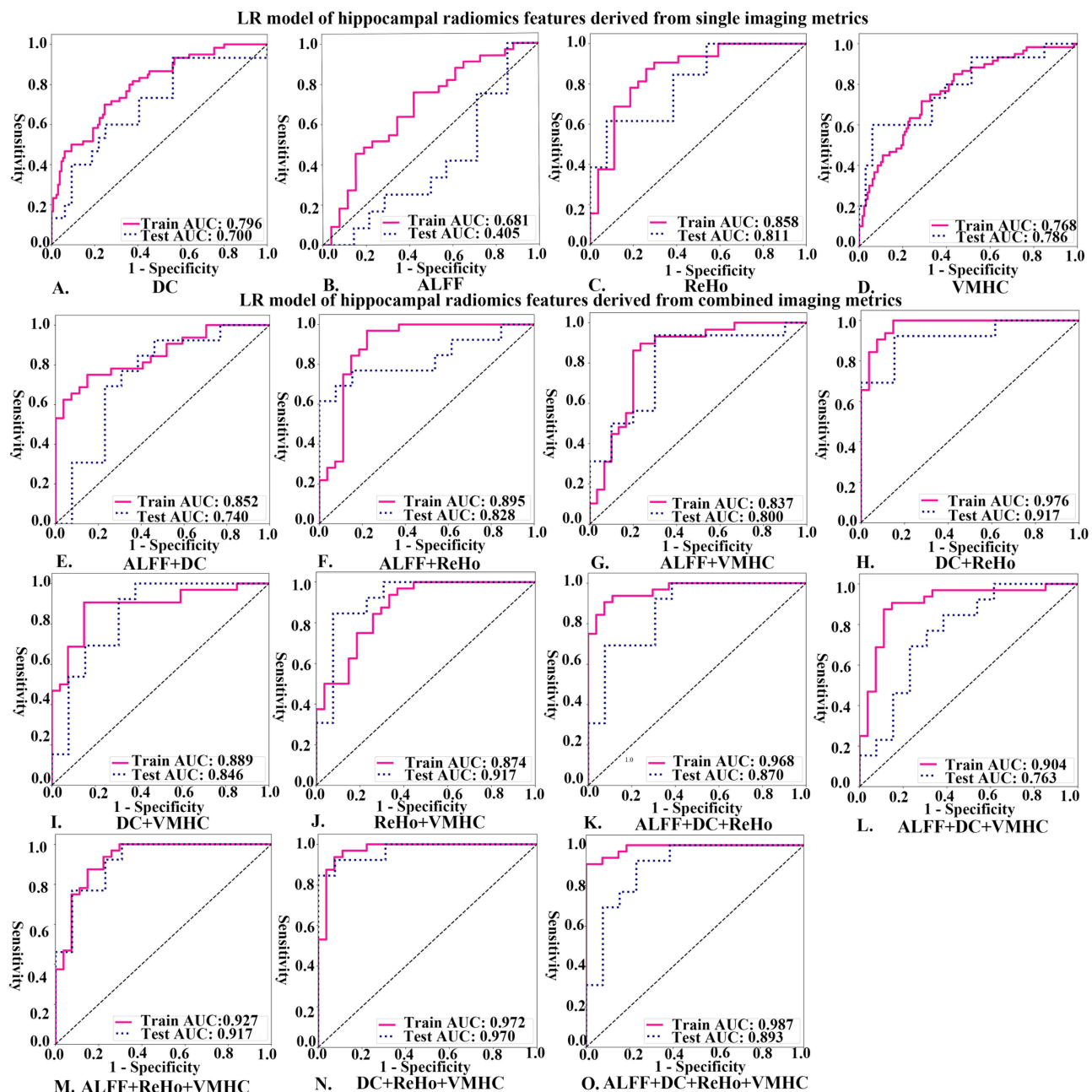


Figure 3 The ROC curve of the hippocampal functional radiomic models developed by LR algorithms. **(A-D)** The ROC curve of hippocampal radiomic features derived from single imaging metrics by LR algorithms. **(E-J)** The ROC curve of hippocampal radiomic features derived from two imaging metrics by LR algorithms. **(K-N)** The ROC curve of hippocampal radiomic features derived from three imaging metrics by LR algorithms. **(O)** The ROC curve of hippocampal radiomic features derived from four imaging metrics by LR algorithms.

Abbreviations: ROC, receiver operating characteristic; ALFF, amplitude of low-frequency fluctuations; ReHo, regional homogeneity; VMHC, voxel-mirrored homotopic connectivity; DC, degree centrality.

LBLP. Furthermore, we found that the hippocampal functional radiomic features in CI-LBLP patients were significantly correlated with clinical pain intensity, cognitive status, and anxiety status scores.

Combined Modeling of Hippocampal Multilevel Functional Radiomic Features Rather Than Single Feature

In this study, 31 potential discriminative features were identified by using Spearman rank correlation test and LASSO regression. Except in the DC imaging has 2 “Gray Level Size Zone Matrix (glszm)” and 1 “Neighbouring Gray Tone

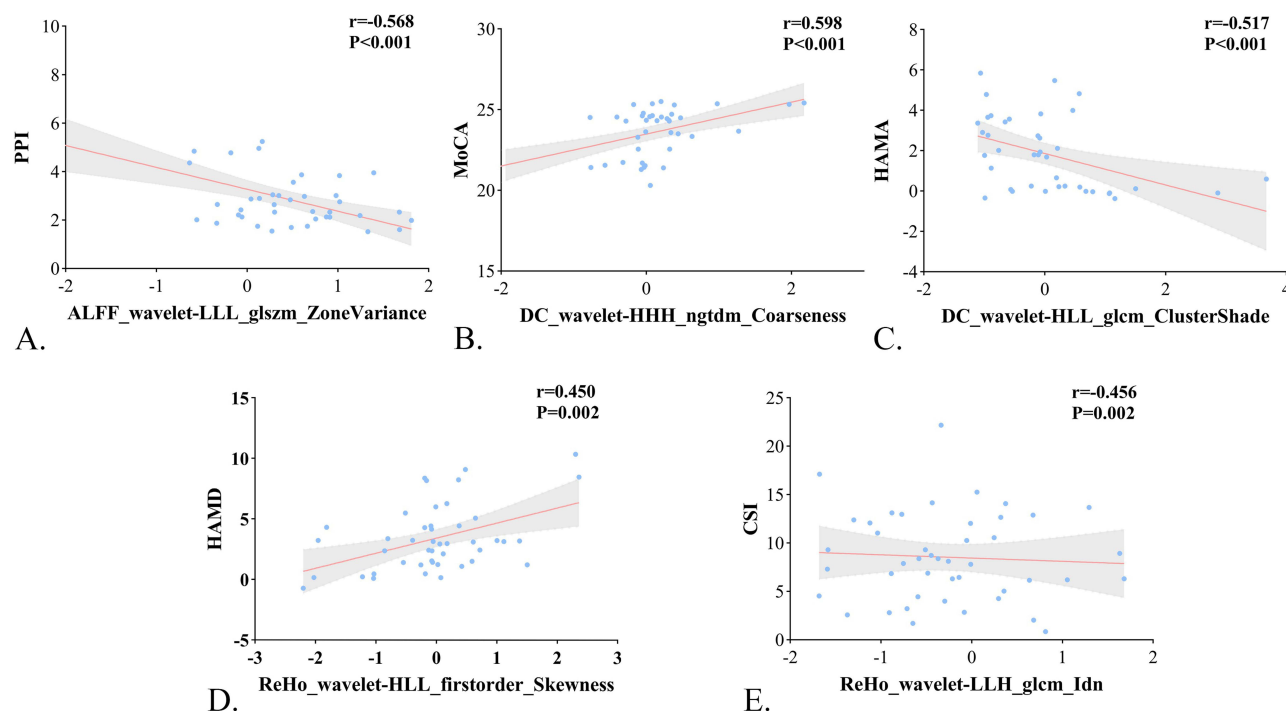


Figure 4 Partial correlation analysis between clinical scores and textural features in CI-LBLP and CP-LBLP. (A–C) Partial correlation analysis between clinical scores and textural features in CI-LBLP. (D and E) Partial correlation analysis between clinical scores and textural features in CP-LBLP.

Abbreviations: MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PPI, present pain intensity; CSI, central sensitization inventory. ALFF, amplitude of low-frequency fluctuations; ReHo, regional homogeneity; DC, degree centrality.

Difference Matrix (ngtdm)” texture features, and the rest are “wavelet” features. In terms of distinguishing cognitively preserved patients from LBLP, the features that made the greatest contribution came from the wavelet features of DC imaging (HLL_glszm_SmallAreaEmphasis) and ReHo imaging (LHL_glm_Correlation), respectively. Previous studies have confirmed that the wavelet transform features provided by PyRadiomics can help to improve the diagnostic efficiency of radiomic features.^{25,26} In this study, the optimization of valuable features may reveal the heterogeneity and spatial change rate in the strength of hippocampal functional connectivity strength, and help to understand the alteration of hippocampal function.

However, in this study, the AUC value of the machine learning algorithm model constructed by the radiomic features of a hippocampal single imaging metric (such as ReHo, etc.) was not high (AUC in the test set: 0.556–0.811), indicating that the altered higher order feature of hippocampal single function metric could not well distinguish cognitively impaired patients from those with LBLP. In previous studies including individuals with low back pain with radicular pain, these patients have demonstrated significant alterations in hippocampal volume,²⁷ hippocampal structural covariance,²⁸ and functional connectivity.²⁹ It has been suggested that hippocampus can serve as a potential diagnostic biomarker for chronic back pain.^{30–32} However, its diagnostic efficiency is not high, which may be due to the limited information of included image or insufficient information mining, which inevitably ignores other potentially useful information.^{3,31,33}

The combination of multilevel functional image features can improve classification performance, which seems to be a reasonable hypothesis in fMRI studies of chronic pain. Different types of features can provide complementary information to highlight the differences between the two groups of patients. Moreover, radiomic features further excavate its higher-order information, especially the wavelet features, which reflect the functional change patterns in different spaces. The combination of radiomic features from two functional images can significantly improve discrimination ability (AUC in the test set: 0.741–0.917). The improvement in diagnostic efficiency of machine learning models based on hippocampal radiomic features is mainly affected by the contribution degree from the features derived from DC and ReHo imaging. Combined with the radiomic feature of homotopy connectivity (VMHC), an exceptional discriminatory

capacity can be attained, with an AUC of 0.970 and a sensitivity of 0.923. This thoroughly demonstrates that in the combination of DC and ReHo, VMHC radiomic features are more complementary than ALFF radiomic features.

Combined with the following findings: (1) neuroimaging studies have shown that there are varying degrees of morphological, (microscopic) structural, metabolic and functional changes in the hippocampus of patients with cognitive impairment;³ (2) recent studies using radiomics to evaluate hippocampal texture features are more effective than hippocampal volume measurement.²⁶ We have reason to believe: based on the features of hippocampal functional radiomic modeling of machine learning algorithm, it can effectively distinguish cognitively impaired patients from those with LBLP.

Hippocampal Functional Radiomic Features and Clinical Relevance

According to the results of correlation analysis, DC imaging's "wavelets" feature (wavelets-hhH_NGTDm_coarseness) has significant correlation with the MoCA scores of CI-LBLP patients. It represents the texture roughness of the rapid grayscale change between a DC's pixel or voxel and its adjacent pixel or voxel. This suggests that the heterogeneity of degree centrality changes is closely associated with cognitive impairment in LBLP patients. In this study, it was also found that hippocampal functional radiomic features of patients in both groups were related to pain intensification and anxiety state, indicating that pain stimulation and pain-induced anxiety participated in the functional changes of the hippocampus.

Hippocampus is involved in pain processing, pain-related attention and anxiety, and stress response.³⁴ Intrinsic connectivity between chronic pain and limbic systems, such as the hippocampus, has been proposed to explain the association between chronic pain and cognitive function.²⁹ In the state of chronic pain, multiple factors such as nervous system sensitization, imbalance between ascending stimulation and descending inhibition, and dysregulation of regulatory circuits can aggravate the decline of cognitive functions related to the limbic system, such as executive function, language, memory and attention.^{3,29,31,35} Recent studies indicated tape containing magnetic particles (TCMP) and tape with magnetic particles (MPT) applied to the lumbar area have an immediate effect on the autonomic nervous system (ANS) and can reduce perceived chronic low back pain.^{25,35} The innovative application of this technique in comparative studies of CI-LBLP and CP-LBLP highlights the robust neurobiological foundation underlying the altered hippocampal functional radiomic. The differentiation between cognitively impaired patients and those with LBLP may provide valuable insights for clinical practice.

Limitations

There are several limitations to this study. First, this is a prospective recruitment study, the recruited LBLP patients come from the pain clinical department. When the patients first develop cognitive disorders, their family members are more willing to seek medical treatment, and with the prolongation of the disease course, they will gradually accept this reality or lose patience and reduce the behavior of seeking medical treatment, or transfer to the neurology department. In addition, age may be a risk factor for cognitive impairment. Second, as a pain study, the cognitive assessment was limited (only MoCA), and no specific scale assessment, such as memory scale, was performed. Further prospective studies with comprehensive clinical and specific cognitive information such as working memory to explore the clinical significance of these hippocampal imaging markers. Finally, as a preliminary, exploratory study, it was not verified by external data. The model requires careful application. This model based on the hippocampal function radiomic features still needs to be careful in clinical application.

Conclusion

In this study, based on the hippocampal functional radiomic features, an LR algorithm classifier was constructed, which can effectively distinguish cognitively impaired patients from those with LBLP, and is helpful to clinical practice and explain the pathologic mechanisms of patients.

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Disclosure

The authors report no conflicts of interest in this work.

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