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Abnormal Functional Connectivity of Thalamic Subdivisions in Alzheimer's Disease: A Functional Magnetic Resonance Imaging Study

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Abstract—Alzheimer's disease (AD) is characterized by global cognitive impairment in multiple cognitive domains. Thalamic dysfunction during AD progression has been reported. However, there are limited studies regarding dysfunction in the functional connectivity (FC) of thalamic subdivisions and the relationship between such dysfunction and clinical assessments. This study examined dysfunction in the FC of thalamic subdivisions and determined the relationship between such dysfunction and clinical assessments. Forty-eight patients with AD and 47 matched healthy controls were recruited and assessed with scales for multiple cognitive domains. Group-wise comparisons of FC with thalamic subdivisions as seed points were conducted to identify abnormal cerebral regions. Moreover, correlation analysis was conducted to evaluate the relationship between abnormal FC and cognitive performance. Decreased FC of the intralaminar and medial nuclei with the left precuneus was observed in patients but not in heathy controls. The abnormal FC of the medial nuclei with the left precuneus was correlated with the Mini Mental State Examination score in the patient group. Using the FC values showing between-group differences, the linear support vector machine classifier achieved quite good in accuracy, sensitivity, specificity and area under the curve. Dysfunction in the FC of the intralaminar and medial thalamus with the precuneus may comprise a potential neural substrate for cognitive impairment during AD progression, which in turn may provide new treatment targets.

Key words: Alzheimer's disease, thalamus, subdivisions, functional magnetic resonance imaging.

INTRODUCTION

Alzheimer's disease (AD) is characterized by insidious and progressive cognitive impairment and is the most common cause of dementia (Arvanitakis et al., 2019). This neurodegenerative disease is prevalent worldwide. Episodic memory impairment is the core clinical symptom of AD (Dubois et al., 2014), involving failure to remember past events.

AD typically involves amyloid-beta and tau pathology in neurofibrillary tangles that are associated with cognitive decline (Jack et al., 2018). Tau pathologies contribute to cognitive impairment in AD (Malpetti et al., 2020) and can be directly observed in post-mortem studies. Moreover, neuro-fibrillation is generally observed in the spatiotemporal cortex and other neocortical areas associated with memory (Murray et al., 2011; Gefen et al., 2012). Tauopathy associated with sporadic AD may possibly begin in the locus coeruleus, the subcortical nuclei of the low brainstem, rather than in the cortical region (Braak et al., 2011). In addition, tauopathy influences structures located in the Papez circuit (Aggleton et al., 2016), including the thalamus. Researchers have also observed

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Abbreviations: AD, Alzheimer's disease; BOLD, blood oxygen level-dependent; FC, functional connectivity; HCs, healthy controls; LOOCV, leave-one-out cross-validation; MRI, magnetic resonance imaging; rs-fMRI, resting-state functional MRI; SVM, support vector machine; TMS, transcranial magnet stimulation.

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marked thalamic neurofibrillary deposits at similar stages as that involving the hippocampus (stages III–IV), ahead of changes in other regions (Braak and Braak, 1991). Therefore, AD is a degenerative disease where both the cerebral cortex and subcortical nuclei are affected (McDuff and Sumi, 1985; Landin-Romero et al., 2017). The pathologies can be revealed during autopsy, but the procedure is expensive.

With the development of noninvasive neuroimaging methods to observe the disease (Soleimani-Meigooni et al., 2020), we can assess patients *in vivo* (Matsuda, 2016). Numerous studies have shown cortical dysfunction in AD. However, most studies have focused on the subcortical nuclei, i.e., deep gray-matter structures (de Jong et al., 2008; Kenny et al., 2013; Yi et al., 2016). More recently, several AD studies have shifted the focus from the medial temporal lobe to the thalamus (Aggleton et al., 2016) because of marked pathologies in the Papez circuit and thalamus at the early stage of AD.

The thalamus is a crucial brain region involved in the coordination and integration of cerebral processes (Saalmann and Kastner, 2015). Growing evidence has shown that the thalamus comprises a complicated structure, i.e., individual thalamic subnuclei are distinct in their morphology, function, and neural connectivity. In other words, different parts of the thalamus play varied roles in cognitive processes, including attention, speed of information processing, and memory (Fama and Sullivan, 2015; Saalmann and Kastner, 2015). Considering the complicated thalamic functions of coordination and integration, contact between the thalamus and other brain regions is vital for such cognitive processes. However, the structural or functional connectivity (FC) of the thalamus is vulnerable in both normal aging and disease progression, which are associated with cognitive decline (Menegaux et al., 2020; Das et al., 2021). The thalamus is regarded as a putative biomarker considering that abnormalities are noted in this area in different neurodegenerative disorders (Power and Looi, 2015), as supported by research on mild cognitive impairment and AD (Cai et al., 2015). The connectivity pattern of the thalamus is different in the AD progression (Dai et al., 2015; Ng et al., 2021). The abnormal FC of thalamus with brain regions including frontal and parietal lobe is observed (Zhou et al., 2013). However, for the complication of the thalamus, the information derived from the thalamic subdivisions may demonstrate increased sensitivity to pathological changes in AD and its clinical correlates, necessitating observation of the connectivity of different thalamic subareas in patients with AD.

Parcellation of the thalamic nuclei based on a novel probabilistic atlas with previously described ex vivo brain magnetic resonance imaging (MRI) scans and histological data has been performed (Iglesias et al., 2018) based on high-resolution MRI, detailed brain atlases, probabilistic models of neuroanatomy, and advanced neuroimaging segmentation tools. According to this parcellation, the atlas demonstrates excellent test–retest reliability, robustness to changes in the input MRI contrast, and the ability to detect differential thalamic effects in patients with AD (Low et al., 2019).

In this study, we used blood oxygen level-dependent (BOLD) signal-based resting-state functional MRI (rs-fMRI) (Biswal et al., 1995) and estimated regional correlations in spontaneous low-frequency fluctuations (at <0.1 Hz) in the BOLD signal. The latter is interpreted as FC to depict the activity integration of distinct cerebral regions (Fox and Raichle, 2007). We compared the FC of different thalamic subdivisions between patients with AD and sex- and age-matched healthy controls (HCs). We attempted to observe FC abnormalities of the thalamic subdivisions and to determine the relationship between abnormal FC and clinical measures. We hypothesized the following: (1) not all thalamic subdivisions would show FC differences between the groups; (2) abnormal FC would be correlated with poor cognitive test results; and (3) abnormal FC could be considered a good marker to classify patients with AD and HCs.

EXPERIMENTAL PROCEDURES

Participants

We recruited 48 patients with AD from the First Affiliated Hospital of the Anhui Medical University, China, between September 2017 and May 2020. Patients with AD were clinically diagnosed by a specialist in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984) as follows: (a) meeting the criteria of possible or probable AD; (b) Mini-Mental State Examination (MMSE) score <24; and (c) Clinical Dementia Rating (CDR) scores ranging from 0.5 to 2. The exclusion criteria were as follows: substance use disorder, other neurological diseases, and life-threatening somatic disease. We included 47 matched HCs who were recruited from the local community through advertisements or were spouses of the study subjects. They fulfilled the following criteria: normal cognitive function, no neurological or psychiatric disorders, no psychoactive medication use, MMSE score ≥ 27, and CDR scores equivalent to 0.

All participants were right-handed and provided written informed consent. The study was conducted in accordance with the latest revision of the Declaration of Helsinki, and the experimental procedures were approved by the local ethics committees of Anhui Medical University.

Neuropsychological assessment

All subjects underwent clinical evaluation and neuropsychological assessment. We conducted the following neuropsychological tests to establish a clinical diagnosis: (i) the MMSE test and Montreal Cognitive Assessment- Beijing Version (MoCA) to assess general cognitive functions, (ii) CDR as a proxy of disease severity, (iii) the Lawton-Brody Activities of Daily Living (ADL) scale to assess daily functions, (iv) the Hamilton Anxiety Scale and Hamilton Depression Rating Scale to evaluate affective symptoms, and (v) the Auditory Verbal Learning Test (AVLT), including AVLT–

immediate (AVLT-I), AVLT– delay (AVLT-D), and AVLT–recognition (AVLT-R) for memory evaluation. The Clock Drawing Test (CDT) was used for visual spatial and executive assessment, Verbal Fluency Test-Animal (VFT) for language assessment, and Digital Span Forward (DS-F) and Digital Span Backward (DS-B) tests for attention assessment.

MRI data acquisition

We performed structural and functional MRI for each participant using a 3T scanner (Signa HDxt 3.0T, General Electric HD 750 w, Buckinghamshire, UK) at our institution. During rs-fMRI scanning, we instructed the participants to keep their eyes closed. However, they were requested not to fall asleep and to not think of anything in particular. We acquired sagittal three-dimensional high spatial resolution T1-weighted images using a brain volume sequence with the following parameters: repetition time = 8.676 ms, echo time ratio = 3.184 ms, flip angle = 8°, field of view = 256 × 256 mm^2, matrix size = 256 × 256, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3, and number of sections = 188. The rs-fMRI images were acquired using a standard echo planar imaging sequence as follows: repetition time = 2000 ms, echo time ratio = 2 2.5 ms, flip angle = 30°, matrix size = 64 × 64, field of view = 220 × 220 mm^2, and slice thickness = 4.0 mm, with 33 continuous slices (one voxel = 3.4 × 3.4 × 4.6 mm^3). The duration of the resting state fMRI sequence lasted for 6 minutes and 10 seconds.

MRI preprocess

We acquired the rs-fMRI data using the advanced edition of Data Processing Assistant for Resting-State Functional MR Imaging toolkit, a package in the Data Processing & Analysis for (Resting-State) Brain Imaging software (Yan et al., 2016), based on the Resting State Functional MR Imaging Toolkit (REST; https://www.restfmri.net), and a statistical parametric mapping software package (SPM12; https://www.fil.ion.ucl.ac.uk/spm). We discarded the 10 initial volumes to avoid unsteady states. This was followed by slice timing correction and realignment. Following realignment, the individual functional images were coregistered to the respective structural images. We performed spatial normalization based on the unified segmentation of the structural images. Nuisance regressors with 24 Friston motion parameters, white-matter high signal, and cerebrospinal fluid signal as regressors were subsequently conducted. In addition, we included linear trends as a regressor to account for drifts in the BOLD signal. Temporal bandpass filtering (0.01–0.1 Hz) was performed after nuisance regression. Moreover, we performed motion scrubbing to remove the time points with high motion.

FC analysis

Subdivisions of the thalamus were selected as seeds to calculate the FC. The subdivisions were selected from the third version of the automated anatomical labelling atlas (Rolls et al., 2020). The parcellation of the thalamic nuclei we adopted was based on the probabilistic atlas. In this version of the atlas, the thalamus is divided into six subareas, namely the anterior, lateral, ventral, intralaminar, medial, and posterior nuclei. Fig. 1 depicts the location of the thalamus in the Montreal Neurological Institute space. To obtain the FC value, we extracted the mean time series of the left and right thalamic subdivisions and computed Pearson's correlations with voxels in the remaining whole brain within each individual. Fisher's *z* *r*-to-*z* transformation was then applied to improve normality. The result was displayed with a connectivity map for each individual. We then performed the FC metrics with spatial smoothing (Gaussian kernel, full width at half maximum = 8 mm). We compared the FC maps between the AD and HC groups within a gray-matter mask excluding the cerebellum. The permutation test (5,000 permutations for the analysis) was performed in the comparison using the toolbox in SPM12, Statistic Non-Parametric Mapping (SnPM13) (Nichols and Holmes, 2002), with the head motion parameter and total intracranial volume as covariates. To control for the family-wise error in multiple comparisons, we first set a voxel level threshold of $p < 0.0001$. Then, only clusters larger than a given volume would be reported as having survived the cluster-level correction, $p_{corr} < 0.004$ (0.05/12, for there were 12 thalamic subfields). To show the FC differences in detail and for further analyses, FC showing significant differences was extracted and centered at the peak point of the cluster with a 6-mm radius.

Statistical analyses

The clinical and demographic data were analyzed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Parametric data are presented as means and standard deviations and were analyzed with two sample *t*-tests for the neuropsychological assessments. Nonparametric data are presented as medians and interquartile distances and were analyzed with the Mann–Whitney *U* test. Furthermore, we conducted a correlation analysis between the FC and neuropsychological assessment to further explore the association between the neuroimaging indices and cognitive impairment. A value of $p < 0.05$ was considered statistically significant.

FC pattern classification analysis using a support vector machine approach

To test whether the identified neural indices may serve as imaging biomarkers to differentiate patients with AD from HCs, a linear support vector machine (SVM) approach within a library for the SVMs (LIBSVMs) toolkit running on MATLAB was performed with the linear kernel setting for classification (Chang and Lin, 2011). FC showing significant differences between the two groups was used as the feature for classification. The leave-one-out cross-validation (LOOCV) strategy was employed. Briefly, in a fold of LOOCV, one participant was left out and used as the testing set, whereas the remaining participants were used as the training set. Thus, each participant was left out only once, and the number of folds was equal

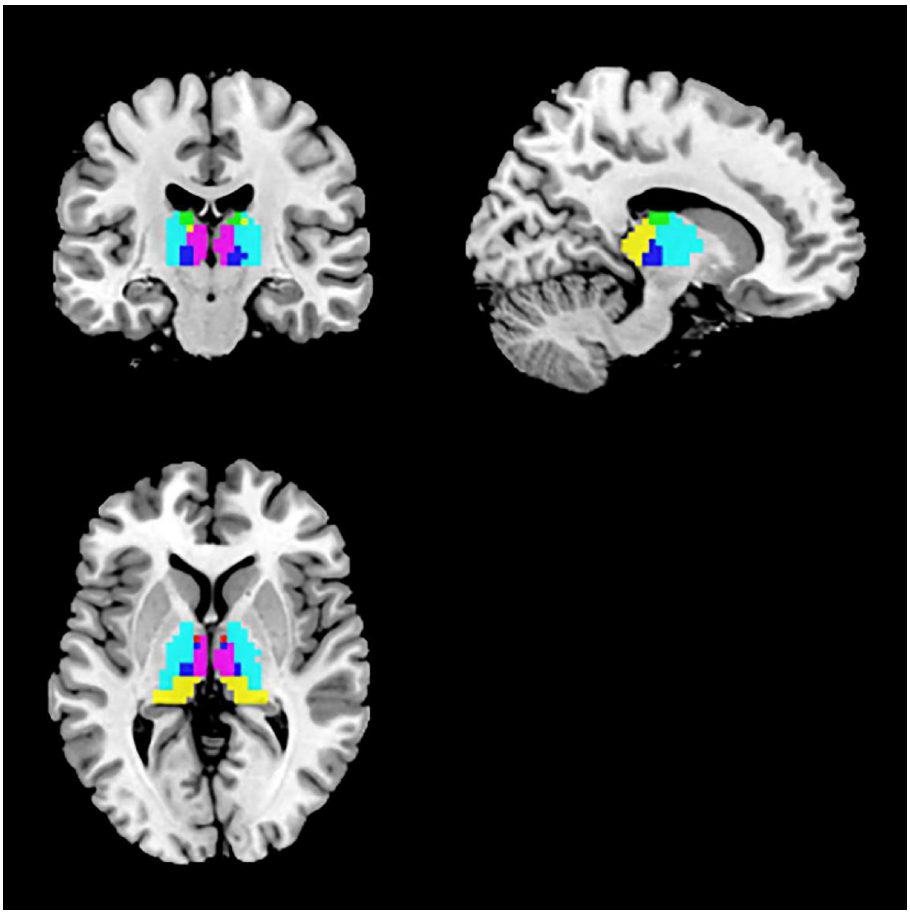

Fig. 1. Position of thalamic subdivions in MNI Space. Red: the Anterior Subdivion; Blue: the Intralaminar Subdivion; Green:the Lateral Subdivision; Violet: the Medial Subdivision; Yellow: the Posterior Subdivion; Cyan: the Ventral Subdivision.

to the number of total participants. There was a label (AD or HC) for each individual in training set and testing set. With the SVM procedure, a predicted label was obtained in each fold. By comparing true labels and predicted labels, the classification accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were obtained. The performance of the classifier was assessed based on the results of the cross-validation. The significance of the accuracy was determined using permutation test (5000 permutations). In the permutation test, the label of the individuals was shuffled randomly at first. Then the LOOCV strategy was employed based on the new label. Thus, a new accuracy of classification was obtained in one permutation. Based on the distribution of these 5,000 values of the accuracy, the accuracy in the real labeling condition can be inferred as significant or not. The p-value of <0.05 was considered significant.

RESULTS

Demographic and clinical characteristics

There were no significant differences in either age or sex between the AD and HC groups. The MMSE ($p<0.001$), MoCA ($p<0.001$), CDR ($p<0.001$), ADL ($p<0.001$), AVLT-I ($p<0.001$), AVLT-D ($p<0.001$), AVLT-R ($p=0.002$), DS-F ($p=0.004$), DS-B ($p=0.001$), CDT ($p<0.001$), and VFT ($p<0.001$) scores markedly differed, with significantly worse performance in the AD group (Table 1).

Functional connectivity of thalamic subdivisions

The FC of the left intralaminar nuclei with the left precuneus (peak t-value = −4.96, Montreal Neurological Institute (MNI) coordinates = [−6, −66, 54], cluster size = 147 voxels) and inferior parietal cortex (peak t-value = −4.70, MNI coordinates = [−36, −57, 51], cluster size = 70 voxels) differed between the groups; FC was lower in the AD group than in the HC group. In addition, the FC of the right medial nuclei with the left precuneus and occipital cortex, where the calcarine and lingual cortices were mainly included (peak t-value = −5.35, MNI coordinates = [−6, −48, 9], cluster size = 63 voxels), differed between the groups; FC was lower in the AD group than in the HC group. There were no significant differences in the FC of the other thalamic subdivisions between the groups (Table 2, Fig. 2, and Figs. S1–S3).

Correlation analyses

The FC of the right medial nuclei with the left precuneus was positively correlated with the MMSE scores ($r=0.30$, $p=0.042$) in the AD group. There was no significant correlation between the FC and other clinical characteristics in AD. Fig. 3 depicts the results of the correlation analyses.

Classification results

Using the FC values that displayed differences in brain regions, the linear SVM classifier achieved accuracy of 76.8%, sensitivity of 76.6%, specificity of 77.1%, and AUC of 81%. The SVM was significant based on the permutation test ($p<0.001$). The classification results are shown in Fig. 4.

DISCUSSION

In the present study, we explored abnormalities in the FC of thalamic subdivisions in patients with AD. We observed dysfunction in the FC of the intralaminar and medial nuclei with the left precuneus between the groups. The FC of patients with AD was lower than that of the matched HCs. Meanwhile, FC abnormalities were correlated with

Table 1. Demografic data and neuropsychological assessment

Variable	HC	AD	$t/Z/\chi^2$	p
Demographic				
Age	63.26(9.40)[a]	65.65(10.35)[a]	1.17	.242[c]
Gender(M/F)	20/27	19/29	0.87	.769[d]
Neuropsychological assessment				
MMSE	29.00(3.00)[b]	16.17(4.59)[a]	8.42	< .001[e]
MoCA	26.00(4.00)[b]	9.40(4.30)[a]	8.28	< .001[e]
CDR	0.00(0.00)[b]	1.00(1.00)[b]	8.01	< .001[e]
ADL	20.00(0.00)[b]	32.33(10.33)[a]	8.08	< .001[e]
HAMA	4.15(2.69)[a]	6.79(4.42)[a]	3.41	.001[c]
HDRS	2.59(2.60)[a]	5.25(4.20)[a]	3.68	< .001[c]
ALVT-I	8.46(1.90)[a]	2.36(1.60)[a]	16.78	< .001[c]
ALVT-D	9.22(2.83)[a]	0.00(0.00)[b]	8.61	< .001[e]
ALVT-R	14.00(1.00)[b]	8.52(5.08)[a]	6.42	< .001[e]
DS-Forward	6.91(1.41)[a]	5.50(2.00)[b]	3.97	< .001[e]
DS-Backward	4.22(1.15)[a]	3.00(1.00)[b]	4.80	< .001[e]
CDT	4.00(1.00)[b]	1.00(1.00)[b]	5.96	< .001[e]
VFT	18.37(4.00)[a]	8.04(3.84)[a]	12.78	< .001[c]

a: Parametric variables.
b: Nonparametric variables.
c: Two sample *t* test.
d: Chi-square test.
e: Mann–Whitney *U* test.
Abbreviation: MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment- Beijing Version; CDR: Clinical Dementia Rating; ADL: Activities of Daily Living; HAMA: the Hamilton Anxiety Scale; HDRS: Hamilton Depression Rating Scale; AVLT-I: Auditory Verbal Learning Test – immediate; AVLT-D: Auditory Verbal Learning Test – delay; AVLT-R: Auditory Verbal Learning Test – recognition; DS-F: Digital Span Forward; DS-B: Digital Span Backward; CDT: The Clock Drawing Test; VFT: Verbal Fluency Test.

Table 2. Brain Regions of FC differences between groups

Seed point[a]	Brain region	Peak MNI coordinates			Voxels	t	$p_{FWE\text{-corr}}$
		x	y	z			
L-Intra[b]							
	L Precuneus	−6	−66	54	140	12.80	0.001
	L Parietal Cortex	−36	−57	51	70	9.64	0.003
R-Media[c]							
	L Precuneus	−6	−48	9	63	5.35	0.004

a: Subdivisions of Thalamus as seed points for FC analysis.
b: Left intralaminar thalamus; L means Left.
c: Right Medial thalamus; R means Right.

the cognitive assessment scores in patients with AD, i.e., lower FC was associated with more severe cognitive performance deficits.

Interestingly, our results showed that the FC of the intralaminar nuclei was abnormal in the AD group. This might be associated with the specific function of the intralaminar nuclei, which have been found to be affected in other neurodegenerative disorders, such as Parkinson's disease and progressive supranuclear palsy (Henderson et al., 2000). Therefore, the thalamic intralaminar nuclei could be a region of interest in neurodegenerative disorders (Power and Looi, 2015). The intralaminar nuclei are considered part of the higher-order thalamus and have been implicated in various cognitive functions (Saalmann, 2014). Some patients experience cognitive impairment following stroke affecting the intralaminar nuclei (Mennemeier et al., 1992; Van der Werf et al., 2003). The involvement of the intralaminar thalamus in memory processing could be verified by some animal-model studies. A study found that intralaminar-nucleus modulation with deep brain stimulation enhanced spatial memory in healthy rodents (Tsai et al., 2016). In a rat study using an AD model, intralaminar thalamic deep brain stimulation was found to ameliorate memory deficits (Tsai et al., 2020). The aforementioned results could partially explain our findings of intralaminar nucleus FC abnormality and its association with cognitive impairment. The intralaminar nuclei do not comprise an isolated cerebral structure; they send projections to the basal ganglia, most notably the striatum (Lacey et al., 2007), a structure involved in cognitive processes (Landau et al., 2009). Dopamine released by the striatum is considered an important neurotransmitter associated with such processes. Previous studies have reported on cognitive impairment treatment with dopamine supplements (Floel et al., 2008; MacDonald et al., 2011). The connection between the intralaminar nuclei and the striatum may direct cholinergic interneuron activity *in vivo* to shape

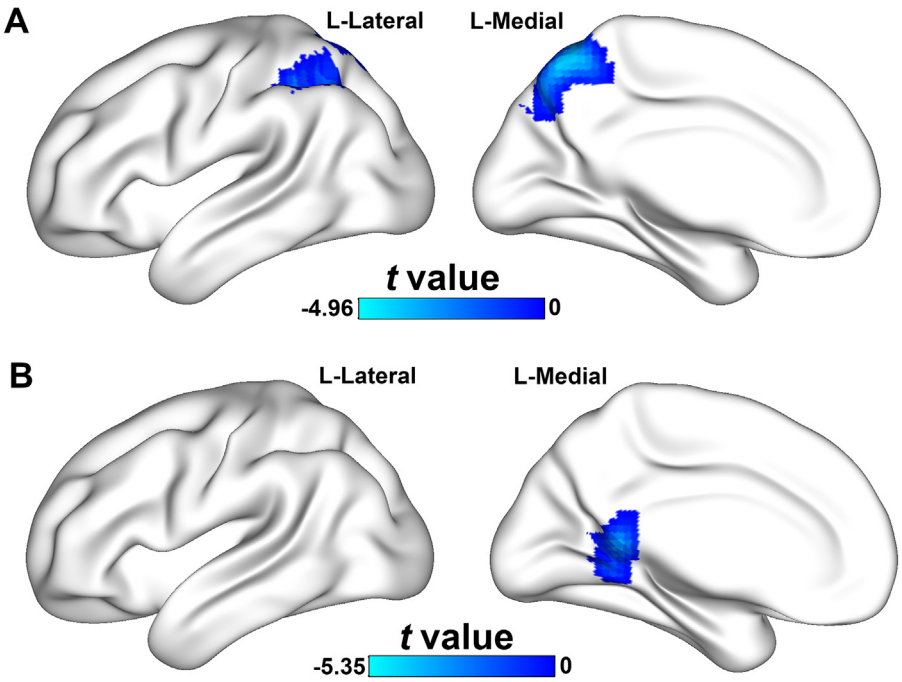

Fig. 2. Brain regional differences between groups. **(A)** FC of the left intralaminar thalamus with left precuneus and left parietal cortex was different between groups; **(B)** FC of the right medial thalamus with left precuneus was different between groups.

action learning through local striatal dopamine-release mechanisms (Cover et al., 2019). Moreover, the dysfunction of the intralaminar nuclei might influence their connection with the striatum, which might eventually affect dopamine. Dysfunction of the intralaminar nuclei, together with other connected brain regions, might lead to cognitive impairment in patients with AD.

Abnormal FC between the medial nuclei and precuneus was also observed in this study. The medial thalamus was considered a sensory-functional hub in previous studies (Domin et al., 2021; Franzini et al., 2022). However, research has increasingly focused on its cognitive functions in recent years (Saalmann, 2014; Jin et al., 2020). The medial nuclei are connected with different parts of the prefrontal cortex but also parts of the hippocampus and entorhinal cortex (Saalmann, 2014), and structural and functional abnormalities in these areas have been observed during AD progression (Kobro-Flatmoen et al., 2021; Ruan et al., 2021). Our results supported the cognitive function of the medial thalamus. Interestingly, we did not find abnormal FC of the medial thalamus with these cerebral regions, which were structurally connected with the medial nuclei, highlighting the possibility of functional compensation for these structural connections. This could be confirmed by future studies aiming at elucidating the relationship between FC and structural connectivity in AD progress. Perhaps because of the cognitive function of the intralaminar and medial thalamus, abnormal FC between these subareas, but not other subfields, was observed in this study. This could also help delineate relevant machine learning results; FC abnormalities could be considered effective features for classification.

The FC of the precuneus with the thalamic intralaminar and medial nuclei was low in patients with AD, which may inform probable diagnostic methods and therapies. The precuneus, a brain region located in the default mode network (DMN) (Raichle, 2015), is vital for cognitive processes (Cavanna and Trimble, 2006). Previous researchers observed that the connections within the DMN are modulated by the thalamus and weaken during

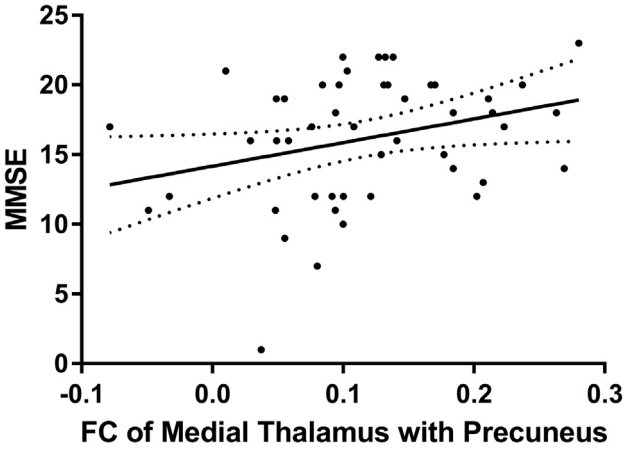

Fig. 3. Correlation between FC of right medial thalamus with precuneus and cognition scales. The FC of the right medial nuclei with the left precuneus was positively correlated with the MMSE scores ($r = 0.30$, $p = 0.042$) in the AD group.

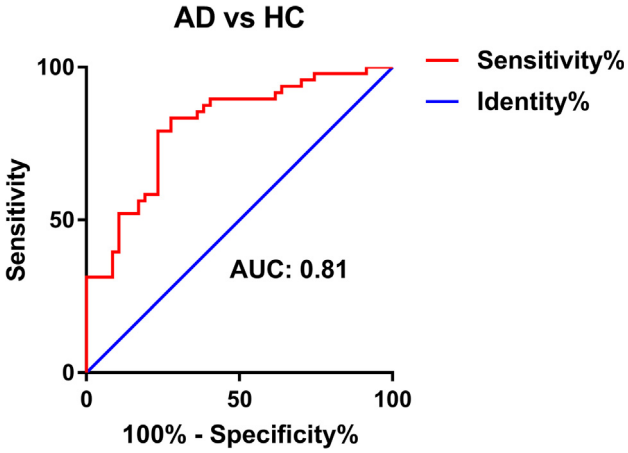

Fig. 4. Classification results based on the FC. The linear SVM classifier achieved accuracy of 76.8%, sensitivity of 76.6%, specificity of 77.1%, and AUC of 81%.

aging (Das et al., 2021). Our results suggested that the connections among these brain areas may be abnormally weakened during disease progression. This might comprise a possible auxiliary diagnostic method, thus helping us differentiate among patients in the future. Our results also showed that the integration of distinct brain regions, which might become abnormal in disease processes, is crucial for brain function. Some studies on AD have proposed that transcranial magnet stimulation (TMS) may comprise an effective means of supplemental therapy. The precuneus was recommended as a stimulation target in the TMS therapy guidelines (Lefaucheur et al., 2020). Despite TMS stimulating the surface cortex alone, the deep cerebral nuclei, functionally connected with the stimulated surface, could be effectively activated or deactivated (Fox et al., 2014). Our results provided partial evidence for a suitable TMS substrate for AD treatment. By stimulating the precuneus, deep gray-matter nuclei, such as the intralaminar nuclei, might also become activated. Moreover, symptoms could be relieved.

Despite showing the abnormal FC of thalamic nuclei with precuneus, which was in line with the previous study (Zhou et al., 2013), our results were not showing the abnormal FC of thalamic nuclei with the frontal lobe. Such different result compared with other study might be associated with the sample size of the study and the severity of AD participants. Our results also did not show the abnormal FC of the anterior thalamus, which was reported the atrophy and functional abnormalities (Perry et al., 2021). This did not mean that the interaction between the anterior thalamus and cortex was normal in the AD progression. For metric of FC was defined by the correlation of the BOLD signal, which was an indirect way to calculate the interaction between brain regions. Our results indicated that the blood flow of the anterior thalamus was relatively normal in AD patient, which was in line with some cerebral blood flow study not showing abnormal blood flow in AD (Camargo and Wang, 2021; Duan et al., 2021). Thus, metric of white matter might be used to assess the direct interaction in our future studies.

Low FC of the thalamus with the precuneus corresponded to poor cognitive performance, possibly comprising a substrate of cognitive impairment in AD. A previous study indicated that DMN dysfunction plays an important role in AD (Greicius et al., 2004). Researchers have observed abnormal connectivity within the network, associated with cognitive impairment. According to a systematic review, some studies have regarded the AD process as a network imbalance (Badhwar et al., 2017). In contrast, there are explicit connections of the thalamus with the DMN in healthy individuals, and such connections could be regarded as dynamic shifts for the cortical hubs of consciousness (Cunningham et al., 2017). Thus, our results could be interpreted as abnormal shifts of cognition-related hubs, and such dysfunctions were correlated with cognitive impairment. In this study, we did not find a correlation between FC and other clinical assessments, indicating that functional integration between the precuneus and thalamus might not be the reason for cognitive impairment in domains such as of vision and language. Structural metrics might be more greatly correlated with cognitive impairment with cognitive impairment in AD. The relationship between structural connectivity and cognitive impairment could be studied in future studies on AD progress. Negative results do not deny a relationship between cognition and the thalamus.

In the present study, we used fMRI to evaluate the integration between brain regions. The sample size and statistical methods were appropriate to control result reproducibility. Previous biomedical and psychological research (Prinz et al., 2011) has examined the reproducibility of rs-fMRI (Poldrack et al., 2017) and found it to be appropriate for basic, translational, and clinical neuroscience (Biswal et al., 1995). fMRI is being increasingly used because of the relative ease of data acquisition and amenability to aggregation across studies and sites (Zuo et al., 2014). However, the relatively small sample size in most studies and great amount of flexibility in data analysis would threaten the reproducibility of the results (Button et al., 2013; Eklund et al., 2016). Previous studies have shown a relationship between replicability and sample size. The PT, a strict multiple comparison correction strategy, reaches the best balance between the family-wise error rate and replicability. In addition, at least 40 subjects per group have been suggested for ensuring result stability (Chen et al., 2018). Therefore, we selected the PT as a multiple comparison correction strategy and controlled our sample size. We also used an SVM approach to support our results. The moderate accuracy also showed that the results were reliable.

Our study has some limitations. First, we recruited patients based on the NINCDS-ADRDA criteria. Thus, the study subjects were patients with clinically probable AD. The lack of biomarkers might have introduced bias. Second, the white matter is associated with symptoms in patients with AD and MCI. This necessitates applying methods to analyze the white matter in the future, such as tract-based spatial statistics. Third, only one cohort was collected in our study, results could be validated in other cohort such as Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

Dysfunction in the FC of the intralaminar and medial thalamus with the precuneus may be a potential neural substrate for cognitive impairment during AD progression, which in turn may provide new treatment targets in the future.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University. The patients/participants provided their written informed consent to participate in this study.

IMPACT STATEMENT

Decreased functional connectivity of the intralaminar and medial thalamus with the precuneus was observed in our patients, highlighting the different functions of each thalamic subdivision and different disease process for each subnucleus. Our results suggested that

dysfunction of the intralaminar and medial thalamus is instrumental in Alzheimer's disease. Our findings could contribute to advancements in precision medicine, i.e., the fact that there is dysfunction in the functional connectivity of the intralaminar and medial thalamus with the precuneus could be considered in target-based therapy such as repetitive transcranial magnetic stimulation or deep brain stimulation.

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There is no interest of conflict. We thank all the participants for their cooperation during this study.

AUTHORSHIP CONFIRMATION STATEMENT

Y Wu and XQ Wu analyzed the data and wrote the manuscript. LY Gao, YB Yan, and Z Geng collected the demographic data and assessed the scales. SS Zhou and YH Tian diagnosed patients. WQ Zhu collected the MRI data. YQ Yu, L Wei, and K Wang designed the experiment.

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APPENDIX A. SUPPLEMENTARY DATA

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