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Trajectories of amyloid beta accumulation – Unveiling the relationship with *APOE* genotype and cognitive decline

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ABSTRACT

Amyloid beta (Aβ) follows a sigmoidal time function with varying accumulation rates. We studied how the position on this function, reflected by different Aβ accumulation phases, influences *APOE* ε4's association with Aβ and cognitive decline in 503 participants without dementia using Aβ-PET imaging over 5.3-years. First, Aβ load and accumulation were analyzed irrespective of phases using linear mixed regression. Generally, ε4 carriers displayed a higher Aβ load. Moreover, Aβ normal (Aβ-) ε4 carriers demonstrated higher accumulation. Next, we categorized accumulation phases as "decrease", "stable", or "increase" based on trajectory shapes. After excluding the Aβ-/decrease participants from the initial regression, the difference in accumulation attributable to genotype among Aβ- individuals was no longer significant. Further analysis revealed that in increase phases, Aβ accumulation was higher among noncarriers, indicating a genotype-related timeline shift. Finally, cognitive decline was analyzed across phases and was already evident in the Aβ-/increase phase. Our results encourage early interventions for ε4 carriers and imply that monitoring accumulating Aβ- individuals might help identify those at risk for cognitive decline.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common dementia cause (Du et al., 2018). The disease displays a considerable variety of temporally and phenotypically diverse clinical courses (Wang et al., 2019). Amyloid beta (Aβ) load, one of the major pathological hallmarks of AD (Villemagne et al., 2013), might be especially relevant with respect to these disease heterogeneities. Aβ aggregation over decades has been suggested to occur years before salient symptom onset and triggers further disease-related changes (Hardy and Selkoe, 2002; Hardy and Higgins, 1992; Jack et al., 2013a, b). Consequently, currently ongoing prevention trials either target the removal of plaque deposition or the halting of its further progression (Huang et al., 2020). Thus, a proper understanding of longitudinal Aβ trajectories, its major influencing factors, and how it is related to cognitive decline might be especially important for clinical trial designs.

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Studies using repeated PET suggest that the trajectories of Aβ load follow a sigmoidal shape over time and may reach a plateau towards later stages of the AD course (Jack et al., 2013a,b; Jagust et al., 2021; Knopman et al., 2021). The *APOE* gene might be one factor influencing these Aβ trajectories. The gene has been repeatedly described as one of the most important genetic AD risk factors (Belloy et al., 2019; Corder et al., 1993; Strittmatter et al., 1993). The *APOE* ε4 allele lowers the age of onset in a dose-dependent manner and increases the risk of developing AD (Khachaturian et al., 2004). Moreover, *APOE* might act as a disease modifier (Williams et al., 2020; Zhao et al., 2018) and is hypothesized to have a pleiotropic effect on AD across the lifespan (Henson et al., 2020). However, uncertainty remains about how exactly *APOE* influences Aβ progression. Until now, Aβ-PET imaging research has consistently demonstrated *APOE* ε4's effects on elevated brain Aβ load when measured cross-sectionally (Fouquet et al., 2014). However, the association between longitudinal Aβ accumulation, which is the increase of Aβ load over time, and the *APOE* genotype is controversial (e.g., Lim and Mormino, 2017; Lopresti et al., 2020; Mishra et al., 2018). While some researchers found no association at all (Lopresti et al., 2020; Resnick et al., 2015), others reported ε4 carriers to show higher Aβ accumulation rates (e.g., Jack et al., 2013a,b; Villemagne et al., 2011). A relatively recent study by Lim and Mormino (2017) found an *APOE* ε4 effect only in a subgroup who displayed still normal Aβ levels at the baseline measurement. So far, however, these investigations lack a consideration of the varying increase rates across the previously mentioned Aβ function over time. That is, the sigmoidal shape suggests different slopes and, therefore, different Aβ accumulation phases ranging from no or little to high accumulation. Accordingly, an *APOE* association with Aβ load and with accumulation might differ depending on the accumulation phase under investigation. An understanding of *APOE*'s exact contribution across the sigmoid function might be particularly important for current advances in therapies that aim to modify the effects of *APOE* and/or targeting Aβ.

In a similar way, the position on the sigmoidal function might influence the association of Aβ and cognitive decline. Previous literature has shown that an abnormal Aβ level is associated with cognitive decline (Donohue et al., 2017; Landau et al., 2012; Mormino et al., 2014). However, in participants with still normal levels the association is controversial and a few recent studies suggested that Aβ accumulation rather than Aβ load alone might improve the prediction of cognitive decline, especially in the memory domain (e.g., Collij et al., 2021; Farrell et al., 2018; Insel et al., 2020). Therefore, cognitive decline profiles might differ across the accumulation phases of the proposed sigmoid function. A better understanding might offer practical advantages for proper patient selection for clinical trials.

The current study examined longitudinal Aβ trajectories measured by PET imaging and the relation with the *APOE* genotype and cognitive decline. The study used data from a large longitudinal multicenter study by the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Australian Imaging, Biomarker & Lifestyle Flagship Study of Aging (AIBL) including older adults without dementia who had received Aβ-PET imaging at three or more time points. Our primary objective was to assess whether Aβ load and accumulation differ between the *APOE* genotype groups. We hypothesized that *APOE* ε4 carriage has an association not only with higher Aβ load, but also with higher accumulation. However, we expected that the relationship between Aβ accumulation and the *APOE* genotype might vary depending on the accumulation phases. We intended to target inconsistencies in the previous literature regarding the predictive value of *APOE* genotype for Aβ load and accumulation by initially analyzing the whole sample irrespective of the accumulation phases considering only the Aβ baseline status as normal or abnormal. Subsequently, we individually examined the distinct accumulation phases and performed comprehensive analyses that involved combining certain phases to gain a better understanding. Our second aim was to investigate the relation of different accumulation phases with cognition, including the domains of memory, executive function, and language. We hypothesized that cognitive decline might especially vary across baseline Aβ normal individuals depending on accumulation phases. Moreover, Aβ abnormal individuals were assumed to generally indicate considerable cognitive declines and *APOE* genotype was predicted to exert phase-dependent associations. Our results might contribute to the understanding of the highly heterogeneous dynamics of AD progression and might have important implications for the selection of high-risk participants for AD prevention trials.

2. Materials and methods

2.1. Study population

The cohort was acquired from a large longitudinal multi-center cohort study. That is, data were obtained from the ADNI data repository encompassing data from various protocols (ADNI 1, 2, 3, ADNI Go, AIBL). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. ADNI's primary goal has been to assess whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For our analysis, we had access to 543 datasets of participants who received an Aβ-PET at three or more time points (female = 260). The downloaded data included MRI, Aβ-PET scans, *APOE* genotyping, demographics, and clinical information for all participants. 237 participants were characterized as cognitively normal (CN), and 306 participants were characterized as cognitively impaired (CI) with a diagnosis of mild cognitive impairment (MCI) (early or late subgroups) or subjective memory concern (SMC) at baseline. SMC individuals were included into the CI group as they might represent an early disease stage (Lista et al., 2015) with heightened risk for developing objective cognitive impairment (Amieva et al., 2008) and AD (e.g., Jessen et al., 2010). Group classification was based on the criteria set by the ADNI consortium. Participants were defined as CN based on a Mini Mental State Examination (MMSE) score between 24 and 30, a Clinical Dementia Rating (CDR) of 0; they had to be non-MCI and to have no objective memory loss based on the delayed recall of one paragraph from the Wechsler Memory Scale (WMS) Logical Memory II. SMC was defined based on MMSE scores between 24 and 30, a significant subjective memory concern reported by the participant, an informant, or a clinician, a Charlson Comorbidity Index score $\geq$ 16, a CDR of 0; participants had to be non-MCI and had to have no objective memory loss based on the delayed recall of one paragraph from the WMS Logical Memory II. MCI was defined by MMSE scores between 24 and 30, a memory complaint, participants had to have objective memory loss measured by the WMS Logical Memory II, a CDR of 0.5, no impairment in other cognitive domains, and preserved activities of daily living. All participants had to have an absence of depression and of dementia. At baseline, patients were aged between 55 and 90 years. Full information regarding the ADNI inclusion/exclusion criteria and recruitment can be accessed at http://adni.loni.usc.edu/.

2.2. Standard protocol approvals, registrations, and patient consents

The ADNI data are available to the scientific community without embargo at http://adni.loni.usc.edu/data-samples/access-data/ after approval by the Data Sharing and Publications Committee and adherence to the ADNI Data Use Agreement and publication policies. AIBL study methodology has been reported previously (Ellis et al., 2009). Institutional review boards of participating centers of ADNI granted ethical approval. All participants provided written consent. The analysis of the obtained data was preregistered at https://osf.io/x9dh4/.

2.3. APOE genotyping

Detailed description of *APOE* genotyping methods can be retrieved from https://adni.loni.usc.edu/data-samples/data-types/. *APOE*

genotypes were grouped according to the presence of one or two ε4 alleles into ε4 carriers and ε4 noncarriers. Participants that displayed the ε2/ε4 genotype were excluded from analysis due to the combination of a potentially protective and risk allele that demonstrated conflicting findings in the literature (e.g., Insel et al., 2021). Thus, participants with the ε2/ε3 and the ε3/ε3 genotypes were grouped together as the ε4 noncarriers (n = 353), and participants with the ε3/ε4 and the ε4/ε4 genotypes were grouped together as the ε4 carriers (n = 189).

2.4. Imaging analysis

[^{11}C]-Pittsburgh Compound B (PiB), [^{18}F]florbetapir (FBP), and temporally corresponding 3D T1 MRI images were downloaded from ADNI. Additional details of ADNI methods for image acquisition can be obtained from https://adni.loni.usc.edu/methods/. PET images were processed using PMOD 4.2 NeuroTool (Pmod Technologies). We extracted globally calculated Aβ values by applying the centiloid (CL) method developed by Klunk et al. (2015). This method has been proven to achieve comparable results across different Aβ tracers (Klunk et al., 2015; Navitsky et al., 2018; Su et al., 2019). The CL approach is based on the concept to linearly scale the outcome data of any Aβ-PET method to zero in "high-certainty" amyloid negative individuals and to 100 in "typical" AD patients. Thus, we applied the CL atlas implemented in NeuroTool and determined rigid-body transformation parameters by using each participant's temporally closest anatomical image to co-register with its Aβ-PET images. Generated transformation parameters were applied and resulting images were normalized to the common Montreal Neurological Institute (MNI152) standard space. We used the whole cerebellum as a reference area to quantitatively normalize the PET scans. Resulting images were smoothed using a 4 mm full-width at half maximum (FWHM) Gaussian kernel and masked to exclude voxels outside the brain. To convert normalized values into CL units, we used the equation by Klunk et al. (2015) for the PiB images and conducted a level-2 calibration as described by Klunk et al. (2015) for the FBP images. Participants were defined as baseline Aβ+ or Aβ- using a CL cut-off 30 which has been proven to indicate the presence of established pathology (Salvadó et al., 2019). We additionally performed control analyses using a lower Aβ baseline threshold of 20 CL to test the influence of the abnormality cut-off (Royse et al., 2021).

2.5. Neuropsychological scores

For all ADNI participants (n = 439), repeated cognitive composite scores based on the ADSP Phenotype Harmonization Consortium were available. We obtained memory, executive function, and language composite scores and matched each participant's neuropsychological assessment timepoint to the closest Aβ scan in time. Further information about the exact calculation of these composite scores can be retrieved from https://ida.loni.usc.edu/.

2.6. Statistical analysis

Statistical analyses were performed in SPSS 28 and R (R version 4.2.2., R Foundation for Statistical Computing, Vienna, Austria, available at https://cran.r-project.org/). Except for demographics, we analyzed all data using linear mixed effects models. This regression approach has been described to be especially suited for longitudinal data in the case of dependency within observations (Liu et al., 2012; Moerbeek et al., 2003). Thus, this method was most appropriate for three or more available measurement time points. Moreover, the linear mixed regression allowed us to consider inter-subject differences in slopes and intercepts (individual starting points). The fixed and random effects of the models were defined based on the goal of the analyses. A classical forward selection process for the inclusion of model terms was applied comparing models' goodness of fit using the likelihood ratio test and a *p*-value of 0.05 (Morrell, 1998). We reported Type III tests of fixed effects as main effects and estimates of fixed effects as simple effects. For all analyses, statistical assumptions were met, and significance was defined as $p \leq 0.05$. Formulas of the models will be displayed in line with the Wilkinson notation (Wilkinson and Rogers, 1973). The sum of model terms is represented by "+", only interaction effects are represented by ":", sum of terms and interaction effects are represented by "*", and random effects are represented by using the vertical bar symbol "(|)".

2.6.1. APOE genotype association with Aβ load and accumulation irrespective of the accumulation phase

To examine the association of *APOE* genotype with Aβ load and accumulation, we first used linear mixed regression in the whole sample. The major outcome variable was CL which reflects the Aβ load. Accordingly, we tested Aβ accumulation as the change in CL values over time. We fitted models based on the factors ε4 carrier (coded as 0 for noncarriers and 1 for carriers), baseline clinical group (coded as 0 for CN and 1 for CI), and Aβ baseline status (coded as 0 for Aβ- and 1 for Aβ+), and the covariates time and baseline age. These terms and their interactions were the fixed effects. Individually varying slopes and intercepts were added as random effects. Time was computed as years relative to each individual's baseline Aβ scan. Baseline age was mean centered. We tested for the linear, quadratic, and cubic terms of age, and all two-way and three-way interactions. Based on the likelihood ratio test the different models were compared and terms that did not improve the fit were not included. The final best fitting model included the following terms: *Centiloids* ~ *E4Carrier*Time* + *ClinicalGroup* + *AβBaselineStatus* + *BaselineAge* + *E4Carrier:AβBaselineStatus* + *AβBaselineStatus:BaselineAge* + *AβBaselineStatus:Time* + *E4Carrier:AβBaselineStatus:Time* (*Time* | *Patient*)

2.6.2. Clustering of accumulation phases and phase-dependent analyses of APOE genotype association with Aβ load and accumulation

Next, we predicted a difference in Aβ load and accumulation between *APOE* genotypes dependent on the accumulation phase. To identify the accumulation phases, we applied a k-means clustering algorithm for longitudinal data using shape respecting distance in R (package 'kmlShape' version 0.9.5) to classify the differences in the shape of individuals' CL trajectories. Due to the assumption of Aβ to follow a sigmoid function (Jack et al., 2013a,b), the algorithm was specified to create six clusters based on Aβ baseline abnormality (Aβ+ or Aβ-) and the assumption of decreasing, stable, or increasing trajectories over time (Guo et al., 2018) (Figure 1a & b). Accordingly, we termed the clusters as: (1) Aβ-/decrease (n = 87); (2) Aβ-/stable (n = 193); (3) Aβ-/increase (n = 61); (4) Aβ+/increase (n = 43); (5) Aβ+/stable (n = 93); and (6) Aβ+/decrease (n = 26) (Figure 1a & b and Supplementary Figure 1). As a controlling measure, annual change rates based on the baseline and the last follow-up CL values divided by the time interval between the measurement timepoints were calculated per cluster. The mean CL annual change rate was −2.33 (sd = 1.26) for the Aβ-/decrease phase, 0.61 (sd = 1.31) for the Aβ-/stable phase, 5.66 (sd = 2.67) for the Aβ-/increase phase, 8.13 (sd = 3.14) for the Aβ+/increase phase, 2.20 (sd = 2.17) for the Aβ+/stable phase, and −5.77 (sd = 6.91) for the Aβ+/decrease phase. Clinical characteristics and demographics of each cluster are summarized in Table 1. For robustness, we also assessed the influence using a lower Aβ baseline threshold of 20 CL (Royse et al., 2021) and using no threshold at all for the cluster assignment. The clustering based on 20 CL led to 96.66% of participants receiving the same accumulation phase categorization, including the individuals that received the same categorization but changed from negative to positive. When using no threshold, the clustering led to a matching classification of 93.71%. The linear mixed regression approach was repeated separately within the clusters (based on 30 and 20 CL) using the same variables except for Aβ baseline status, which was already coded in the clustering. Thus, the final per cluster models included: *Centiloids* ~ *E4Carrier*Time* + *ClinicalGroup* + *AβBaselineStatus* + *BaselineAge* + *(1* |

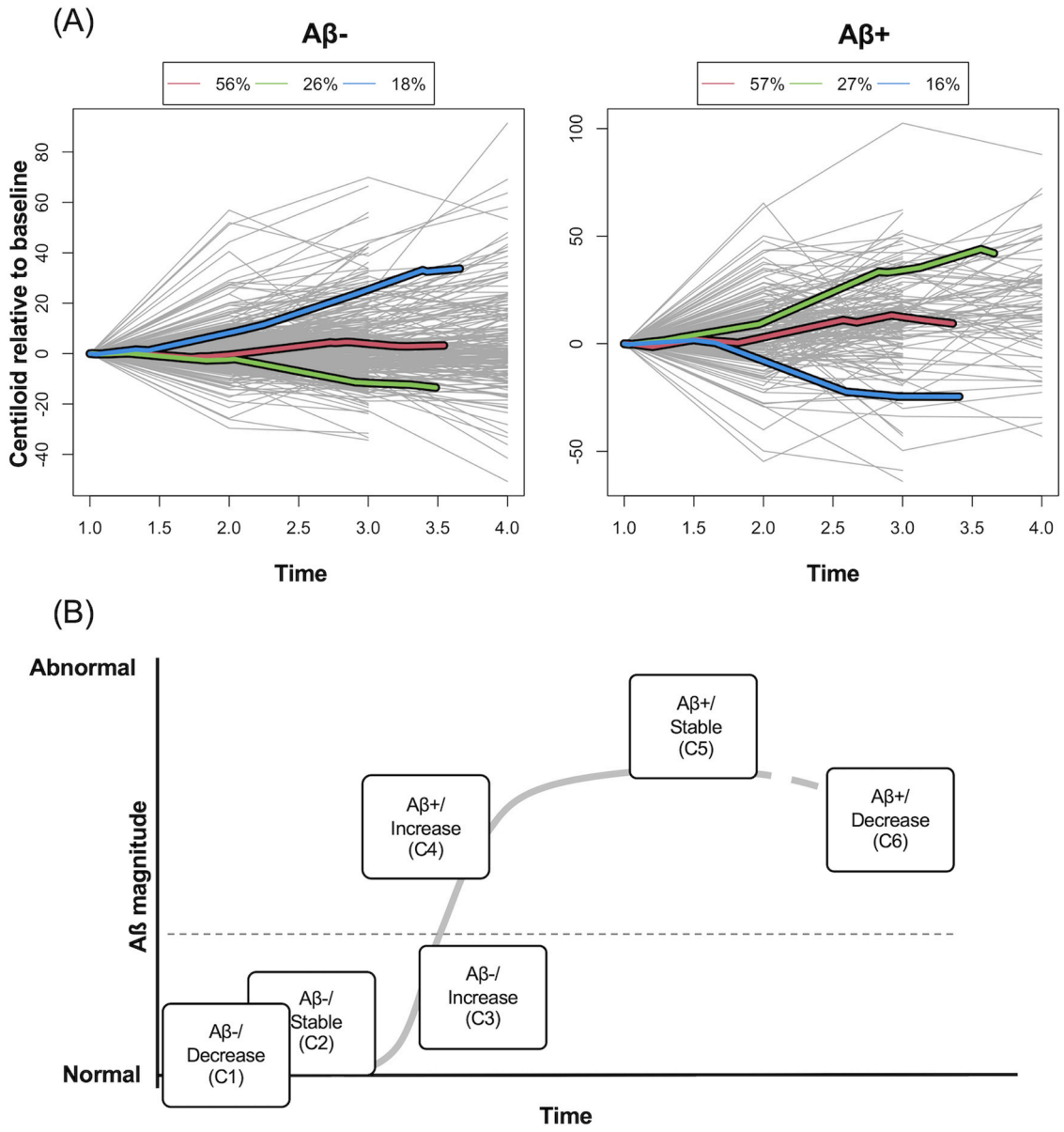

Fig. 1. Distinct amyloid beta accumulation phases over time. (A) kmlShape clustering to specify accumulation phases. The sample was first divided by a centiloid threshold of 30 into baseline amyloid negative (Aβ-) and baseline amyloid positive (Aβ+). Within these subgroups the clustering algorithm assigned each individual to a decrease, stable, and increase cluster based on the amyloid progression shape. Percentages indicate the number of participants that were assigned to the respective group. The colour code is dependent on the group size determined by the algorithm. (B) Subgroup placement to describe the resulting accumulation phases along the suggested model by Jack et al. (2013a, 2013b).

Patient)

For exploratory reasons, we conducted two additional analyses. First, we combined the increasing clusters into a "high accumulator phase" and tested the same variables as for the whole sample to directly discern the dependence of the interaction between *APOE* genotype and time on the Aβ baseline status. Second, the influence of excluding the Aβ-/ decrease cluster from the initial whole sample mixed regression approach was examined as it might represent measurement inaccuracies (e.g., Flores et al., 2023; Villain et al., 2012; Villemagne et al., 2013).

2.6.3. Cognitive progression in different accumulation phases

To test the influence of the Aβ cluster assignment on cognitive decline, we conducted separate linear mixed regressions per cluster for each cognitive domain. The composite scores were the dependent variable and time was the major predictor. Additional models tested the association of *APOE* genotype and baseline clinical group with cognitive progression. Fixed and random effects were adjusted based on the fit. A Bonferroni correction for multiple testing was used.

*Domain specific composite score ~ Time*E4Carrier + ClinicalGroup + ClinicalGroup:Time + (Time | Patient)*

3. Results

3.1. Demographics and clinical parameters

We included 543 participants into the initial examination pipeline. Due to faulty scans or tracer changes within subject we had to exclude 30 participants from further analysis. All participants performed a baseline Aβ-PET scan and at least two follow-up scans. Overall, participants were followed over an average time of 5.27 years. The time interval between

Table 1
Demographics and clinical variables for the whole sample and for the amyloid accumulator phases.

Groups (N)	Values	All (503)	Aβ-/Decrease (87)	Aβ-/Stable (193)	Aβ-/Increase (61)	Aβ+/Increase (43)	Aβ+/Stable (93)	Aβ+/Decrease (26)	Test statistic
Baseline Age	Mean (sd)	72.66 (7.02)	70.77 (7.51)	73.32 (7.32)	73.17 (7.25)	71.12 (6.69)	73.37 (6.06)	72.88 (4.85)	F=3; p=0.01
Sex	Female (%)	241(47.91)	39 (44.83)	97 (50.26)	23 (37.70)	23 (53.49)	46 (49.46)	13 (50.00)	X^2=4; p=0.55
Diagnosis Baseline	CI (%)	279 (55.47)	48 (55.17)	87 (45.08)	30 (49.18)	31 (72.09)	61 (65.59)	22 (84.62)	X^2=27;p<0.001
MMSE Baseline	Mean (sd)	28.01(3.13)	27.01 (4.74)	28.23 (2.70)	28.28 (2.13)	28.00 (3.84)	28.17 (2.42)	28.46 (1.30)	X^2=2; p=0.84
APOE Genotype	ε4 carrier (%)	169 (33.60)	8 (9.20)	40 (20.73)	22 (36.07)	28 (65.12)	54 (58.06)	17 (65.38)	X^2=94; p<0.001
Baseline CL	Median (IQR)	9.99 (51.20)	2.83 (13.76)	-0.02 (14.43)	9.75 (16.49)	61.38 (39.85)	68.81 (36.03)	93.79 (50.80)	X^2=340, p<0.001
Annual CL Change Rate	Mean (sd)	1.32 (4.17)	-2.33 (1.26)	0.61 (1.31)	5.66 (2.67)	8.13 (3.14)	2.20 (2.17)	-5.77 (6.91)	F=296; p<0.001

CI = Mild Cognitive Impairment and Subjective Memory Concerns; CL = Centiloid.

Table 2
Whole sample estimates of fixed effects (simple effects).

	Estimates of Fixed Effects				
				95% Confidence Interval	
Parameter	β	t	p	Minimum	Maximum
Intercept	80.47	41.01	<0.001	76.61	84.32
E4 Carrier=0	-13.34	-4.22	<0.001	-19.55	-7.13
Baseline Clinical Group=0	-1.21	-0.67	0.49	-4.69	2.26
Amyloid Baseline Status=0	-76.82	-24.95	<0.001	-82.86	-70.78
Baseline Age	0.49	2.16	0.03	0.05	0.94
Time	2.49	6.50	<0.001	1.74	3.25
E4 Carrier=0 * Amyloid Baseline Status=0	12.05	2.94	<0.01	4.00	20.10
E4 Carrier=0 * Time	0.47	0.77	0.44	-0.72	1.65
Amyloid Baseline Status=0 * Baseline Age	-0.86	-3.21	0.001	-1.39	-0.33
Amyloid Baseline Status=0 * Time	-0.67	-1.18	0.24	-1.77	0.42
E4 Carrier=0 * Amyloid Baseline Status=0 * Time	-1.93	-2.53	0.01	-3.42	-0.43

E4 Carrier was coded as noncarrier = 0 and carrier = 1; Baseline Clinical Group was coded as cognitively normal = 0 and mild cognitive impairment = 1; Amyloid Baseline Status was coded as Aβ- = 0 and Aβ+ = 1; Baseline Age = mean centered baseline age; Time depicts Aβ accumulation.

baseline and first follow-up was on average 2.00 years (sd = 0.67). The second follow-up was on average 4.14 years (sd = 1.09) after the baseline visit. 260 Participants received a third follow-up. The time interval between third follow-up and baseline comprised an average of 6.07 years (sd = 1.25). 170 participants were characterized as ε4 carriers and 333 participants as ε4 noncarriers. 10 participants with an ε2/ε4 genotype were excluded from regression analyses. Demographics are summarized in Table 1. A Mann-Whitney-U test demonstrated a significant difference between baseline diagnostic groups and baseline CL values with CI patients (n = 280) having higher baseline values (U = 37222, $p < 0.001$) than CN participants (n = 223).

3.2. *APOE genotype association with Aβ load and accumulation irrespective of the accumulation phase*

Linear mixed regression was first applied to the whole sample. The parameter estimates of the fixed effects (simple effects) are displayed in

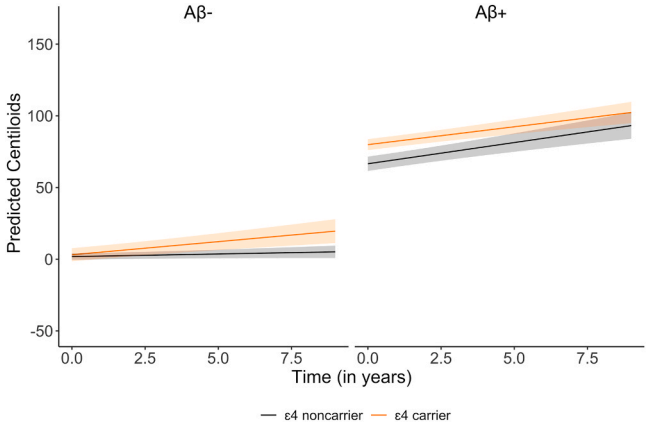

Fig. 2. Model predictions irrespective of accumulation phase. Significant three-way interaction between Aβ baseline status, *APOE* genotype, and time. In the baseline Aβ normal (Aβ-) group, ε4 carriers displayed more accumulation than noncarriers. Shaded areas represent the confidence intervals of the fixed effects.

Table 2. The *APOE* genotype had a significant fixed effect on CL ($F(495) = 12.80$, $p < 0.001$). The parameter estimates show that ε4 carriers presented higher CL values than ε4 noncarriers ($\beta = -13.34$, $se = 3.16$) (Table 2). Additionally, the regression demonstrated a significant interaction between Aβ baseline status (Aβ- or Aβ+) and *APOE* genotype on CL ($F(495) = 8.64$, $p = 0.003$) with a larger CL difference between genotype groups in Aβ+ than in Aβ- (Table 2). This interaction was expected given a narrower range of baseline CL values in the Aβ- group (IQR = 15.05) in comparison to the Aβ+ group (IQR = 43.61). Baseline age had a significant overall interaction with Aβ baseline status ($F(493) = 10.29$, $p = 0.001$). In the Aβ+ group, lower ages are associated with lower CL values, whereas, in the Aβ- group lower ages are associated with higher CL values (Table 2). Table 2 presents Aβ accumulation as the covariate variable time on CL values. The mixed model demonstrated a significant three-way interaction between *APOE* genotype, Aβ baseline status, and time ($F(469) = 6.39$, $p = 0.012$). Fig. 2 visualizes this interplay, demonstrating that in the Aβ- group, ε4 carriers demonstrated higher accumulation. A control analysis showed that these results are not solely due to participants that convert from Aβ- to Aβ+ over the study period (Fig. S2). Therefore, this initial analysis incorporating the whole sample disregarding a differentiation of accumulation phases confirmed the hypothesized higher Aβ load of *APOE* ε4 carriers and suggested a three-way relation of *APOE* genotype and Aβ baseline status with Aβ accumulation.

3.2.1. *Clustering of accumulation phases and APOE genotype association with amyloid load and accumulation in the different phases*

To sort participants into different accumulation phases based on their Aβ trajectory shapes over time, a k-means cluster analysis was performed, and six phases were identified: (1) Aβ-/decrease; (2) Aβ-/stable; (3) Aβ-/increase; (4) Aβ+/increase; (5) Aβ+/stable; and (6) Aβ+/decrease. Linear mixed regression analysis was repeated separately in each accumulator phase (Tables S1 & S2). Focusing on Aβ load, a fixed effect of baseline age on CL ($F_{dec}(82) = 9.01$, $p_{dec} = 0.004$; $F_{sta}(190) = 18.99$, $p_{sta} < 0.001$) was found in the Aβ-/decrease and stable phases, with younger ages having higher CL values ($\beta_{dec} = -0.49$, $se_{dec} = 0.16$, $\beta_{sta} = -0.53$, $se_{sta} = 0.12$). Additionally, in the Aβ-/stable phase, CN participants displayed higher CL values than CI participants ($F(245) = 4.14$, $p = 0.043$, $\beta = 3.40$, $se = 1.67$). No direct association of baseline age, baseline diagnosis, or *APOE* genotype with Aβ load was observed in any other cluster. The predicted Aβ accumulation difference between *APOE* genotypes was not significant when investigating the phases separately. Trends have been visualized in the Fig. S3. The same results were found when the analyses were repeated in phases based on the lower 20 CL abnormality threshold. We subsequently conducted an exploratory analysis combining the two increasing phases into a high accumulator phase. This analysis displayed a significant interaction of *APOE* genotype and time ($F(95) = 4.40$, $p = 0.039$), however contrary to expectations, with noncarriers displaying higher accumulation than carriers independent of Aβ baseline status ($\beta = 1.14$, $se = 0.55$) (Tables S3 & S4, Fig. 3). In contrast to the whole sample analysis, the three-way interaction between Aβ baseline status, time, and *APOE* genotype was not significant and did not improve the fit. The regression displayed a general difference in accumulation between Aβ+ and Aβ- ($F(102) = 21.11$, $p < 0.001$) with Aβ+ participants demonstrating higher accumulation than Aβ- participants ($\beta = -2.58$, $se = 0.56$). Further, we explored the influence of excluding the Aβ-/decrease cluster from the initial regression due to its potential to represent measurement inaccuracies. That is, all phases except for the Aβ-/decrease phase were analyzed together. Again, the originally observed three-way interaction between Aβ baseline status, *APOE* genotype, and Aβ accumulation was not significant and did not improve the fit anymore. Furthermore, *APOE* genotype displayed no direct effect on Aβ accumulation (Tables S5 & S6), while Aβ+ participants had significantly more accumulation than Aβ- participants ($F(276) = 4.29$, $p = 0.039$, $\beta = -0.81$, $se = 0.39$). In sum, the second analysis part demonstrated clusters with distinctive accumulation patterns. In a high accumulator phase, a difference in Aβ accumulation between *APOE* genotypes was detected with noncarriers demonstrating higher accumulation. Moreover, excluding the Aβ-/decrease individuals from the initial regression altered the relation between *APOE* genotype, Aβ baseline status, and Aβ accumulation.

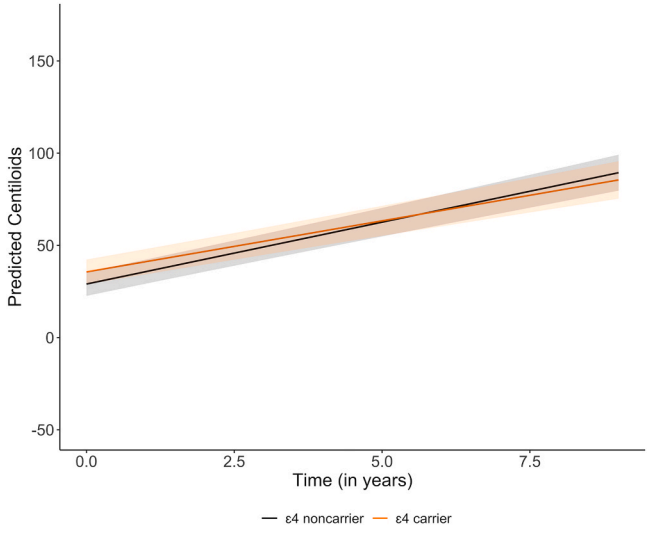

Fig. 3. Model predictions in high accumulator phase. The Aβ increasing clusters presented a significant association of the *APOE* genotype with longitudinal amyloid accumulation. In these clusters ε4 noncarriers had more accumulation than carriers.

Table 3
LME results of cognitive domains.

Cognitive domain	Aβ accumulation phase	Simple time model			Complete model including significant or improving predictors: *Cognitive score ~ Time*E4Carrier + ClinicalGroup + ClinicalGroup:Time + (Time | Patient)*
		β	t	*p*	
Memory	Aβ-/Stable	-0.01	-1.68	0.28	Baseline Clinical Group (Main & Interaction effect)*
	Aβ-/Increase	-0.03	-2.59	0.04	-
	Aβ+/Increase	-0.10	-4.46	<0.001	-
	Aβ+/Stable	-0.13	-7.91	<0.001	Baseline Clinical Group (Main effect)*
	Aβ+/Decrease	-0.12	-7.40	<0.001	Baseline Clinical Group (Main effect)*
Executive function	Aβ-/Stable	-0.01	-1.23	0.67	-
	Aβ-/Increase	-0.02	-2.60	0.03	-
	Aβ+/Increase	-0.06	-2.81	0.03	-
	Aβ+/Stable	-0.08	-5.71	<0.001	-
	Aβ+/Decrease	-0.13	-4.74	0.001	-
Language	Aβ-/Stable	-0.01	-1.85	0.20	Baseline Clinical Group (Main & Interaction effect)*
	Aβ-/Increase	-0.02	-2.48	0.04	*APOE* Genotype (Main effect)°
	Aβ+/Increase	-0.06	-3.18	0.01	-
	Aβ+/Stable	-0.09	-5.77	<0.001	-
	Aβ+/Decrease	-0.10	-4.06	<0.001	Baseline Clinical Group (Main effect)°

*=significant effect and improvement of fit; ° = improvement of fit, but no significance. *p*-values are Bonferroni corrected.

3.3. Cognitive progression in different accumulation phases

We assessed the influence of the Aβ accumulation phase categorization on cognitive decline. Therefore, decline in the memory, executive function, and language domain was tested for each Aβ accumulation phase. Results of all tested linear mixed regression models per cluster can be found in Table 3. We did not include the Aβ-/decrease cluster into this analysis, as we assumed this cluster to reflect measurement inaccuracies. In the Aβ-/stable phase, participants demonstrated no significant change in scores over time for all three domains when time was used as the only predictor. Adding baseline clinical group to the model improved the fit for memory and language and resulted in a significant main and interaction effect with time. That is, in this Aβ-/stable phase, CN participants had significantly higher baseline memory scores ($\beta = 0.32$, se $= 0.10$, $p = 0.004$) and language scores ($\beta = 0.25$, se $= 0.08$, $p = 0.007$) and demonstrated a memory decline ($\beta = -0.04$, se $= 0.01$, $p > 0.001$) and language decline ($\beta = -0.03$, se $= 0.01$, $p = 0.009$) compared to already cognitively impaired individuals that had no decline. For the executive function domain, no such difference was found. In the Aβ-/increase phase, the final models showed that a significant decline in performance was observable for memory ($\beta = -0.03$, se $= 0.01$, $p = 0.039$), executive functions ($\beta = -0.02$, se $= 0.01$, $p = 0.025$), and the language scores ($\beta = -0.02$, se $= 0.01$, $p = 0.039$). Aβ + phases (stable/increase/decrease) demonstrated a significant decline in all domains over time (Table 3). CN participants had significantly higher memory scores in the Aβ+/stable phase ($\beta = 0.43$, se $= 0.13$, $p = 0.003$) and in the Aβ+/decrease phase ($\beta = 1.20$, se $= 0.38$, $p = 0.014$) compared to CI participants. Fig. S4 visualizes the slope per Aβ cluster based on the separate regressions for each cognitive domain using only time. *APOE* genotype showed no significant association with the decline over time in any domain. Repeating the analysis in the Aβ accumulation phases based on the lower 20 CL abnormality threshold offered similar results.

4. Discussion

We examined longitudinal trajectories of amyloid beta deposition in the brain of individuals without dementia using Aβ-PET imaging and follow-ups over 5.27-years. The major goal of our examination was to investigate the *APOE* genotype association with both amyloid beta load and longitudinal amyloid beta accumulation assuming that the latter might be dependent on the specific accumulation phase under investigation. Additionally, we examined the predictive value of these Aβ accumulation phases regarding cognitive decline in the domains of memory, executive function, and language and the respective relation with the *APOE* genotype.

In this study, we first focused on the entire sample irrespective of the accumulation phases. This step aimed at replicating studies that addressed *APOE*'s relation with longitudinal Aβ accumulation (Lim and Mormino, 2017; Lopresti et al., 2020; Resnick et al., 2015) as there exists an ongoing debate about the association between the *APOE* genotype and Aβ accumulation. Previous research has shown mixed results; while some investigations found an influence of *APOE* genotype on longitudinal Aβ accumulation with a trend toward stronger accumulation in cognitively healthy and MCI ε4 carriers (Mishra et al., 2018; Villemagne et al., 2013), others did not observe genotype differences in Aβ accumulation (Lopresti et al., 2020; Resnick et al., 2015). The current investigation extends the previous examinations in several ways, especially by including a longer time interval of on average 5.27 years and by considering Aβ baseline status as direct factor. This extended timeframe provides a more comprehensive view of Aβ accumulation dynamics and by incorporating the Aβ baseline status as a direct factor, our study enhances the understanding of how initial Aβ levels influence subsequent accumulation patterns and interactions. Our first analysis indicated a higher Aβ load in *APOE* ε4 carriers. Moreover, *APOE* genotype and Aβ baseline status displayed an interacting effect on Aβ accumulation. Specifically, *APOE* ε4 carriage seemed to predict higher Aβ accumulation in baseline Aβ normal (Aβ-) individuals. This difference was not observable in Aβ+ individuals. These results replicate a previous observation by Lim and Mormino (2017). The researchers examined FBP data of ADNI participants without dementia. Our study extends their research by considering FBP and PiB data combined with a longer observational period and the consideration of Aβ baseline status as direct factor.

For the second analysis step, we clustered the Aβ trajectories based on their individual progression shapes into distinctive accumulation phases. We were able to extract six phases which comply with the previously proposed model of Aβ progression (Figure 1b) (Jack et al., 2013a,b). Surprisingly, separate analyses in the different accumulation phases did not confirm the previously reported genotype differences in Aβ- individuals. This discrepancy to our initial analysis might be explained by the Aβ-/decrease phase, where a trend towards decreasing Aβ trajectories in ε4 noncarriers was observed. This trend might have influenced the overall results of our first analysis by counterbalancing increasing trajectories observed in Aβ-/increase noncarriers. Notably, the Aβ-/decrease phase might represent measurement noise (e.g., Villain et al., 2012; Villemagne et al., 2013) or other inaccuracies based on age-related changes in off-target retention or cerebral blood flow (Flores et al., 2023; Mattsson et al., 2014; Mino et al., 2017; Tosun et al., 2017). Consequently, we repeated the initial analysis excluding this Aβ-/decrease phase, which altered the three-way interaction between baseline Aβ status, *APOE* genotype, and accumulation nonsignificant. This adjustment might highlight the importance of carefully extracting and potentially excluding these individuals from analyses concerning dynamic Aβ accumulation patterns.

The current investigation additionally observed that when focusing on participants actively accumulating Aβ (summing Aβ- and the Aβ+ increasing phases into a high accumulator phase), ε4 noncarriers exhibited higher accumulation rates than ε4 carriers. This finding might be explained by a leftward shift of the Aβ curve due to the ε4 carrier status and the aspect that Aβ accumulation has been proposed to have an inverted U-shape in relation to Aβ load (Guo et al., 2018; Jack et al., 2013a,b; Knopman et al., 2021), hence, to slow down at higher values (Villemagne et al., 2013). That is, ε4 carriers might have an earlier Aβ accumulation onset but might also demonstrate an earlier stagnation. In line with this interpretation, Koychev et al. (2020) used PiB-PET data and reported that healthy ε4 carriers started to accumulate Aβ at a faster rate around the age of 60 years, whereas noncarriers started to increase their accumulation at the age of 69 years. Other research that aimed to develop models that estimated the onset age of Aβ accumulation suggested that ε4 homozygotes reach an abnormal Aβ status approximately a decade before ε4ε3 heterozygotes and approximately two decades before ε3 homozygotes. The models were based on cognitively healthy, MCI, and AD individuals (Betthauser et al., 2022). Similarly, different work applying an accelerated failure time model in participants along the whole AD continuum reported a 6.1-years leftward shift of the amyloid curve due to *APOE* ε4 (Therneau et al., 2021). Additionally, Jagust et al. (2021) demonstrated that Aβ accumulation begins to slow down 3.8 years after reaching the positivity threshold and before dementia onset in a sample consisting of CN, MCI, and AD participants. Given these previous findings, it might be assumed that the carriers in our data set are already demonstrating a slowing of accumulation, whereas the noncarriers are still at the highest point. Our sample presenting an average age of 72.66 years might thus have missed earlier effects of carriers on accumulation. Together, strong evidence exists suggesting a displacement of timelines between *APOE* genotype groups that influence an earlier onset of accumulation but does not influence the slope.

From a biological perspective, the *APOE* genotype has been observed to be involved in a variety of Aβ related pathological aspects. The presence of an ε4 allele was associated with higher synthesis, greater fibrillization, and less effective inhibition of Aβ aggregation. Mouse models suggest genotype dependent effects on Aβ load which might be due to differential effects on Aβ clearance (Huynh et al., 2017; Zuroff

et al., 2017). Other research proposed *APOE*-expressing microglia to be involved in alterations of early Aβ plaque deposition (e.g., Muth et al., 2019; Parhizkar and Holtzman, 2022; Ulrich et al., 2018). One study observed the ε4 allele to cause an upregulation of phagocytosis of apoptotic cells while downregulating those of Aβ *in vitro* (Muth et al., 2019). The ε4 allele additionally demonstrated an impact on neurons by increasing the release of neurotransmitter and elevating synaptic density (Lin et al., 2018). These findings parallel neuroimaging studies implying a higher metabolic activity in asymptomatic younger ε4 carriers (Filippini et al., 2011; Thambisetty et al., 2010; Wierenga et al., 2013). The higher neuronal activity may be accompanied by higher Aβ levels (Bero et al., 2011; Lin et al., 2018). All of these mechanisms suggest a major *APOE* genotype role in altering the early stages of Aβ pathology (Parhizkar and Holtzman, 2022) and causing a shift in the time course of *APOE* ε4 carriers. Thus, early initiation of therapies directed at attenuating Aβ accumulation is particularly crucial for individuals with the *APOE* ε4 allele. Consequently, ε4 carriers might need to be examined and monitored at an earlier stage than noncarriers.

Last, the influence of the position on the sigmoidal Aβ function on cognition, comprising memory, executive function, and language, was tested. Consistent with other studies, a strong cognitive decline for all domains was predicted in the Aβ+ phases (e.g., Donohue et al., 2017; Insel et al., 2020; Landau et al., 2012; Mormino et al., 2014). In the Aβ-/stable phase, CN participants demonstrated a decrease in memory and language scores, while no further worsening was observable in MCI patients. The executive scores revealed no decline at all in this phase. In the Aβ-/increase phase, all three tested cognitive domains presented general longitudinal decreases. These results support evidence from recent cross-sectional and longitudinal reports suggesting an association between Aβ accumulation and cognitive decline in preclinical participants with normal Aβ levels (Collij et al., 2021; Farrell et al., 2018; Guo et al., 2020; Insel et al., 2020; Landau et al., 2018). Unexpectedly, *APOE* genotype had no relation with the cognitive decline in any phase. The literature of cross-sectional and longitudinal genotype effects on cognition is controversial (O'Donoghue et al., 2018). Some studies observed a stronger cognitive decline in ε4 carriers, especially in the domain of episodic memory (e.g., Andrews et al., 2016; Bretsky et al., 2003; Duchek et al., 2006; Foster et al., 2013); however, other investigations found no such difference (e.g., Batterham et al., 2013; Bunce et al., 2014). Together, the consideration of individual Aβ increase rates, in particular when Aβ levels are still in the normal range, might be of therapeutic relevance and aid clinical trial design. On the one hand, it might help to identify individuals which will display a stable cognitive status over time; on the other hand, it might facilitate the selection of individuals at risk for cognitive decline in an early preclinical stage.

This study has several limitations. Due to the division into distinctive accumulation phases that were theoretically corresponding to the sigmoidal Aβ function, the sample size of each phase was relatively small. The study used data obtained from ADNI and AIBL allowing for a large sample size and a long time interval to be analyzed. However, using a multicenter cohort may introduce several methodological variabilities. Particularly, participants were assessed on different scanner types varying between study centers and across time points. Moreover, Aβ data of two different tracers, PiB and FBP, were used. We tried to reduce intraindividual variability by excluding participants with tracer changes. Using the centiloid method allowed for tracer independent Aβ values (Klunk et al., 2015; Navitsky et al., 2018; Su et al., 2019). However, following the standard centiloid protocol, we did not correct for partial volume effects which might occur due to atrophy especially at older ages and more severe disease stages (Rullmann et al., 2020). A further consideration when applying the centiloid approach might be that this method uses global Aβ values averaged across the brain which we used to examine longitudinal Aβ trajectories and the relation with *APOE*. However, an important aspect might be the regional variation of Aβ progression over time and how *APOE* genotype might affect this accumulation differently depending on the brain area. Future studies considering the regional variation of Aβ progression and *APOE*'s effect are therefore warranted.

5. Conclusion

The purpose of the current study was to examine longitudinal Aβ trajectories and the relation with the *APOE* genotype and cognitive decline. Initially, we were able to replicate previous research that suggested higher accumulation rates of ε4 carriers compared to noncarriers in baseline Aβ normal individuals. However, this observation was mainly due to the inclusion of Aβ normal individuals that displayed decreasing trajectories. Moreover, among actively accumulating individuals, ε4 noncarriers demonstrated higher Aβ increase rates. Thus, our study highlights the importance of identifying individuals in active accumulation phases to accurately understand Aβ dynamics. Additionally, the findings suggest a timeline shift in Aβ accumulation between *APOE* genotypes, which supports the view that therapies aiming at modifying ε4 effects on Aβ need to be initiated very early during the disease process. A further major finding was that cognitive decline could be already predicted in Aβ-/increase phases independent of genotypes. Thus, the general identification of Aβ- individuals with trajectories of rapid Aβ accumulation might aid selecting high-risk participants for cognitive decline, thereby identifying the most eligible candidates for disease-modifying therapies or prevention trials. Future research focusing on different accumulation phases is needed to acquire detailed knowledge and to fully predict which trajectories would benefit most from interventions.

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Andreas Buchmann: Writing – review & editing. **Maha Wybitul:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Anton Gietl:** Writing – review & editing, Resources, Methodology, Conceptualization. **Valerie Treyer:** Writing – review & editing, Resources, Methodology, Conceptualization. **Christoph Hock:** Writing – review & editing, Supervision, Resources, Conceptualization. **Nicolas Langer:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Valerie Treyer reports financial support was provided by Vontobel Foundation. Christoph Hock reports a relationship with Neurimmune that includes: board membership, employment, and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.03.007.

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