Journal of Psychiatric Research 158 (2023) 382–391

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

The effect of hippocampal radiomic features and functional connectivity on the relationship between hippocampal volume and cognitive function in Alzheimer's disease

Yang Du [a,b], Shaowei Zhang [a,b], Qi Qiu [a,b], Jianye Zhang [c], Yuan Fang [a,b], Lu Zhao [a,b], Wenjing Wei [a,b], Jinghua Wang [a,b], Jinhong Wang [c,**], Xia Li [a,b,*]

[a] Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, 200030, China
[b] Alzheimer's Disease and Related Disorders Center, Shanghai Jiao Tong University, Shanghai, 200030, China
[c] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, 200030, China

ARTICLE INFO

Keywords:
Alzheimer's disease
Radiomic features
Hippocampal volume
Functional connectivity
Mediation effect
Moderation effect

ABSTRACT

Hippocampal volume is associated with cognitive function in Alzheimer's disease (AD). Hippocampal radiomic features and resting-state functional connectivity (rs-FC) are promising biomarkers and correlate with AD pathology. However, few studies have been conducted on how hippocampal biomarkers affect the cognition-structure relationship. Therefore, we aimed to investigate the effects of hippocampal radiomic features and resting-state functional connectivity (rs-FC) on this relationship in AD. We enrolled 70 AD patients and 65 healthy controls (HCs). The FreeSurfer software was used to measure hippocampal volume. We selected hippocampal radiomic features to build a model to distinguish AD patients from HCs and used a seed-based approach to calculate the hippocampal rs-FC. Furthermore, we conducted mediation and moderation analyses to investigate the effect of hippocampal radiomic features and rs-FC on the relationship between hippocampal volume and cognition in AD. The results suggested that hippocampal radiomic features mediated the association between bilateral hippocampal volume and cognition in AD. Additionally, patients with AD showed weaker rs-FC between the bilateral hippocampus and right ventral posterior cingulate cortex and stronger rs-FC between the left hippocampus and left insula than HCs. The rs-FC between the hippocampus and insula moderated the relationship between hippocampal volume and cognition in AD, suggesting that this rs-FC could exacerbate or ameliorate the effects of hippocampal volume on cognition and may be essential in improving cognitive function in AD. Our findings may not only expand existing biological knowledge of the interrelationships among hippocampal biomarkers and cognition but also provide potential targets for treatment strategies for AD.

1. Introduction

Alzheimer's disease (AD), characterized by hippocampal atrophy, is a progressive neurodegenerative disorder (Josephs et al., 2020). The role of hippocampal atrophy in AD has become increasingly important owing to its part of the diagnostic criteria and correlation with the severity of cognitive impairment (Lazarov and Hollands, 2016). Recently, studies have shown a positive relationship between hippocampal volume and cognitive performance, as measured by the Mini-Mental State Examination (MMSE), in patients with AD (Yang et al., 2021; Yamashita et al., 2022). More importantly, few studies have investigated the biological mechanisms underlying the relationship between hippocampal volume and cognitive impairment in patients with AD. In addition to identifying the correlation, determining how and when this relationship holds are more influential in our understanding of the mechanism (Fairchild and MacKinnon, 2009). However, most studies have not considered whether this association is affected by hippocampal biomarkers by conducting moderation and mediation analyses.

Recently, radiomic features have shown great potential as non-

* Corresponding author. Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, 200030, China.
** Corresponding author.
E-mail addresses: jinhongw2004@foxmail.com (J. Wang), lixia11111@sjtu.edu.cn (X. Li).

https://doi.org/10.1016/j.jpsychires.2023.01.024
Received 10 June 2022; Received in revised form 9 January 2023; Accepted 10 January 2023
Available online 11 January 2023
0022-3956/

invasive neuroimaging biomarkers for AD, opening new avenues for precision medicine (Jiang et al., 2022). Radiomic features describe the spatial distribution of voxel intensity levels, including the gray-level co-occurrence matrix (GLCM), gray-level dependence matrix (GLDM), gray-level run-length matrix (GLRLM), and neighborhood gray-tone difference matrix (NGTDM) (Mayerhoefer et al., 2020). Briefly, the GLCM contains spatial information about the relationship of pixel pairs with similar intensity, the GLDM describes the relationships between the intensities of a pixel and those of its neighbors, the GLRLM measures the zone of uniform pixels, and the NGTDM evaluates the differences between pixel intensities (Abbasian Ardakani et al., 2022). Several magnetic resonance imaging (MRI) studies have found that hippocampal volume could distinguish healthy controls (HCs) from AD patients with an area under the curve (AUC) of 0.80–0.88, while hippocampal radiomic features achieved an AUC of 0.90–0.95 in distinguishing AD patients from HCs (Luk et al., 2018; Park et al., 2021). Although much evidence suggests that radiomic features have promising clinical applications in diagnosis and prognosis, their roles in the neurobiological mechanisms of AD still need to be fully understood.

Radiomic features contain microstructural information that reflects the underlying pathophysiology (Chaddad et al., 2018). Interestingly, AD-related alterations in radiomic features may be affected by the properties or distribution of gray matter volume, and nearly 30% of radiomic features strongly correlate with volume (Traverso et al., 2020). Moreover, recent studies have shown that radiomic features are also significantly associated with changes in amyloid-β (Aβ) and Tau deposition and cognitive function in AD (Zhao et al., 2020). In addition to Aβ and Tau, hippocampal atrophy is a valuable biomarker of AD and is associated with cognitive function. However, it is unclear how hippocampal radiomic features affect the relationship between hippocampal volume and cognitive function in AD. Mediation analysis establishes the extent to which the independent variable influences the dependent variable through the mediators (Igartua and Hayes, 2021). Considering the close relationship between hippocampal radiomic features and AD pathology, we had a rationale to put radiomic features in the mediation analysis when analyzing hippocampal volume to cognitive function in AD. Accordingly, we spectate hippocampal radiomic features that may mediate the effect of hippocampal volume on cognitive function in patients with AD. Conducting this mediation analysis may provide a basis for the indirect influence of radiomic features on cognition in AD, bridge the connection between microstructural information and cognition, and clarify the role of radiomic features in the progression of AD.

Resting-state functional connectivity (rs-FC) is a valid neuroimaging biomarker for AD that reflects the synchrony of functional activities between non-adjacent brain regions within the brain without tasks (Zhang et al., 2021). One study found that the earliest accumulation of Aβ fibrils is associated with altered rs-FC patterns, suggesting that the rs-FC and AD pathology are biologically relevant (Hahn et al., 2019). Of note, the hippocampus is affected early in AD, and hippocampal rs-FC plays an essential role in episodic and autobiographical memory (Frank et al., 2019). Most studies have found extensive decreased hippocampal rs-FC with frontal, parietal, occipital, and temporal lobes in patients with AD (Allen et al., 2007). Furthermore, one study found a widespread decrease in hippocampal rs-FC patterns and a weak correlation between hippocampal volume and MMSE scores in AD patients with a Pearson's correlation coefficient of 0.28 (Subramanian et al., 2020). However, many studies have shown a moderate to strong correlation between hippocampal volume and MMSE scores in AD patients of similar age, education, and disease severity, with a Pearson's correlation coefficient of 0.35–0.67 (Nakata et al., 2009; Feng et al., 2021). Based on the above findings, it is likely that the magnitude of the association between hippocampal volume and cognitive function in patients with AD depends on hippocampal rs-FC. Therefore, we speculate that hippocampal rs-FC may moderate the association between hippocampal volume and cognitive function in AD. That is, different hippocampal rs-FC may correspond to different structure-cognitive correlation patterns. Moreover, hippocampal rs-FC represents an early neuroimaging biomarker for AD and can predict clinical response to AD treatment (Wei et al., 2022). Elucidating the moderation effect of hippocampal rs-FC on the relationships between hippocampal volume and cognitive function in AD may not only provide potential explanations for the pattern of non-fixed structure-cognition relationships in AD but help to clarify the potential target for intervention strategies for AD.

First, we aimed to verify the relationship between hippocampal volume and cognitive impairment in AD patients. Second, we explored hippocampal radiomic features for distinguishing AD patients from HCs and compared hippocampus-based rs-FC in AD patients and HCs. Finally, we investigated the mediation effect of hippocampal radiomic features and the moderation effect of hippocampal rs-FC on the association between hippocampal volume and cognition in AD.

2. Methods

2.1. Participants

In total, 70 patients with AD from the Shanghai Action of Dementia Prevention for the Elderly (SHAPE) cohort (Fang and Li, 2021) were recruited. Moreover, we recruited 65 healthy controls (HCs) matched for age, sex, and education. Patients with AD were diagnosed based on the revised National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 2011). Additionally, HCs were required to have an MMSE score $\geq$27 (O'Bryant et al., 2008). Furthermore, we included 135 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to validate the findings of the SHAPE cohort.

This retrospective study was approved by the Ethics Committee of the Shanghai Mental Health Center, School of Medicine, Shanghai Jiao Tong University, and all participants provided written informed consent. The institutional review board approved using ADNI data at each site, and all participants provided written permission.

2.2. MRI data acquisition and preprocessing

All subjects from the SHAPE cohort were scanned using a 3.0-T MRI system (Siemens, Munich, Germany) with an 8-channel phase-array head coil. A 3D magnetization-prepared rapid gradient-echo imaging (MPRAGE) sequence was used with the following parameters:176 sagittal slices, slice thickness = 1.2 mm, flip angle = 9°, repetition time (TR) = 2530 ms, and echo time (TE) = 3.5 ms. Moreover, resting-state functional MRI (rs-fMRI) data were obtained using a gradient-echo echo-planar imaging sequence with the following parameters:50 slices, slice thickness = 3 mm, flip angle = 90°, TR = 2000 ms, TE = 30 ms.

Structural MRI scans were preprocessed using the free software, FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer provides a full processing stream of structural MRI data. The bias field of the images was corrected using a non-uniform intensity normalization algorithm. Images were registered to the Montreal Neurological Institute (MNI) 152 atlas for the next step of fMRI analysis.

The rs-fMRI data were preprocessed and analyzed using the Data Processing and Analysis for Brain Imaging Toolkit (Yan et al., 2016). First, we discarded the first ten time points. Second, we performed slice timing and head motion corrections. We then used the Friston 24-parameter model to minimize the effects of head motion. Finally, we calculated the mean framewise displacement (FD) to measure microscale head motion. All subjects met the criteria of a mean FD < 0.2 mm. The images were spatially normalized into the standard MNI space. Subsequently, we removed the linear trend from the fMRI data and performed bandpass filtering (0.01–0.08 Hz). Furthermore, we regressed the white matter and cerebrospinal fluid signals.

2.3. Hippocampal volume and correlation analysis

The absolute hippocampal volume was obtained from FreeSurfer hippocampus segmentation and was comparable in accuracy to manual labeling (Srinivasan et al., 2020). We normalized regional brain volumes by the total intracranial volume (ICV) to estimate the degree of atrophy (Voevodskaya et al., 2014). Therefore, we normalized the hippocampal volume from the absolute hippocampal volume divided by the ICV. Bilateral hippocampal volumes were compared between the AD and HC groups using a two-sample *t*-test, controlling for age, sex, and educational level. Finally, we performed a partial correlation analysis to explore the correlations between hippocampal volume and MMSE scores with age, sex, and education as covariates.

2.4. Radiomics analysis

In our study, the hippocampus was a critical region of interest. The preprocessed 3D T1-weighted MPRAGE images were used for hippocampal segmentation, and the open-source software 3D-slicer (https://www.slicer.org/) was used to visualize the images. Two expert radiologists worked together to label the hippocampus for each subject manually. Image features were extracted using the "pyradiomics" package in the software (http://www.jetbrains.com/pycharm/).

The SHAPE data were randomly divided into training and test datasets at ratios of 0.7 and 0.3, respectively. We used t-tests and Mann–Whitney U tests to select significantly different features ($p < 0.05$). Since the least absolute shrinkage and selection operator (LASSO) method is a commonly applied feature selection method (Lee et al., 2016), we used the LASSO regression analysis method with 10-fold cross-validation to select the valuable features and the corresponding lambda values with minimum mean-squared error (MSE) values.

Support vector machines (SVM) are extensively employed in machine learning algorithms (Kavzoglu and Colkesen, 2009); therefore, we chose the SVM model to establish a classification model based on selected features of the bilateral hippocampus. We then used ADNI data as an external validation set to verify the generalization and robustness of the classification model. The model's classification performance was assessed using the following metrics: accuracy, sensitivity, specificity, and AUC. Finally, we performed a partial correlation analysis to explore the correlations between hippocampal radiomic features, hippocampal volume, and MMSE scores with age, sex, and education as covariates.

2.5. Resting-state FC analysis

The bilateral hippocampal regions defined by the automated anatomical labeling atlas were selected as seeds. Moreover, seed-based rs-FC analysis was performed using the Resting-State fMRI Data Analysis Toolkit (REST) (http://www.restfmri.net/forum, version 1.8). First, we calculated the Pearson's correlation coefficients between the mean time course of each seed and voxel in the whole brain. Next, we conducted a voxel-wise correlation analysis between each seed and all other brain voxels to acquire the FC maps. Fisher's Z-transformation was used to standardize Pearson's correlation coefficient. We then compared the Z-score FC maps of the bilateral hippocampus between the AD and HC groups using a two-sample *t*-test with age, sex, and education as covariates. Gaussian random field (GRF) correction (voxel-level $p < 0.001$, cluster-level $p < 0.05$, two-tailed) was used to correct for multiple comparisons for statistical analyses.

2.6. Moderation and mediation analysis

Mediation analysis is a statistical method for multivariate studies that explain how the mediator mediates the effect of the independent variable (X) on the dependent variable (Y) (Preacher and Hayes, 2004). In a simple mediation model, c denotes the total effect of X on Y and c' estimates the direct effect of X on Y. Moreover, the indirect effect of X on Y through the mediator is ab, which can be calculated as ab = c – c'. The moderation analysis describes how X's effect on Y depends on the moderator. In other words, moderation analysis refers to the effect of X on Y being moderated if its size, sign, or strength depends on the moderator (Hayes and Rockwood, 2017).

We conducted moderation and mediation analyses using PROCESS v3.4 macro in SPSS (Hayes, 2013). We used the variance inflation factor (VIF) to assess multicollinearity and chose a threshold of VIF >10 to indicate multicollinearity. We explored the moderation effect of hippocampal rs-FC and the mediation effect of hippocampal radiomic features on the relationship between hippocampal volume and cognitive function in AD. A bias-corrected bootstrap approach with 5000 iterations was used to test the significance of moderation and mediation effects in AD. Bootstrapped 95% confidence intervals (CIs), not including zero, were considered significant (Hayes, 2018), with age, sex, and education as covariates. To demonstrate the moderation effect more visually, we conducted a simple slope analysis (Dawson, 2014) to depict how the positive relationship between the left hippocampal volume and MMSE scores in patients with AD changes as one standard deviation below and above the mean level for our low and high values of the hippocampal rs-FC.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics are presented in Table 1. In the SHAPE data, the AD group showed significantly higher Clinical Dementia Rating (CDR) scores ($p < 0.001$) and significantly lower MMSE scores ($p < 0.001$) than the HC group, which is consistent with the results of the ADNI data. There were no differences in age, sex, or education between the patients with AD and HCs in the SHAPE and ADNI data. Similarly, we included patients with mild-to-severe AD in the SHAPE and ADNI data. Additionally, the mean AD duration in patients from the SHAPE dataset was 1.83 ± 1.21 years, while it was 2.04 ± 1.14 years in the ADNI dataset (Table 1). Moreover, all patients with AD received combined treatment with memantine and donepezil.

3.2. Hippocampal volume and correlation analysis results

The AD group showed a significantly lower volume of bilateral hippocampus than the HC group ($p < 0.001$) (Table 1, Fig. 1A). At the same time, there was no difference in the ICV between patients with AD and HCs. Additionally, we observed a positive correlation between the left hippocampal volume and MMSE scores ($r = 0.4649$, $p < 0.001$). In contrast, the right hippocampal volume was positively associated with MMSE scores ($r = 0.3858$, $p = 0.001$) in AD (Fig. 1B and C).

3.3. Radiomics analysis results

In total, 282 features were extracted from the bilateral hippocampus. After t-tests and Mann–Whitney U tests, 102 bilateral hippocampal features were retained. The values of the coefficients and the corresponding lambda values, and the MSE values and the corresponding lambda values for the AD and HC groups are shown in Fig. 2A and B, respectively. Moreover, the LASSO regression model yielded six features in the left hippocampus and seven in the right hippocampus (Fig. 2C, Table 2). In the test set, the accuracy, sensitivity, specificity, and AUC were 0.94, 0.98, 0.88, and 0.96, respectively, and 0.93, 0.96, 0.88, and 0.95 in the validation set, respectively, to differentiate between AD patients and HCs (Fig. 2D).

Furthermore, in patients with AD, we found that radiomic features, including IV ($r = 0.2511$, $p = 0.038$) and IDN ($r = 0.3708$, $p = 0.002$), were positively correlated with left hippocampal volume (Fig. 3A). The right hippocampal volume positively and negatively correlated with IV ($r = 0.3368$, $p = 0.005$) and contrast ($r = -0.3093$, $p = 0.010$),

Table 1
The demographic and clinical characteristics of the two groups.

	SHAPE			ADNI		
Characteristic	AD	HC	*P* value	AD	HC	*P* value
N	70	65	–	70	65	–
Age, y	72.27 ± 6.96	72.23 ± 4.49	0.97	72.82 ± 4.49	72.27 ± 4.43	0.92
Sex, F (%)	45 (64.3%)	40 (61.5%)	0.72	45 (64.3%)	40 (61.5%)	0.72
Education, y	10.92 ± 3.40	10.08 ± 3.19	0.84	11.12 ± 2.47	11.17 ± 2.62	0.96
Duration, y	1.83 ± 1.21	–	–	2.04 ± 1.14	–	–
CDR	1.22 ± 0.56	0.00 ± 0.00	<0.0001	1.14 ± 0.41	0.00 ± 0.00	<0.0001
MMSE	13.18 ± 6.32	27.42 ± 0.95	<0.0001	13.75 ± 3.24	27.93 ± 0.83	<0.0001
ICV (cm^3)	1469.57 ± 216	1512.12 ± 158	0.28	1493.80 ± 174	1545.54 ± 157	0.32
Left hippocampal volume (%)	0.18 ± 0.04	0.24 ± 0.03	<0.001	0.18 ± 0.02	0.25 ± 0.03	<0.0001
Right hippocampal volume (%)	0.19 ± 0.04	0.25 ± 0.03	<0.001	0.18 ± 0.02	0.26 ± 0.03	<0.0001

Abbreviations: CDR, Clinical Dementia Rating Scale; MMSE, Mini-Mental State Examination; AD, Alzheimer's disease; HC, healthy control; ICV, total intracranial volume.

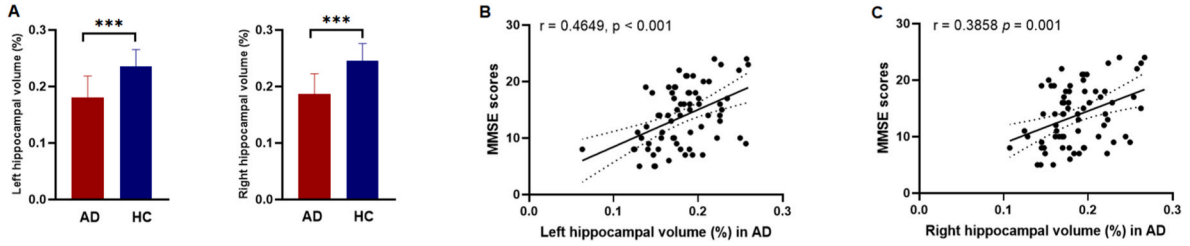

Fig. 1. The difference in bilateral hippocampal volume between AD patients and healthy subjects (A) and correlation analysis between the left hippocampal volume (B) and right hippocampal volume (C) and the Mini-Mental State Examination (MMSE) scores in AD patients.

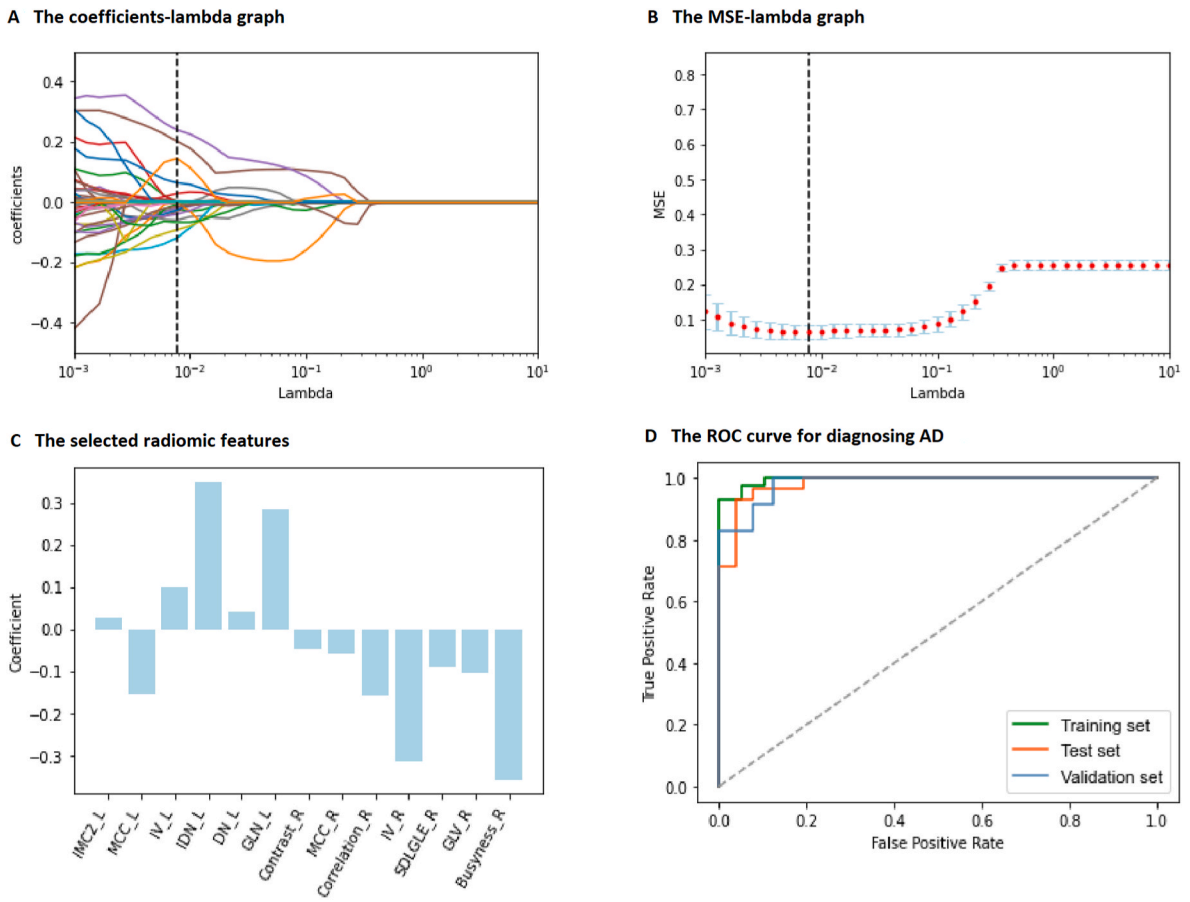

Fig. 2. The coefficients-lambda graph (A) and the MSE-lambda graph (B) in the AD-HC groups, the selected radiomic features for the bilateral hippocampus following LASSO regression (C), the ROC curve of the training and test and validation sets of the hippocampus for diagnosing AD (D).

Table 2
The selected radiomic features for the left and right hippocampus used in the current study following LASSO regression.

Type of features	The left hippocampus	The right hippocampus
GLCM	IMC2	Contrast
	MCC	MCC
	IV	Correlation
	IDN	IV
GLDM	DN	SDLGLE
GLRLM	GLN	GLV
NGTDM		Busyness

Abbreviations: GLCM, Gray Level Co-occurrence Matrix; GLDM, Gray Level Dependence Matrix; GLRLM, Gray Level Run Length Matrix; NGTDM, Neighbouring Gray Tone Difference Matrix; IMC, Informational Measure of Correlation; MCC, Maximal Correlation Coefficient; IV, Inverse Variance; IDN, Inverse Difference Normalized; DN, Dependence Non-Uniformity; SDHGLE, Small Dependence High Gray Level Emphasis; GLN, Gray Level Non-Uniformity; GLV, Gray Level Variance.

respectively (Fig. 3B). Moreover, the left hippocampal radiomic features of IV ($r = 0.4934$, $p < 0.001$) and IDN ($r = 0.4427$, $p < 0.001$) were positively correlated with the MMSE scores (Fig. 3C). The right hippocampal radiomic features of IV ($r = 0.4117$, $p < 0.001$) were positively associated with MMSE scores, and contrast ($r = -0.3880$, $p = 0.001$) was negatively associated with MMSE scores (Fig. 3D).

3.4. Resting-state FC results

Regarding the left hippocampus, we observed weaker rs-FC between the left hippocampus seed, left dorsal anterior cingulate cortex (ACC), and the right ventral posterior cingulate cortex (PCC) and stronger rs-FC between the left hippocampus seed and the left insula in patients with AD as compared to those of HCs (Table 3, Fig. 4A and B). Regarding the right hippocampus, we observed weaker rs-FC between the right hippocampus seed and the right ventral PCC in AD patients compared to HCs (Table 3, Fig. 4C). However, there was no statistical correlation between hippocampal rs-FC and MMSE scores ($p = 0.28$), duration of illness ($p = 0.53$), and radiomic features ($p = 0.18$) in AD.

3.5. Moderation and mediation analysis results

In this study, no multicollinearity was found in any of the models. Our findings demonstrated that hippocampal radiomic features in AD patients mediated the relationship between left hippocampal volume and cognitive impairment, including IV (indirect effect = 0.1029, bootstrapped 95% CI = [0.0272, 0.2025]; $p < 0.05$) and IDN (indirect effect = 0.1204, bootstrapped 95% CI = [0.0348, 0.2274]; $p < 0.05$), with an approximate proportion of mediation of 22% and 26%, respectively (Fig. 5A and B). Additionally, IV (indirect effect = 0.1145, bootstrapped 95% CI = [0.0349, 0.2089]; $p < 0.05$) and contrast (indirect effect = 0.0960, bootstrapped 95% CI = [0.0221, 0.1854]; $p < 0.05$) mediated the association between the right hippocampal volume and cognitive function in AD patients, with the percentage of mediation ranging from 25% to 30% (Fig. 5C and D).

Moreover, we observed that the rs-FC between the left hippocampus and left insula moderated the positive relationship between the left hippocampal volume and cognitive function measured using MMSE scores in AD patients (bootstrapped 95% CI = [2012.83, 54798.79]; $p = 0.0353$). In brief, the positive relationship between left hippocampal volume and MMSE scores varied according to the strength of the rs-FC between the left hippocampus and left insula in patients with AD. A simple slope graph depicting the moderation effect of hippocampal rs-FC is shown in Fig. 6.

4. Discussion

In the present study, we aimed to explore the effect of hippocampal radiomic features and rs-FC on the relationship between hippocampal

Table 3
Group comparison of rs-FC between the bilateral hippocampus and whole brain.

Cluster location	Number of voxels	MNI coordinates (x, y, z)			*T*-value	*p*-GRF
Seed: Left Hippocampus						
AD < HC						
Left dorsal anterior cingulate cortex	351	−3	54	15	−4.84	<0.001
Right ventral posterior cingulate cortex	111	9	−18	33	−4.35	0.004
AD > HC						
Left insula	148	−39	3	−12	4.89	0.002
Seed: Right Hippocampus						
AD < HC						
Right ventral posterior cingulate cortex	67	9	−21	30	−4.41	0.036

Abbreviations: AD, Alzheimer's disease; HC, healthy control; MNI, the Montreal Neurological Institute; GRF, Gaussian random field.

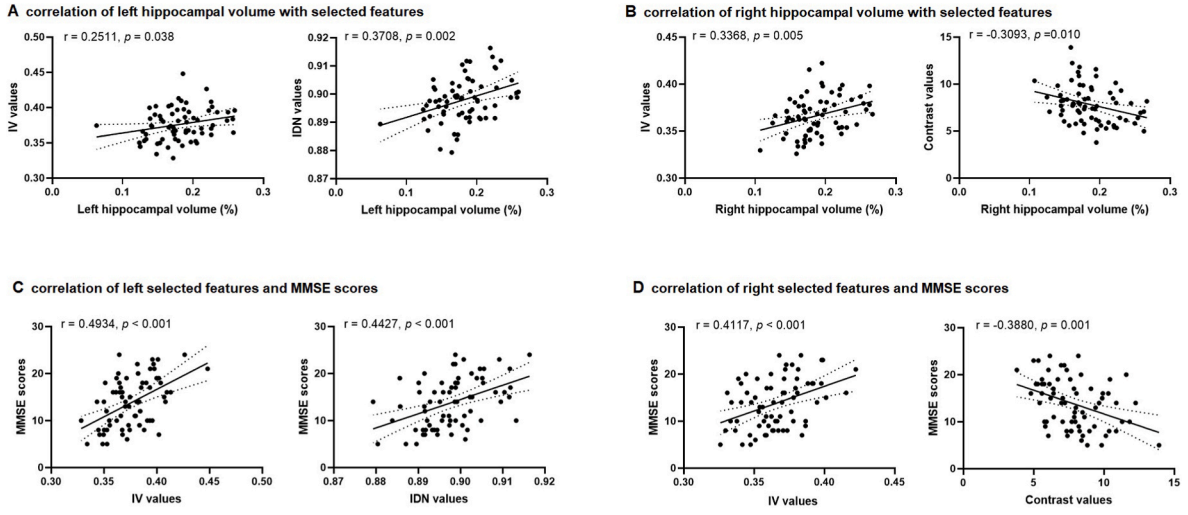

Fig. 3. Correlation analysis between the left hippocampal volume (A) and right hippocampal volume (B) and selected radiomic features in AD; correlation analysis between the left selected radiomic features (C) and right selected radiomic features (D) and MMSE scores in AD patients.

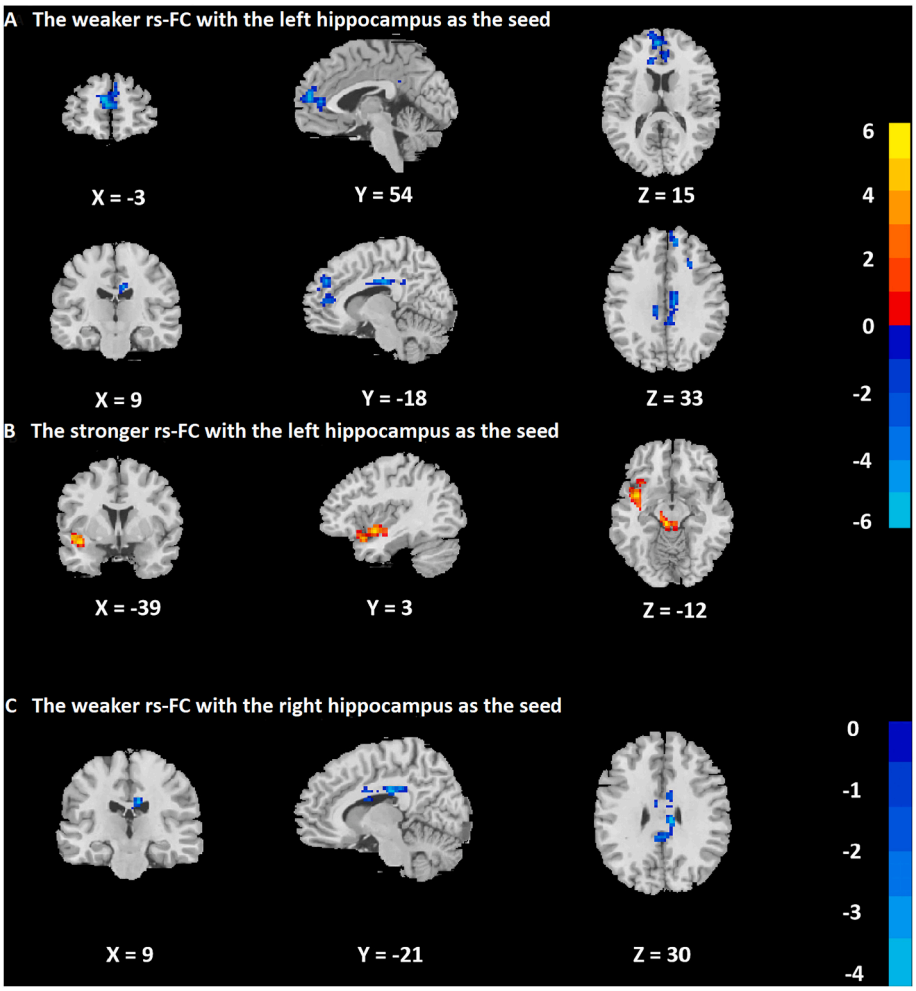

Fig. 4. Differential rs-FC of the bilateral hippocampus between AD group and HCs group. Weaker rs-FC between the left hippocampus and the left dorsal anterior cingulate cortex and the right ventral posterior cingulate cortex (A), and stronger rs-FC between the left hippocampus and the left insula (B), weaker rs-FC between the right hippocampus and the right ventral posterior cingulate cortex (C) in AD patients compared to HCs.

volume and cognitive function, yielding insights into hippocampal biomarkers in the neurobiological mechanisms underlying AD. Our study observed that hippocampal radiomic features mediated the relationship between bilateral hippocampal volume and cognition in AD, which may serve as a neural substrate in the association between hippocampal volume and cognition. Moreover, we found a weaker rs-FC between the left hippocampus and the left dorsal ACC and the right ventral PCC and a stronger rs-FC between the left hippocampus and the left insula in AD. Additionally, the rs-FC between the left hippocampus and left insula moderated the relationship between left hippocampal volume and cognitive function in AD, indicating that the higher the hippocampal rs-FC was, the stronger the positive association was between hippocampal volume and cognitive function.

We found that the influence of hippocampal volume on cognition is mediated by radiomic features, including IV, IDN, and contrast, in patients with AD. IV measures the homogeneity of image features, IDN quantifies the local homogeneity, and contrast estimates the local intensity variation (Yip et al., 2017). Notably, the features of IV and IDN in the left hippocampus and IV and contrast in the right hippocampus were all GLCM features. Several radiomics analyses have shown that GLCM texture features are one of the most accurate for diagnosing AD (Dhruv et al., 2019). Moreover, existing evidence has demonstrated that the accumulated effect of neurofibrillary tangles and Aβ plaques leads to changes in the statistical properties of the image intensities, which could be reflected by radiomic features (Sorensen et al., 2016). In this study, hippocampal volume affected cognitive impairments indirectly through the mediation effect of GLCM features, which varied from 22% to 30%. This finding suggests that hippocampal volume affects cognition directly and indirectly through structural changes reflected by hippocampal volume and microstructural changes reflected by radiomic features, highlighting the indirect pathway for hippocampal radiomic features to affect cognitive function.

Moreover, the mediation effect of hippocampal radiomic features suggests that cognitive decline may be caused by structural changes detected by hippocampal volume and microstructural changes detected by hippocampal radiomic features in AD. These findings suggest that hippocampal volume affects hippocampal radiomic features, which drives cognitive decline and highlights a potential pathway in which hippocampal volume affects cognition by changing hippocampal radiomic features. Hippocampal volume is often used clinically to assess the degree of brain atrophy in AD patients qualitatively. Combined with our findings, combining hippocampal volume and radiomic features in the clinical assessment of morphological changes may facilitate a more accurate and personalized assessment of AD patients. However, this speculation needs to be applied and generalized with caution. Further studies to demonstrate this are warranted. In general, the present study indicates that hippocampal radiomic features act as crucial mediators of cognition in AD, which is critical in revealing the pathological mechanisms of radiomic features involved in AD.

Compared with HCs, patients with AD showed weaker rs-FC between

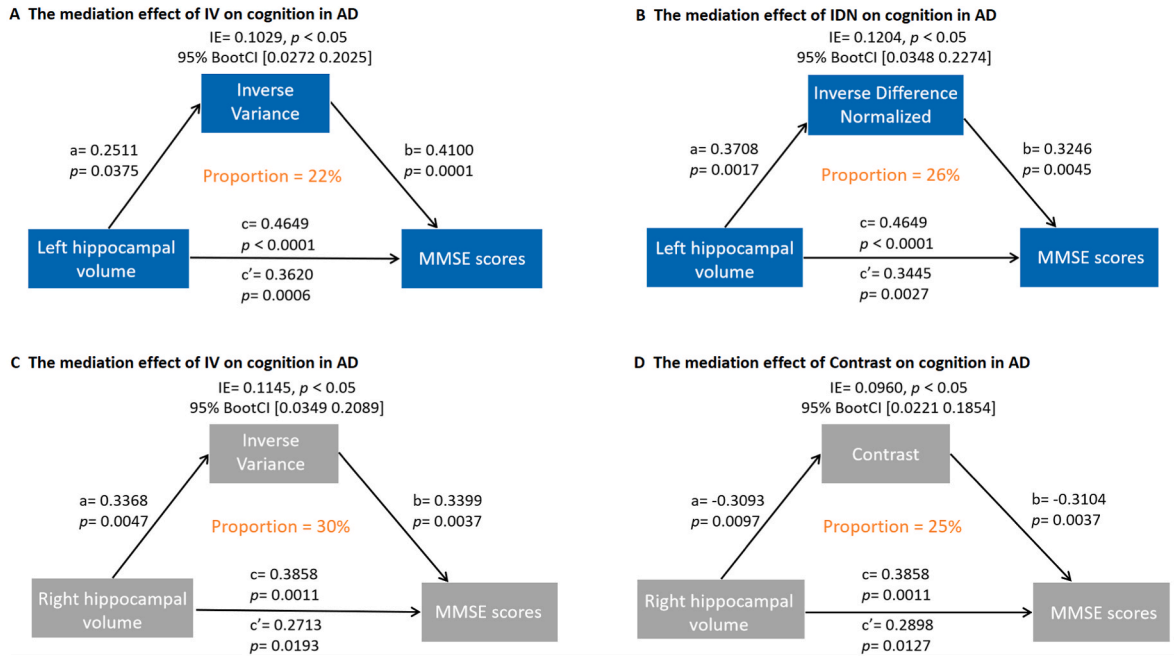

Fig. 5. The mediation effect of IV and IDN on the positive relationship between the left hippocampal volume and cognitive function (A–B), and the mediation effect of IV and contrast on the positive relationship between the right hippocampal volume and cognitive function in patients with AD (C–D). IE, indirect effect; CI, confidence interval; IV, inverse variance; IDN, inverse difference normalized; MMSE scores, scores on the Mini-Mental State Exam.

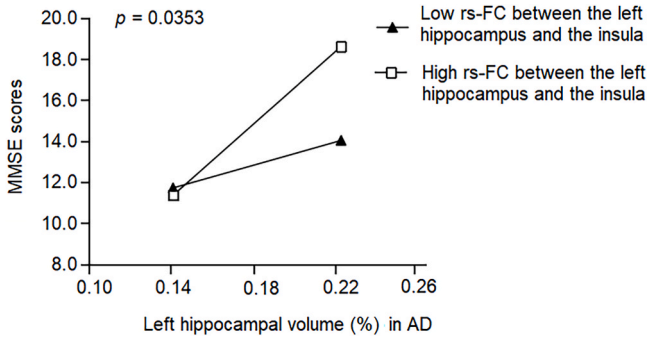

Fig. 6. A visual representation of the moderation effect of the rs-FC between the left hippocampus and insula on the positive relationship between the left hippocampal volume on cognitive function measured by MMSE scores in AD. Low rs-FC between the left hippocampus and insula: one standard deviation below the mean level of the rs-FC; High rs-FC between the left hippocampus and insula: one standard deviation above the mean level of the rs-FC.

the left hippocampus and the left dorsal ACC and between the bilateral hippocampus and the right ventral PCC. The rs-FC between the hippocampus and the ACC plays a vital role in cognitive control processes, such as attention control in the elderly (Cao et al., 2014). Moreover, a previous study indicated that hippocampal rs-FC with the dorsal ACC may be related to stimulus responses and memory encoding (Chen et al., 2019). Similar to our findings, an rs-fMRI study showed decreased rs-FC between the hippocampus and the ACC in AD patients (Wang et al., 2006). Our finding of weaker connectivity between the left hippocampus and the dorsal ACC provides additional information on AD pathology from a network perspective. Moreover, the rs-FC between the hippocampus and the PCC is involved in cognitive processes such as retrieval of episodic and semantic memories, spatial memory, and navigation (Rolls, 2019). Consistent with our findings, several studies have also found weaker functional connectivity between the hippocampus and PCC (Soldner et al., 2012). Therefore, disrupted hippocampal rs-FC with the dorsal ACC and the ventral PCC may contribute to the underlying pathophysiology of AD, providing a reference for further understanding of AD.

Furthermore, patients with AD demonstrate a stronger left hippocampal rs-FC with the left insula. The evidence indicates that the rs-FC between the hippocampus and the insula is related to the encoding and memory systems (Tsukiura et al., 2013). A previous study showed stronger hippocampal rs-FC with the insula in patients with AD (Zhu et al., 2022), further supporting our findings. Moreover, a study showed that instantaneous memory scores were positively correlated with rs-FC between the hippocampus and insula, providing neuroimaging evidence for understanding the mechanisms of cognitive impairment (Shen et al., 2019). The evidence showed that changes in rs-FC may reflect pathology; however, altered rs-FC may also reflect adaptive mechanisms that compensate for the underlying pathology (Geddes et al., 1985). Therefore, we hypothesized that stronger rs-FC between the hippocampus and insula in patients with AD might represent a compensatory mechanism for mounting neuropathologic changes involving memory mechanisms. In summary, stronger rs-FC between the hippocampus and insula may indicate adaptation to compensate for impaired cognitive function.

Notably, our study did not find a relationship between abnormal hippocampal rs-FC and cognitive function. Several previous studies have shown that the hippocampal rs-FC with the prefrontal cortex, olfactory cortex, and inferior temporal gyrus is significantly related to cognitive function in AD (Xue et al., 2019). However, the patients with AD in the aforementioned studies had relatively good cognitive function, with a mean MMSE score ≥21. In contrast, the patients with AD in our study had relatively poor cognitive function, with a mean MMSE score of 13. A previous study showed a bidirectional change in the increase and decrease of rs-FC as AD staging progressed (Zhang et al., 2010). On the one hand, the decreased rs-FC may be associated with disconnection in these AD-affected brain regions, which play an extraordinary role in the degeneration of brain networks during AD. On the other hand, the increased rs-FC may be related to compensation for the loss and brain remolding due to its plasticity after the damage of original neural networks. Moreover, this study also found that hippocampal rs-FC was not associated with cognitive function in patients with severe AD, which is consistent with our findings. Therefore, we speculated that the

bidirectionally altered rs-FC disrupted the significant correlation between hippocampal rs-FC and cognitive function in patients with severe AD.

Moreover, we used the MMSE to assess the severity of global cognitive impairment, which has shown good longitudinal stability and has been widely used in previous studies assessing hippocampal volume and cognitive function in AD (Chishiki et al., 2020). Of note, previous studies found that abnormal hippocampal rs-FC correlated with Rey auditory verbal learning test (RAVLT) scores, which reflect subdomains of cognitive function for verbal learning and memory rather than global cognitive function (Lu et al., 2019). Thus, the lack of a more refined assessment of cognitive function subdomains in this study may have influenced our inability to detect a correlation between hippocampal rs-FC and cognition in patients with AD. Furthermore, we included patients taking AD medications of donepezil and memantine. Several studies have found the increased rs-FC between the hippocampus and the PCC after donepezil treatment in patients with AD (Goveas et al., 2011). Moreover, studies showed increased rs-FC between the hippocampus and frontal cortical structures in moderate-severe AD patients after memantine treatment (Guo et al., 2018). The above evidence suggests that hippocampal functional connectivity patterns in AD patients taking medications may be disturbed by medications. Therefore, we hypothesized that hippocampal rs-FC in AD patients is not associated with cognitive function, possibly due to medication interference.

This study found the moderation effect of rs-FC between the left hippocampus and left insula on the relationship between left hippocampal volume and cognition measured using MMSE scores in AD. Several studies have found that disrupted hippocampal rs-FC with the insula may underlie the lack of information integration and memory processing in AD (Berlingeri et al., 2015). Therefore, connectivity still works in patients with AD with higher rs-FC between the left hippocampus and left insula, resulting in a significant correlation between hippocampal volume and cognitive function. Conversely, in AD patients with lower rs-FC, connectivity dysfunction leads to an insignificant association between hippocampal volume and cognition, which suggests that even if the hippocampal volume is larger in these patients, the MMSE score is not equally significant. Generally, the association between hippocampal volume and cognitive function is not static or fixed; however, it is moderated by the hippocampal rs-FC to varying degrees. Specifically, AD patients with a larger hippocampal volume and higher hippocampal rs-FC tended to be associated with higher MMSE scores, suggesting that the interaction between hippocampal volume and rs-FC additionally affects cognitive function in AD patients. This finding indicates that this rs-FC could exacerbate or ameliorate the effects of hippocampal volume on cognitive function and may play an essential role in improving cognitive function in AD patients. Additionally, one study has shown that abnormal functional connectivity provides a generalizable and interpretable neuroimaging biomarker, which may be used as an individual target for different therapeutic strategies in AD, such as non-invasive stimulation technology (Ren et al., 2020). Therefore, the rs-FC between the hippocampus and the insula is abnormal in AD patients compared to HCs and plays a moderator role in the structure-cognition relationship, suggesting a potential and promising brain target for treatment strategies for AD.

This study has some limitations. First, the samples used for moderation and mediation analyses were obtained from individuals of the Han race. Evidence has shown different neuropathological mechanisms of AD across different racial backgrounds (Qin et al., 2021). For example, older African Americans are more likely to develop AD than older Caucasians are, and this difference is associated with AD phenotypes downstream of cerebral amyloid deposition (Misiura et al., 2020). Therefore, it is difficult to generalize our findings to other ethnic populations. In brief, the sample homogeneity limits our findings' generalization. Further studies with more diverse samples are required. Second, MMSE measures general cognitive function and does not assess cognitive function across subdomains (Arevalo-Rodriguez et al., 2015). Therefore, this study's use of only the MMSE to assess global cognitive function may not provide more comprehensive information. Future research needs to focus on subdomains of cognitive function by adding assessments of cognitive scales that reflect memory and learning functions, such as the RAVLT and logical memory tests. Third, future studies on individuals with preclinical AD who are not taking medication are warranted because the medication may interfere with the functional connectivity pattern. Additionally, we conducted a cross-sectional mediation analysis. However, using cross-sectional instead of longitudinal data for mediation analyses should be performed cautiously (O'Laughlin et al., 2018). Literature on moderation and mediation analyses in future longitudinal studies should be explored. Finally, the limited sample size may have affected the stability of the radiomic model, resulting in the relatively poor performance of the model in distinguishing patients with AD from HC (Won et al., 2020). Future studies with larger sample sizes are necessary to ensure the robustness of the model performance.

In conclusion, hippocampal radiomic features could mediate the positive relationship between hippocampal volume and cognitive impairment in AD, indicating that radiomic features may be associated with the pathogenesis of AD. Moreover, hippocampal rs-FC moderated the association between the left hippocampal volume and cognitive function in AD, providing insights into the interaction between hippocampal biomarkers and cognition and a new therapeutic target for AD.

Funding

This study was supported by grants from the technology promotion project of Shanghai Municipal Health Commission (2019SY045), Shanghai Fifth Round of Public Health Three-year Action Plan (GWV-9.2), Clinical Research Plan of SHDC (SHDC2020CR1044B), and National Key R&D Program of China (2017YFC1310500 and 2020YFC2005200).

Author statements

XL, JHW and YD conceived and designed the study. YD, SWZ, QQ, and JYZ acquired and analyzed the data. YF, WJW, and LZ performed and checked the image quality of hippocampal segmentation data. YD, JHW, and XL interpreted the results. YD and JHW drafted the manuscript. All authors contributed to the article and approved the submitted version.

Data availability statement

The data from ADNI can be found in www.adni-info.org. The data form the SHAPE cohort analyzed in this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

None of the authors in this study had any conflict of interest to declare.

Acknowledgements

The authors are most grateful to the Alzheimer's Disease Neuroimaging Initiative (ADNI) and all the study participants for their involvement.

References

Abbasian Ardakani, A., Bureau, N.J., Ciaccio, E.J., Acharya, U.R., 2022. Interpretation of radiomics features-A pictorial review. Comput. Methods Progr. Biomed. 215 (1), 106609.

Allen, G., Barnard, H., McColl, R., Hester, A.L., Fields, J.A., Weiner, M.F., Ringe, W.K., Lipton, A.M., Brooker, M., McDonald, E., Rubin, C.D., Cullum, C.M., 2007. Reduced

hippocampal functional connectivity in Alzheimer disease. Arch. Neurol. 64 (10), 1482–1487.
Arevalo-Rodriguez, I., Smailagic, N., Figuls, M.R.I., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O.L., Cosp, X.B., Cullum, S., 2015. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev. (3), 010783, 2015.
Berlingeri, M., Ravasio, A., Cranna, S., Basilico, S., Sberna, M., Bottini, G., Paulesu, E., 2015. Unrealistic representations of "the self": a cognitive neuroscience assessment of anosognosia for memory deficit. Conscious. Cognit. 37 (1), 160–177.
Cao, W., Luo, C., Zhu, B., Zhang, D., Dong, L., Gong, J., Gong, D., He, H., Tu, S., Yin, W., Li, J., Chen, H., Yao, D., 2014. Resting-state functional connectivity in anterior cingulate cortex in normal aging. Front. Aging Neurosci. 6 (1), 280.
Chaddad, A., Desrosiers, C., Niazi, T., 2018. Deep radiomic analysis of MRI related to Alzheimer's disease. IEEE Access 6 (1), 58213–58221.
Chen, H.J., Zhang, L., Ke, J., Qi, R., Xu, Q., Zhong, Y., Pan, M., Li, J., Lu, G.M., Chen, F., 2019. Altered resting-state dorsal anterior cingulate cortex functional connectivity in patients with post-traumatic stress disorder. Aust. N. Z. J. Psychiatr. 53 (1), 68–79.
Chishiki, Y., Hirano, S., Li, H., Kojima, K., Nakano, Y., Sakurai, T., Mukai, H., Sugiyama, A., Kuwabara, S., 2020. Different patterns of gray matter volume reduction in early-onset and late-onset Alzheimer disease. Cognit. Behav. Neurol. 33 (4), 253–258.
Dawson, J.F., 2014. Moderation in management research: what, why, when, and how. J. Bus. Psychol. 29 (1), 1–19.
Dhruv, B., Mittal, N., Modi, M., 2019. Study of Haralick's and GLCM texture analysis on 3D medical images. Int. J. Neurosci. 129 (4), 350–362.
Fairchild, A.J., MacKinnon, D.P., 2009. A general model for testing mediation and moderation effects. Prev. Sci. 10 (2), 87–99.
Fang, Y., Li, X., 2021. Developing a whole-course management system for older adults with cognitive impairment in ShangHai. IPA Bulletin 38 (2), 17–19.
Feng, F., Huang, W., Meng, Q., Hao, W., Yao, H., Zhou, B., Guo, Y.e., Zhao, C., An, N., Wang, L., Huang, X., Zhang, X., Shu, N., 2021. Altered volume and structural connectivity of the Hippocampus in Alzheimer's disease and amnestic mild cognitive impairment. Front. Aging Neurosci. 13 (1), 705030.
Frank, L.E., Bowman, C.R., Zeithamova, D., 2019. Differential functional connectivity along the long Axis of the Hippocampus Aligns with differential role in memory specificity and generalization. J. Cognit. Neurosci. 31 (12), 1958–1975.
Geddes, J.W., Monaghan, D.T., Cotman, C.W., Lott, I.T., Kim, R.C., Chui, H.C., 1985. Plasticity of hippocampal circuitry in Alzheimer's disease. Science 230 (4730), 1179–1181.
Goveas, J.S., Xie, C., Ward, B.D., Wu, Z., Li, W., Franczak, M., Jones, J.L., Antuono, P.G., Li, S.J., 2011. Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. J. Magn. Reson. Imag. 34 (4), 764–773.
Guo, H., Grajauskas, L., Habash, B., D'Arcy, R.C., Song, X., 2018. Functional MRI technologies in the study of medication treatment effect on Alzheimer's disease. Aging medicine (Milton (N.S.W)) 1 (1), 75–95.
Hahn, A., Strandberg, T.O., Stomrud, E., Nilsson, M., van Westen, D., Palmqvist, S., Ossenkoppele, R., Hansson, O., 2019. Association between earliest amyloid uptake and functional connectivity in cognitively unimpaired elderly. Cerebr. Cortex 29 (5), 2173–2182.
Hayes, A.F., 2013. Introduction to mediation, moderation, and conditional process analysis. J. Educ. Meas. 51 (3), 335–337.
Hayes, A.F., 2018. Partial, conditional, and moderated moderated mediation: quantification, inference, and interpretation. Commun. Monogr. 85 (1), 4–40.
Hayes, A.F., Rockwood, N.J., 2017. Regression-based statistical mediation and moderation analysis in clinical research: observations, recommendations, and implementation. Behav. Res. Ther. 98 (1), 39–57.
Igartua, J.J., Hayes, A.F., 2021. Mediation, moderation, and conditional process analysis: concepts, computations, and some common confusions. Spanish J. Psychol. 24 (1), e49.
Jiang, J.H., Wang, M., Alberts, I., Sun, X.M., Li, T.R., Rominger, A., Zuo, C.T., Han, Y., Shi, K.Y., I. Alzheimer's Dis Neuroimaging, 2022. Using radiomics-based modelling to predict individual progression from mild cognitive impairment to Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imag. 49 (7), 2163–2173.
Josephs, K.A., Martin, P.R., Weigand, S.D., Tosakulwong, N., Buciuc, M., Murray, M.E., Petrucelli, L., Senjem, M.L., Spychalla, A.J., Knopman, D.S., Boeve, B.F., Petersen, R. C., Parisi, J.E., Dickson, D.W., Jack, C.R., Whitwell, J.L., 2020. Protein contributions to brain atrophy acceleration in Alzheimer's disease and primary age-related tauopathy. Brain 143 (11), 3463–3476.
Kavzoglu, T., Colkesen, I., 2009. A kernel functions analysis for support vector machines for land cover classification. Int. J. Appl. Earth Obs. Geoinf. 11 (5), 352–359.
Lazarov, O., Hollands, C., 2016. Hippocampal neurogenesis: learning to remember. Prog. Neurobiol. 138–140 (2), 1–18.
Lee, J.D., Sun, D.L., Sun, Y., Taylor, J.E., 2016. Exact post-selection inference, with application to the lasso. Ann. Stat. 44 (3).
Lu, J., Testa, N., Jordan, R., Elyan, R., Kanekar, S., Wang, J., Eslinger, P., Yang, Q.X., Zhang, B., Karunanayaka, P.R., 2019. Functional connectivity between the resting-state olfactory network and the Hippocampus in Alzheimer's disease. Brain Sci. 9 (12), 1–14.
Luk, C.C., Ishaque, A., Khan, M., Ta, D., Chenji, S., Yang, Y.H., Eurich, D., Kalra, S., I. Alzheimer's Disease Neuroimaging, 2018. Alzheimer's disease: 3-Dimensional MRI texture for prediction of conversion from mild cognitive impairment. Alzheimers Dement (Amst) 10 (1), 755–763.
Mayerhoefer, M.E., Materka, A., Langs, G., Haggstrom, I., Szczypinski, P., Gibbs, P., Cook, G., 2020. Introduction to radiomics. J. Nucl. Med. 61 (4), 488–495.
McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack Jr., C.R., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7 (3), 263–269.
Misiura, M.B., Howell, J.C., Wu, J., Qiu, D., Parker, M.W., Turner, J.A., Hu, W.T., 2020. Race modifies default mode connectivity in Alzheimer's disease. Transl. Neurodegener. 9 (8), 1–15.
Nakata, Y., Sato, N., Nemoto, K., Abe, O., Shikakura, S., Arima, K., Furuta, N., Uno, M., Hirai, S., Masutani, Y., Ohtomo, K., Barkovich, A.J., Aoki, S., 2009. Diffusion abnormality in the posterior cingulum and hippocampal volume: correlation with disease progression in Alzheimer's disease. Magn. Reson. Imaging 27 (3), 347–354.
O'Laughlin, K.D., Martin, M.J., Ferrer, E., 2018. Cross-sectional analysis of longitudinal mediation processes. Multivariate Behav. Res. 53 (3), 375–402.
O'Bryant, S.E., Humphreys, J.D., Smith, G.E., Ivnik, R.J., Graff-Radford, N.R., Petersen, R.C., Lucas, J.A., 2008. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch. Neurol. 65 (7), 963–967.
Park, Y.W., Choi, D., Park, M., Ahn, S.J., Ahn, S.S., Suh, S.H., Lee, S.K., I. Alzheimer's Disease Neuroimaging, 2021. Predicting amyloid pathology in mild cognitive impairment using radiomics analysis of magnetic resonance imaging. J Alzheimers Dis 79 (2), 483–491.
Preacher, K.J., Hayes, A.F., 2004. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav. Res. Methods Instrum. Comput. 36 (4), 717–731.
Qin, W., Li, W.W., Wang, Q., Gong, M., Li, T.T., Shi, Y.Q., Song, Y., Li, Y., Li, F.Y., Jia, J. P., 2021. Race-related association between APOE genotype and Alzheimer's disease: a systematic review and meta-analysis. J. Alzheim. Dis. 83 (2), 897–906.
Ren, H., Zhu, J., Su, X., Chen, S., Zeng, S., Lan, X., Zou, L.Y., Sughrue, M.E., Guo, Y., 2020. Application of structural and functional connectome mismatch for classification and individualized therapy in Alzheimer disease. Front. Public Health 8 (1), 1–12.
Rolls, E.T., 2019. The cingulate cortex and limbic systems for emotion, action, and memory. Brain Struct. Funct. 224 (9), 3001–3018.
Shen, Y., Li, Z., Wu, X., Zou, Z., Wang, E., Dou, S., Yan, F., Zhang, H., Li, Y., 2019. Resting-state fMRI observation on functional connectivity of insula in patients with chronic insomnia based on Chinese brain template. Chin. J. Med. Imaging Technol. 35 (1), 15–19.
Soldner, J., Meindl, T., Koch, W., Bokde, A.L., Reiser, M.F., Moller, H.J., Burger, K., Hampel, H., Teipel, S.J., 2012. Structural and functional neuronal connectivity in Alzheimer's disease: a combined DTI and fMRI study. Nervenarzt 83 (7), 878–887.
Sorensen, L., Igel, C., Liv Hansen, N., Osler, M., Lauritzen, M., Rostrup, E., Nielsen, M., I. Alzheimer's Disease Neuroimaging, B. the Australian Imaging & A. Lifestyle Flagship Study of, 2016. Early detection of Alzheimer's disease using MRI hippocampal texture. Hum. Brain Mapp. 37 (3), 1148–1161.
Srinivasan, D., Erus, G., Doshi, J., Wolk, D.A., Shou, H., Habes, M., Davatzikos, C., I. Alzheimer's Disease Neuroimaging, 2020. A comparison of Freesurfer and multi-atlas MUSE for brain anatomy segmentation: findings about size and age bias, and inter-scanner stability in multi-site aging studies. Neuroimage 223 (1), 117248.
Subramanian, S., Rajamanickam, K., Prakash, J.S., Ramachandran, M., I. for Alzheimer's Disease Neuroimaging, 2020. Study on structural atrophy changes and functional connectivity measures in Alzheimer's disease. J. Med. Imaging 7 (1), 016002.
Traverso, A., Kazmierski, M., Zhovannik, I., Welch, M., Wee, L., Jaffray, D., Dekker, A., Hope, A., 2020. Machine learning helps identifying volume-confounding effects in radiomics. Phys. Med. 71 (1), 24–30.
Tsukiura, T., Shigemune, Y., Nouchi, R., Kambara, T., Kawashima, R., 2013. Insular and hippocampal contributions to remembering people with an impression of bad personality. Soc. Cognit. Affect Neurosci. 8 (5), 515–522.
Voevodskaya, O., Simmons, A., Nordenskjold, R., Kullberg, J., Ahlstrom, H., Lind, L., Wahlund, L.O., Larsson, E.M., Westman, E., I. Alzheimer's Disease Neuroimaging, 2014. The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. Front. Aging Neurosci. 6 (1), 264.
Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., Wu, T., Jiang, T., Li, K., 2006. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage 31 (2), 496–504.
Wei, L.L., Zhang, Y.C., Wang, J.T., Xu, L.Y., Yang, K.H., Lv, X.H., Zhu, Z.W., Gong, Q., Hu, W.M., Li, X., Qian, M.C., Shen, Y.D., Chen, W., 2022. Parietal-hippocampal rTMS improves cognitive function in Alzheimer?s disease and increases dynamic functional connectivity of default mode network. Psychiatr. Res. 315 (1), 114721.
Won, S.Y., Park, Y.W., Park, M., Ahn, S.S., Kim, J., Lee, S.K., 2020. Quality reporting of radiomics analysis in mild cognitive impairment and Alzheimer's disease: a roadmap for moving forward. Korean J. Radiol. 21 (12), 1345–1354.
Xue, J., Guo, H., Gao, Y., Wang, X., Cui, H., Chen, Z., Wang, B., Xiang, J., 2019. Altered directed functional connectivity of the Hippocampus in mild cognitive impairment and Alzheimer's disease: a resting-state fMRI study. Front. Aging Neurosci. 11 (1), 326.
Yamashita, K., Kuwashiro, T., Ishikawa, K., Furuya, K., Harada, S., Shin, S., Wada, N., Hirakawa, C., Okada, Y., Noguchi, T., 2022. Right entorhinal cortical thickness is associated with Mini-Mental State Examination scores from multi-country datasets using MRI. Neuroradiology 64 (2), 279–288.
Yan, C.G., Wang, X.D., Zuo, X.N., Zang, Y.F., 2016. DPABI: data processing & analysis for (Resting-State) brain imaging. Neuroinformatics 14 (3), 339–351.
Yang, C., Ren, J., Li, W., Lu, M., Chu, T.J.B., Cognition, 2021. Individual-level morphological hippocampal networks in patients with Alzheimer's disease. Brain and Cognition 151 (2), 105748.

Yip, S.S., Kim, J., Coroller, T.P., Parmar, C., Velazquez, E.R., Huynh, E., Mak, R.H., Aerts, H.J., 2017. Associations between somatic mutations and metabolic imaging phenotypes in non-small cell lung cancer. J. Nucl. Med. 58 (4), 569–576.

Zhang, H.Y., Wang, S.J., Liu, B., Ma, Z.L., Yang, M., Zhang, Z.J., Teng, G.J., 2010. Resting brain connectivity: changes during the progress of Alzheimer disease. Radiology 256 (2), 598–606.

Zhang, J., Kucyi, A., Raya, J., Nielsen, A.N., Nomi, J.S., Damoiseaux, J.S., Greene, D.J., Horovitz, S.G., Uddin, L.Q., Whitfield-Gabrieli, S., 2021. What have we really learned from functional connectivity in clinical populations? Neuroimage 242 (1), 118466.

Zhao, K., Ding, Y.H., Han, Y., Fan, Y., Alexander-Bloch, A.F., Han, T., Jin, D., Liu, B., Lu, J., Song, C.Y., Wang, P., Wang, D.W., Wang, Q., Xu, K.B., Yang, H.W., Yao, H.X., Zheng, Y.J., Yu, C.S., Zhou, B., Zhang, X.Q., Zhou, Y.Y., Jiang, T.Z., Zhang, X., Liu, Y., Alzheimers Dis Neuroimaging, I., Multi-Ctr Alzheimer Dis Imaging, C., 2020. Independent and reproducible hippocampal radiomic biomarkers for multisite Alzheimer?s disease: diagnosis, longitudinal progress and biological basis. Sci. Bull. 65 (13), 1103–1113.

Zhu, Q., Wang, Y., Zhuo, C., Xu, Q., Yao, Y., Liu, Z., Li, Y., Sun, Z., Wang, J., Lv, M., Wu, Q., Wang, D., 2022. Classification of Alzheimer's disease based on abnormal hippocampal functional connectivity and machine learning. Front. Aging Neurosci. 14 (1), 754334.