Alzheimer's Research & Therapy

RESEARCH

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Amyloid deposition and its association with depressive symptoms and cognitive functions in late-life depression: a longitudinal study using amyloid-β PET images and neuropsychological measurements

Kiwon Kim[1†], Yoo Jin Jang[2†], Jeong-Hyeon Shin[3], Mi Jin Park[4], Hyun Soo Kim[5], Joon-Kyung Seong[6,7] and Hong Jin Jeon[2,8*]

Abstract

Background Although depression is linked to an increased risk of dementia, the association between late-onset depression (LOD) and amyloid burden remains unclear. This study aimed to determine amyloid deposition in patients with LOD compared to healthy controls (HC) using amyloid-beta (Aβ) positron emission tomography (PET) images and neuropsychological assessments.

Methods Forty patients first diagnosed with major depressive disorder after the age of 60 (LOD) and twenty-one healthy volunteers (HC) were enrolled. Depression and anxiety were evaluated using the 17-item Hamilton Depression Scale, Hamilton Anxiety Rating Scale, and Clinical Global Impression Scale. Cognitive function was assessed using the Korean versions of the Mini-Mental Status Examination, Montreal Cognitive Assessment, and Seoul Neuropsychological Screening Battery at baseline and 3-month follow-up. ^{18}F-florbetapir PET images were co-registered with T1-weighted magnetic resonance images.

Results There was no significant difference in Aβ deposition between LOD and HC groups. No significant correlation between Aβ burden and depressive symptom severity was found in LOD patients. Higher somatic anxiety was correlated with lower Aβ burden in multiple brain regions, including the left inferior frontal lobe ($p=0.009$), right anterior cingulate ($p=0.003$), and right superior frontal lobe ($p=0.009$). Despite cognitive recovery in areas such as attention (Digit Span Forward, $p=0.026$), memory (Auditory Verbal Learning Test Recall Total, $p=0.010$; Rey Complex Figure Test Delayed Recall, $p=0.039$), and frontal executive function (Contrasting Program, $p=0.033$) after three months of antidepressant treatment, cognitive improvement showed no association with amyloid deposition.

Conclusions These findings suggest distinct mechanisms may underlie amyloid deposition in neurodegenerative changes associated with depression. While amyloid burden in specific brain regions negatively correlated with somatic anxiety, it showed no significant correlation with the severity of depression or overall cognitive function.

[†]Kiwon Kim and Yoo Jin Jang contributed equally to this work.

*Correspondence:
Hong Jin Jeon
jeonhj@skku.edu
Full list of author information is available at the end of the article

Keywords Late-life depression, Amyloid deposition, PET imaging, Somatic anxiety, Cognitive recovery

Background

Depression is associated with an increased risk of dementia [1]. Due to the heterogeneity of late-life depression (LLD), many researchers have attempted to classify its phenotypes [2]. Among these, late-onset depression (LOD) and early-onset depression (EOD) distinguished by the age of first onset appear to have distinct characteristics [3–5]. While a systematic review has indicated no clinical differences between EOD and LOD groups except for a family history of depression [6], other comparative studies have shown higher prevalence of cognitive decline, somatic complaints, and vascular risk factors in LOD than in EOD [3, 7, 8]. LOD also demonstrates distinct functional network patterns, suggesting that it has different pathological changes from EOD, as evidenced by functional magnetic resonance imaging (MRI) studies [9]. Investigations into the relationship between LOD and dementia risk have led some researchers to propose that LOD might be a prodrome of dementia [10]. While some researchers have differing views [11, 12], other longitudinal cohort studies have reported that LOD carries a greater risk of dementia than EOD [4, 13]. Additionally, Gujral et al. have performed a case–control study with 278 participants aged over 50 years and found that late-onset suicidal behavior is linked to cognitive decline and memory impairment, reinforcing the hypothesis of depression as a prodrome of dementia [14]. A population-based cohort study has indicated that aspirin use in LOD might reduce the incident risk of dementia, highlighting the role of vascular factors in the link between LOD and dementia [15].

The accumulation of amyloid-beta (Aβ) plaques in the brain is a hallmark of Alzheimer's disease (AD), the most common cause of dementia [16]. Aβ burden begins to accumulate in the pre-clinical stage of AD, even before significant cognitive impairments appear. It is used as an auxiliary tool for AD diagnosis [17]. Dementia patients frequently experience depression both before and after disease onset [18]. Findings that AD patients with comorbid major depression exhibit more amyloid deposition and neurofibrillary tangles compared to those without depression suggest a link between depression and AD pathology [19, 20]. Some researchers have hypothesized that amyloid accumulation may induce depressive symptoms, implying that LOD could be a prodrome of AD [21].

Studies investigating the relationship between amyloid pathology in vivo and depression prior to dementia onset have produced inconsistent results. Sun et al. [21] have found elevated plasma Aβ levels in LLD patients. Yamazaki et al. [22] have reported that higher plasma Aβ40 levels in LLD are associated with parahippocampal atrophy and greater cognitive decline. However, measuring plasma Aβ, particularly single markers such as Aβ42 or Aβ40 alone, is generally considered less sensitive and specific than Aβ-positron emission tomography (PET) scans, the current gold standard biomarker of early AD [23]. A few previous studies have demonstrated differences in amyloid burden using more reliable measurements between patients with depression and healthy controls [24, 25]. However, these studies included patients with mild cognitive impairment or applied a dichotomous approach for amyloid deposition. Other studies have either failed to find an association between amyloid binding and depressive symptoms [26] or observed a negative correlation, with the LLD group showing lower Aβ deposition than healthy controls [27]. Another study has reported that LLD is associated with lower gray matter volume but not higher amyloid burden [28].

These inconsistent findings of previous studies might be due to the heterogeneity of LLD. Not differentiating based on the age of depression onset potentially could confound the relationship between depressive symptoms and amyloid burden. Enrollment of participants with mild cognitive impairment (MCI) can result in the inclusion of undiagnosed dementia cases. Additionally, depression with psychotic features has a stronger familial and genetic connection to major psychoses, such as schizophrenia and bipolar disorder, than non-psychotic depression [29]. These genetic differences may complicate the relationship being studied. Moreover, employing a simple and broad method to measure associations between amyloid burden and cognition as well as depressive symptoms could obscure which specific domains of cognitive decline or depressive symptoms are most impacted by amyloid burden. Previous studies that have identified an association between treatment response and Aβ burden have primarily focused on the alleviation of depressive symptoms without exploring its relationship with cognitive improvement [30]. Therefore, rigorous research with segmented and comprehensive cognitive assessments at baseline and after antidepressant treatment, along with quantitative measurement of amyloid deposition, is necessary.

In this study, we recruited a more homogeneous group of LLD individuals, specifically cognitively normal LOD patients, with the aim of: (1) investigating the

relationship between Aβ burden and major depression in late-life using Aβ-PET scans by comparing them with healthy controls; (2) determining which domains of cognitive decline or depressive symptoms Aβ predominantly affects in LOD using comprehensive neuropsychological batteries; and (3) examining the association with Aβ burden and cognitive recovery following antidepressant treatment in LOD.

Methods

Participants

A total of 61 participants were enrolled in this study, including 40 patients with LOD and 21 healthy volunteers without a history of psychiatric disease. Forty patients with LOD (5 males and 35 females) were recruited from the outpatient clinic of the Depression Center at Samsung Medical Center between May 2016 and January 2018. All patients were clinically referred. They maintained their psychotropic medication, including antidepressants, mood stabilizers, benzodiazepines, and zolpidem, during the study.

Inclusion criteria for patients were: being 65 years of age or older, experiencing a current unipolar major depressive episode verified by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depressive disorder (MDD), with onset after 60 years of age [31]. The baseline minimum 17-item Hamilton Scale for Depression (HAM-D) [32] score required for enrollment was 16. Exclusion criteria were: presence of psychotic disorders (e.g., schizophrenia or delusional disorder), bipolar affective disorder, neurological illnesses including significant cognitive impairment and Parkinson's disease, mental retardation, significant medical conditions, epilepsy, history of alcohol or drug dependence, personality disorders, brain injury, and individuals currently taking or requiring antipsychotics, choline esterase inhibitors, memantine, Ginkgo biloba, or acetyl-L-carnitine.

The control group comprised 21 healthy volunteers aged 65 years or older. They were recruited through advertisement. Volunteers with a positive family history of mood disorders were excluded. Screening assessments were conducted to rule out individuals with a history of current or past depressive episodes.

The study protocol was approved by the Ethics Review Board of Samsung Medical Center, Seoul, Korea. All research procedures were performed in accordance with relevant guidelines. Signed informed consent was obtained from all participants.

Clinical evaluation

The Korean version of the Mini-Mental Status Examination (K-MMSE) [33] and the Korean version of the Montreal Cognitive Assessment (MoCA-K) [34] were applied to test eligibility of each participant for this study. To assess 'cognitive normality', clinical psychiatrists interviewed participants regarding their daily life activities following K-MMSE and MoCA-K assessments, considering the impact of depression on cognition. Psychiatrists with more than three years of clinical experience evaluated past psychiatric and physical history of participants to confirm their eligibility for this study.

After enrollment, participants were evaluated twice: at 1 month and 3 months after the initial assessment. During these follow-ups, a professional clinical psychologist at the Depression Center performed the Mini International Neuropsychiatric Interview (MINI) [35] to evaluate psychiatric comorbidities. The psychologist also assessed participants' severity of depression and anxiety using the 17-item Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) [36]. In addition to the K-MMSE and MoCA-K, the Clinical Global Impression Scale (CGI-S) and the Seoul Neuropsychological Screening Battery (SNSB-II) [37] were used to assess the overall state and cognitive function of participants. The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) was used to assess clinically relevant cognitive and physical symptoms associated with depression as a subjective cognitive domain [38].

The LOD group was treated according to evidence-based treatment guidelines for Korean MDD, initiating antidepressant treatment at the first visit. If augmentation was needed, mood stabilizers, benzodiazepine, and zolpidem were allowed to be used. However, antipsychotics, choline esterase inhibitors, memantine, Ginkgo biloba, and acetyl L-carnitine were not allowed.

One month after the initial visit, all participants were evaluated using the HAM-D and CGI-S. After 3 months, they were re-evaluated with the HAM-D, CGI-S, SNSB-II, and MoCA-K.

Outcomes of interest

The primary outcome of this study was to compare amyloid deposition levels between patients with LOD and healthy controls (HC) using Aβ-PET scans. Secondary outcomes included examining the relationships between amyloid deposition and the severity of depressive symptoms in LOD individuals, as well as the association between amyloid deposition and cognitive changes following antidepressant treatment.

MRI data acquisition

Structural images of brains of all 61 participants were acquired at the Samsung Medical Center using a 3.0 T Achieva MRI scanner (Philips, Amsterdam, The

Netherlands) within one month of the second visit. T1-weighted MRI data were recorded using the following imaging parameters: sagittal slice thickness of 1 mm, contiguous slices with 50% overlap, no gap, repetition time (TR) of 9.9 ms, echo time (TE) of 4.6 ms, flip angle of 8°, and matrix size of 240×240 pixels. Images were reconstructed to 480×480 pixels over a 240 mm field of view.

PET imaging analyses

Participants underwent ^{18}F-florbetaben PET scanning at Samsung Medical Center using a Discovery STe PET/Computed tomography (CT) scanner (GE Medical Systems, Milwaukee, WI, USA) (47 slices of 3.3 mm in thickness, spanning the entire brain). For attenuation correction, CT images were acquired using a 16-slice helical CT (140 keV, 80 mA; 3.75 mm section width). Ninety minutes after injecting 300 MBq ± 20% ^{18}F-florbetaben, a 20-min emission PET scan in a dynamic mode (consisting of 4×5 min frames) was performed. Using the ordered-subsets expectation maximization algorithm (iteration = 4 and subset = 20), 3-dimensional PET images were reconstructed in a 128×128×48 matrix with a 2×2×3.27 mm voxel size.

Image processing steps

T1-weighted MR images were processed to obtain anatomical parcellations based on the Desikan-Killiany atlas [39] using the FreeSurfer software package (version 5.1.0, http://surfer.nmr.mgh.harvard.edu). Each florbetaben image was co-registered to the T1 image through affine coregistration (FSL-FLIRT) and normalized by the mean value of cerebellar gray matter to measure standardized uptake value ratios (SUVRs) in 61 participants. SUVR values were then measured as means of each Desikan-based region of interest (ROI). In the present study, amyloid deposition data were analyzed using ROI and metaROI approaches [40]. Group comparisons utilized both ROI and metaROI approaches. Based on group comparison results, correlational analysis also used metaROI approach. This method comprised 13 metaROIs (medial temporal lobe, anterior cingulate, middle frontal lobe, medial occipital lobe, lateral occipital lobe, inferior parietal lobe, posterior cingulate, orbitofrontal cortex, lateral temporal lobe, inferior frontal lobe, precuneus, superior frontal lobe, and superior parietal lobe). Applying bilateral metaROIs could reduce the number of estimated correlations.

Statistical analysis

SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, with a significance level set at $p < 0.05$. The false discovery rate (FDR) procedure was applied to multiple comparison.

Clinical and demographic profiles of the 61 participants are presented as either categorical or continuous variables, as appropriate. Categorical variables are presented as frequencies and proportions, while continuous variables are presented as mean ± standard deviation (SD). Student's t-test, Mann-Whitney test, or Fisher's exact test was applied after evaluating the normality of distributions. To compare neurocognitive functions between the two groups, SNSB-II and MoCA-K results were subjected to multiple analyses of covariance, adjusting for age, sex, and years of education.

We used permutation-based analysis of covariance (ANCOVA) to compare amyloid depositions in cortical and subcortical structures between the LOD group and the healthy control (HC) group, controlling for the effects of age, sex, and education. Significance level of the group difference was estimated as the fraction of permutations whose F values were not less than those from the original dataset. We used 5,000 permutations. We performed correlation tests between amyloid deposition in each brain structure and depressive symptom severity as well as each item of the depression scale (HAM-D) in LOD individuals. Since amyloid deposition often does not follow a normal distribution, we used Spearman partial correlation to control for effects of age, sex, and years of education. Additionally, we evaluated the correlation of amyloid deposition with baseline neurocognitive assessments and cognitive changes following antidepressant treatment after adjusting for the severity of depression, age, sex, and years of education.

Based on previous amyloid PET studies with effect sizes of 0.48 [41] and 0.55 [42], we estimated a medium effect size (Cohen's d = 0.5) for the difference in amyloid deposition between the LOD and HC group. With an alpha level of 0.05 and a power of 0.80, the required sample size for each group was calculated to be approximately 32 participants.

Results

Clinical and neurocognitive characteristics

Baseline clinical and neurocognitive characteristics of participants are summarized in Table 1. Male gender was significantly less prevalent in the LOD group (12.2%) than in the control group (65%) ($p < 0.001$). There was no significant difference in age or years of education between the two groups, although the LOD group had fewer participants having more than 12 years of education (17.1%) than the control group (35%) ($p = 0.247$). LOD patients showed higher suicidality (mean score = 4.07) as measured by the Mini-International Neuropsychiatric Interview Suicidality Module (MINI SM) ($p < 0.001$), higher depression severity (HAM-D score = 17.90) ($p < 0.001$), and higher anxiety levels (HAM-A score = 11.54)

Table 1 Baseline clinical and neurocognitive characteristics of participants

Clinical Characteristics	**Late-Onset Depression**		**Healthy Control**		***p***
	(*n* = 41)		**(*n* = 20)**		
Gender, male (%)[a]		5 (12.2%)		13 (65%)	**< 0.001**
Age, years[b]		73.54 ± 5.85		74.25 ± 5.27	0.646
Education, years[c]		8.88 ± 4.05		11.00 ± 5.16	0.132
> 12 Years[d]		7 (17.1%)		7 (35.0%)	0.247
Suicidality measured by MINI SM[d]		4.07 ± 5.19		0	**< 0.001**
HAM-D[c]		17.90 ± 6.00		3.89 ± 1.88	**< 0.001**
≥ 24[d]		6 (14.6%)		0	0.230
HAM-A[c]		11.54 ± 4.89		3.94 ± 2.78	**< 0.001**
SFGDS[c]		6.07 ± 3.37		2.41 ± 2.74	**0.002**
≥ 8[d]		15 (36.6%)		1 (5%)	**0.018**
K-MMSE[b]		24.02 ± 5.48		25.39 ± 3.05	0.382
MGH-CPFQ[b]		21.85 ± 5.77		13.65 ± 5.07	**< 0.001**
CGI-S[c]		3.95 ± 0.84		1.06 ± 0.24	**< 0.001**
Amyloid-β (Global SUVR)		1.46 ± 0.30		1.42 ± 0.22	0.580
Items of Neurocognitive Tests	**Mean**	**SD**	**Mean**	**SD**	***Adjusted p*** [**]
Attention; Digit Span Forward	5.08	1.73	5.89	2.00	**0.033**
Language & Related; S-K-BNT	8.73	3.23	11.00	2.57	**< 0.001**
Visuospatial; RCFT Copy	28.00	10.91	31.19	6.92	**0.034**
Memory					
AVLT Recall Total	27.48	8.52	28.56	7.43	**< 0.001**
AVLT Delayed Recall	4.88	3.84	4.83	3.15	0.131
AVLT Recognition	9.78	2.94	10.06	3.72	0.160
RCFT Immediate Recall	7.61	7.66	13.22	7.80	**0.004**
RCFT Delayed Recall	8.23	7.46	13.86	6.61	**0.011**
RCFT Recognition	17.71	2.94	18.56	2.87	0.057
Frontal					
Contrasting Program	18.08	4.39	18.89	2.40	0.057
GoNoGo Test	15.78	5.77	18.28	3.05	0.177
COWAT Animal	10.46	3.31	12.56	4.36	**0.004**
COWAT Phonemic Total	13.17	8.99	14.28	9.43	**< 0.001**
K-CWST Word Reading Time	93.44	23.64	77.72	27.36	**< 0.001**
K-CWST Color Reading Correct	57.68	28.09	71.89	21.49	**0.003**
K-CWST Color Reading Error	2.95	4.68	4.72	6.99	**0.031**
Digit Symbol Coding Correct	30.53	16.88	41.83	18.69	**< 0.001**
K-TMT-E Part B Success Time	84.97	63.20	47.83	25.27	**0.004**
K-TMT-E Part B Success Error	1.53	2.11	0.44	1.42	0.091

SD Standard deviation, *MINI SM* The Mini-International Neuropsychiatric Interview Suicidality Module, *HAM-D* Hamilton Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale, *SFGDS* Short Form Geriatric Depression Scale, *K-MMSE*, Korean version of Mini-Mental Status Examination, *MGH-CPFQ* The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, *CGI-S* Clinical Global Impression Scale, *SUVR* Standardized uptake value ratio, *S-K-BNT* Short-Korean-Boston Naming Test, *RCFT* Rey Complex Figure Test, *AVLT* Auditory Verbal Learning Test, *COWAT* Controlled Oral Word Association Test, *K-CWST* Korean-Color Word Stroop Test, *K-TMT-E* Korean-Trail Making Test-Elderly's version

[a] Chi square test was used

[b] Student's t-test was used. Data are given as mean and standard deviation

[c] Mann–Whitney test was used

[d] Fisher's exact test was used

[**] Multiple analyses of covariance were performed to test for differences in neurocognitive test results between groups after controlling for age, sex, and years of education. The false discovery rate procedure was applied for multiple comparisons, with significance set at $p < 0.05$

($p < 0.001$) than the control group. The LOD group also had significantly higher scores on the Short Form Geriatric Depression Scale (SFGDS) (mean = 6.07) ($p = 0.002$). CGI-S scores reflected this trend, showing a higher severity in the LOD group ($p < 0.001$).

There was no significant difference in simple cognitive function as measured by K-MMSE between the two groups. However, subjective cognitive decline, as measured by MGH-CPFQ, was significantly more pronounced in the LOD group than in the HC group ($p < 0.001$). Specific neurocognitive assessments revealed significantly more impairments in the LOD group than in healthy controls in several domains, including attention (Digit Span Forward, $p = 0.033$), language (Short-Korean-Boston Naming Test (S-K-BNT), $p < 0.001$), visuospatial function (Rey Complex Figure Test (RCFT) Copy, $p = 0.034$), memory (Auditory Verbal Learning Test (AVLT) Recall Total, $p < 0.001$; RCFT Immediate Recall, $p = 0.004$; RCFT Delayed Recall, $p = 0.011$), and frontal executive functions (Controlled Oral Word Association Test (COWAT) Animal, $p = 0.004$; COWAT Phonemic Total, $p < 0.001$; Korean-Color Word Stroop Test (K-CWST) Word Reading Time, $p < 0.001$; K-CWST Color Reading Correct, $p = 0.003$; K-CWST Color Reading Error, $p = 0.031$; Digit Symbol Coding Correct, $p < 0.001$; Korean-Trail Making Test-Elderly's version (K-TMT-E) Part B Success Time, $p = 0.004$), after controlling for age, sex, and education years.

Correlation of amyloid deposition with depressive symptoms in LOD

Group comparisons for amyloid deposition between the LOD group and the control group using permutation-based ANCOVA with the Desikan-ROI approach showed no significant difference (Fig. 1). Although LOD individuals had higher quantitative levels of amyloid deposition than HC individuals, the difference was not statistically significant (Table 1 and Fig. 1).

Table 2 presents the correlations between amyloid deposition and depressive symptoms in LOD patients after adjusting for multiple comparisons. In LOD patients, the overall HAM-D score did not show a significant correlation with amyloid deposition in any brain region (adjusted $p = 0.625$), despite an unadjusted negative correlation observed with the right anterior cingulate. In contrast, somatic anxiety, a specific item of the HAM-D, showed significant negative correlations with amyloid deposition in various brain regions. Significant negative correlations were observed in the left inferior frontal lobe (adjusted $p = 0.009$), left inferior parietal lobe (adjusted $p = 0.040$), left middle frontal lobe (adjusted $p = 0.040$), left superior parietal lobe (adjusted $p = 0.040$), right anterior cingulate (adjusted $p = 0.003$), right inferior parietal lobe (adjusted $p = 0.042$), right lateral temporal lobe (adjusted $p = 0.040$), right middle frontal lobe (adjusted $p = 0.042$), right orbitofrontal cortex (adjusted $p = 0.042$), right posterior cingulate (adjusted $p = 0.042$), and right superior frontal lobe (adjusted $p = 0.009$).

Correlation of amyloid deposition with neurocognitive function in LOD

Correlations between Aβ deposition and neurocognitive function in LOD patients after adjusting for depressive symptom severity (overall HAM-D score), are illustrated in Table 3. No correlation reached the significance threshold of $p < 0.05$ after adjusting for depressive symptom severity, age, sex, and years of education, although some nominally significant correlations were observed in a few brain regions before adjustment.

Three months after antidepressant treatment, LOD participants showed small but significant improvements in several cognitive domains, including attention (Digit Span Forward, $p = 0.026$), memory (AVLT Recall Total, $p = 0.010$; RCFT Delayed Recall, $p = 0.039$), and frontal executive function (Contrasting Program, $p = 0.033$) (Supplementary Table 1). However, correlations between Aβ deposition and neurocognitive recovery after 3 months of treatment in LOD patients after adjusting for age, sex, and years of education (Table 4) were not significant. Although unadjusted correlations suggested improvements in several neurocognitive measures were related to amyloid deposition in various brain regions, these associations did not remain significant after adjustment.

Discussion

This longitudinal study utilizing quantitative measurements of Aβ burden and comprehensive neurocognitive assessments found no significant difference in Aβ deposition between LOD and control groups. While it identified a negative correlation between somatic anxiety and Aβ burden in specific brain regions, there were no significant correlations between Aβ burden and the severity of depressive symptoms, cognitive dysfunction, or cognitive recovery following treatment in LOD patients.

LOD is often discussed in the context of prodromal AD due to its accompanying cognitive dysfunction in information processing speed, executive function, and episodic memory [43]. We also observed cognitive declines in these domains in the LOD group compared to healthy controls. Even so, we did not find a difference in amyloid deposition between LOD and HC groups. Our findings were consistent with several studies showing no association between amyloid deposition and major depression in late-life, suggesting a non-amyloid pathway to dementia [27, 44, 45]. Despite shared possible pathophysiologies

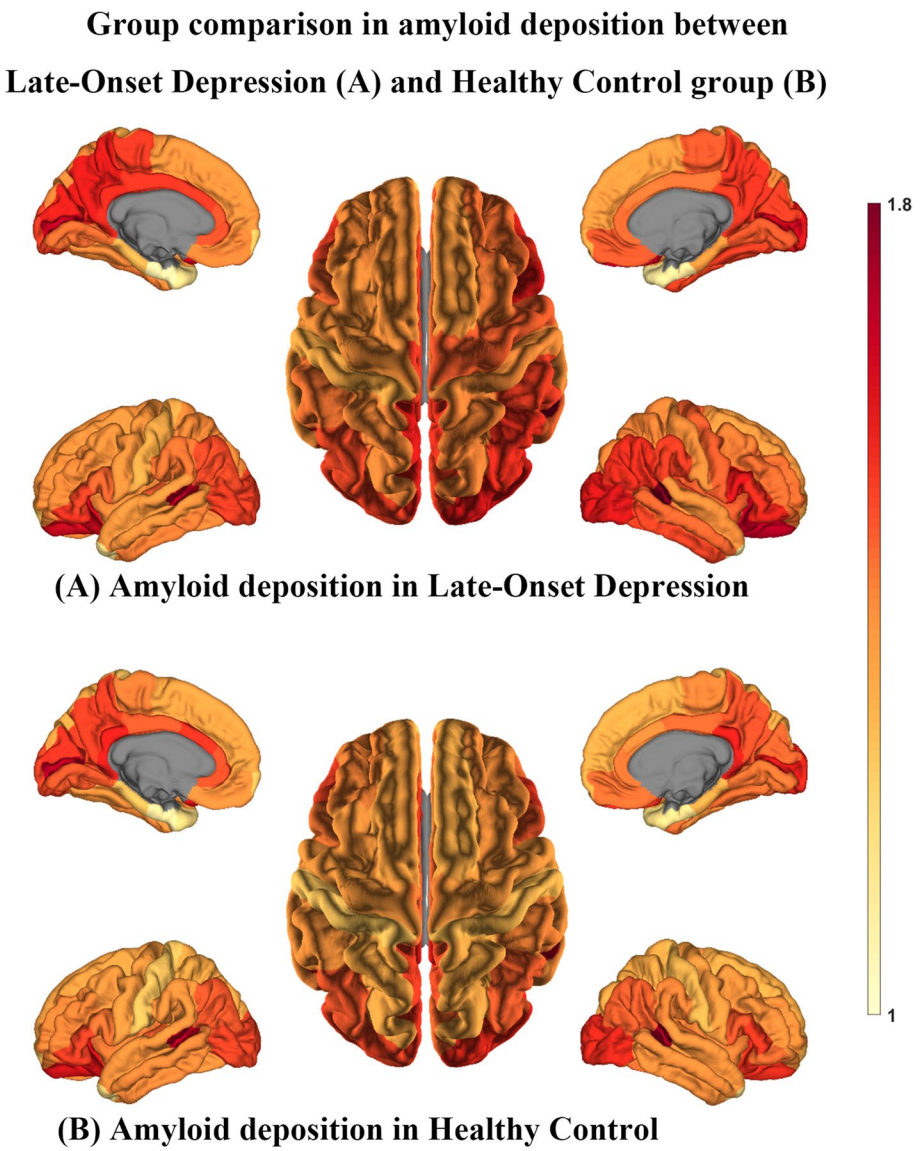

Fig. 1 Group comparison in amyloid desposistion between Late-Onset Depression (**A**) and Healthy Control Group (**B**)

between depression and AD [46], the no significant difference in the amount of amyloid deposition between LLD and HC groups supports the existence of an independent pathology for LLD, different from the AD component, as suggested by other study groups [47–49]. The poor accuracy of Alzheimer's dementia diagnosis may lead to misinterpretations. With current diagnostic standards, the diagnosis of Alzheimer's dementia is based on clinical presentation. Confirming AD pathology with biomarkers is not a necessary criterion. The sensitivity and specificity of clinical diagnosis of Alzheimer's dementia using the neuropathologic diagnosis were only around 70–80% [50]. Another study has reported that 20% of clinical Alzheimer's dementia patients do not have Alzheimer pathology [49]. Although prospective studies have accumulated evidence that LOD can increase the risk of Alzheimer's dementia [4, 51–53], cognitive impairment through mechanisms other than amyloid pathogenesis could be misclassified as Alzheimer's dementia.

Another possible explanation is that LOD, classified by the age of depression onset, is not a sufficiently homogeneous group. We conducted analyses on cognitively normal individuals under the assumption that amyloid beta accumulated before significant cognitive impairment could induce LOD, and failed to find an association. However, some studies reporting an

Table 2 Correlation between amyloid deposition and depressive symptoms in late-onset depression

Depression Severity	Structure Name	*rho*	*p*	*Adjusted p*[*]
HAM-D	Right Anterior Cingulate	-0.409	0.031	0.625
Items of HAM-D				
4. Insomnia; Early in the night	Left Lateral Occipital Lobe	0.399	0.035	0.521
	Right Medial Occipital Lobe	0.390	0.040	0.521
8. Retardation	Left Anterior Cingulate	-0.378	0.047	0.338
11. Anxiety Somatic	Left Inferior Frontal Lobe	-0.591	0.001	**0.009**
	Left Inferior Parietal Lobe	-0.475	0.011	**0.040**
	Left Middle Frontal Lobe	-0.484	0.009	**0.040**
	Left Precuneus	-0.396	0.037	0.074
	Left Superior Parietal Lobe	-0.500	0.007	**0.040**
	Right Anterior Cingulate	-0.667	0.000	**0.003**
	Right Inferior Parietal Lobe	-0.459	0.014	**0.042**
	Right Lateral Temporal Lobe	-0.483	0.009	**0.040**
	Right Middle Frontal Lobe	-0.445	0.018	**0.042**
	Right Orbitofrontal Cortex	-0.447	0.017	**0.042**
	Right Posterior Cingulate	-0.449	0.017	**0.042**
	Right Superior Frontal Lobe	-0.585	0.001	**0.009**
	Right Superior Parietal Lobe	-0.419	0.027	0.057
13. General Somatic Symptoms	Left Inferior Frontal Lobe	-0.413	0.029	0.322
	Left Medial Temporal Lobe	-0.381	0.046	0.322
	Right Anterior Cingulate	-0.483	0.009	0.239
	Right Superior Frontal Lobe	-0.375	0.050	0.322
16. Loss of Weight	Left Inferior Frontal Lobe	0.408	0.031	0.344
	Right Orbitofrontal Cortex	0.382	0.045	0.344
17. Insight	Left Middle Frontal Lobe	-0.443	0.018	0.125
	Left Posterior Cingulate	-0.491	0.008	0.119
	Left Precuneus	-0.484	0.009	0.119
	Left Superior Frontal Lobe	-0.385	0.043	0.125
	Right Inferior Parietal Lobe	-0.430	0.022	0.125
	Right Lateral Temporal Lobe	-0.414	0.029	0.125
	Right Middle Frontal Lobe	-0.405	0.032	0.125
	Right Orbitofrontal Cortex	-0.387	0.042	0.125

HAM-D Hamilton Depression Rating Scale

[*] Spearman correlational analyses were performed after adjusting for age, sex, and years of education with false discovery rate for multiple comparisons

association between LLD and amyloid burden have found this link only in groups with MCI. Wu et al. [54] have reported higher Aβ burden in depressed patients than in healthy controls using ^{18}F-florbetapir PET, but it was only associated with LLD in those with amnestic MCI. They could not find any significant association in cognitively normal LLD patients or those with non-amnestic MCI. Eyre et al. [55] have illustrated a positive correlation between apathy symptoms and Aβ levels using ^{18}F-FDDNP PET in LLD patients. However, they defined non-dementia using the MMSE score of 24 or higher, which could include MCI cases that performed relatively well on the MMSE. A study has found that 60% of MCI patients are ^{11}C-PIB positive, with 75% of these being amnestic MCI and none of the non-amnestic MCI patients showing ^{11}C-PIB uptake, although the study did not enroll depressed patients [56]. A certain subgroup of LOD that we excluded, for example, those with pronounced amnestic cognitive impairment, might be associated with AD. Mackin et al. [27] have found lower amyloid deposition in LLD patients with MCI than in healthy controls. However, their sample predominantly comprised patients with EOD, making direct comparisons difficult. Wen et al. [57] have highlighted the heterogeneity of LLD by reporting that some LLD individuals have more preserved brain structures than healthy controls, while the others exhibit diffuse brain abnormalities and more significant

Table 3 Correlation between amyloid deposition and baseline neurocognitive assessments in late-onset depression

Items of Neurocognitive Tests	Structure Name	*rho*	*p*	*Adjusted p*[*]
COWAT Animal	Right Precuneus	-0.442	0.031	0.334
COWAT Phonemic Total	Right Posterior Cingulate	-0.418	0.047	0.391
	Right Precuneus	-0.441	0.035	0.391
K-CWST Word Reading Time	Left Inferior Frontal Lobe	-0.530	0.008	0.142
	Left Orbitofrontal Cortex	-0.419	0.042	0.142
	Right Inferior Frontal Lobe	-0.457	0.025	0.142
	Right Inferior Parietal Lobe	-0.455	0.026	0.142
	Right Medial Temporal Lobe	-0.430	0.036	0.142
	Right Orbitofrontal Cortex	-0.442	0.031	0.142
	Right Precuneus	-0.467	0.022	0.142
K-CWST Color Reading Correct	Left Lateral Occipital Lobe	0.422	0.045	0.293
	Right Lateral Temporal Lobe	0.478	0.021	0.183
	Right Posterior Cingulate	0.497	0.016	0.183
	Right Precuneus	0.485	0.019	0.183
K-TMT-E Part B Success Time	Left Inferior Parietal Lobe	-0.493	0.017	0.080
	Left Medial Occipital Lobe	-0.516	0.012	0.076
	Left Middle Frontal Lobe	-0.432	0.040	0.114
	Left Posterior Cingulate	-0.461	0.027	0.097
	Left Precuneus	-0.555	0.006	0.076
	Left Superior Parietal Lobe	-0.571	0.004	0.076
	Right Anterior Cingulate	-0.519	0.011	0.076
	Right Superior Frontal Lobe	-0.487	0.018	0.080
	Right Superior Parietal Lobe	-0.453	0.030	0.097

COWAT Controlled Oral Word Association Test, *K-CWST* Korean-Color Word Stroop Test, *K-TMT-E* Korean-Trail Making Test-Elderly's version

[*] Spearman correlational analyses were performed after adjusting for depressive symptom severity, age, sex, and years of education with false discovery rate for multiple comparisons

cognitive impairment. Even though we did not find an association with the phenotype of 'cognitively normal LOD', further research should explore the relationship between amyloid deposition and LLD across various phenotypes, taking into account other clinical features, genetic characteristics, and structural brain changes.

Our finding of a negative correlation between somatic anxiety and Aβ burden in several brain regions, including the right anterior cingulate, left inferior frontal lobe, and right superior frontal lobe, contrasted with a previous study that observed higher Aβ burden in the subcortical area of cognitively normal older adults with anxious depression [58]. In a study by Morin et al. [59], which recruited participants with baseline HAM-D scores similar to those in our study, older adults with high levels of somatic anxiety were found to have an increased risk of disability. Physical disability or frailty is prone to degeneration, and higher Aβ accumulation has also been found in these cases [60]. While it is possible, as suggested by few researchers, that the early inflammatory phase of depression may prevent or delay the formation of Aβ neuritic plaques [27, 61], our results could also be partially due to measurement errors inherent to PET scans [62]. Since those brain regions have been reported to show selective hypoperfusion with increasing severity of depressive symptoms in depressed AD patients [63], it is possible that major depression or depressive symptoms can alter the activity of specific brain regions, leading to reduced perfusion or neurodegeneration-induced brain atrophy, which can result in a lower PET signal. However, Sinclair et al. [44] did not find any evidence of hypoperfusion or Alzheimer pathology in brain tissues of LLD patients compared to controls or early Alzheimer's dementia patients. The use of antidepressants might have also influenced our results, as some studies have suggested that certain antidepressants can inhibit the aggregation of Aβ in animal models and healthy humans [64, 65]. However, in studies on LLD patients, adjusting for antidepressant use did not change the study results [27, 54]. There was no significant association between the length of lifetime antidepressant treatment and amyloid burden [27].

Our study has several limitations. First, the short follow-up period hindered our ability to establish a direct association between depressive symptoms, Aβ burden, and future development of dementia. We could

Table 4 Correlation between amyloid deposition and neurocognitive changes after three months in late-onset depression

Items of Neurocognitive Tests	Structure Name	*rho*	*p*	*Adjusted p*[*]
AVLT Delayed Recall Difference	Left Lateral Occipital Lobe	-0.475	0.004	0.090
	Left Lateral Temporal Lobe	-0.424	0.010	0.109
	Left Medial Temporal Lobe	-0.412	0.013	0.109
	Left Middle Frontal Lobe	-0.363	0.030	0.112
	Right Lateral Temporal Lobe	-0.387	0.020	0.112
	Right Medial Occipital Lobe	-0.362	0.030	0.112
	Right Posterior Cingulate	-0.345	0.039	0.128
	Right Precuneus	-0.372	0.026	0.112
RCFT Recognition Difference	Left Lateral Temporal Lobe	-0.366	0.043	0.427
Contrasting Program Difference	Right Posterior Cingulate	0.364	0.041	0.423
	Right Precuneus	0.410	0.020	0.423
COWAT Animal Difference	Left Lateral Temporal Lobe	-0.398	0.024	0.074
	Left Orbitofrontal Cortex	-0.374	0.035	0.076
	Left Superior Frontal Lobe	-0.357	0.045	0.078
	Left Superior Parietal Lobe	-0.376	0.034	0.076
	Right Inferior Frontal Lobe	-0.398	0.024	0.074
	Right Inferior Parietal Lobe	-0.388	0.028	0.074
	Right Lateral Occipital Lobe	-0.388	0.028	0.074
	Right Lateral Temporal Lobe	-0.429	0.014	0.074
	Right Medial Occipital Lobe	-0.418	0.017	0.074
	Right Medial Temporal Lobe	-0.420	0.017	0.074
	Right Middle Frontal Lobe	-0.367	0.039	0.078
	Right Orbitofrontal Cortex	-0.389	0.028	0.074
	Right Precuneus	-0.419	0.017	0.074
	Right Superior Frontal Lobe	-0.388	0.028	0.074
K-CWST Word Reading Time Difference	Left Inferior Frontal Lobe	-0.426	0.017	0.064
	Left Inferior Parietal Lobe	-0.439	0.014	0.064
	Left Medial Occipital Lobe	-0.436	0.014	0.064
	Left Middle Frontal Lobe	-0.399	0.026	0.064
	Left Orbitofrontal Cortex	-0.361	0.046	0.079
	Left Precuneus	-0.417	0.020	0.064
	Left Superior Parietal Lobe	-0.411	0.022	0.064
	Right Anterior Cingulate	-0.439	0.014	0.064
	Right Lateral Temporal Lobe	-0.376	0.037	0.074
	Right Medial Occipital Lobe	-0.361	0.046	0.079
	Right Orbitofrontal Cortex	-0.413	0.021	0.064
	Right Posterior Cingulate	-0.393	0.029	0.064
	Right Precuneus	-0.392	0.029	0.064
	Right Superior Frontal Lobe	-0.440	0.013	0.064
	Right Superior Parietal Lobe	-0.400	0.026	0.064

AVLT Auditory Verbal Learning Test, *COWAT* Controlled Oral Word Association Test, *K-CWST* Korean-Color Word Stroop Test, *K-TMT-E* Korean-Trail Making Test-Elderly's version

[*] Spearman correlational analyses were performed after adjusting for age, sex, and years of education with false discovery rate for multiple comparisons

not confirm that our sample included individuals who would develop dementia in the future. Furthermore, we could not rule out the possibility that Aβ levels might significantly increase later in LOD patients, eventually leading to dementia. Nonetheless, our study aimed to investigate whether the core AD pathology, Aβ, contributed to depressive symptoms, based on the premise that LOD might be a prodrome of AD. Confirming

the role of depression as a risk factor for dementia was beyond the scope of our study. Second, stringent exclusion criteria might affect the generalizability of our study. Although cognitive impairment is common in LLD, our strict cognitive criteria led to the inclusion of only a specific subgroup of depressed patients without significant cognitive symptoms. Additionally, excluding antipsychotics users resulted in the exclusion of patients with severe non-psychotic depression who augment antipsychotics to enhance the effects of antidepressants. Nonetheless, to minimize the impact of LLD heterogeneity, we aimed to focus on the effect of amyloid pathology on 'pure' depressive symptoms before significant cognitive decline. Therefore, we chose to implement these criteria despite the potential impact on generalizability. Third, our small sample size reduced the statistical power of our findings. Despite statistically significant results in some analyses, the small sample size not only affected statistical significance but also might have led to sampling bias, as mentioned above. Our post hoc power calculation revealed an effect size of 0.145. However, it is comparable to the effect size (Cohen's $d = 0.09$) recently reported in a systematic review [66], and post hoc effect size can be misleading and does not provide a clear measure of the practical significance of findings [67]. Fourth, we did not account for important risk factors influencing dementia, such as ApoE, vascular risk factors, or health behaviors. Although we failed to collect genetic information on ApoE, previous studies have found no differences in results after adjusting for ApoE [28, 45] or comparing ApoE-matched controls [27]. Additionally, our study was conducted in a single clinic of a tertiary hospital with specific socioeconomic characteristics and more severe disease cases, potentially limiting generalizability and introducing selection bias. Repetitive cognitive measurements using the same tools might also have influenced the cognitive performance of participants.

In conclusion, we did not find a difference in Aβ deposition between LOD and control groups. We observed a significant negative correlation between somatic anxiety and Aβ deposition in multiple brain regions. Our findings support the hypothesis that non-amyloid pathology might play a role in the progression from depression to dementia. Due to the increasing burden of geriatric depression and dementia, further research is needed to elucidate pathophysiological mechanisms and specific neuropathological manifestations of LLD. This understanding could lead to the development of early interventions and appropriate LLD-specific management strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01562-0.

Supplementary Material 1: Supplementary Table 1. Baseline vs post-treatment neurocognitive assessments in late-onset depression.

Acknowledgements
We would like to thank Harrisco (https://www.harrisco.net) for the English language editing.

Role of funding source
The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit this paper for publication.

Authors' contributions
KK, YJJ, JHS, JKS, and HJJ have full access to all data of this study and take responsibility for the integrity of the data and accuracy of the data analysis. KK, YJJ, JHS, JKS, and HJJ conceived and designed the study. KK, YJJ, and JHS performed statistical analyses. KK, YJJ, JHS, MJP, HSK, JKS, and HJJ drafted the manuscript. JKS and HJJ supervised the entire study. All authors contributed to the interpretation of the data and have read and approved the final draft for submission.

Funding
This study was supported by a Samsung Medical Center grant (SMO1161491, PI Hong Jin Jeon). This work was supported by the Technology Innovation Program (or Industrial Strategic Technology Development Program-Source Technology Development and Commercialization of Digital Therapeutics) (20014967, Development of Digital Therapeutics for Depression from COVID19) funded By the Ministry of Trade, Industry & Energy (MOTIE, Korea), and by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HR21C0885).

Availability of data and materials
Data of this study have not been previously presented orally or by poster at scientific meetings.

Data Availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Review Board of Samsung Medical Center, Seoul, Korea. All research procedures were performed in accordance with relevant guidelines. Signed informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Workplace Mental Health Institute, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea. [2]Department of Psychiatry, Depression Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea. [3]Bio Medical Research Center, Bio Medical and Health Division, Korea Testing Laboratory, Seoul, South Korea. [4]Department of Psychiatry, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea. [5]Department of Psychiatry, Dong-A University College of Medicine, Busan, South Korea. [6]School of Biomedical Engineering, College of Health Science, Korea University, Seoul, South Korea. [7]Department of Artificial Intelligence, Korea

University, Seoul, South Korea. [8]Department of Health Sciences and Technology, Department of Medical Device Management and Research, and Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, 81 Irwon-Ro, Gangnam-Gu, Seoul 06351, South Korea.

Received: 16 June 2024 Accepted: 18 August 2024
Published online: 19 October 2024

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