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Original Article

Reductions in neuropsychiatric symptoms after lecanemab treatment and their associations with imaging markers of β-amyloid clearance

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ABSTRACT

Background: Anti–amyloid-β (Aβ) therapies can slow cognitive decline and reduce cerebral amyloid burden in Alzheimer's disease (AD). Neuropsychiatric symptoms (NPS) are highly prevalent across the disease course and substantially contribute to disability and caregiver burden. However, whether Aβ clearance translates into improvements in NPS remains unclear.

Method: We enrolled 144 individuals with AD-related mild cognitive impairment or AD dementia who received intravenous lecanemab infusions. Standardized clinical rating scales, including the Neuropsychiatric Inventory, and amyloid PET were assessed at baseline (V0), 6 months (V1), and 12 months (V2). Longitudinal changes in clinical function and amyloid burden were analyzed.

Results: Lecanemab treatment was associated with robust reductions in amyloid PET biomarkers and significant short-term reductions in NPS scores in patients who completed follow-up. Longitudinal analyses showed that reductions in total NPI scores were significantly associated with amyloid-β clearance in the insular cortex. Reductions in the hyperactivity subsyndrome were associated with amyloid reduction across a broader network, including the frontal and temporal lobes, striatum, and insular cortex.

Conclusions: In this real-world cohort, lecanemab was associated with short-term reductions in NPS. Changes in NPS severity were linked to regional amyloid-β clearance.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder, profoundly impairing patients' daily functioning and imposing a substantial societal and healthcare burden [1]. Over the past decades, major advances in diagnostic biomarkers and disease-modifying therapies have reshaped the therapeutic landscape of AD. The advent of anti–amyloid-β immunotherapies has marked a new era in AD treatment. Lecanemab, the first monoclonal antibody approved by the US Food and Drug Administration for disease modification in AD, has been shown to slow cognitive decline and substantially reduce cerebral amyloid burden as measured by amyloid PET centiloid scales [2].

While memory impairment is the hallmark symptom of AD, neuropsychiatric symptoms (NPS) are highly prevalent throughout the disease course and tend to worsen over time. Accumulating evidence suggests that the presence of NPS is closely associated with AD and is linked to

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faster cognitive decline, poorer clinical prognosis, and reduced quality of life [3–6]. Consequently, in clinical practice, managing behavioural, psychological, and somatic symptoms is often considered as important as—if not more urgent than—targeting cognitive impairment alone [7].

Mechanistically, the impact of NPS on cognitive dysfunction and neurodegeneration may be partially related to amyloid-β (Aβ) pathology, as indicated by cerebrospinal fluid (CSF) studies [3]. In addition, neuroimaging studies have shown that regional fibrillar Aβ burden may act as a risk factor for NPS [8]. However, whether therapeutic clearance of Aβ can effectively alleviate NPS remains unclear.

In this study, we aimed to evaluate the safety profile of lecanemab and to examine its short-term effects on amyloid PET biomarkers, cognitive performance, and NPS in individuals with AD dementia and mild cognitive impairment (MCI). Based on previous evidence linking NPS to amyloid pathology, we hypothesized that reductions in amyloid-β burden following anti–Aβ disease-modifying therapy would be associated with improvements in NPS.

2. Methods

2.1. Participants

Between July 2024 and November 2025, a total of 144 participants with AD-related MCI or AD dementia was prospectively recruited from the Department of Neurology at The Second Affiliated Hospital of Zhejiang University School of Medicine. The study protocol was approved by the local Ethics Committee (No. 2025-0938). Written informed consent was obtained from all participants or their legally authorized caregivers for those with dementia.

The diagnosis and clinical staging of AD was established according to the most recent diagnostic criteria [9]. Participants with other neurological or psychiatric disorders, a history of alcoholism or significant brain injury, or contraindications to MRI were excluded.

All participants received intravenous lecanemab infusions in the outpatient clinic. To monitor infusion-related reactions, patients were observed for one hour after each of the first three infusions, followed by a telephone follow-up on the next day. Clinical assessments were repeated at 6-month intervals. At the time of analysis, 73 participants had completed the 6-month follow-up, and 32 participants had completed the 12-month follow-up. The study flowchart was shown in Fig. 1.

2.2. Clinical assessment

All participants underwent a comprehensive cognitive assessment, including the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating (CDR; range, 0–3, with higher scores indicating greater impairment), the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0–18, with higher scores indicating greater impairment), and the Activities of Daily Living scale (ADL; range, 0–80, with lower scores indicating greater functional impairment). APOE ε4 carrier status was classified into three groups: APOE ε4 non-carriers, APOE ε4 heterozygotes, and APOE ε4 homozygotes.

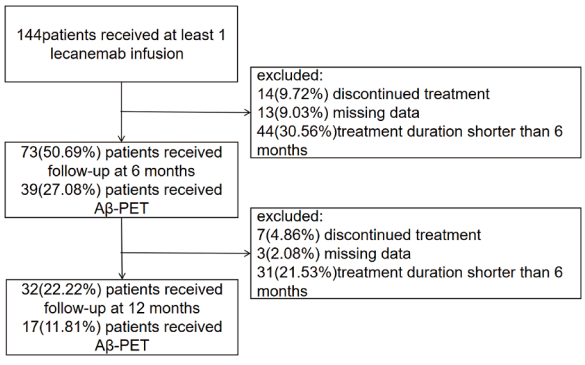

Fig. 1. Flowchart of patient selection and follow-up for the study.

NPS were assessed using the Neuropsychiatric Inventory (NPI), a structured caregiver interview designed to evaluate behavioral and psychological symptoms of dementia. The total NPI score ranges from 0 to 144, with higher scores indicating more severe NPS. Each NPI domain score (0–12) was calculated by multiplying symptom frequency (0–4) by symptom severity (0–3) [10].

According to recommendations from the European Alzheimer's Disease Consortium, NPI domains were further grouped into four neuropsychiatric subsyndromes: (1) hyperactivity (agitation, elation, disinhibition, irritability, and aberrant motor behavior); (2) psychosis (delusions, hallucinations, and night-time behavioral disturbances); (3) affective symptoms (anxiety and depression); and (4) apathy (apathy and appetite disturbances) [11,12].

2.3. MRI acquisition and safety monitoring

Magnetic resonance imaging (MRI) was performed at baseline prior to treatment initiation and during follow-up visits (before the 5th, 7th, 14th, and 26th infusions), in accordance with the prescribing information for lecanemab. MRI was an integral component of safety monitoring, together with regular clinical assessments, and was conducted according to recommended protocols to detect amyloid-related imaging abnormalities (ARIA), including ARIA with edema or effusion (ARIA-E) and ARIA with hemorrhage (ARIA-H) [2,7].

If ARIA was identified, lecanemab treatment was temporarily suspended in some cases according to published guidelines [13], and follow-up MRI examinations were performed as recommended. Resumption of therapy was guided by radiological resolution of ARIA and the patient's clinical status.

2.4. PET acquisition and preprocessing

Each participant received an intravenous injection of 185–370 MBq of ^{18}F-Flobetapir tracer. PET acquisition commenced 40 min after tracer injection and was preceded by a low-dose CT scan for attenuation correction. PET data were acquired over 10 min and reconstructed using the TrueX+TOF (Ultra HD-PET) algorithm, with a matrix size of 400 × 400 × 148 and a voxel size of 1 × 1 × 1.5 mm^3.

All ^{18}F-Flobetapir PET images were spatially normalized to the Montreal Neurological Institute (MNI) space and resampled to a resolution of 2 × 2 × 2 mm^3 using the Spatial Normalization of Brain PET Images (SNBPI) toolbox implemented in MATLAB R2022a. This toolbox is based on the DARTEL framework and enables PET-only spatial normalization without the need for accompanying structural T1-weighted MRI images [14] .

To standardize tracer uptake, standardized uptake value ratios (SUVRs) were calculated using the whole cerebellum mask from the Global Alzheimer's Association Interactive Network (GAAIN) repository as the reference region [15]. Cortical SUVRs were extracted using the GAAIN-provided cortical mask (Supplementary Figure S1). A two-step procedure was applied to derive a Centiloid (CL) conversion formula specific to the present dataset, resulting in the following relationship: CL = 185 × SUVR – 195 (Supplementary Figure S2). Details of the CL calibration procedure are provided in the Supplementary Methods S1.

To further quantify regional amyloid-β deposition, seven composite regions of interest (ROIs) were constructed by combining anatomically related regions defined in the Desikan–Killiany (DK) atlas (Supplementary Table S1). These composite ROIs included the frontal, parietal, temporal, occipital, and insular lobes, as well as the striatum and precuneus. SUVRs were calculated for each composite ROI. The specific DK atlas region labels corresponding to each composite region are detailed in the Supplementary Methods S2.

2.5. Statistical analysis

Statistical analyses were performed using R software (version 4.2.3) and GraphPad Prism (version 9). Continuous variables with normal distributions are presented as means ± standard deviations (SDs), whereas categorical variables are presented as counts and percentages. One-way analysis of variance (ANOVA) or paired-sample t tests, as appropriate, were used to compare baseline and post-treatment clinical scale scores and PET biomarkers.

To investigate factors associated with NPS, we adopted a combined cross-sectional and longitudinal analytical framework. For cross-sectional analyses at baseline, multivariable linear regression models were used to examine the associations between clinical variables (age, sex, education level, APOE ε4 carrier status, CDR-SB score, and age at disease onset) and neuropsychiatric outcomes, including the total NPI score and the four neuropsychiatric subsyndromes. Partial correlation analyses (Pearson or Spearman correlation, depending on data distribution) were subsequently performed to assess the associations between regional amyloid PET SUVRs and NPS, adjusting for the aforementioned clinical covariates.

For longitudinal analyses, changes in regional SUVRs (ΔSUVR = follow-up minus baseline) and changes in NPS (ΔNPI = follow-up minus baseline) were calculated. Partial correlation analyses were applied to examine the relationships between longitudinal changes in regional SUVRs and changes in NPS, with adjustment for the same set of clinical covariates.

All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Given the exploratory nature of this study, no correction for multiple comparisons was applied.

3. Results

3.1. Participants

Baseline demographic and clinical characteristics of the study participants are summarized in Table 1. A total of 144 patients were included, comprising 95 females and 49 males, with a mean age at enrollment of 67.28 ± 9.00 years. The mean educational attainment was 8.82 ± 4.76 years. Notably, due to the prospective, real-world enrollment design, some patients had not yet reached their scheduled 6-month or 12-month follow-up time points at the time of data analysis.

Overall, 57.64% of participants were carriers of the APOE ε4 allele, including 45.83% heterozygous and 11.81% homozygous carriers. Based on CDR scores, 38.19% of participants were classified as AD-related MCI (CDR = 0.5), 40.97% as mild AD dementia (CDR = 1), and 20.83% as moderate AD dementia (CDR = 2). Baseline medical comorbidities and cerebrovascular risk factors, including hypertension, diabetes, hyperlipidemia, and smoking status, were summarized in Supplementary Table S2. Among all participants, seven were taking antidepressant medications before the initiation of lecanemab treatment and continued these medications during the treatment period.

Table 1
Baseline characteristics of patients.

Characteristics	Total (n = 144)	MCI due to AD (n = 55, 38.19%)	Mild AD (n = 59, 40.97%)	Moderate AD(n = 30 20.83%)	p
Age at first infusion,y, mean(SD)	69.97 (8.44)	69.40 (7.94)	71.56 (7.97)	67.90 (9.83)	0.127
Age at onset,y, mean(SD)	67.28 (9.00)	66.96 (8.30)	69.19 (8.33)	64.00 (10.73)	0.036
Disease duration, y,mean(SD)	2.91 (2.10)	2.78 (1.96)	2.57 (2.04)	3.83(2.25)	0.016
Education,y, mean(SD)	8.82 (4.76)	9.19 (4.14)	8.85 (5.05)	8.10(5.27)	0.649
Sex(F/M)	95/49	29/26	45/14	21/9	0.027
APOE 4					0.336
E4 non-carrier, n (%)	61 (42.36)	21(38.18)	23 (38.98)	17(56.67)	
E4 heterozygotes, n (%)	66 (45.83)	27(49.09)	29 (49.15)	10(33.33)	
E4 homozygotes, n (%)	17 (11.81)	7(12.73)	7(11.86)	3(10.00)	
MMSE,mean(SD)	17.10 (4.76)	22.94 (3.95)	16.46 (5.72)	7.73(4.39)	<0.001
ADL,mean(SD)	29.71 (9.01)	23.15 (3.57)	29.28 (5.11)	41.9(9.09)	<0.001
NPI,mean(SD)	9.83 (12.68)	4.29 (6.20)	11.14 (12.57)	17.43 (16.84)	<0.001
Hyperactivity, mean(SD)	3.69 (6.97)	1.38 (2.42)	4.10 (6.91)	7.10 (10.53)	0.004
Psychosis,mean (SD)	1.83 (3.69)	0.96 (2.18)	1.44 (3.10)	4.17(5.62)	0.008
Affective symptoms, mean(SD)	2.15 (4.57)	1.00 (3.60)	2.95 (5.46)	2.70(3.91)	0.013
Apathy,mean (SD)	2.17 (4.42)	0.95 (2.95)	2.64 (5.19)	3.47(4.96)	0.083
Infusion reaction, n (%)	30 (20.83)	13(23.64)	13 (20.03)	4(13.33)	0.515
ARIA, n (%)	19 (13.19)	5(9.09)	11 (18.64)	3(10.00)	0.274
Isolated ARIA-H, n (%)	18 (12.50)	4(7.27)	11 (18.64)	3(10.00)	
Concurrent ARIA-E and ARIA-H, n (%)	1(0.69)	1(1.82)	0	0	
Cerebral infarction, n (%)	2(1.39)	1(1.82)	1(1.69)	0	0.766

3.2. Safety

Lecanemab demonstrated a favorable overall safety profile. Infusion-related reactions occurred in 20.83% of participants (Table 1). Most infusion-related reactions were mild in severity and occurred during the first two infusions; only four patients required symptomatic treatment.

In the overall cohort, ARIA were identified in 19 patients (13.19%), including one case of ARIA-E with concomitant ARIA-H and 18 cases of isolated ARIA-H. The incidence of ARIA did not differ significantly across clinical subgroups. All ARIA cases were asymptomatic and were incidentally detected on scheduled MRI examinations. Among patients with ARIA-H, only four individuals exhibited more than four cerebral microhemorrhages on MRI, two of these patients were MCI and the other two had moderate AD.

In addition, new cerebral infarctions occurred in two patients, both of whom exhibited mild neurological symptoms and had risk factors for cerebrovascular diseases such as hypertension or diabetes. No spatial correspondence was observed between the location of infarct and the region with ARIA.

3.3. Efficacy of lecanemab treatment

Longitudinal data were collected from all treated participants at baseline (V0, $n = 144$), 6 months (V1, $n = 73$), and 12 months (V2, $n = 32$) (Table 2; Fig. 2). Changes in cognitive performance, activities of daily living, and NPS are summarized in Table 2.

Cognitive function and functional status remained stable during follow-up, with no significant changes observed in MMSE, CDR, CDR-SB, or ADL scores at either the 6-month or 12-month assessments. In contrast, NPS showed significant reductions, as reflected by reductions in total NPI scores at both follow-up time points (6-month follow-up, $p = 0.006$; 12-month follow-up, $p = 0.020$). Subsyndrome analyses revealed a significant improvement in hyperactivity symptoms at the 6-month follow-up ($p = 0.019$), whereas no significant changes were observed

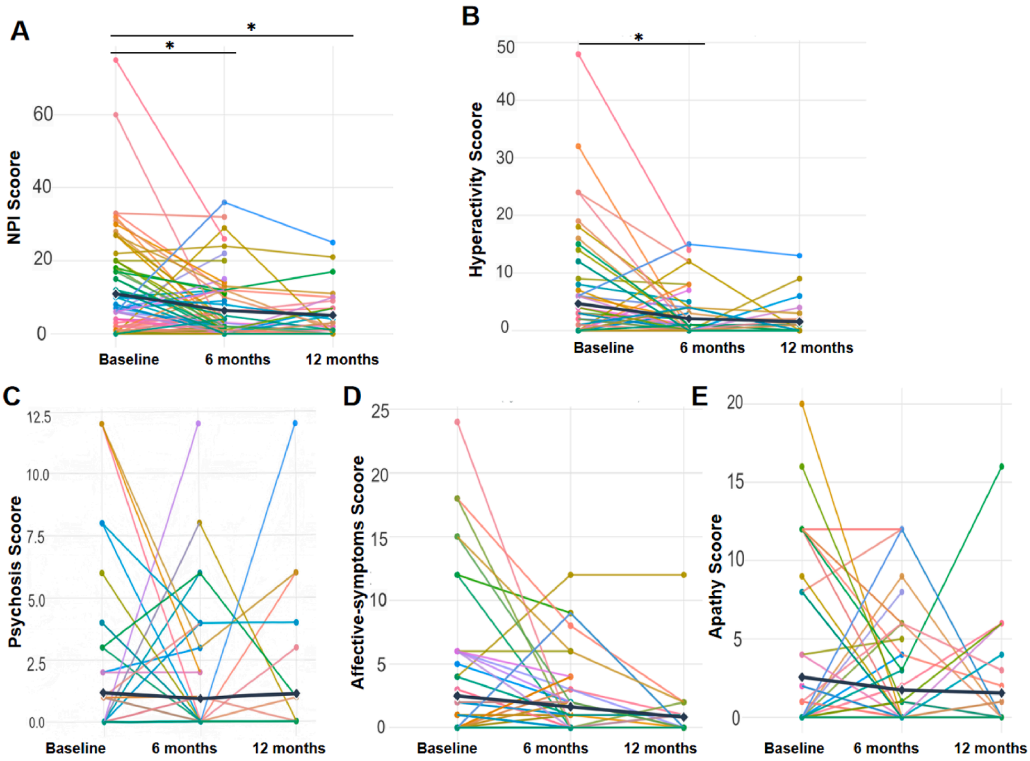

Fig. 2. Longitudinal changes in Neuropsychiatric Inventory (NPI) total score and its subdomains during treatment with lecanemab. Five items (A-E) were assessed at baseline, 6 months, and 12 months. Significant changes from baseline are indicated with asterisks (*$p < 0.05$).

Table 2
Patient clinical characteristics at baseline,6-month, and 12-month follow-up.

Variables	6-month follow-up N = 73			12-month follow-up N = 32		
	V0	V1	*p*	V0	V2	*p*
Age at first infusion, y, mean(SD)	68.95(8.12)	/		68.53(9.04)	/	
Age at onset, y, mean(SD)	66.03(8.95)	/		65.51(9.78)	/	
Disease duration, y, mean(SD)	3.12(2.16)	/		3.48(2.13)	/	
Education, y, mean(SD)	9.69(4.35)	/		10.97(3.39)	/	
Sex(F/M)	46/27	/		21/11	/	
APOE 4						
E4 non-carrier, n (%)	34(46.58)	/		15(46.88)	/	
E4 heterozygotes, n (%)	31(42.47)	/		13(40.63)	/	
E4 homozygotes, n (%)	8(10.96)	/		4(12.50)	/	
MMSE,mean(SD)	18.07(7.09)	17.78(8.00)	0.810	18.97(5.19)	18.36(6.36)	0.649
CDR,mean(SD)	1.08(0.56)	1.06(0.65)	0.805	1.02(0.48)	0.97(0.64)	0.333
CDR-SB,mean(SD)	5.81(3.24)	5.89(3.78)	0.935	5.62(2.90)	5.48(3.41)	0.500
ADL,mean(SD)	28.81(7.41)	30.49(10.19)	0.107	27.73(6.15)	29.37(10.21)	0.658
NPI,mean(SD)	10.92(13.93)	6.34(9.07)	**0.006**	11.94(12.90)	6.34(10.47)	**0.020**
Hyperactivity,mean(SD)	4.68(8.53)	2.08(3.72)	**0.019**	3.719(6.213)	1.84(3.48)	0.117
Psychosis,mean(SD)	1.18(2.84)	0.93(2.25)	0.485	1.47(2.98)	1.61(3.60)	0.928
Affective symptoms,mean(SD)	2.49(5.07)	1.65(2.76)	0.331	3.84(6.78)	1.19(3.09)	0.105
Apathy,mean(SD)	2.56(4.87)	1.76(3.50)	0.429	2.91(5.19)	1.81(3.82)	0.264
Infusion reaction n (%)		14(19.18)			6(18.75)	>0.999
AIRA n (%)		14(19.18)			8(25.00)	0.605

in psychosis, affective symptoms, or apathy during the follow-up period.

To examine whether antidepressant medication use may have contributed to the observed reductions in NPS, we performed sensitivity analyses excluding the seven participants that were taking antidepressant. NPI scores remained significantly reduced at both the 6-month and 12-month follow-ups ($p = 0.029$ and $p = 0.008$, respectively).

A total of 39 participants (53.42% of those with 6-month follow-up data) underwent follow-up amyloid PET/CT imaging at 6 months. Regional and whole-brain SUVR values, including the frontal, parietal, temporal, occipital, and insular lobes, as well as the precuneus and striatum, are summarized in Fig. 3 and Table S3. Significant reductions in SUVRs were observed across all regions after treatment.

At approximately 12 months of treatment, a sustained reduction in mean whole-brain SUVR was still evident among patients with available follow-up imaging. Amyloid clearance was most pronounced during the first 6 months of treatment and sustained throughout the subsequent lecanemab treatment period (Fig. 4). The occipital lobe showed the least amyloid clearance, while the precuneus, striatum, and frontal lobes were the brain regions with the greatest amyloid clearance.

To investigate whether ARIA was associated with changes in clinical

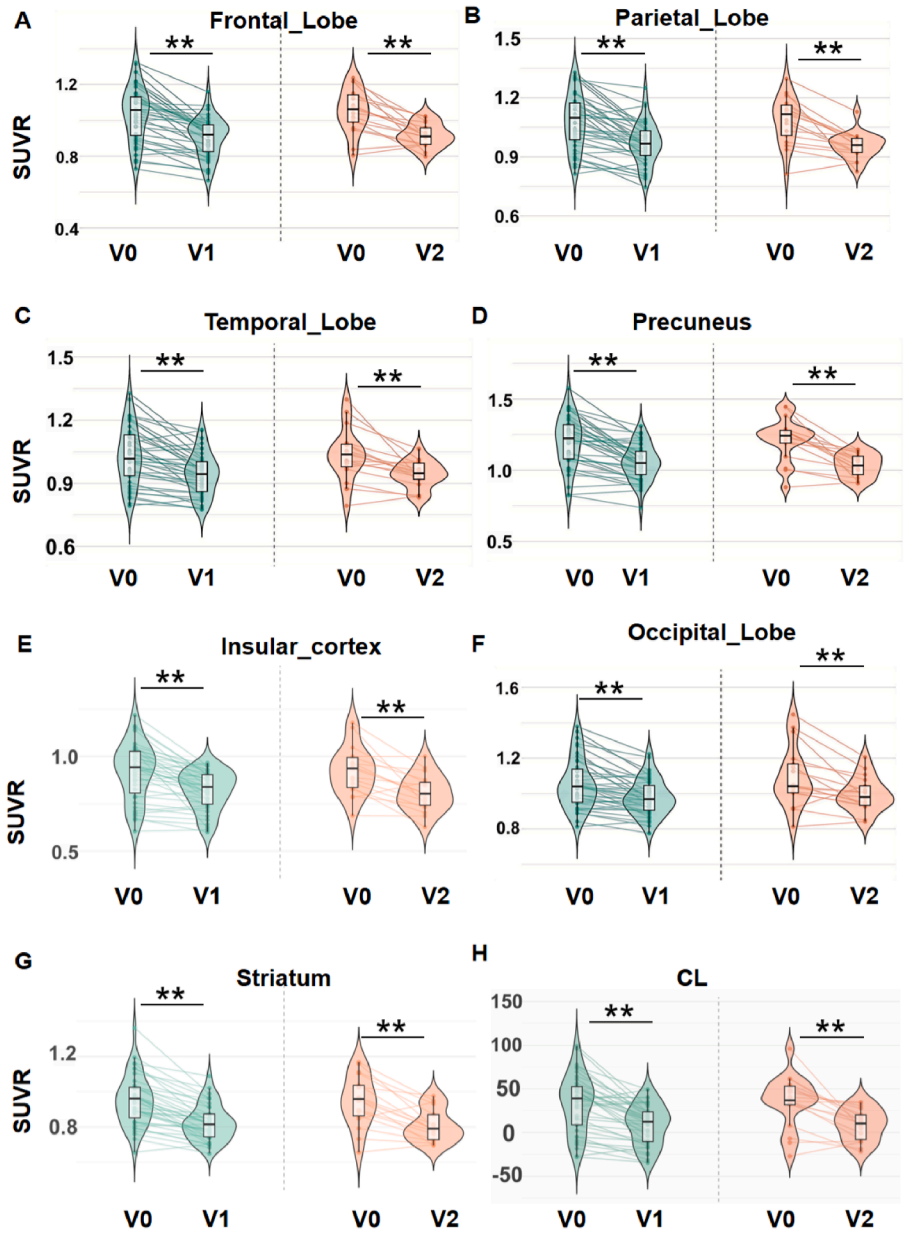

Fig. 3. Longitudinal changes in brain regional Aβ-PET SUVR and Centilod (CL) during lecanemab treatment. Violin graphs show changes at baseline (V0), 6 months (V1), and 12 months (V2) in seven pre-specified brain regions including frontal (A), parietal (B), temporal (C), precuneus (D), and insular (E), occipital (F) and striatum (G) as well as CL (H). Significant reductions from baseline at V1 or V2 are marked with asterisks (**$p < 0.001$).

function, we compared changes in cognitive outcomes, including MMSE and CDR-SB, as well as NPI scores, between patients with and without ARIA at the 6-month follow-up. No significant differences were observed between the two groups (Table S4).

3.4. Subgroup analyses by disease severity

To evaluate the consistency of observed changes across disease stages, we performed subgroup analyses stratified by AD-related MCI, mild AD dementia, and moderate AD dementia at the 6-month follow-up. Baseline demographic and clinical characteristics differed significantly among the three subgroups in terms of age, age at disease onset, and APOE ε4 carrier status (Table S5). At 6 months, cognitive and functional scores, including MMSE, CDR-SB, and ADL, remained stable in all subgroups, with no significant changes observed (Table S6). The total NPI score was significantly reduced in the mild AD dementia subgroup ($p = 0.003$), but not in the MCI or moderate AD dementia subgroups. The hyperactivity subsyndrome was also significantly reduced in the mild AD dementia subgroup ($p = 0.013$), but not in the other two subgroups. Amyloid PET analyses showed significant reductions in SUVR and Centiloid values across all three subgroups, including in the frontal, temporal, parietal, insular, and occipital lobes, as well as the precuneus and striatum (all $p < 0.05$; Table S7).

3.5. Factors associated with NPS at baseline

Associations between baseline NPS scales and clinical variables are summarized in Table S8, whereas associations between NPS and Aβ biomarkers are presented in Table S9. At baseline, longer disease duration ($r = 0.275$, $p = 0.021$) and higher CDR ($r = 0.251$, $p = 0.035$) were significantly associated with higher total NPI scores. In addition, disease duration was positively correlated with affective symptom subsyndrome scores ($r = 0.280$, $p = 0.019$).

In contrast, other demographic and genetic variables, including age

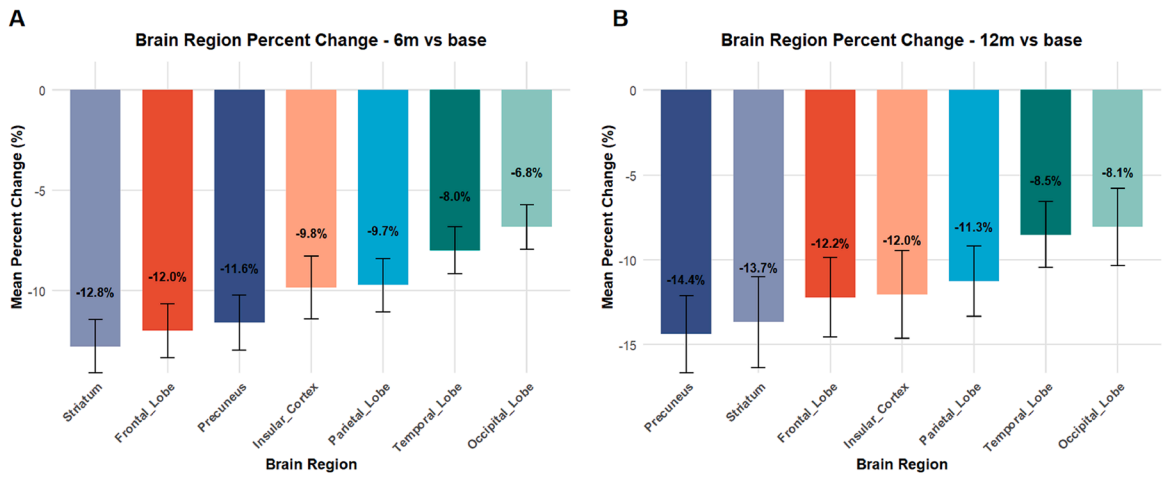

Fig. 4. Regional percentage reduction in Aβ-PET SUVR during lecanemab treatment. Bar graphs show the mean percent reduction in SUVR from baseline to (A) 6 months and (B) 12 months across seven brain regions. The reduction rate was calculated as (SUVR_follow-up - SUVR_baseline) / SUVR_baseline × 100%.

at first infusion, age at disease onset, years of education, sex, and APOE ε4 carrier status, showed no significant associations with baseline NPS scores (Table S8). Furthermore, no significant associations were observed between Aβ and NPS scales at baseline after adjustment for age, sex, education, APOE ε4 carrier status, and age at disease onset (Table S9).

3.6. *Factors associated with longitudinal NPS changes*

At the 6-month follow-up, reductions in total NPI scores were significantly associated with Aβ clearance in the insular cortex (Fig. 5; Table S10). In addition, reductions in the hyperactivity subsyndrome were correlated with reductions in Aβ burden across multiple brain regions, including the frontal lobe, temporal lobe, insular cortex, and striatum.

Associations between changes in NPS and Aβ reduction at the 12-month follow-up are presented in the Supplementary Materials (Table S11). Owing to the limited sample size at 12 months, these correlation analyses did not yield statistically robust results (Figure S3).

4. Discussion

In this prospective longitudinal study, we evaluated the short-term clinical and imaging effects of lecanemab in patients with AD and AD-related MCI, with a particular focus on NPS. Our findings demonstrate that lecanemab treatment was associated with robust and sustained amyloid-β clearance on PET imaging. While cognitive performance remained largely stable over the follow-up period, NPS showed

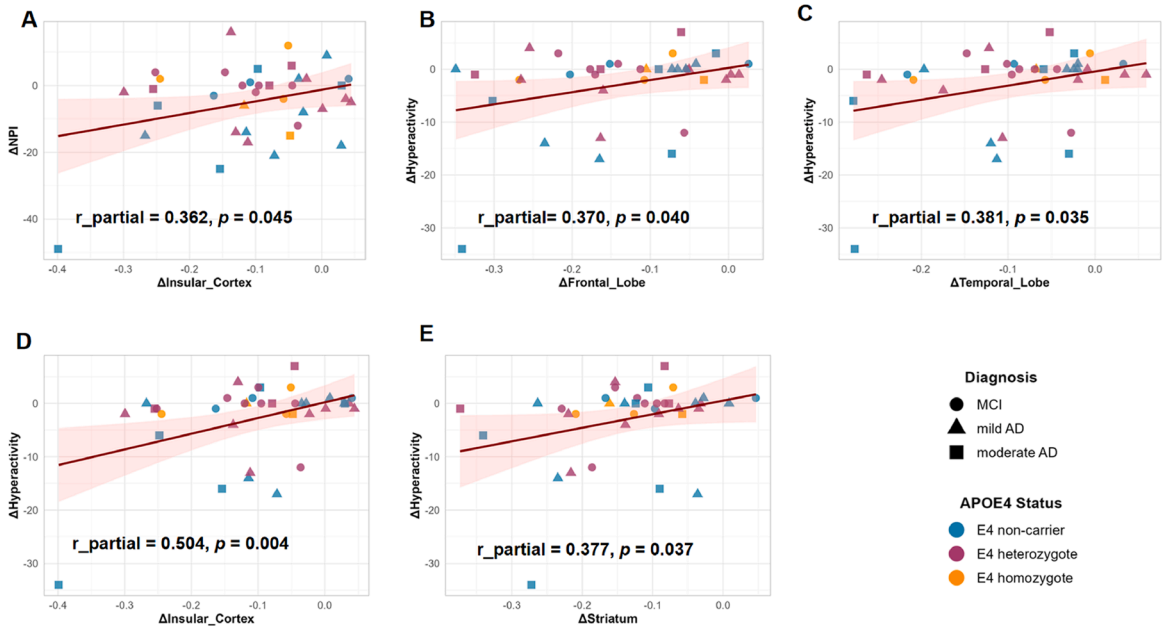

Fig. 5. Partial correlations between Aβ clearance and neuropsychiatric reduction at 6 months of lecanemab treatment. Scatter plots showing significant associations between changes in neuropsychiatric symptoms and reductions in regional Aβ burden (measured by SUVR) from baseline to the 6-month follow-up. Δ values represent change from baseline (i.e., value at follow-up minus value at baseline). Data points are stratified by clinical diagnosis (mild cognitive impairment [MCI]), mild Alzheimer's disease [AD], moderate AD; shown by shape) and APOE ε4 carrier status (non-carrier, heterozygote, homozygote; shown by color). (A) shows total NPI scores were significantly associated with Aβ clearance in the insular cortex. (B-E) shows reductions in the hyperactivity subsyndrome were correlated with reductions in Aβ Aβ clearance in frontal lobe, temporal lobe, insular cortex, and striatum. All analyses were adjusted for clinical covariates. Detailed partial correlation coefficients (r_partial) and p values for all regions are provided in Supplementary Table S10.

significant reduction, particularly within the hyperactivity subsyndrome. Importantly, reductions in NPS were linked to treatment-related Aβ reduction in the insular cortex and fronto–temporal–striatal regions. Together, these results suggest that dynamic changes in amyloid pathology may be relevant to short-term reduction in NPS following anti–Aβ therapy.

The observed incidences of infusion-related reactions and ARIA in our cohort fell within the range reported in previous Chinese studies [16–19], confirming the known safety profile of lecanemab. Most infusion-related reactions were mild, occurred early in the treatment course, and typically resolved by the third infusion; only a small proportion of patients required symptomatic management. In addition, all ARIA cases were asymptomatic and were detected incidentally on scheduled MRI monitoring. Importantly, ARIA events were predominantly ARIA-H, and the burden of cerebral microhemorrhages was generally low, with fewer than four microhemorrhages observed in most affected individuals.

Two patients had cerebral infarctions during lecanemab treatment course. Recent case reports suggest that ischemic infarction may represent an underrecognized vascular manifestation associated with ARIA following anti-amyloid therapy. In one report, ischemic strokes occurred repeatedly within or adjacent to regions of severe ARIA-E, supporting a localized inflammatory vasculopathy mechanism related to cerebral amyloid angiopathy–related inflammation [20]. In contrast, another case described multifocal cerebellar infarctions spatially remote from cortical ARIA, suggesting that anti-amyloid therapy may also induce a more global microvascular vulnerability rather than strictly focal injury [21]. Together, these observations indicate that ARIA-associated ischemic injury may arise through both local inflammatory effects and systemic microvascular dysfunction. Nonetheless, we did not observe any clear spatial relationship between ARIA and newly developed infarcts, and our patients had pre-existing vascular risk factors prior to lecanemab treatment. Therefore, whether the new infarctions were attributable to lecanemab remains inconclusive.

In our cohort, cognitive performance remained largely stable following lecanemab treatment, which is broadly consistent with prior reports [16,19]. In the phase 3 CLARITY AD trial, lecanemab was associated with a modestly slower decline in cognition and function compared with placebo [2]. Notably, we observed a short-term reduction in NPS during follow-up, suggesting that the potential benefits of anti–Aβ therapy may extend beyond cognitive outcomes. Given that NPS are strongly linked to functional disability and caregiver distress, reductions in patients' behavioral and psychological status may have meaningful implications for daily functioning and the overall caregiving burden.

Consistent with previous studies [22,23], our findings demonstrate that the severity of NPS is positively associated with both disease duration and disease severity. Patients with longer disease duration and higher CDR scores tended to exhibit higher NPI scores. In contrast, no significant associations were observed between baseline NPS and baseline Aβ pathology. These findings suggest that neuropsychiatric manifestations may be more closely related to clinical disease progression than to static amyloid burden at a single time point, although studies with larger sample sizes are required to confirm this observation.

In line with prior reports, our study demonstrated robust Aβ clearance following lecanemab treatment across the whole brain. Furthermore, treatment-related reductions in Aβ pathology were associated with NPS reductions. Previous work has shown that changes in cerebrospinal fluid Aβ42 levels are inversely and independently associated with the frequency and severity of NPS [24], supporting a potential link between amyloid dynamics and behavioral manifestations. From a neurobiological perspective, Aβ plays a modulatory role in synaptic activity and neurotransmission under physiological conditions, whereas pathological accumulation of Aβ is associated with early synaptic dysfunction and dysregulation of key neurotransmitter systems [25]. Neurotransmitters such as norepinephrine, dopamine, and serotonin have been implicated in the development of NPS [26].

More specifically, reductions in total NPI scores after 6 months of lecanemab treatment were specifically associated with Aβ clearance in the insular cortex, while reductions in hyperactivity symptoms were linked to Aβ reduction across a broader network involving the frontal and temporal lobes, striatum, and insular cortex. These regions—particularly the orbitofrontal cortex and temporal lobe—are known to play critical roles in emotional regulation and behavioral control, and have been repeatedly implicated in the pathophysiology of NPS [27]. These findings suggest that regional amyloid clearance within emotion- and behavior-related neural circuits may contribute to short-term reductions in NPS following anti–Aβ therapy. However, these findings are exploratory and require further validation with fluorodeoxyglucose (FDG) PET or structural MRI to confirm underlying neurobiological mechanisms.

5. Limitation

This study has several important limitations. First, this was a prospective, open-label, real-world observational study without a randomized, blinded control group, which inherently limits our ability to establish causal efficacy or treatment benefit. Second, patients were consecutively enrolled in a clinical setting, and some had not yet reached their scheduled 6-month or 12-month follow-up time points at the time of data analysis. This resulted in relatively high follow-up attrition and a small sample size at the 12-month follow-up. Third, the lack of CSF Aβ42 measurements limited a comprehensive interpretation of amyloid homeostasis and its relationship with NPS. Fourth, the disproportionate representation of female and male participants may limit the external validity of the present findings. Furthermore, the study cohort included participants with depression and cerebrovascular risk factors, such as hypertension, diabetes, and hyperlipidemia, which may have acted as potential confounders. Nonetheless, these conditions frequently co-occur with AD, and excluding all patients with such comorbidities would have reduced the real-world representativeness of the cohort. Therefore, our results should be interpreted as observational findings reflecting clinical and imaging changes associated with lecanemab treatment in a real-world setting. Finally, this was a single-center study, which may further restrict the generalizability of our findings to other populations and clinical settings.

6. Conclusion

Lecanemab treatment was associated with substantial reductions in Aβ and reductions in NPS. Notably, longitudinal changes in NPS were linked to regional Aβ clearance, suggesting that Aβ dynamics within specific neural circuits may be relevant to behavioral outcomes.

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AI has not been used at all in the preparation of this manuscript.

CRediT authorship contribution statement

Yaping Yan: conception, study design, data collection or acquisition, statistical analysis, writing, review & editing. **Daoyan Hu**: data collection or acquisition, statistical analysis, writing, review & editing. **Linlin Kong**: data collection or acquisition. **Kaichen Li**: data collection

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Declaration of competing interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100600.

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