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Association of circulating proteasome activity with Alzheimer's pathology and cognitive functions in APOE ε4 carriers

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Abstract

Background The proteasome is a major intracellular protease complex, but the significance of circulating proteasome activity in Alzheimer's disease (AD) is not well established. Because APOE ε4 is the strongest genetic risk factor for AD, we examined whether plasma proteasome activity is associated with AD-related pathology, neurodegeneration, and cognitive decline, focusing on APOE ε4 carriers.

Methods In this observational study, participants were classified as cognitively normal (CN), mild cognitive impairment (MCI), and dementia. All underwent 3.0-T MRI, [^{18}F]flutemetamol PET for amyloid, [^{18}F]MK-6240 PET for tau, APOE genotyping, and neuropsychological testing. Circulating proteasome activity was measured using fluorogenic substrates. Associations between proteasome activity and imaging or clinical features were assessed after stratifying by APOE ε4 status. Mediation analyses evaluated whether amyloid or tau burden indirectly linked proteasome activity with hippocampal volume or cognition.

Results A total of 148 individuals were included (58 CN, 39 MCI, 38 AD dementia, and 13 other dementia). Significant associations appeared only in APOE ε4 carriers ($n=55$). Higher proteasome activity was associated with lower amyloid burden ($\beta=-0.336$, $p=0.009$), lower global tau burden ($\beta=-0.268$, $p=0.047$), and reduced tau in Braak I/II ($\beta=-0.298$, $p=0.033$) and Braak III/IV regions ($\beta=-0.296$, $p=0.033$). Proteasome activity was positively associated with hippocampal volume ($\beta=0.374$, $p=0.001$) and with cognitive performance, including MMSE ($\beta=0.294$, $p=0.026$), CDR-SOB ($\beta=-0.365$, $p=0.005$). No significant associations were found in noncarriers. Mediation analyses showed that amyloid burden explained ~ 29% and Braak I/II tau ~ 23% of the proteasome–hippocampal volume relationship, while tau in Braak I/II and III/IV regions mediated 24–41% of the associations between proteasome activity and global cognition.

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Conclusions Downregulated proteasome activity is strongly associated with amyloid burden, early tau accumulation, hippocampal atrophy, and cognitive impairment only in APOE ε4 carriers. These findings suggest that plasma proteasome activity may serve as a noninvasive marker of AD-related vulnerability in genetically at-risk individuals. Further studies are needed to clarify whether proteasome activity contributes to or results from amyloid and tau aggregation.

Trial registration KCT0005428. Registered September 24, 2020.

Study subjects included in this analysis were those recruited from November 2018 onwards (retrospectively registered).

Keywords Alzheimer's disease, Amyloid, APOE ε4, Biomarker, Cognition, PET, Plasma, Proteasome, Tau

Background

The ubiquitin (Ub)-proteasome system (UPS) plays a principal role in degrading misfolded and aggregation-prone proteins in cells. Given that many neurodegenerative diseases, including Alzheimer's disease (AD), manifest with the accumulation of proteotoxic proteins, UPS dysfunction is expected to be pathologically associated with the onset and progression of these disorders [1, 2]. For example, postmortem analyses of AD brains have revealed significantly reduced proteasome activity in the hippocampal region compared to healthy controls [3, 4]. The 26 S proteasome is the sole adenosine triphosphate (ATP)-dependent protease in the cytoplasm, consisting of two functionally distinct compartments: the catalytic complex (20 S) for substrate hydrolysis and the regulatory complex (19 S) for substrate recognition, processing, and translocation into the 20 S chamber [5]. Notably, more than half of all proteasomes exist as a free 20 S form [6]. The contribution of 20 S-mediated proteolysis to global protein homeostasis, i.e., proteostasis, has been increasingly recognized, particularly in the degradation of misfolded proteins in a Ub-independent manner [7, 8].

While intracellular proteostasis via proteolysis has been extensively studied, how extracellular proteostasis is regulated remains poorly understood. Yet, the presence of protein aggregates in the blood or cerebrospinal fluid, such as amyloid β (Aβ) and tau proteins, underscores the importance of extracellular protein quality control (PQC), especially in neurodegenerative conditions [9]. With more than one-third of protein encoding genes involved in producing membrane-bound and secreted proteins [10, 11], extracellular PQC may be particularly critical in preventing the accumulation of misfolded proteins in the extracellular environment, where ATP is depleted. We previously observed that circulating proteasomes in human plasma predominantly exist as 20 S proteasomes and that their activity is significantly reduced in patients with mild cognitive impairment (MCI) and chronic tinnitus, compared to those with tinnitus alone [10]. We also found a significant negative association between Aβ levels and circulating proteasome activity, which was not observed with other plasma enzymes.

The ε4 allele of apolipoprotein E (APOE) is the strongest risk factor for late-onset AD [11–13]. APOE, present in lipoprotein particles in the human brain, plays critical roles in amyloid precursor protein processing, Aβ clearance, and tau phosphorylation [14]. Among the three gene variants (APOE ε2, ε3, and ε4), the ε4 isoform increases AD risk by 2- to 3-fold with one ε4 allele and up to 12-fold with two alleles [15]. While APOE ε4 appears critically implicated in Aβ and tau pathologies, the precise mechanism of how it contributes to AD risk and prognosis remains to be determined. We hypothesized that proteasomes in the circulatory system may dynamically respond to systemic stress caused by accumulated proteotoxic proteins, potentially serving as an adaptive response mechanism linked to neuropathological characteristics. In addition, APOE ε4 status strengthens the association between plasma proteasome activity and AD pathology indices. Accordingly, this study aimed to investigate the association between circulating proteasome activity and key Alzheimer's disease–related pathological, structural, and cognitive markers, with a particular focus on the modifying role of APOE ε4 status.

Material and methods

Participants

Participants were enrolled in a prospective cohort study conducted at the memory disorder clinic within the Department of Neurology at Gachon University Gil Medical Center. Patients with cognitive impairment, including those with MCI or dementia, were recruited through this neurology-based clinic. Community-dwelling cognitively normal (CN) individuals were recruited as control participants from volunteers engaged in aging-related research. All participants underwent the same standardized clinical evaluation by a single board-certified neurologist (Y.N.), and each completed a detailed neuropsychological assessment administered by an experienced neuropsychologist to confirm the diagnosis.

We recruited a total of 180 participants composed of patients with MCI, dementia and CN individuals. They performed 3.0-Tesla MRI, [^{18}F]flutemetamol (FLUTE) and [^{18}F]MK-6240 (MK-6240) PET scans,

APOE genotyping, comprehensive neuropsychological tests, and plasma collection for blood-based proteasome activity assessment. Among them, 15 individuals were excluded due to incomplete evaluation, 11 due to motion defects on PET imaging and 6 due to hemolyzed blood. The final cohorts consisted of 38 patients with AD dementia, 39 with MCI, 13 with other dementia (3 with subcortical vascular dementia, 1 with corticobasal syndrome, and 9 with clinically probable AD who showed negative findings on amyloid PET imaging), and 58 CN individuals.

AD dementia were diagnosed with probable AD according to the framework criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS–ADRDA) [16]. AD patients with a history of other neurological or psychiatric disorders were not recruited in the study. Patients with structural abnormalities on MRI, such as cerebral, cerebellar, or brainstem infarction, intracranial hemorrhage, hydrocephalus, severe white matter hyperintensities, white matter hyperintensities associated with radiation, traumatic brain injury, tumors, multiple sclerosis, and vasculitis, were excluded. Furthermore, patients with cognitive impairment due to metabolic or systemic causes were excluded after assessment with laboratory tests, which included complete blood count, thyroid function, syphilis serology, folate levels, vitamin B12, and metabolic profile.

Participants were classified as MCI according to Petersen's criteria [17], objective cognitive decline in neuropsychological tests, indicated by a clinical dementia rating (CDR) score of 0.5, and their ability to independently perform activities of daily living at a sufficient level. CN participants were either healthy volunteers or individuals who did not exhibit objective cognitive decline, with mean z-scores within 1.5 standard deviations of age- and education-corrected norms on neuropsychological tests and a CDR score of 0.

Written informed consent was obtained from all participants and their guardians (for dementia patients). This study was approved by the Institutional Review Board (IRB # GBIRB2018-350) and registered at the Clinical Research Information Service of Korea (CRIS: KCT0005428).

Neuropsychological assessment

All participants underwent cognitive function evaluations using the Mini-Mental State Examination (MMSE), CDR, and comprehensive neuropsychological tests, assessing attention, language, verbal and visual memory, visuospatial skills, and frontal/executive functioning. Detailed items of the comprehensive test battery have been described in the previous study [18, 19]. For comprehensive neuropsychological test results, we used z-scores which were standardized for age and years of education. Details of the specific tests administered are provided in Supplementary Text 1.

Image acquisition and quantification

MR imaging acquisition and segmentation

MRI scans were performed using a Magnetom Skyra 3.0-Tesla MRI scanner (Siemens, Erlangen, Germany), equipped with a 32-channel Siemens matrix head coil. We acquired 3D T1 magnetization-prepared rapid gradient echo (T1-MPRAGE): repetition time = 1,810 ms, echo time = 2.91 ms, flip angle = 9°, pixel bandwidth = 340 Hz/pixel, matrix size = 256 × 256, field of view = 250 mm, NEX = 1, total acquisition time = 3 min 37 s, voxel size = 0.49 × 0.49 × 1.0 mm3, and fluid attenuated inversion recovery (FLAIR): repetition time = 9,000 ms, echo time = 122 ms, flip angle = 150°, pixel bandwidth = 287 Hz/pixel, matrix size = 256 × 224, field of view = 256 mm, NEX = 1, total acquisition time = 2 min 44 s, voxel size = 0.5 × 0.5 × 2.0 mm3. 3D susceptibility weighted imaging (SWI) was conducted with TR = 40 ms and dual echo times of 13.70 ms and 30.50 ms. The flip angle was 15°, bandwidth was 120 Hz/pixel, matrix = 230 × 202, FOV = 230 mm, and NEX = 1. The scan duration was about 109 s, with voxel dimensions of 0.8 × 0.8 × 2.0 mm^3.

MR imaging quantification

Structural MRI processing and volumetric measurements were performed using FreeSurfer 6.0 (www.surfer.nmr.mgh.harvard.edu). The standard recon-all processing pipeline was applied to 3D-T1 MPRAGE images for cortical surface reconstruction and volumetric segmentation. Mean cortical thickness was calculated by averaging vertex-wise cortical thickness across bilateral hemispheres. Intracranial volume (ICV) and hippocampal volume (HV) were automatically derived using the aseg (automated segmentation) output. All segmentations were visually inspected for accuracy and manual corrections were performed, when necessary, in accordance with FreeSurfer guidelines [20]. Assessment of white matter hyperintensity volume, microbleeds and lacunes are described in the Supplementary Text 2.

PET imaging acquisition

All participants acquired FLUTE and MK-6240 PET scans using a Siemens Biograph 6 Truepoint PET/computed tomography (CT) scanner (Siemens, Knoxville, TN, USA) with a list-mode emission acquisition. MK-6240 scans were acquired from 70 to 90 min after the intravenous injection of 185 MBq of [^{18}F]MK-6240, which was prepared as described previously [21] with a modified method at the cyclotron facility, Gachon University. FLUTE scans were acquired from 90 to 110 min after the intravenous injection of 185 MBq of [^{18}F]

FLUTE, which was purchased from Carecamp Inc. We used a low-dose CT scan for attenuation correction. PET data was reconstructed onto a 256 × 256 × 109 matrix with a voxel size of 1.3 × 1.3 × 1.5 mm^3 using a 2D ordered subset expectation maximization algorithm with 8 iterations and 16 subsets.

PET quantification

Individual MK-6240 and FLUTE PET images were co-registered onto individual T1 MPRAGE images using FreeSurfer. We calculated regional mean values of PET images after region-based partial volume correction using PETSurfer and acquired weighted-average values of pre-defined ROIs [22, 23]. For amyloid PET, the cortical retention of FLUTE was quantified in AD-associated regions, including the prefrontal, superior parietal, lateral temporal, inferior parietal, occipital, anterior cingulate, mesial temporal, precuneus, and posterior cingulate cortices. FLUTE SUVR was evaluated using the pons as a reference region [24]. FLUTE images were also visually evaluated for amyloid positivity based on a standardized visual rating protocol [25].

Tau burden was quantified using MK-6240 SUVR. ROIs for MK-6240 included global MK-6240 (frontal pole, pars orbitalis, lateral orbitofrontal, pars triangularis, pars opercularis, rostral middle frontal, superior frontal, caudal middle frontal, medial orbitofrontal, superior parietal, inferior parietal, supramarginal, precuneus, cuneus, pericalcarine, lateral occipital, banks of superior temporal, inferior temporal, middle temporal, superior temporal, hippocampus, amygdala, parahippocampal, entorhinal, nucleus accumbens, caudal anterior cingulate, rostral anterior cingulate and posterior cingulate), Braak I/II (entorhinal and hippocampus regions), Braak III/IV (parahippocampal, fusiform, lingual, amygdala, inferior temporal, middle temporal, temporal pole, thalamus, caudal, rostral, isthmus, posterior cingulate and insula regions) and Braak V/VI (frontal, parietal, occipital, transverse, superior temporal, precuneus, banks of superior temporal, nucleus accumbens, caudate nucleus, putamen, precentral, postcentral, paracentral, cuneus and pericalcarine regions) [26, 27]. Regional standardized uptake value ratios (SUVRs) of MK-6240 were computed using cerebellar gray matter as a reference region [28].

Plasma preparation and processing

Whole blood was collected in two EDTA vacuum tubes from study participants between 9:00 and 10:00 AM after a 6-hour fasting period. Blood was processed independently as technical duplicates. Plasma was isolated by centrifugation at 3,000 rpm using a benchtop centrifuge for 15 min, aliquoted into 1.5 mL tubes in 0.5–1.0 mL volumes and stored at – 80°C until analyzed. Hemolytic samples were identified and discarded through visual inspection. Previous studies have confirmed that proteasome activity in plasma remains comparable across multiple freeze-thaw cycles [10].

Proteasome activity measurement

Circulating proteasome activity in plasma was assessed using a standardized method employing a fluorogenic reporter substrate, succinyl-Leu-Leu-Leu-Val-Tyr-7-amino-4-methylcoumarin (suc-LLVY-AMC; Bachem, Bubendorf, Switzerland.) [29, 30]. This peptide is cleaved by the proteasome subunit (β5) with chymotrypsin-like catalytic activity, and the fluorescence intensity from free AMC is considered as a representative measure of overall proteasome activity [31]. Briefly, 20 µL of human plasma was combined with 250 µM of suc-LLVY-AMC in an assay buffer (50 mM Tris-HCl [pH 7.5], 1 mg/mL BSA, 1 mM EDTA, 1 mM fresh ATP, and 1 mM fresh DTT) in a black 96-well plate. The hydrolysis of the fluorogenic peptides was monitored every three min at 380/460 nm (excitation/emission wavelength) at 30°C. Each sample was assayed in triplicate. All fluorescence intensities from plasma samples were normalized to those obtained in the presence of the proteasome inhibitor MG132 (10 µM), and the resulting circulating proteasome activity was expressed as relative fluorescence units (RFU).

Statistical analysis

To analyze the demographics and clinical characteristics of the study population, continuous variables were assessed through group comparisons using the independent samples t-test. For nominal variables, the chi-square test or Fisher's exact test was applied. After dividing the study participants as APOE ε4 carriers (having at least one APOE ε4 allele) and noncarriers, we assessed associations of clinical variables (MMSE, CDR-SOB, mean cortical thickness, hippocampal volume, cortical FLUTE retention, global MK-6240 retention, and MK-6240 SUVR based on Braak stages) with proteasome activity using multivariable linear regression models in each group. In the linear regression models, age, sex, and years of education were included as covariates. The difference in the associations between APOE ε4 carriers and noncarriers was tested by the method described elsewhere and expressed as p for interaction [32].

To examine whether amyloid or tau burden ('M') mediated the associations between proteasome activity ('X') and global cognition or hippocampal volume ('Y'), we performed mediation analyses. Indirect effects were quantified through a series of regression models evaluating: (1) the association between X and Y, (2) the association between X and M, and (3) the joint influence of X and M on Y. After controlling for age, sex, and years of education, we derived the estimates for the indirect, direct, and total effects (direct plus indirect), as well as

the percentage of the total effect explained by mediation (indirect effect/total effect × 100). Confidence intervals for the beta coefficients were obtained using non-parametric bootstrapping with 1,000 resamples. All mediation procedures were implemented in R (version 3.4.1, R Foundation) using the "mediation" package [33].

All statistical analyses were conducted using PASW Statistics 19 (SPSS Inc, Chicago, IL, USA) with a significance at $p < 0.05$ (two-way).

Results

Demographics and clinical characteristics of study population

The demographics and clinical characteristics of the study population are shown in Table 1. There was no significant difference in age, sex, and years of education. In contrast, APOE ε4 carriers and noncarrier groups showed a clear statistical difference in clinical diagnoses ($p = 0.002$). The APOE ε4 carrier group had a higher number of AD dementia patients, while the noncarrier group included a higher proportion of CN individuals. In the APOE ε4 carrier group, the majority of participants were ε3/ε4 ($n = 39$ [70.9%]), followed by ε4/ε4 ($n = 13$ [23.6%]), and ε2/ε4 ($n = 3$, [5.5%]). By comparison, the APOE ε4 noncarrier group mainly consisted of ε3/ε3 individuals ($n = 76$, 81.7%), with a smaller proportion of ε2/ε3 ($n = 17$[18.3%]).

MMSE and CDR-SOB scores did not significantly differ between APOE ε4 carrier and noncarriers. In addition, there were no significant differences in the prevalence of comorbidities, such as hypertension, diabetes, dyslipidemia, coronary artery disease, and history of stroke, between the two groups. Proteasome activity in plasma also did not differ between the groups. However, we found that hippocampal volume was significantly smaller in APOE ε4 carriers. Both cortical FLUTE retention and

Table 1 Demographics and clinical characteristics of the study subjects

Variables	All participants ($N = 148$)	APOE ε4 carrier ($n = 55$)	APOE ε4 noncarrier ($n = 93$)	*p* value
CN/MCI/ADD/OD (%)	58/39/38/13 (39.2/26.4/25.7/8.8)	15/18/21/1 (27.3/32.7/38.2/1.8)	43/21/17/12 (46.2/22.6/18.3/12.9)	0.002
Age	70.80 ± 8.01	70.47 ± 7.95	70.99 ± 8.09	0.706
Sex (Female, n [%])	97(65.5)	35(63.6)	62(66.7)	0.724
Education(year)	9.09 ± 4.25	9.58 ± 4.02	8.81 ± 4.37	0.284
APOE genotype				< 0.001†
ε2/ε3	17 (11.5)		17 (18.3)	
ε3/ε3	76 (51.4)		76 (81.7)	
ε2/ε4	3 (2.0)	3 (5.5)		
ε3/ε4	39 (26.4)	39 (70.9)		
ε4/ε4	13 (8.8)	13 (23.6)		
MMSE	24.53 ± 5.09	24.18 ± 4.52	24.73 ± 5.41	0.527
CDR-SOB	2.53 ± 2.87	2.75 ± 2.46	2.39 ± 3.09	0.460
Hypertension (%)	67(45.3)	23(41.8)	44(47.3)	0.609
Diabetes mellitus (%)	44(29.7)	13(23.6)	31(33.3)	0.265
Dyslipidemia (%)	62(41.9)	27(49.1)	35(37.6)	0.227
Coronary artery disease (%)	8(5.4)	6(10.9)	2(2.2)	0.052†
History of stroke (%)	2(1.4)	0(0.0)	2(2.2)	0.530†
Amyloid Positivity (%)	64(43.2)	38(69.1)	26(28.3)	< 0.001
Cortical FLUTE SUVR	0.5955 ± 0.27	0.7136 ± 0.24	0.5230 ± 0.27	< 0.001
Global MK-6240 SUVR	1.4010 ± 0.93	1.6216 ± 0.95	1.2759 ± 0.90	0.034
Mean cortical thickness (mm)	2.35 ± 0.18	2.37 ± 0.16	2.34 ± 0.19	0.346
ICV (L)	1.42 ± 0.18	1.38 ± 0.17	1.44 ± 0.19	0.052
Hippocampal volume (mL)	3.25 ± 0.48	3.10 ± 0.54	3.35 ± 0.43	0.004*
WMHV (mL)	10.07 ± 11.60	9.28 ± 12.28	10.54 ± 11.21	0.523
Proteasome activity (RFU/1,000)	1.215 ± 0.56	1.239 ± 0.56	1.201 ± 0.56	0.690

Abbreviations: *CN* Cognitive normal, *MCI* Mild cognitive impairment, *ADD* Azheimer's disease dementia, *OD* Other dementia, *MMSE* Mini-Mental State Examination, *CDR-SOB* Clinical Dementia Rating-Sum Of Boxes, *FLUTE* Flutemetamol, *SUVR* Standardized uptake value ratio, *ICV* Intracranial volume, *WMHW* White matter hyperintensity volume, *RFU* Relative fluorescence units

Values are presented as mean ± standard deviation for continuous variables and as number (%) for nominal variables. Group comparisons were performed between the APOE ε4 carrier and noncarrier groups using an independent samples *t*-test for continuous variables and chi-square test for categorical variables. All group comparisons were considered significant when $p < 0.05$

*The assumption of equal variances was not met (Levene's test), so the results of Welch's *t*-test were reported. †Mean group differences were assessed by Fisher's exact test

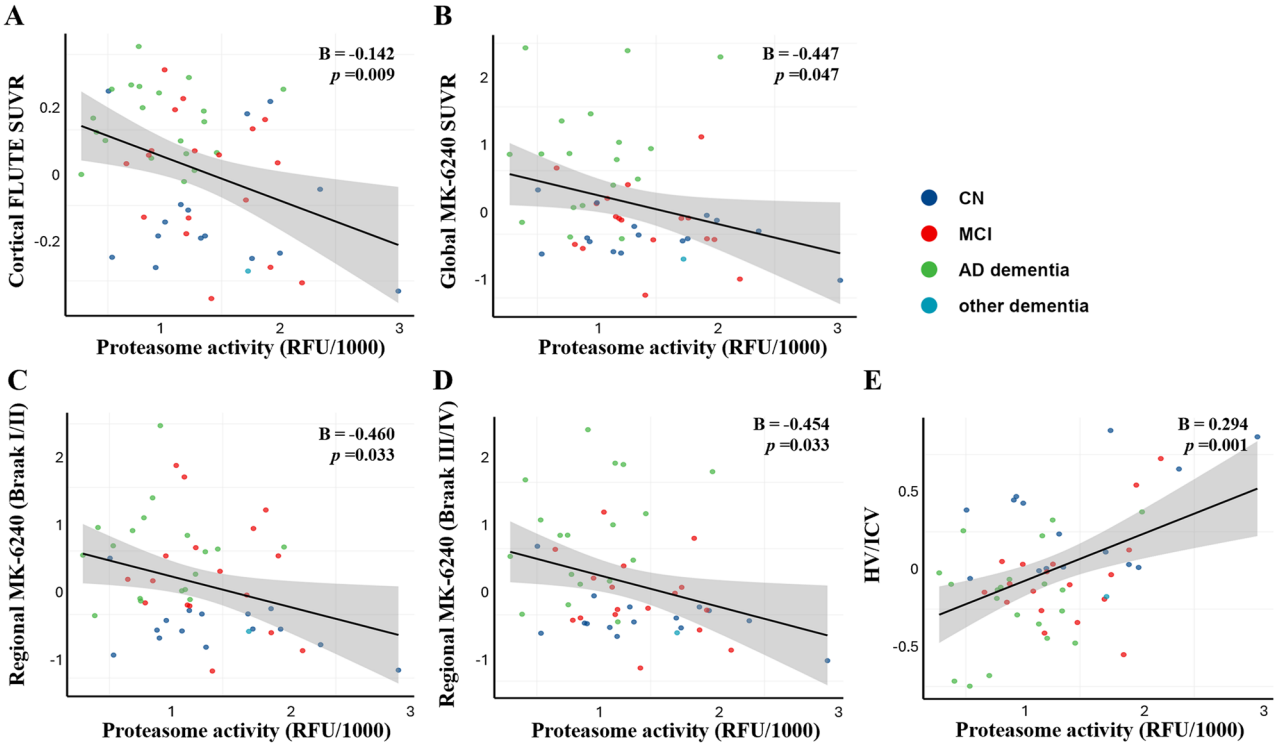

Fig. 1 Associations of proteasome activity with amyloid burden, tau burden, and hippocampal volume in APOE ε4 carriers. **A** A partial regression plot showing the association between proteasome activity in plasma and cortical FLUTE SUVR. **B** A partial regression plot showing the association between proteasome activity and global MK-6240 SUVR. **C** A partial regression plot showing the association between proteasome activity and regional MK-6240 SUVR in the brain areas for Braak I/II. **D** A partial regression plot showing the association between proteasome activity and regional MK-6240 PET SUVR in the brain areas for Braak III/IV. **E** A partial regression plot showing proteasome activity and hippocampal volume (HV) normalized to intracranial volume (ICV). All analyses were performed with adjustment of age, sex and years of education

Table 2 Association between proteasome activity and amyloid, tau and neurodegeneration

Variables (*N* = 148)	APOE ε4 carrier (*n* = 55)			APOE ε4 noncarrier (*n* = 93)			
	B (SE)	β	*p* value	B (SE)	β	*p* value	*p* for interaction
Cortical FLUTE SUVR	-0.142(0.052)	-0.336	0.009	-0.028(0.050)	-0.059	0.582	0.114
Global MK-6240 SUVR	-0.447(0.219)	-0.268	0.047	0.011(0.163)	0.007	0.945	0.093
Regional MK-6240 SUVR in Braak I/II	-0.460(0.209)	-0.298	0.033	-0.010(0.116)	-0.010	0.930	0.060
Regional MK-6240 SUVR in Braak III/IV	-0.454(0.206)	-0.296	0.033	-0.017(0.128)	-0.014	0.895	0.072
Regional MK-6240 SUVR in Braak V/VI	-0.336(0.192)	-0.232	0.087	0.013(0.143)	0.009	0.930	0.145
Mean cortical thickness	0.047(0.032)	0.171	0.151	0.016(0.037)	0.047	0.664	0.523
HV/ICV	0.294(0.083)	0.374	0.001	-0.123(0.078)	-0.156	0.119	< 0.001

Values are presented as unstandardized coefficients (B) with standard errors (SE) and Standardized coefficients (*β*) from multivariable linear regression models adjusted for age, sex, and years of education

global MK-6240 PET retention were greater in APOE ε4 carriers than in noncarriers.

Associations between circulating proteasome activity and amyloid, tau, and neurodegeneration in APOE ε4 carriers and noncarriers

Among APOE ε4 carriers, higher proteasome activity was significantly associated with lower cortical amyloid burden (β = -0.336, $p = 0.009$) and lower global tau burden measured by MK-6240 SUVR (β = -0.268, $p = 0.047$) (Fig. 1A and B; Table 2). Regional tau deposition in Braak I/II and Braak III/IV areas also showed significant negative associations (β = -0.298, $p = 0.033$; β = -0.296, $p = 0.033$, respectively) (Fig. 1C and D). In contrast, none of these associations reached significance in APOE ε4 noncarriers.

Proteasome activity was further associated with neurodegeneration in APOE ε4 carriers, as reflected by a strong positive association with hippocampal volume normalized to intracranial volume (HV/ICV; β = 0.374, $p = 0.001$) (Fig. 1E), whereas no such association was observed in noncarriers (β =-0.156, $p = 0.119$). The interaction term for APOE ε4 status was highly significant for HV/ICV (*p* for interaction < 0.001), indicating that the

Table 3 Association of cognitive functions and proteasome activity

Variables	APOE ε4 carrier			APOE ε4 noncarrier			
	B (SE)	β	*p* value	B (SE)	β	*p* value	*p* for interaction
MMSE	2.375(1.034)	0.294	0.026	-1.162(0.999)	-0.121	0.248	0.014
CDR-SOB	-1.604(0.544)	-0.365	0.005	0.618(0.578)	0.112	0.288	0.005
Digit span test: forward	-0.044(0.207)	-0.029	0.833	0.161(0.201)	0.084	0.425	0.477
Digit span test: backward	0.097(0.219)	0.061	0.659	-0.031(0.205)	-0.016	0.882	0.670
Boston Naming Test	0.637(0.351)	0.242	0.075	-0.167(0.343)	-0.051	0.628	0.101
Rey Complex Figure Test-copy	0.573(0.635)	0.123	0.371	-0.089(0.651)	-0.014	0.891	0.467
SVLT immediate recall	0.590(0.311)	0.252	0.063	0.217(0.302)	0.076	0.474	0.391
SVLT delayed recall	0.749(0.321)	0.305	0.023*	0.143(0.301)	0.050	0.637	0.168
SVLT recognition	0.579(0.483)	0.163	0.236	0.191(0.308)	0.065	0.538	0.497
RCFT immediate recall	0.553(0.237)	0.306	0.023*	-0.052(0.249)	-0.022	0.837	0.079
RCFT delayed recall	0.514(0.249)	0.273	0.044*	0.003(0.255)	0.001	0.991	0.151
RCFT recognition	0.589(0.343)	0.230	0.091	0.027(0.276)	0.010	0.924	0.201
COWAT animal	0.412(0.250)	0.221	0.105	0.048(0.232)	0.022	0.835	0.286
COWAT supermarket	0.413(0.297)	0.188	0.170	-0.133(0.231)	-0.060	0.567	0.147
COWAT phonemic total	0.175(0.267)	0.089	0.516	-0.021(0.212)	-0.011	0.921	0.566
Color-Word Stroop Test	0.401(0.310)	0.175	0.202	0.215(0.269)	0.084	0.428	0.651
Digit Symbol Coding	0.608(0.326)	0.248	0.068	0.194(0.311)	0.066	0.533	0.358
TMT-A	0.249(0.246)	0.137	0.318	-0.284(1.656)	-0.018	0.864	0.750
TMT-B	1.389(0.878)	0.212	0.119	-0.507(0.957)	-0.056	0.598	0.144

Abbreviations: *MMSE* Mini-Mental State Examination, *CDR-SOB* Clinical Dementia Rating-Sum of Boxes, *SVLT* Seoul verbal language test, *RCFT* Rey complex figure test, *COWAT* Controlled Oral word association test, *TMT* Trail making test

Values are presented as unstandardized coefficients (B) with standard errors (SE) and Standardized coefficients (*β*) from multivariable linear regression models adjusted for age, sex, and years of education

*data which did not survive domain-wise FDR correction for multiple comparisons, $P > 0.05$

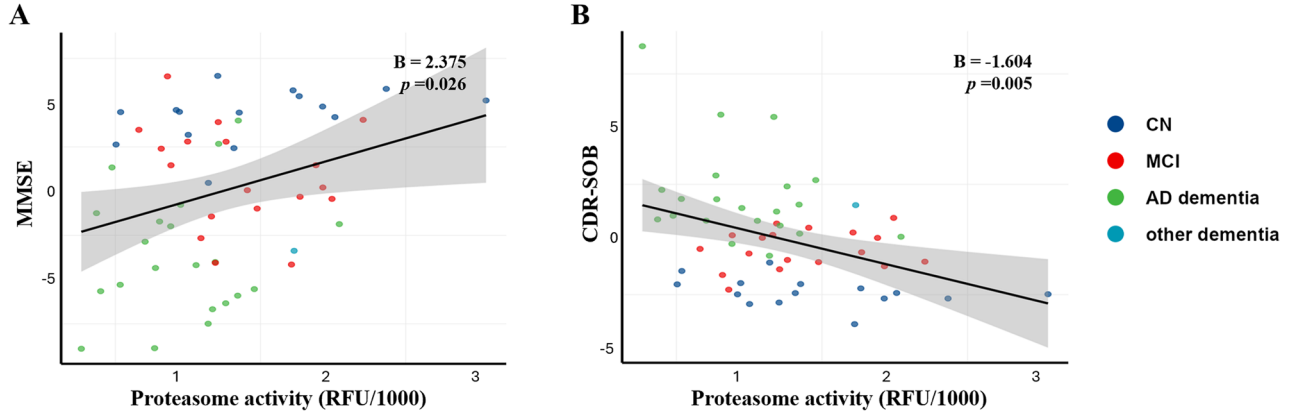

Fig. 2 Associations of proteasome activity with cognitive functions in APOE ε4 carriers **A**. A partial regression plot showing the association between proteasome activity and MMSE scores. **B**. A partial regression plot showing the association between proteasome activity and clinical dementia rating-sum of boxes (CDR-SOB) scores. All analyses were performed with adjustment for age, sex, and years of education

effect of proteasome activity on hippocampal atrophy differed markedly by genetic risk.

Interaction effects for tau burden were also observed, with trend-level significance in Braak I/II and Braak III/IV regions (p for interaction = 0.060 and 0.072, respectively), suggesting that the association between proteasome activity and tau deposition is stronger in APOE ε4 carriers than in noncarriers.

When APOE ε4 carriers and noncarriers were analyzed together, no significant associations were observed between proteasome activity and amyloid/tau burden or structural brain atrophy (Supplementary Table 2).

Associations between circulating proteasome activity and cognitive functions in APOE ε4 carriers

In APOE ε4 carriers, global cognitive functions were significantly associated with circulating proteasome activity (Table 3). MMSE scores showed a positive association (β = 0.294, p = 0.026), and CDR-SOB scores were inversely associated (β = -0.365, p = 0.005) with proteasome

activity, but not in APOE ε4 noncarriers (Fig. 2A and B; Table 3). These group differences were statistically significant (p for interaction = 0.014 for MMSE, p for interaction = 0.005 for CDR-SOB). In addition, although memory-domain measures showed nominal associations with circulating proteasome activity in APOE ε4 carriers in the uncorrected analyses, these associations did not remain statistically significant after correction for multiple comparisons. Specifically, the associations with verbal memory assessed by the Seoul Verbal Learning Test (SVLT) delayed recall, and visual memory assessed by the Rey Complex Figure Test (RCFT) immediate and delayed recall, were attenuated after false discovery rate correction (Table 3). No significant correlations between proteasome activity and cognitive functions were observed in APOE ε4 noncarriers. When both carriers and noncarriers were analyzed together, no significant association was observed between proteasome activity and cognitive functions (Supplementary Table 3).

We additionally examined whether the associations differed between APOE ε3/ε4 and ε4/ε4 carriers using interaction analyses, and found no significant effect modification by APOE ε4 subcategory (Supplementary Table 5).

Mediation effects of amyloid and tau burden on the associations between proteasome activity and cognitive function and hippocampal volume in APOE ε4 carriers

In the mediation analysis, the associations of proteasome activity with hippocampal volume and cognitive function in APOE ε4 carriers were differentially mediated by amyloid and tau burden (Fig. 3, Supplementary Table 4). Cortical FLUTE SUVR significantly mediated the relationship between proteasome activity and hippocampal volume, showing a significant indirect effect (p = 0.02) and accounting for approximately 29.3% of the total effect.

Regional MK-6240 corresponding to Braak I/II demonstrated significant indirect effects for the associations of proteasome activity with hippocampal volume, MMSE, and CDR-SOB, indicating that early-stage tau burden mediates both neurodegeneration and global cognitive impairment. The proportion mediated ranged from 23% to 28% across outcomes.

In contrast, regional MK-6240 corresponding to Braak III/IV significantly mediated the associations of proteasome activity with MMSE and CDR-SOB, whereas the indirect effect for hippocampal volume was not significant. Mediation proportions for these cognitive measures ranged from 30% to 41%.

Discussion

In this study, we found that plasma proteasome activity is significantly associated with AD–related biomarkers in individuals carrying the APOE ε4 allele, but not in noncarriers. Specifically, higher proteasome activity in APOE ε4 carriers was linked to lower amyloid and tau burden, larger hippocampal volume, and better cognitive performance (MMSE and CDR-SOB). In sharp contrast, these correlations were absent or negligible in APOE ε4 noncarriers, suggesting that peripheral proteasome activity might reflect underlying neuropathology and cognitive decline only in individuals genetically predisposed to AD. Therefore, changes in proteasome activity may function as a genotype-specific biomarker that is potentially manifested from AD-linked proteostasis dysfunction in neurons. Mediation analysis showed that in APOE ε4 carriers, amyloid burden primarily mediates proteasome-related hippocampal atrophy, whereas tau burden, particularly in Braak I/II and III/IV regions, mediates the associations between proteasome dysfunction and cognitive decline.

The monomeric component of proteotoxic proteins, such as Aβ and tau, major hallmarks of AD, have been identified as direct substrates for 20 S proteasomes, degraded in a Ub- and ATP-independent manner [31, 34, 35]. These findings might be in line with clinical studies where 20 S activity and levels in plasma were altered in diverse disease states [5–10, 36, 37]. Proteasome impairment in AD has been attributed to the degradation-resistant proteins, such as oligomeric Aβ and tau, that may clog the proteasome and initiate a vicious cycle producing excess aggregation-prone proteins [38–40]. More recently, the 20 S proteasome was reported to be packaged into extracellular vesicles, delivered to recipient cells, and contributed to the degradation of excess tau proteins [41]. Overall, our finding that circulating proteasome activity is inversely associated with amyloid and tau PET signals in ε4 carriers aligns with these mechanistic models of UPS dysfunction in AD.

The APOE genotype appears to modulate this activity-pathology relationship. APOE ε4 is known to enhance amyloid-related tau pathology and neuronal damage [42]. Recent quantitative proteomic analysis using humanized APOE ε4 mice also demonstrated inadequate proteasome and autophagy function, thus indicating extensively disrupted proteostasis in the mouse brain [43]. Our human data parallel these findings, suggesting that ε4 impairs UPS-mediated clearance of pathological proteins, unlike ε2 or ε3 variants. This may explain why proteasome function correlates with AD pathology only in APOE ε4 carriers. Along with this notion, it seems plausible that proteasome inactivation is a central feature of neurodegeneration and that proteasome augmentation reduces related cognitive deficits [44]. The pro-inflammatory

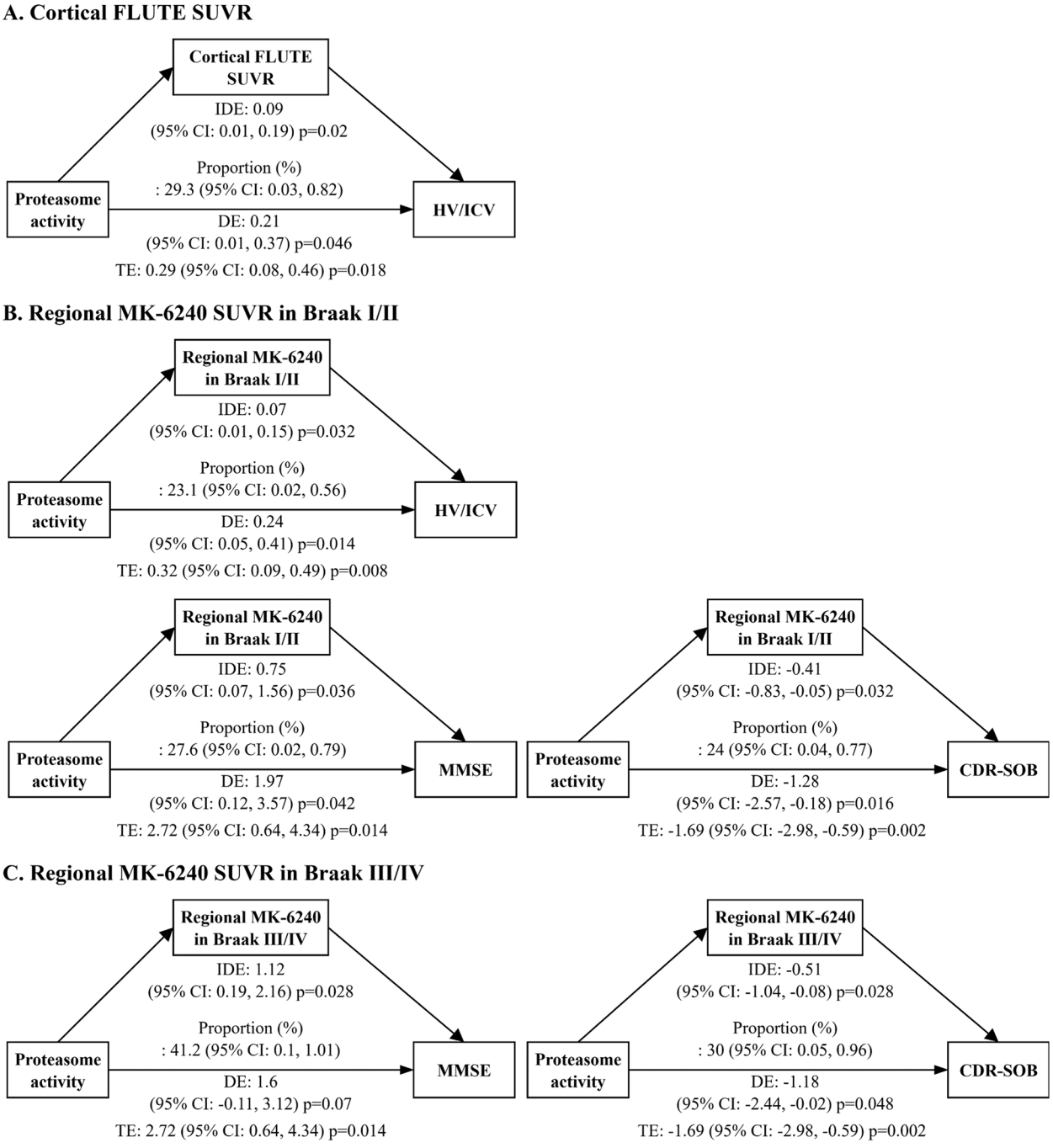

Fig. 3 Mediation effects of amyloid and tau on the associations of proteasome activity with neurodegeneration and cognition. **A** Cortical FLUTE retention, **B** Regional MK-6240 retention in the brain regions for Braak I/II, **C** Regional MK-6240 retention in the brain regions for Braak III/IV mediate the associations between proteasome activity hippocampal atrophy and global cognition (MMSE, CDR-SOB). Abbreviations, SUVR, standardized uptake value ratio; IDE, indirect effect; DE, direct effect; TE, total effect; HV, hippocampal volume; ICV, intracranial volume; MMSE, mini-mental state examination; CDR-SOB, clinical dementia rating-sum of boxes

effect of APOE ε4 in the brain may further exacerbate dysregulation of proteasome pathways, although this remains to be fully elucidated [45].

Our study demonstrates that circulating proteasome activity is selectively associated with pathologic changes at the early stages of AD. Significant correlations with tau burden were confined to Braak I/II and III/IV regions, but absent in Braak V/VI, suggesting that proteasome dysfunction is preferentially linked to early tau deposition. This aligns with the Braak model, where initial tau accumulation in medial temporal regions is most closely tied to episodic memory impairment, whereas widespread

neocortical tau (Braak V/VI) reflects more advanced disease. The lack of association at Braak V/VI may indicate that once tau pathology becomes widespread, systemic proteasome activity no longer tracks disease severity, possibly due to saturation of proteostasis impairment.

Similarly, proteasome activity was positively correlated with hippocampal volume, but not with mean cortical thickness. Since hippocampal atrophy emerges in prodromal stages of AD, whereas diffuse cortical thinning typically manifests later, these results suggest that plasma proteasome activity reflects early medial temporal neurodegeneration rather than global cortical atrophy. The concordance of these findings with tau PET results supports the hypothesis that systemic proteasome dysfunction mirrors early, region-specific AD changes.

In terms of cognition, proteasome activity was robustly associated with global cognitive function, including MMSE and CDR-SOB, but not with attention, language, visuospatial, or executive functions. Although nominal associations with memory-domain measures were observed in APOE ε4 carriers, these associations did not remain statistically significant after correction for multiple comparisons. Nevertheless, it is noteworthy that proteasome activity was associated with hippocampal volume as well as with key pathological markers of early Alzheimer's disease, including amyloid burden and early-stage tau deposition. Given the central role of the hippocampus in memory processing, these findings suggest a biologically plausible link between proteasome alterations and memory-related neurodegeneration, even though the association with memory performance did not withstand FDR correction in the present sample. The attenuation of statistical significance after correction may, at least in part, reflect limited statistical power. Taken together, these findings suggest that circulating proteasome activity is more closely related to global cognitive function than to specific cognitive domains in APOE ε4 carriers, while its association with early Alzheimer's disease pathology and hippocampal structure may provide a biological context for this relationship.

Mediation analyses further clarified these genotype-specific relationships. In APOE ε4 carriers, amyloid burden partially mediated the association between proteasome activity and hippocampal volume, suggesting that reduced amyloid accumulation may be one pathway through which preserved proteasome function relates to medial temporal structural integrity. Moreover, tau burden played a critical and region-specific mediating role: Braak I/II MK-6240 SUVR significantly mediated the associations between proteasome activity and hippocampal volume, MMSE, and CDR-SOB, indicating that early-stage tau deposition is a key intermediary linking proteasome dysfunction to both neurodegeneration and global cognition. In contrast, Braak III/IV MK-6240 SUVR mediated only the relationships with MMSE and CDR-SOB, but not hippocampal volume, suggesting that limbic-stage tau primarily contributes to cognitive impairment rather than structural atrophy in this group. Together, these findings suggest that both amyloid and early tau burden lie on the pathway between systemic proteasome dysfunction and AD-related clinical outcomes, reinforcing the centrality of proteostasis impairment in APOE ε4 carriers.

This study's strengths lie in its rigorously characterized cohort with multimodal imaging and detailed cognitive function data, genotype stratification, and quantitative measurement of plasma proteasome activity. These design features enabled us to detect genotype-specific associations that would have been missed in pooled analyses. Clinically, plasma proteasome activity could offer a noninvasive readout of proteostatic stress in AD in APOE ε4 carriers. Previously, we have reported that proteasome activity is lower in MCI patients and that proteasome activity negatively correlates with plasma Aβ levels [10]. Current findings extend this by showing that in ε4 carriers, proteasome activity not only reflects amyloid and tau burdens but also predicts cognitive performance. This suggests that systemic decline in proteostasis may mirror synaptic dysfunction in the brain, particularly in neurons predisposed by APOE ε4-related pathologic stress. A blood-based enzymatic assay would be far more accessible and cost-effective than PET scans or CSF analyses. Thus, combining plasma proteasome measurements with APOE genotyping could help identify high-risk individuals in prodromal stages more efficiently.

Limitations include the cross-sectional data, which preclude causal inference; the modest sample size, particularly of APOE ε4 carriers; and the single-center, ethnically homogeneous cohort, which may limit generalizability. While our cohort was powered to detect significant effects in ε4 carriers, replication in larger and more diverse populations is essential. In addition, we do not yet know the sequence of events at present; a longitudinal study will determine whether proteasome decline drives pathology or results from it. The origin of plasma proteasomes also remains unclear. Therefore, in a follow-up work, it would be interesting to design in vivo experiments to address these questions in AD model mice. In addition, we do not yet know the origin of circulating proteasomes. While some studies suggest that proteasomes are passively released as 'free' particles, others propose that they are actively transported within extracellular vesicles. Based on our previous findings, proteasomes in the blood may be present in an encapsulated form within extracellular vesicles. We previously reported that human plasma exhibits enhanced suc-LLVY-AMC hydrolysis in the presence of SDS [29]. It is possible that specific SDS concentrations disrupt phospholipid membrane-like

extracellular vesicles, thereby releasing encapsulated proteasomes. Further studies are needed to clarify the relative contributions of free and extracellular vesicle-associated proteasomes.

In summary, our study reveals an APOE ε4-specific correlation between circulating proteasome activity and AD-related features, which may indicate impaired proteostasis in AD. Plasma proteasome activity therefore emerges as a promising, noninvasive biomarker for genotype-specific AD diagnosis and prognosis. Our data also underscores the therapeutic potential of proteasome-activating strategies in neurodegeneration [46, 47].

Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's Disease
APOE	Apolipoprotein E
ATP	Adenosine Triphosphate
CDR-SOB	Clinical Dementia Rating Sum of Box
CN	Cognitively Normal
CT	Computed Tomography
FLAIR	Fluid Attenuated Inversion Recovery
FLUTE	Flutemetamol
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MPRAGE	Magnetization-Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
NEX	Number of Excitation
PET	Positron Emission Tomography
PQC	Protein Quality Control
ROI	Region of Interest
SUVR	Standardized Uptake Value Ratio
SVLT	Seoul Verbal Learning Test
RCFT	Rey Complex Figure Test
Ub	Ubiquitin
UPS	Ubiquitin Proteasome System

Supplementary Information

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Supplementary Material 1. Supplementary Text 1: Detailed neuropsychological tests. Supplementary Text 2 Assessment of WMHV, lacunes and cerebral microbleeds. Supplementary Table 1 Demographics and APOE genotypes of the diagnostic groups. Supplementary Table 2: Associated of amyloid, tau and neurodegeneration markers and proteasome activity in all participants. Supplementary Table 3: Association of cognitive functions and proteasome activity in all participants. Supplementary Table 4: Mediating effects of amyloid and tau burden on associations between proteasome activity and cognitive function and hippocampal volume. Supplementary Table 5: Interaction effects between proteasome activity and APOE ε4 genotype subcategories on cognitive and neuroimaging markers.

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Authors' contributions

B.G.K.: Investigation, Writing – original draft. H.E.S.: Data curation, investigation. Y.Y.: Investigation, Methodology. D.K.: Data curation, investigation. J.M.K.: Investigation. J.C.: Formal analysis, investigation, methodology. S.Y.L.: Investigation, Methodology. Y.J.L.: Data curation, investigation. K.H.P.: Investigation. M.J.L.: Methodology, Writing – review, Supervision, Funding acquisition. Y.N.: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. All authors have given approval to the final version of the manuscript.

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Data availability

All original data from this manuscript are available from the corresponding author (Y.N.) upon reasonable request.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants and their guardians (in case of dementia patients). This study was approved by the Institutional Review Board (IRB # GBIRB2018-350) and was registered at the Clinical Research Information Service of Korea (CRIS: KCT0005428).

Consent for publication

Not applicable. All figures and tables included in this manuscript have been carefully reviewed. This manuscript does not contain any contents that dispose of any direct or indirect identifiers. Datasets have been fully anonymized and no identifiable personal information is presented.

Competing interests

The authors declare no competing interests.

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