Fluids and Barriers of the CNS

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Blood–brain barrier breakdown in dementia with Lewy bodies

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Abstract

Background Blood–brain barrier (BBB) dysfunction has been viewed as a potential underlying mechanism of neurodegenerative disorders, possibly involved in the pathogenesis and progression of Alzheimer's disease (AD). However, a relation between BBB dysfunction and dementia with Lewy bodies (DLB) has yet to be systematically investigated. Given the overlapping clinical features and neuropathology of AD and DLB, we sought to evaluate BBB permeability in the context of DLB and determine its association with plasma amyloid-β (Aβ) using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Methods For this prospective study, we examined healthy controls (n = 24, HC group) and patients diagnosed with AD (n = 29) or DLB (n = 20) between December 2020 and April 2022. Based on DCE-MRI studies, mean rates of contrast agent transfer from intra- to extravascular spaces (K^{trans}) were calculated within regions of interest. Spearman's correlation and multivariate linear regression were applied to analyze associations between K^{trans} and specific clinical characteristics.

Results In members of the DLB (vs HC) group, K^{trans} values of cerebral cortex ($p = 0.024$), parietal lobe ($p = 0.007$), and occipital lobe ($p = 0.014$) were significantly higher; and K^{trans} values of cerebral cortex ($p = 0.041$) and occipital lobe ($p = 0.018$) in the DLB group were significantly increased, relative to those of the AD group. All participants also showed increased K^{trans} values of parietal ($\beta = 0.391$; $p = 0.001$) and occipital ($\beta = 0.357$; $p = 0.002$) lobes that were significantly associated with higher scores of the Clinical Dementia Rating, once adjusted for age and sex. Similarly, increased K^{trans} values of cerebral cortex ($\beta = 0.285$; $p = 0.015$), frontal lobe ($\beta = 0.237$; $p = 0.043$), and parietal lobe ($\beta = 0.265$; $p = 0.024$) were significantly linked to higher plasma Aβ1-42/Aβ1-40 ratios, after above adjustments.

Conclusion BBB leakage is a common feature of DLB and possibly is even more severe than in the setting of AD for certain regions of the brain. BBB leakage appears to correlate with plasma Aβ1-42/Aβ1-40 ratio and dementia severity.

Keywords Blood brain barrier, Dynamic contrast-enhanced magnetic resonance imaging, Lewy body, Alzheimer's disease, Amyloid-β

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Introduction

Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia, following Alzheimer's disease (AD) [1–6], with the prevalence of 1% in individuals aged 60 years or older [3, 4], and the clinical prevalence of 0–30.5% of all dementia cases in clinical studies [7, 8]. DLB is defined by the presence of intracellular a-synuclein aggregates, but there are similarities to AD with regard to clinical manifestations, genetic risk factors, and neuropathologic hallmarks (ie, Lewy bodies [LBs], amyloid-β [Aβ], and tau) [9]. Although the underpinnings of DLB are controversial, several lines of evidence have implicated blood–brain barrier (BBB) [10] or deposition of co-pathology [11].

The BBB is a selective barrier to diffusion, separating the central nervous system (CNS) from circulating peripheral blood. CNS homeostasis is subsequently maintained by regulating ion balance, facilitating nutritional transport, and preventing influx of potentially neurotoxic molecules within the circulation [12]. Factors impacting BBB integrity in neurodegenerative dementia include old age [13], sex [14], the apolipoprotein E gene (*APOE*) ε4 allele [15], elements of chronic vascular risk [16], Aβ, tau protein, and α-synuclein [17]. Breakdown of the BBB is known to reduce Aβ clearance and trigger Aβ deposition by inducing inflammation, oxidative stress, microglial activation, synaptic dysfunction, and synaptic loss; and the interaction of BBB dysfunction and Aβ deposition promotes the occurrence and progression of AD [18]. Moreover, increased BBB permeability seemingly bears a relation to disease phase. Current studies have shown that the cerebrospinal fluid (CSF)/serum albumin quotient (Q-Alb), a standard and ideal biomarker for BBB permeability, increases during the course of disease and mirrors the Clinical Dementia Rating (CDR) in patients with AD [19]. Our systematic review summarized that Q-Alb was significantly elevated in patients with Lewy body disease than healthy controls (HC) [20], and this finding was consistent with the results of several studies in DLB patients [21–23]. In addition to postmortem [24] and biofluid markers [10], dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is considered to be the most advanced method for noninvasively and quantitatively investigating subtle BBB failure regionally in the living human brain [25]. DCE-MRI images have revealed regional increases of transfer rate of contrast agent from intra- to extravascular spaces (K^{trans}) in normal elderly adults [13]. Increased BBB permeability is also common in cognitively impaired patients, affecting global cortex [26], median temporal lobe or hippocampus

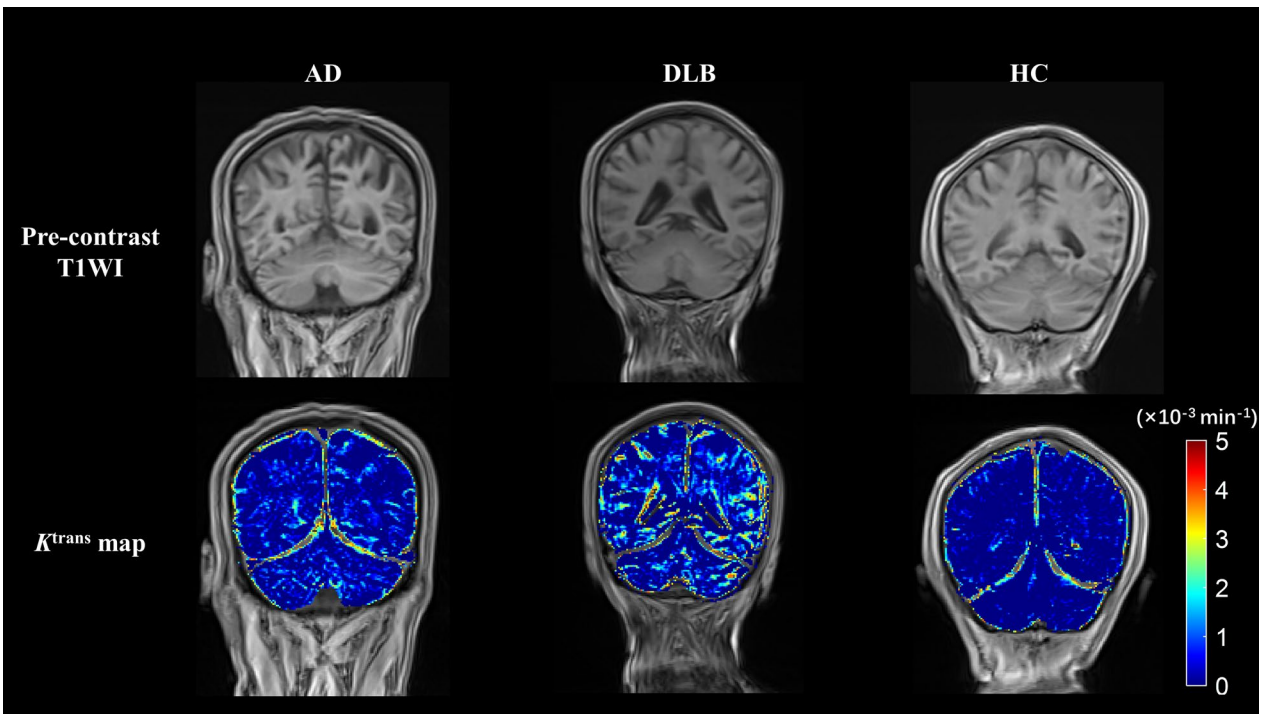

Fig. 1 Representative precontrast T1-weigthed images and K^{trans} maps of AD, DLB and HC groups. This figure showed the representative precontrast T1-weigthed images and K^{trans} maps of the global cerebral cortex in AD (a 72-year-old man with mild AD), DLB (a 75-year-old woman with mild DLB) and HC (a 72-year-old man with no cognitive impairment). *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, *HC* healthy control, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

Table 1 Demographic and clinical characteristics for the HC group, AD group and DLB group

	HC ($n=24$)	AD ($n=29$)	DLB ($n=20$)	p-value
Age, years	68.9 ± 5.5	71.7 ± 7.3	71.7 ± 7.1	0.118
Sex, n (%)				0.493
Men	10 (41.7%)	15 (51.7%)	7 (35.0%)	
Women	14 (58.3%)	14 (48.3%)	13 (65.0%	
Education, years, n (%)				0.715
0	0 (0.0%)	2 (6.9%)	1 (5.0%)	
1–6	6 (25.0%)	5 (17.2%)	5 (25.0%)	
≥ 7	18 (75.0%)	22 (75.9%)	14 (70.0%)	
Time since diagnosis, years	–	3.0 (3.0, 6.6)	3.0 (2.0, 4.0)	0.503
Hypertension, n (%)	7 (29.2%)	7 (24.14%)	10 (50.0%)	0.363
Type 2 diabetes mellitus, n (%)	3 (12.5%)	6 (20.7%)	3 (15.0%)	0.711
Cardiac-cerebral vascular disease, n (%)	2 (8.3%)	4 (13.8%)	6 (30.0%)	0.137
Habits of smoking and/or drinking, n (%)	9 (37.5%)	5 (17.2%)	7 (35.0%)	0.207
APOE ε4 carriers, n (%)	4 (16.7%)	12 (41.4%)	12 (60.0%)	0.012[b]
MMSE	29.0 (27.8, 29.0)	18.5 ± 3.6	15.1 ± 5.4	< 0.001[a,b]
MoCA	25.7 ± 2.2	14.1 ± 4.5	10.7 ± 25.7	< 0.001[a,b]
CDR	0.0 (0.0, 0.0)	2.0 (1.0, 2.0)	2.0 (1.0, 1.8)	< 0.001[a,b]
Visual hallucinations, n (%)	0 (0.0%)	0 (0.0%)	16 (80.0%)	< 0.001[b,c]
Fluctuations, n (%)	0 (0.0%)	0 (0.0%)	12 (60.0%)	< 0.001[b,c]
Parkinsonism, n (%)	0 (0.0%)	0 (0.0%)	12 (60.0%)	< 0.001[b,c]
RBD, n (%)	0 (0.0%)	0 (0.0%)	17 (85.0%)	< 0.001[b,c]
Aβ1-40, pg/ml	100.77 (90.63, 163.48)	118.60 (98.36, 156.31)	182.85 (153.98, 204.85)	< 0.001[b,c]
Aβ1-42, pg/ml	13.75 (9.40, 22.98)	13.44 (8.80, 21.94)	24.09 (17.89, 26.54)	0.009[b]
Aβ1-42/Aβ1-40	0.13 (0.10, 0.16)	0.11 (0.09, 0.14)	0.13 (0.12, 0.13)	0.200

Data are expressed as mean ± SD or median (IQR)

HC healthy controls, *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, *APOE* Apolipoprotein E, *MMSE* Mini-Mental State Examination, *MoCA* the Montreal Cognitive Assessment, *CDR* the clinical dementia rating, *RBD* REM sleep behaviour disorder, *Aβ* amyloid-β

[a] For the comparison between the HC and AD (Bonferroni-corrected $p < 0.05$)

[b] For the comparison between the HC and DLB (Bonferroni-corrected $p < 0.05$)

[c] For the comparison between the AD and DLB (Bonferroni-corrected $p < 0.05$)

[27], and white matter [28] is common in patients with cognitive impairment.

However, there have been few investigations of BBB permeability in patients with DLB, and the volume of available clinical data from DCE-MRI assessments of BBB is meager. Clinical studies targeting associations between BBB and Aβ in patients with DLB are lacking as well. We have therefore chosen to use DCE-MRI for evaluating BBB permeability in the context of DLB and exploring related clinical characteristics. Our findings will hopefully aid in understanding disease mechanisms, yielding precise biomarkers that serve for prevention and management of DLB.

Materials and methods

Study participants

This prospective study took place between December 2020 and April 2022 at Tianjin Huanhu Hospital in Tianjin, China. Selected subjects were healthy controls (HC group, 24) or patients with dementia (AD group, 29; DLB group, 20). Those diagnosed with AD met criteria of the National Institute on Aging and the Alzheimer Association workgroup (NIA-AA 2011) [29], whereas patients with probable DLB satisfied stipulations of the DLB consortium established in 2017 [30]. The following were grounds for patient disqualification: (1) No diagnosis of AD or DLB; (2) inability to undergo DCE-MRI, peripheral blood collection, or neuropsychological assessment; (3) history of mental disorders or illicit drug abuse; or (4) acute or chronic liver or kidney dysfunction, malignant tumors, or other serious comorbidities. The HC group was populated by friends or relatives of these patients who had no histories of psychiatric or neurologic illness or evidence of cognitive decline.

All participants underwent comprehensive clinical interviews and neuropsychological assessments conducted by physicians with expertise in impaired cognition. Various demographics (i.e., sex, age, and education)

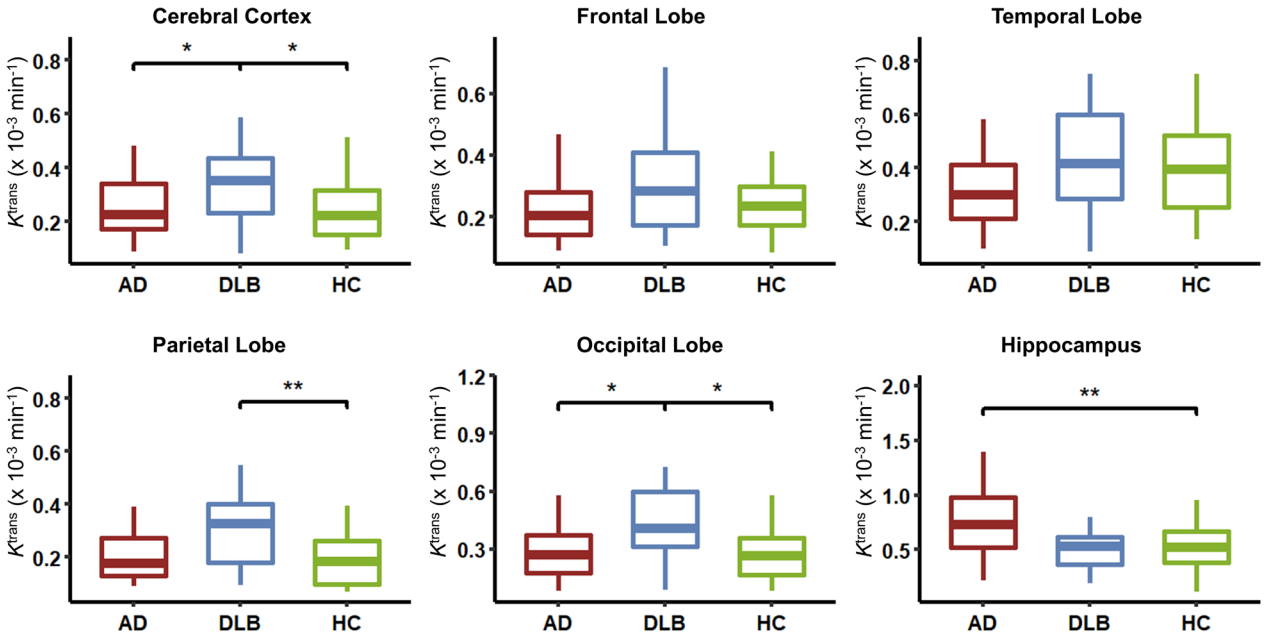

Fig. 2 The BBB permeability in different brain regions among AD, DLB and HC groups. DLB group had the higher BBB permeability constant K^{trans} in cerebral cortex, frontal lobe, temporal lobe, parietal lobe and occipital lobe compared AD group or HC group. While AD group had higher BBB permeability constant K^{trans} in the hippocampus than DLB group and HC group. Boxplots represent the median (thick horizontal line), with the box representing the 25th and 75th percentiles. "*" means the Bonferroni-corrected $p < 0.05$ and "**" means the Bonferroni-corrected $p < 0.01$, all significance by ANOVA tests. *BBB* blood brain barrier, *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, *HC* healthy control, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

and clinical parameters, including course of disease, comorbidities (such as hypertension, type 2 diabetes mellitus [T2DM], cardio- and cerebrovascular disease), and smoking/drinking habits, were contributed by close caregivers. All subjects were tested for global cognitive function by administering the Mini-Mental State Examination (MMSE) [31] and the Montreal Cognitive Assessment (MoCA) [32], using the CDR scale [33] to gauge severity of cognitive impairment. These assessments took place on same days as MRI studies.

Sample collection and measurements

Before providing samples, we mandated a 12- to 14-h overnight fast for all participants, withholding anti-AD drugs during this time. Smoking, alcohol consumption, and vigorous activity were also prohibited for 24 h. On the day of or day after visitation, each participant submitted to venipuncture, filling 6-mL EDTA-coated collection tubes with peripheral blood. Within a 2-h window, each sample was centrifuged (2200 rpm, 10 min) to separate plasma for storage (at -80° C) and later use.

The *APOE* genotyping procedure is detailed elsewhere, in a previous publication [34].

ELISA kits (PK101 and PK102; Beijing 7D Biotech Inc, Beijing, China) served to assay plasma levels of Aβ1-40 and Aβ1-42. The specified detection range of Aβ1-40 was 0–300 pg/mL, with limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) values of 0.9 pg/mL, 1.5 pg/mL, and 2.2 pg/mL, respectively. Intra- and interassay variabilities were < 3% and < 10%, respectively. Each sample was analyzed twice on the same plate, all concentrations falling within the kit's detection linearity range (22–252 pg/mL). The detection range of Aβ1-42 was 0–160 pg/mL (LoB, 0.6 pg/mL; LoD, 1.6 pg/mL; LoQ, 2.3 pg/mL). Intra- and interassay variabilities again were < 3% and < 10%, respectively. Analyzed twice on the same plate (as before), concentrations obtained were within the kit's detection linearity range (34–215 pg/mL).

MRI data acquisition

All participants were scanned using a 3T MRI system (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. Prior to DCE-MRI acquisition, precontrast T1 mapping was achieved using a 3D variable flip-angle sequence. B1 mapping was also obtained to correct for B1 field inhomogeneity. DCE-MRI studies were acquired using 3D T1-weighted spoiled gradient-echo sequences as follows: repetition time/echo time (TR/TE), 5.2/1.8 ms; field of

Table 2 Correlations between MMSE, MoCA and BBB permeability in different brain regions in AD, DLB and HC groups

Groups	K^{trans} ($\times 10^{-3}$ min^{-1})	MMSE		MoCA	
		R	*P* – value	R	*p*-value
AD	Cerebral cortex	– 0.169	0.382	– 0.275	0.148
	Frontal lobe	– 0.287	0.131	– 0.303	0.110
	Temporal lobe	– 0.054	0.780	– 0.154	0.425
	Parietal lobe	– 0.271	0.155	– 0.379	0.043
	Occipital lobe	0.050	0.797	– 0.149	0.441
	Hippocampus	– 0.225	0.240	– 0.233	0.223
DLB	Cerebral cortex	– 0.260	0.268	– 0.197	0.404
	Frontal lobe	– 0.255	0.279	– 0.176	0.457
	Temporal lobe	– 0.116	0.627	– 0.148	0.535
	Parietal lobe	– 0.237	0.314	– 0.193	0.415
	Occipital lobe	– 0.408	0.074	– 0.340	0.143
	Hippocampus	– 0.163	0.492	– 0.139	0.558
HC	Cerebral cortex	0.105	0.627	– 0.001	0.995
	Frontal lobe	0.163	0.446	0.281	0.183
	Temporal lobe	0.060	0.781	0.072	0.739
	Parietal lobe	0.113	0.598	0.081	0.708
	Occipital lobe	0.039	0.858	– 0.307	0.144
	Hippocampus	– 0.009	0.966	0.275	0.194

Spearman correlation analysis was used to evaluate the correlations between MMSE, MoCA and BBB permeability in different brain regions in AD, DLB and HC groups, the Correlation Coefficients (R) and *p*-values were shown. There were no significant correlations between MMSE, MoCA and BBB permeability in different brain regions in DLB

MMSE Mini-Mental State Examination, *MoCA* the Montreal Cognitive Assessment, *BBB* blood brain barrier, *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, *HC* healthy controls, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

view (FOV), 230×187 mm^2; matrix size, 192×156; slice thickness, 3 mm; number of slices, 56; and imaging time, 30×11.7 s. Coincident with the sixth dynamic scan, an intravenous bolus (0.1 mmol/kg) of gadopentetate dimeglumine (Gd-DTPA, Magnevist; Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA) was injected at 2 mL/s, followed by a 12 mL flush of saline at same rate.

MRI data analysis

The global cerebral cortex and areas pertinent to DLB and AD (ie, frontal, temporal, parietal, and occipital lobes and hippocampus) were regarded as regions of interest (ROIs) owing to their critical roles in cognitive function [35]. ROIs were manually delineated on precontrast DCE-MRI images by two experienced radiologists blinded to patient information and analytic results. DCE images were analyzed using the Patlak model [36] (1):

$$C(\mathrm{t}) = K^{trans}\int_0^t C_p(\tau)d\tau + V_pC_p(t), \quad (1)$$

where C(t) denotes the concentration of contrast agent in a selected ROI (calculated from DCE-MRI signal intensities and precontrast T1 mapping data), K^{trans} represents the rate of contrast agent transfer from the intra- to the extravascular space, C_p(t) is the vascular input function (derived from superior sagittal sinus) [37], and V_{p} signifies fractional plasma volume. The kinetic model was fitted pixel by pixel, using least squares method, and then averaged within each ROI. All delineations and analyses relied on conventional software (MATLAB; MathWorks, Natick, MA, USA). Representative precontrast T1-weighted images and K^{trans} maps of AD, DLB, and HC groups were shown in Fig. 1.

Statistical analysis

All continuous variables were assessed for normality via Shapiro–Wilk test and then were described as mean ± standard deviation (SD) or median with interquartile range (IQR). The comparisons between two groups were conducted by Student's t-test or Mann–Whitney U test, and three-way comparisons were achieved through analysis of variance (ANOVA) or Kruskal–Wallis H test. Categorical qualitative variables were presented as proportions and compared using the chi-squared test. Spearman's correlation served to examine the correlations between K^{trans} and clinical characteristics. Parameters of significance in univariate analysis were retested, conducting stepwise multiple linear regression (with Bonferroni correction) to adjust for age and sex. All computations were driven by standard software (IBM SPSS, v26.0; IBM Corp, Armonk, NY, USA), setting significance at $p < 0.05$.

Results

Characteristics of participants

Demographic and clinical characteristics of participating subjects were shown by group (HC, AD, or DLB) in Table 1. There were no significant group differences in age, sex, years of education, various comorbidities (hypertension, T2DM, cardiovascular disease), or habits of smoking/drinking. Although we observed more *APOE* ε4 carriers in the DLB (vs HC) group, the AD and HC groups did not differ significantly in this regard. However, AD and DLB group members scored significantly lower on MMSE and MoCA tests and ranked higher on the CDR scale than did HC group members. In patients with DLB, 80% experienced visual hallucinations, 60% showed cognitive fluctuations, 60% displayed parkinsonism, and 85% exhibited REM sleep behavior disorder (RBD).

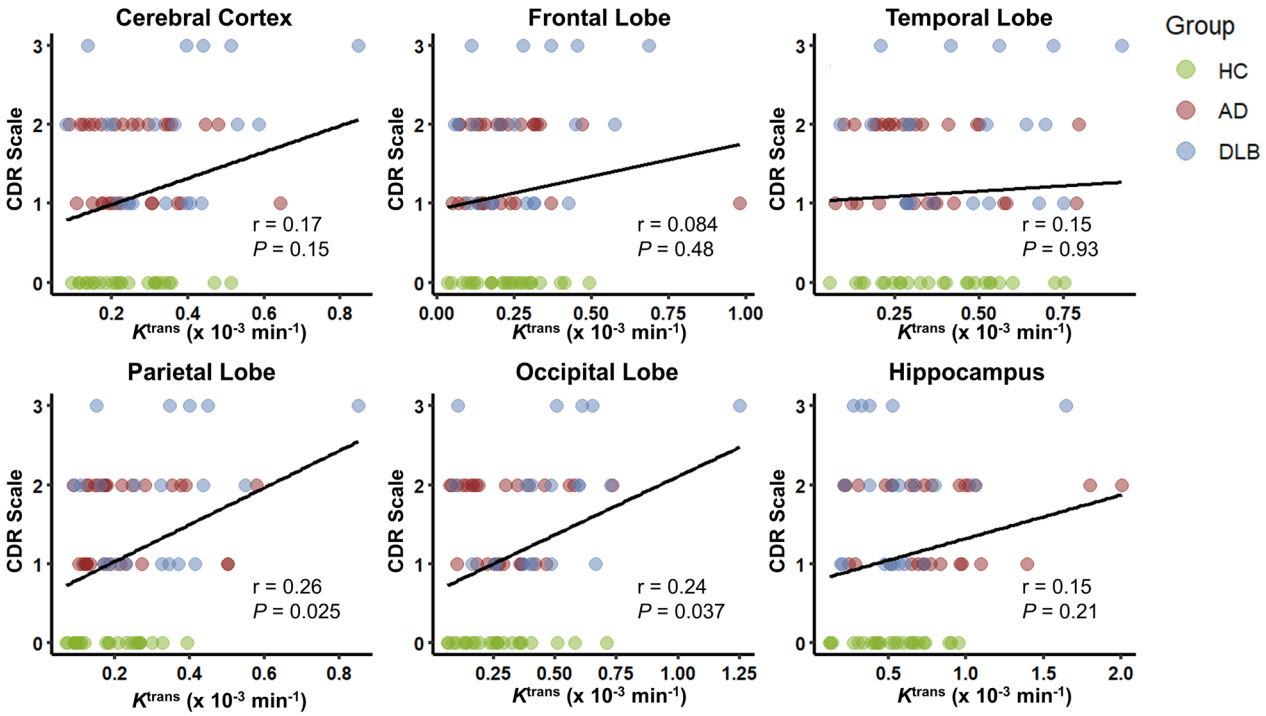

Fig. 3 Correlations between K^{trans} and CDR scale in all participants. The correlation analysis of BBB permeability constant K^{trans} and CDR scale in all participants showed positive correlation trends in cerebral cortex, frontal lobe, temporal lobe, parietal lobe, occipital lobe and hippocampus. Increased BBB permeability constant K^{trans} in the parietal lobe and occipital lobe were significantly correlated to higher CDR score. *CDR* the clinical dementia rating, *BBB* blood brain barrier, *HC* healthy control, *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

We also found the highest median level of Aβ1-40 in the DLB group (182.85 pg/mL, IQR: 153.98–204.85), significantly surpassing levels in both HC (100.77 pg/mL, IQR: 90.63–163.48; $p<0.001$) and AD (118.60 pg/mL, IQR: 98.36–156.31; $p=0.002$) groups. The plasma concentration of Aβ1-42 in the DLB group was significantly higher than that of the HC group ($p=0.012$), while appearing similar to that of the AD group ($p=0.058$). There were no significant differences in Aβ1-42/Aβ1-40 ratios among HC, AD, and DLB groups.

The BBB permeability in HC, AD and DLB groups

As depicted in Fig. 2, the DLB group demonstrated a significantly higher K^{trans} for cerebral cortex, compared with HC ($p=0.024$) and AD ($p=0.041$) groups. In particular, the K^{trans} values of parietal ($p=0.007$) and occipital ($p=0.014$) lobes were significantly higher for the DLB (vs HC) group, with similar values observed for frontal lobe ($p=0.193$), temporal lobe ($p=0.229$), and hippocampus ($p=0.662$). Compared with the AD group, the DLB group registered a significantly higher K^{trans} for occipital lobe ($p=0.018$). Still, the K^{trans} value for hippocampus proved significantly higher ($p=0.006$) in the AD (vs HC) group.

The correlation between BBB permeability and clinical characteristics

Spearman's correlation analysis was used to evaluated the correlation between BBB permeability and scores of MMSE, MoCA and CDR. It indicated no correlations between scores of MMSE, MoCA and K^{trans} of cerebral cortex, frontal lobe, temporal lobe, parietal lobe, occipital lobe and hippocampus in DLB and HC groups (Table 2). There was no relation between K^{trans} of cerebral cortex and CDR score, whereas elevated K^{trans} values for parietal ($p=0.025$) and occipital ($p=0.037$) lobes were significantly linked to higher CDR scores in all participants (Fig. 3). These two brain regions were then subjected to multivariate linear regression analysis, with age and sex as covariates, respectively. Significant associations between increased K^{trans} values of parietal ($\beta=0.391$; $p=0.001$) and occipital ($\beta=0.357$; $p=0.002$) lobes and higher CDR scores emerged as a result. Values of K^{trans} in differing brain regions and CDR scores for AD and DLB groups are delineated in Supplementary Figs. 1, 2 and no significant correlations were found.

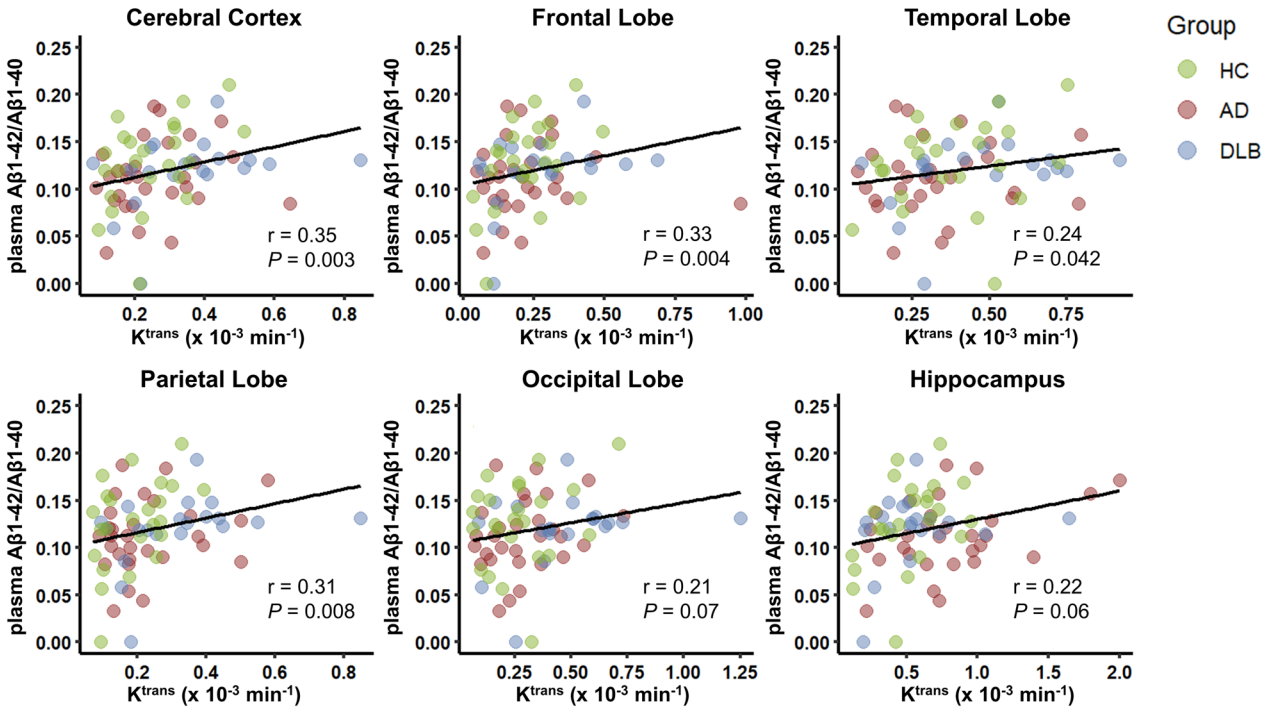

Fig. 4 Correlations between K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in all participants. The correlation analysis of BBB permeability constant K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in all participants showed positive correlation trends in cerebral cortex, frontal lobe, temporal lobe, parietal lobe, occipital lobe and hippocampus. Increased BBB permeability constant K^{trans} in the cerebral cortex, frontal lobe, temporal lobe, and parietal lobe were significantly correlated to higher plasma Aβ1-42/Aβ1-40 ratio. *Aβ* amyloid-β, *BBB* blood brain barrier, *HC* healthy control, *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, *CDR* the clinical dementia rating, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

When analyzing the association between K^{trans} and plasma Aβ1-42/Aβ1-40 ratio, Fig. 4 demonstrated a significant correlation between increased K^{trans} of cerebral cortex and plasma Aβ1-42/Aβ1-40 ratios in all participants ($p=0.003$). Specifically, increased K^{trans} values of frontal lobe ($p=0.004$), temporal lobe ($p=0.042$), and parietal lobe ($p=0.008$) were significantly related to higher plasma Aβ1-42/Aβ1-40 ratios. Upon subjecting these four brain regions to multivariate linear regression analysis (with age and sex as respective covariates), significant associations between increased K^{trans} of cerebral cortex (β = 0.285; $p=0.015$), frontal lobe (β = 0.237; $p=0.043$), and parietal lobe (β = 0.265; $p=0.024$) and higher plasma Aβ1-42/Aβ1-40 ratios emerged.

Specifically, there was no significant correlation between plasma Aβ1-42/Aβ1-40 ratios and K^{trans} in the AD group (Fig. 5). While in the DLB group, correlation analysis showed that increased K^{trans} of cerebral cortex and parietal lobe was significantly associated with higher plasma Aβ1-42/Aβ1-40 ratios (Fig. 6). These two brain regions were included in multiple linear regression analysis with age and sex as covariates, respectively, and the results showed that increased K^{trans} of parietal lobe (β = 0.441, $p=0.031$) was significantly associated with higher plasma Aβ1-42/Aβ1-40 ratios after adjusting for age and sex. In the HC group, correlation analysis showed increased K^{trans} of frontal lobe, parietal lobe and hippocampus was significantly associated with higher plasma Aβ1-42/Aβ1-40 ratios (Fig. 7). These brain regions were included in multiple linear regression analysis with age and sex as covariates, and the results showed that increased K^{trans} of frontal lobe (β = 0.615, $p=0.008$), parietal lobe (β = 0.482, $p=0.030$) and hippocampus (β = 0.468, $p=0.040$) were significantly associated with higher plasma Aβ1-42/Aβ1-40 ratios after adjusting for age and sex.

Discussion

For the present study, we used DCE-MRI studies of test patients (with AD or DLB) and healthy individuals to compare BBB permeability (K^{trans}), investigating its relation to clinical symptoms and plasma Aβ levels. Our findings confirm a greater disruption of BBB within cerebral cortex (especially occipital lobe) of the DLB group, compared with HC and AD groups. Moreover, it was apparent that both CDR scores and plasma Aβ1-42/Aβ1-40 ratios were associated with BBB

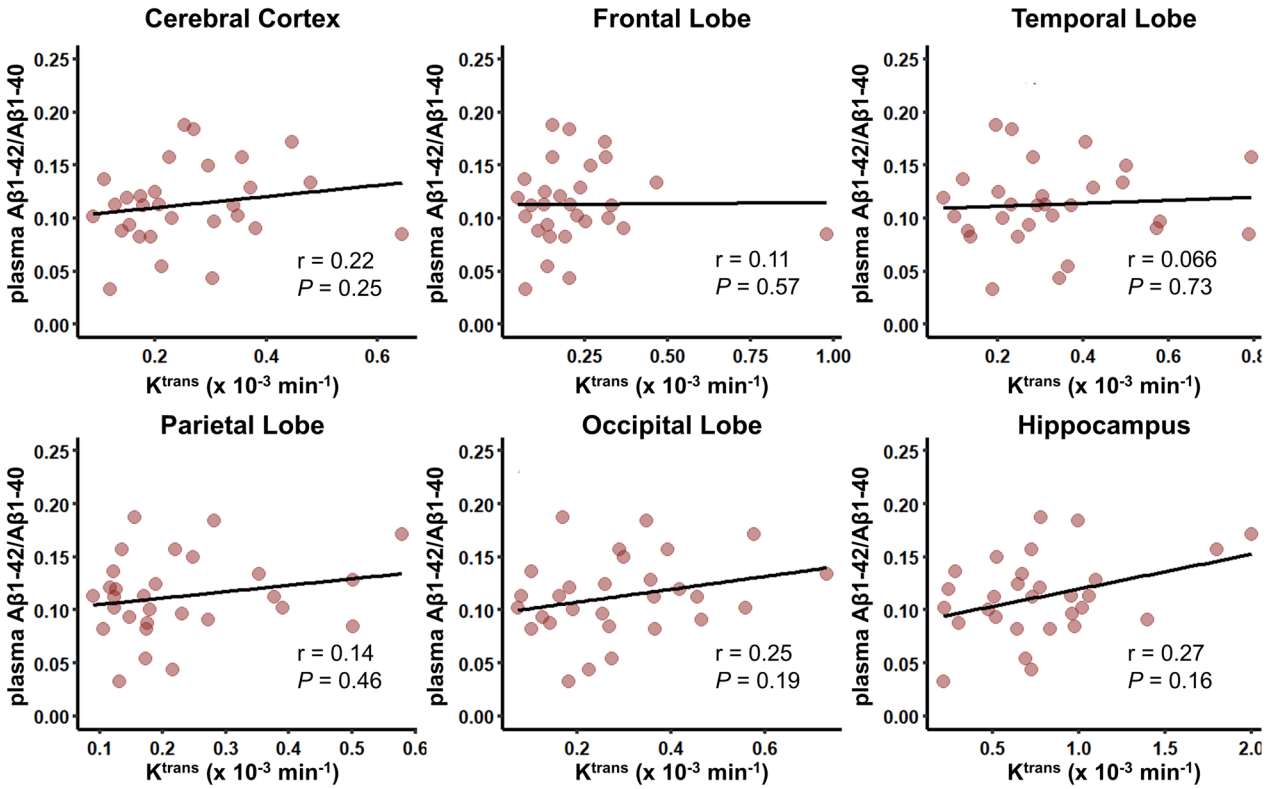

Fig. 5 Correlations between K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in AD patients. The correlation analysis of BBB permeability constant K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in AD patients showed positive but not significant correlation trends in cerebral cortex, frontal lobe, temporal lobe, parietal lobe, occipital lobe and hippocampus. *Aβ* amyloid-β, *BBB* blood brain barrier, *AD* Alzheimer's disease, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

permeability, offering new insights into the evolution of BBB pathology and disease severity.

Initially, we utilized DCE-MRI to assess patients with multiple neurodegenerative dementias, discovering increases in K^{trans} for patients with either AD or DLB. An earlier investigation, based on DCE-MRI studies of patients with AD, has already ascertained a correlation between increased K^{trans} and elevated CSF levels of soluble platelet-derived growth factor receptor β, reflecting BBB damage [38]. In another currently conducted study, patients with DLB similarly showed BBB dysfunction, suggesting a common pathophysiologic mechanism for these two types of dementia. A recent systematic review and meta-analysis [10] had also disclosed significantly higher Q-Alb ratios and blood neurofilament light chain levels in patients with DLB (vs healthy controls), providing evidence that BBB disruption is involved. Notably, the DLB (vs AD) group showed a higher K^{trans} for cerebral cortex, implying a BBB dysfunction of relatively greater magnitude. This result was aligned with that of a prior analysis revealing an increased Q-Alb ratio in patients with DLB (vs AD) [39].

Our efforts had likewise revealed that K^{trans} values among HC, AD, and DLB populations differ for certain brain regions. Specifically, our DLB group demonstrated significantly higher K^{trans} values for parietal and occipital lobes, compared with the HC group, and a higher K^{trans} for occipital lobe, compared with the AD group. On the other hand, the AD group showed a significantly higher K^{trans} for hippocampus than that found in the HC group. As a past report further attests, increased K^{trans} in hippocampus reflects a breakdown in BBB associated with cognitive impairment, so the hippocampus is a critical region in the progression of AD [38].

As for patients with DLB, previous structural imaging and flourine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) studies had documented structural atrophy and hypometabolism of occipital and parietal lobes [40, 41], indirectly supporting our findings. Hypometabolism of this sort had been a consistent feature of DLB for decades, making this specific metabolic signature [42] a viable biomarker of DLB

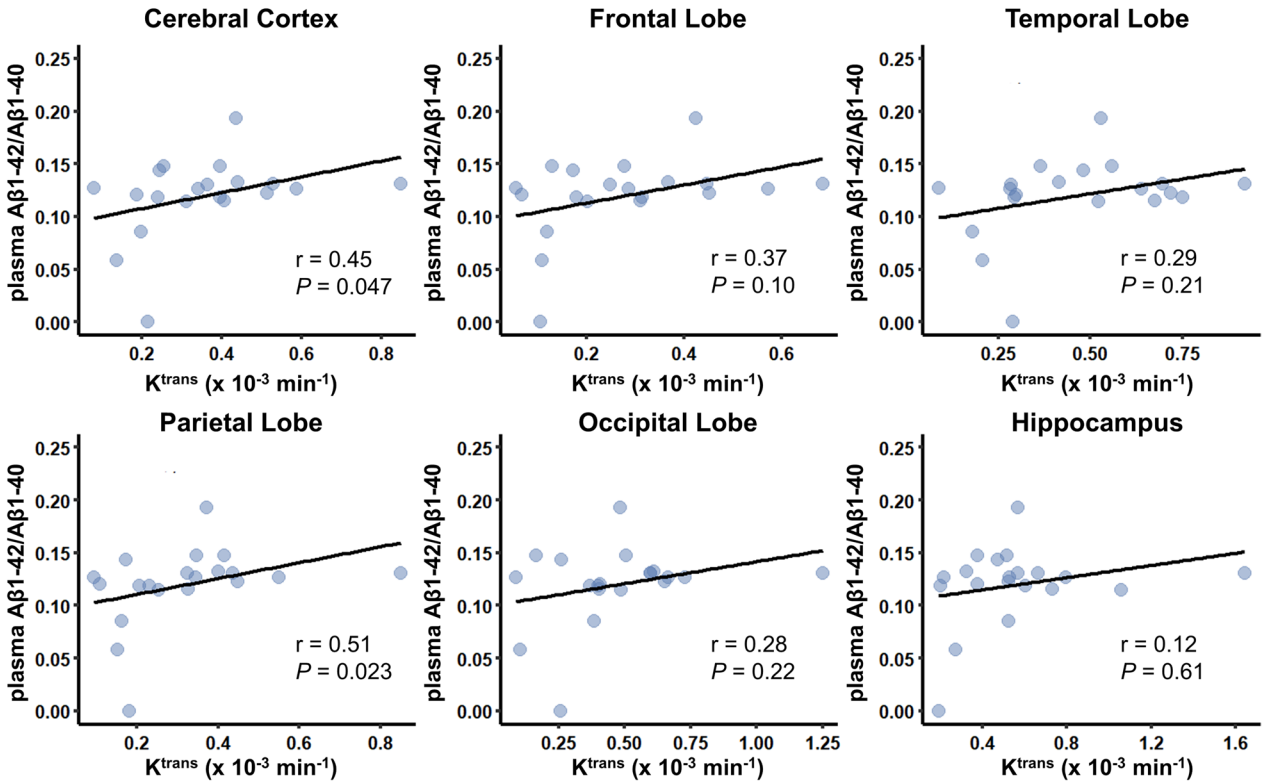

Fig. 6 Correlations between K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in DLB patients. The correlation analysis of BBB permeability constant K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in DLB patients showed positive correlation trends in cerebral cortex, frontal lobe, temporal lobe, parietal lobe, occipital lobe and hippocampus. Increased BBB permeability constant K^{trans} in the cerebral cortex and parietal lobe were significantly correlated to higher plasma Aβ1-42/Aβ1-40 ratio. *Aβ* amyloid-β, *BBB* blood brain barrier, *DLB* dementia with Lewy bodies, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

in diagnostic criteria [30]. Neuropathologic research directed at DLB also seems to indicate a reduced microvessel density within occipital lobe, accompanied by a significant decline in vascular endothelial growth factor. The latter was critical for formation and maintenance of blood vessels and is a biomarker for BBB damage [43]. Hence, K^{trans} qualifies as a direct, non-invasive imaging biomarker for regional BBB deterioration.

We ultimately analyzed correlations between BBB permeability and clinical characteristics. No correlations were found between scores of MMSE, MoCA and K^{trans} of cerebral cortex and five brain regions in DLB and HC groups. The significant associations between increased K^{trans} values in parietal and occipital lobes and higher CDR scores were apparent in all participants, once adjusted for age and sex by multiple linear regression, the significant findings still remained. Nation et al. [44] had observed that CSF levels of soluble platelet-derived growth factor receptor β, a biomarker of pericyte and BBB damage, increased at higher CDR scores; and Lv et al. [19] had determined a trend of increasing CDR scores as Q-Alb levels rose, although significance was not reached. Our data were in general agreement with previous investigations and suggest that K^{trans} values derived through DCE-MRI were likely biomarkers for severity of BBB dysfunction and progression of dementia.

When analyzing the association between K^{trans} values and plasma Aβ1-42/Aβ1-40 ratios, our multivariate linear regression model established significant links between increased K^{trans} values of various brain regions (cerebral cortex, frontal and parietal lobes) and higher plasma Aβ1-42/Aβ1-40 ratios in all participants, after adjusting for age and sex. We also found the increased K^{trans} values of frontal lobe, parietal lobes and hippocampus were correlated with higher plasma Aβ1-42/Aβ1-40 ratios in HC group, reflecting that higher Aβ deposition in the presence of BBB disruption as reported in previous studies [45, 46]. However, several studies suggested the increased BBB permeability in the hippocampus [13, 44], and the reduction of hippocampal volume might be related to Aβ deposition in old adults [47]. There is no more definitive study has elucidated the relationship between Aβ and BBB permeability in various brain regions. Indeed, the

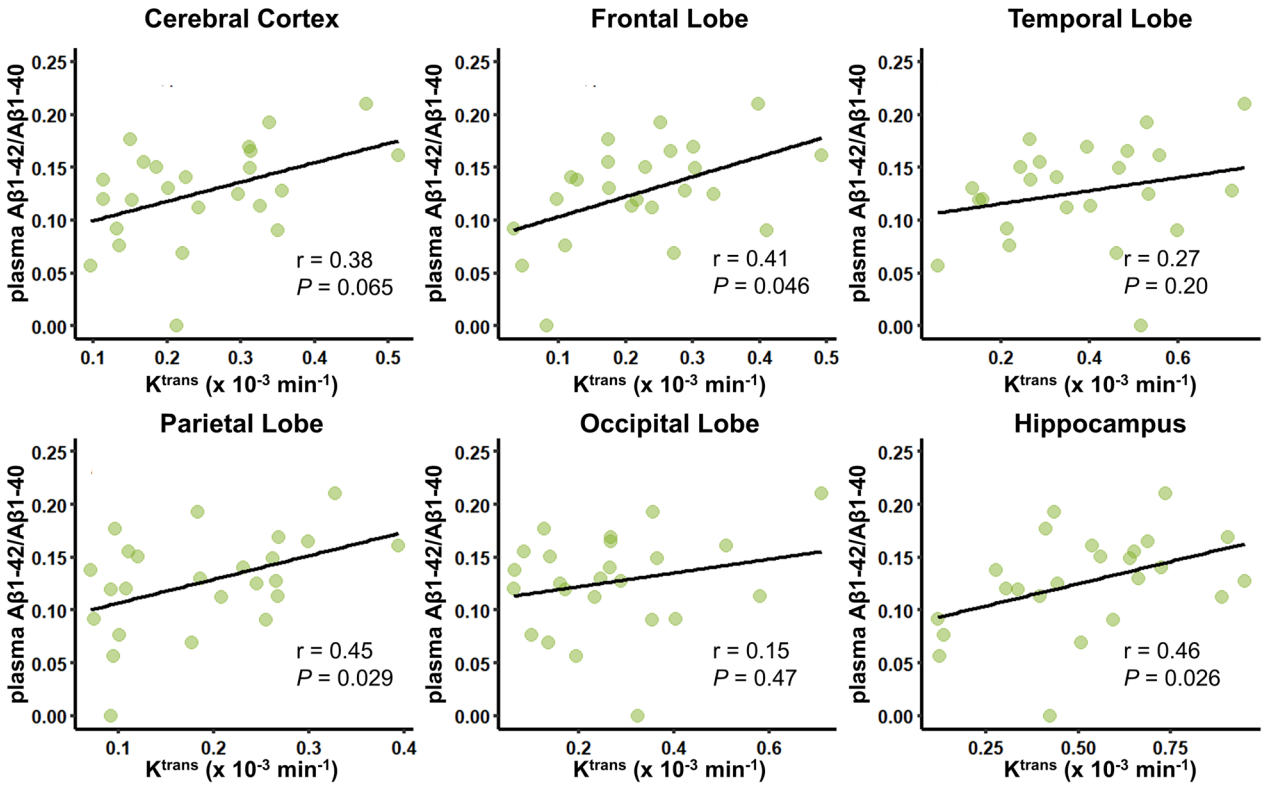

Fig. 7 Correlations between K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in HC group. The correlation analysis of BBB permeability constant K^{trans} and plasma Aβ1-42/Aβ1-40 ratio in HC group showed positive correlation trends in cerebral cortex, frontal lobe, temporal lobe, parietal lobe, occipital lobe and hippocampus. Increased BBB permeability constant K^{trans} in the frontal lobe, parietal lobe and hippocampus were significantly correlated to higher plasma Aβ1-42/Aβ1-40 ratio. *Aβ* amyloid-β, *BBB* blood brain barrier, *HC* healthy control, K^{trans} transfer rate of contrast agent from intra- to extravascular spaces

plasma Aβ1-42/Aβ1-40 ratio had proven to be a robust peripheral biomarker of cerebral amyloid pathology in conjunction with AD [48], AD patients with BBB disruption had low Aβ1-40 levels [49]. Currently, there was no evidence to support a direct connection between Aβ and BBB injury in patients with DLB, despite our initial finding that increased K^{trans} values of cerebral cortex and parietal lobes were correlated with higher plasma Aβ1-42/Aβ1-40 ratios. Aβ deposition had been encountered in roughly one-fourth of such patients, according to neuropathologic data [50]. Aβ levels had correlated as well with levels of α-synuclein and are associated with shorter survival and a heightened rate of cognitive decline [51]. This relation may be attributable to pathophysiologic mechanisms, such as impaired protein homeostasis, whereby compromised protein turnover pathways affect both proteins. In addition, metabolic changes, neuroinflammation, or impaired synaptic function are potential contributors to the accumulation of α-synuclein and Aβ in the setting of DLB. Both Aβ and α-synuclein may independently or jointly play roles in AD and DLB, influencing disease progression or BBB breakdown. This particular realization underscores the potential utility of K^{trans} in evaluating disease burden and cognitive decline for either form of dementia.

Conclusions

Herein, we have detailed the first-time usage of DCE-MRI to directly assess BBB integrity in patients with DLB, while also investigating associations between BBB integrity and significant clinical characteristics. But there are still some limitations. Firstly, the sample size was relatively small, which may explain the fact that 60% DLB patients carried APOE ε4 allele in our data. APOE ε4 allele is a typical risk factor for AD [52], also a strong risk factor across the Lewy body disease spectrum with a proportion of 20–60% in DLB [53–56]. It can enhance the dysfunction of BBB in AD [45] and increase the severity of Lewy body pathology independent of Alzheimer pathology [55, 56], while previous studies did not find significant association between APOE ε4 allele and BBB dysfunction in DLB [23, 57]. Current study showed a slightly higher frequency of APOE ε4 carriers in DLB

patients than HC and AD patients, no significant correlation was found between APOE ε4 allele and K^{trans} values in DLB, which might due to the small sample size with 20 DLB patients. Thus, further validation is needed, drawn from a larger sampling and multiple diagnostic subsets. Secondly, as we did not find a significant difference in plasma Aβ1-42/Aβ1-40 ratio among HC, AD, and DLB groups, suggesting that CSF Aβ1-42/Aβ1-40 ratio may be more accurate as an AD biomarker. The fact that plasma levels of tau or α- synuclein, and CSF testing were lacking also limited our ability to directly and comprehensively investigate the importance of BBB permeability or to pursue pertinent CSF biomarkers. Besides, since there were no subjects in prodromal phase, we must expand our scope of research scope going forward to explore the early diagnostic benefit of DCE-MRI in patients with DLB.

In conclusion, we have found that the BBB leakage within cerebral cortex was common feature of DLB, proving significantly more severe than in AD and HC patient groups (especially at occipital lobe). BBB permeability was also associated with plasma Aβ1-42/Aβ1-40 ratios and CDR scores, which reflect dementia severity. These findings support the potential use of DCE-MRI to monitor patients with DLB in terms of disease progression and declining cognition. They also provide impetus for future investigations of DLB, exploring molecular mechanisms of BBB breakdown and evaluating the merits of targeted therapeutic interventions.

Abbreviations

Aβ	Amyloid β
AD	Alzheimer's disease
APOE ε4	Apolipoprotein E ε4
BBB	Blood–brain barrier
BMI	Body mass index
CDR	Clinical dementia rating
CVD	Cardiac-cerebral vascular disease
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DLB	Dementia with Lewy bodies
^{18}F-FDG-PET	Flourine-18 fluorodeoxyglucose positron emission tomography
FLC	Fluctuating cognition
GFAP	Glial fibrillary acidic protein
HCs	Healthy controls
IQR	Interquartile range
LB	Lewy bodies
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NfLs	Neurofilament light chains
NSE	Neuron-specific enolase
Qalb	CSF/serum albumin quotient
RBD	Rapid eye movement sleep behaviour disorder
ROIs	Regions of interest
S100B	S100 Calcium Binding Protein B
T2DM	Type 2 diabetes mellitus
VEGF	Vascular endothelial growth factor
VHs	Visual hallucinations

Supplementary Information

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Supplementary Material 1.

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Author contributions

YJ and HJC were responsible for the conception and design of the study, and manuscript revision for important intellectual content. JHG and ZCC collected the data and biological samples of all participants, and assisted in the completion of DCE-MRI scanning. JHG also detecting biological samples, and was one of major contributors in writing and re-writing the manuscript. ZMX performed the analysis and interpretation of DCE-MRI, and was one of major contributors in writing the manuscript. YJW assisted in the analysis of DCE-MRI. YJ, HW, and ZHS were responsible for the screening and enrollment of the participants. SL assessed the clinical symptoms of the participants and was responsible for data management. HL performed the scanning of DCE-MRI. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed according to the Helsinki Declaration and approved by the Ethical Review Board of Beijing Tiantan Hospital (KYSQ 2021-068-01). Written informed consents were obtained from all participants and family members of AD and DLB patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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