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RESEARCH ARTICLE

Amyloid-β, cortical thickness, and subsequent cognitive decline in cognitively normal oldest-old

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Abstract

Objective: To investigate the relationship between amyloid-β (Aβ) deposition and markers of brain structure on cognitive decline in oldest-old individuals with initial normal cognition. **Methods**: We studied cognitive functioning in four domains at baseline and change over time in fifty-seven cognitively intact individuals from the EMIF-AD 90+ study. Predictors were Aβ status determined by [^{18}F]-flutemetamol PET (normal = A$\beta-$ vs. abnormal = Aβ+), cortical thickness in 34 regions and hippocampal volume. Mediation analyses were performed to test whether effects of Aβ on cognitive decline were mediated by atrophy of specific anatomical brain areas. **Results**: Subjects had a mean age of 92.7 $\pm$ 2.9 years, of whom 19 (33%) were Aβ+. Compared to A$\beta-$, Aβ+ individuals showed steeper decline on memory ($\beta \pm$ SE = -0.26 ± 0.09), and processing speed ($\beta \pm$ SE = -0.18 ± 0.08) performance over 1.5 years ($P < 0.05$). Furthermore, medial and lateral temporal lobe atrophy was associated with steeper decline in memory and language across individuals. Mediation analyses revealed that part of the memory decline observed in Aβ+ individuals was mediated through parahippocampal atrophy. **Interpretation**: These results show that Aβ abnormality even in the oldest old with initially normal cognition is not part of normal aging, but is associated with a decline in cognitive functioning. Other pathologies may also contribute to decline in the oldest old as cortical thickness predicted cognitive decline similarly in individuals with and without Aβ pathology.

Introduction

Even tough amyloid-β (Aβ) plaques are considered the pathological hallmark of Alzheimer's disease (AD),[1,2] Aβ pathology is observed frequently in cognitively normal (CN) adults. Furthermore, postmortem and in vivo studies have shown that the prevalence of abnormal Aβ in CN individuals increases with age from 16% at the age of 60, up to 44% of CNs in their 90's,[3,4] illustrative of the complex relationship of Aβ deposition with cognitive functioning. While previous studies have reported that Aβ pathology in CN individuals is related to subtle cognitive deficits,[5–7] and an increased risk for cognitive decline and dementia.[8–10] The relationship of Aβ pathology and cognitive decline in the oldest-old, that is, individuals of 90 years and older, is however less clear. Recent

longitudinal studies in the oldest-old suggest a steeper cognitive decline in non-demented Aβ+ compared to Aβ− individuals aged older than 90,[11–13] although one study did not find such an association.[14] Another driver of cognitive decline is cortical atrophy, in particular medial temporal lobe atrophy, which has been observed frequently in the oldest-old as well.[11,13] Medial temporal lobe atrophy is considered a key feature of Aβ pathology, but in the oldest-old other causes of medial temporal lobe atrophy are common, such as hippocampal sclerosis, cerebrovascular disease, TDP-43 pathology, and aging-related tau astrogliopathy (ARTAG).[15,16] It still remains unclear how abnormal Aβ is related to cognitive decline in cognitively normal individuals over age 90 and to what extent such effects are mediated by cortical atrophy. In this study, we investigated if Aβ pathology is associated with cognitive decline in CN oldest-old. Additionally, where this association was present, we further investigated whether the effect of Aβ on cognitive decline was independent or mediated by cortical thickness.

Methods

Participants

Individuals with normal cognition who underwent an amyloid positron emission tomography (PET) were selected from the Innovative Medicine Initiative European Medical Information Framework for AD (EMIF-AD) 90+ Study conducted at the Amsterdam University Medical Center (UMC). Individuals were recruited through general practitioners or via advertisements, see Legdeur et al. (2018)[17] for detailed description of this cohort and overall study design. Normal cognition was defined as a Clinical Dementia Rating (CDR) score of zero, and a Mini-Mental State Examination (MMSE) score of ≥26.

MRI acquisition and processing

3D-T1 weighted and 3D sagittal fluid-attenuated inversion recovery (FLAIR) images were acquired on a Philips 3T Achieva scanner using an 8-channel head coil and a sagittal turbo gradient-echo sequence (T1: 1.00 mm^3 isotropic voxels, repetition time (TR) = 7.9 msec, echo time (TE) = 4.5 msec, flip angle (FA) = 8 degrees; FLAIR: 1.12 mm^3 isotropic voxels, TR = 4800 msec, TE = 279 msec, and inversion time = 1650 msec). Cortical thickness was estimated from 3D T1 MRI using FreeSurfer (v5.3; https://surfer.nmr.mgh.harvard.edu). Non-brain tissue was removed, followed by transformation to MNI space, segmentation and creation of cortical surface meshes.[18] The cortical thickness values were summarized in anatomical regions according to the Desikan–Killiany atlas implemented in FreeSurfer. To reduce dimensionality of the data we averaged cortical thickness values for each brain region across hemispheres, resulting in 34 cortical regions of interest (ROIs). Hippocampal volume was obtained with FMRIB's Software Library (FSL) FIRST (v5.0.1), as reported previously in Patenaude et al (2011).[19] White matter hyperintensities (WMH) segmentation was performed using a previously established algorithm based on a three-level Gaussian mixture model to model healthy tissues and lesions.[20] Because of a skewed distribution, WMH volume was log transformed. Resulting images were visually checked for quality, and data from four subjects had to be excluded due to gross registration or segmentation errors.

Amyloid PET

Dynamic [^{18}F] flutemetamol amyloid-PET scans were performed on a Philips Ingenuity TF PET-MRI scanner (Philips Medical Systems, Cleveland, OH, USA). The tracer was produced by General Electric (GE) Healthcare at the Cyclotron Research Center of the University of Liège (Liège, Belgium). First, a 30 min dynamic emission scan was started simultaneously with a bolus intravenous injection of 185 MBq [^{18}F] flutemetamol. The second part of the scan was performed from 90 to 110 min post injection. Immediately prior to each part of the PET scan a dedicated MR sequence was performed for attenuation correction. During scanning, the head was immobilized to reduce movement artifacts. Data from the two scan parts were coregistered and combined into a single 4D image using VINCI Software 2.56 (https://vinci.sf.mpg.de) and in-house built software for decay correction of the second part. Parametric nondisplaceable binding potential (BP_{ND}) images were generated from the entire image set using the receptor parametric mapping and cerebellar gray matter as reference tissue.[21,22] Global cortical BP_{ND} was calculated as the volume weighted average BP_{ND} of 22 regions located within frontal, parietal, temporal, posterior cingulate, and medial temporal lobes.[23] Dynamic BP_{ND} images were used for visual assessment of [^{18}F] flutemetamol as negative (Aβ−) or positive (Aβ+) by the consensus of three readers, who had been trained according to the manufacturers image interpretation methodology and were blinded to the clinical and demographic data.[24]

Neuropsychological assessment

A trained neuropsychologist administered cognitive tests within the following cognitive domains: memory, language, processing speed, and executive functioning. For each cognitive domain, tests were combined into a

composite score. For memory we included the CERAD 10 words test (delayed recall),[25] the Wechsler Logical Memory Test (delayed recall),[26] the Rey Complex Figure Test (delayed copy),[27] and the Visual Association Test A.[28] For language, we used the 2 min Animal Fluency score,[29] and the Graded Naming Test.[30] For processing speed we included the Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[31] the Trail Making Test A,[32] and the WAIS-III Digit span forward.[33] For executive functioning we included the Trail Making Test B[32], the WAIS-III Digit span backward,[33] Letter Fluency (one minute per letter, three letters),[29] and the Clock drawing test.[34] For a subset (n = 43; 75.4%), neuropsychological tests were repeated once circa 1.5 years (1.0–2.8 y) after baseline assessment. For each test, we calculated Z-scores using the baseline mean and standard deviation of the total group. We created composite scores by averaging test Z-scores for each cognitive domain. Trail Making Test A & B scores were inverted so that for all cognitive tests lower scores indicated worse performance.

APOE genotyping

For all participants, blood samples were collected for DNA analysis. DNA was extracted using the QIAamp® DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany). Apolipoprotein e (APOE) genotype was determined using TaqMan assays (ThermoFisher Scientific, Foster City, CA, USA) on a QuantStudio-12K-Flex system. We classified individuals as APOE ε4 carriers or non-carriers according to their genotype status at rs429358. For three participants, APOE data was missing.

Statistical analysis

We compared demographical characteristics of the Aβ− and Aβ+ groups using X^2 tests for categorical variables and ANOVA for continuous variables. We ran four linear mixed models (LMM) with subject specific intercepts, and fixed slopes: Model 1 tested the effect of baseline Aβ status on cognitive decline with cognitive domain score as the outcome *(Model 1: Cognition ~ Time*Aβ)*. Model 2 tested the effect of Aβ status on cortical thickness of all FreeSurfer ROIs and on hippocampal volume *(Model 2: ROI ~ Aβ)*. Model 3 tested the effect of cortical thickness and hippocampal volume on cognitive decline *(Model 3: Cognition ~ Time*ROI)*. Model 4 tested the combined the effects of Aβ pathology, cortical thickness, and their interactions with each other on cognitive decline *(Model 4: Cognition ~ Time*ROI*Aβ)*. Interaction terms were removed when not significant ($P > 0.05$). All models included sex, education, WMH, and age as covariates, and for hippocampal volume, total intracranial volume was added as a covariate. LMM were corrected for multiple testing using a false discovery rate (FDR) procedure.[35] Effects that did not survive FDR correction are shown as $P_{uncorrected.}$

When Aβ status was significantly associated with both cognitive decline and thickness and/or volume in certain ROIs, we performed causal mediation analyses to assess whether the association between Aβ status and cognitive decline was mediated by grey matter brain atrophy. Mediation analyses provides us with a better understanding of the complex pathways of Aβ deposition toward cognitive decline. To estimate the average causal mediation effect three linear models were fitted: the first model has cognitive decline as the outcome of interest as the dependent variable and thickness/volume as predictor, while controlling for Aβ; the second model that has the mediator variable thickness/volume as the dependent variable and Aβ status as predictor; the third model averages direct and indirect effects of Aβ status on cognitive decline and are estimated based on the quasi-Bayesian Monte Carlo approximation (1000 simulations). Mediation analyses was performed only in individuals who had repeated assessment of cognitive function (n = 43). Finally, we further investigated the effect of other factors known to be associated with cognitive decline, including APOE ε4 genotype, education, and vascular damage. Statistical analyses were performed in R (v4.0.2) using the "lme4" package (v1.1), "mediation" package (v4.5),[36] and group estimates were obtained using the "emmeans" package (v1.5).

Results

Demographics

Participants (n = 57) had an average age of 92.7 years, ranging from 88 to 102 years, were more often female (63%), and 33% had a visually rated abnormal amyloid PET scan (Table 1). The Aβ+ (n = 19) and Aβ− (n = 38) groups did not differ in age, sex, APOE ε4 carriership, vascular burden, or years of education. Moreover the two groups did not differ in availability of follow-up data, nor the time between test assessments. More years of education was associated with better performance on tests related to processing speed, executive functioning, and less steep decline in memory and executive functioning over time ($p_{FDR} < 0.05$; Table S3). Higher WMH volumes were associated with worse performance on language, processing speed, and faster decline on memory ($p_{FDR} < 0.05$). No association between age, sex, or APOE ε4 carriership and cognitive performance or cognitive decline was observed.

Table 1. Subject characteristics according to Aβ status.

	A$\beta-$ (n = 38)	A$\beta+$ (n = 19)	Total (n = 57)	*P*-value
Sex, f (%)	23 (60.5)	13 (68.4)	36 (63.2)	0.771
Age, (y)	92.51 (3.13)	93.00 (2.56)	92.67 (2.94)	0.554
Education, (y)	12.78 (4.53)	11.50 (4.30)	12.35 (4.46)	0.312
Aβ load (BPND)	0.15 (0.12)	0.56 (0.28)	0.29 (0.27)	<0.001*
APOEε4 allele carrier (%)	2 (5.7)	3 (16.7)	5 (9.4)	0.426
WMH volume	9.59 (0.89)	9.71 (0.94)	9.63 (0.90)	0.635
Time between BL and FU, (y)	1.57 (0.57)	1.82 (0.64)	1.66 (0.60)	0.191
FU availability (%)	27 (71.1)	16 (84.2)	43 (75.4)	0.446
Passed away at FU (%)	10 (26.3)	2 (10.5)	12 (21.1)	0.301

Data are presented as mean (SD), or n (%). Aβ, amyloid-β; BPND, nondisplaceable binding potential; APOE, apolipoprotein e; WMH, White matter hyperintensities (log); BL, baseline; FU, follow-up.
*$P < 0.05$.

Associations of amyloid status and cortical thickness with cognitive decline

First, we tested the effects of Aβ status on cognitive decline over time (Model 1). At baseline, Aβ+ individuals tended to show worse performance on memory and language, although this did not reach significance (Fig. 1). Over time, Aβ+ individuals showed steeper decline in memory ($\beta \pm SE = -0.26 \pm 0.09$), and processing speed ($\beta \pm SE = -0.18 \pm 0.08$) than A$\beta-$ individuals ($p_{uncorrected} < 0.05$; Fig. 1). Also, a steeper decline in language performance ($\beta \pm SE = -0.15 \pm 0.08$) was observed at trend level (Table S1a).

Next, we tested effects of Aβ status on cortical thickness (Model 2). Individuals with Aβ+ showed thinner parahippocampal cortex and a thinner medial orbitofrontal cortex compared to A$\beta-$ individuals ($p_{uncorrected} < 0.05$; Fig. 2). Hippocampal volume did not differ between A$\beta-$ and Aβ+ individuals (Table S1c). Then we studied effects of cortical thickness on cognitive decline over time (Model 3). A thinner cortex in predominantly anterior cingulate and multiple lateral temporal regions, including the entorhinal, parahippocampal, fusiform, and superior temporal cortex, was associated with a steeper decline in memory ($p_{FDR} < 0.05$; Fig. 3), with no interaction effects of Aβ status. In addition, smaller hippocampal volume was associated with worse memory and processing speed performance at baseline and a faster decline in memory over time ($p_{uncorrected} < 0.05$), independent of Aβ status. Moreover thinner superior frontal and lateral temporal regions, including the fusiform, inferior and superior temporal, posterior cingulate, and supramarginal cortex, were associated with a steeper decline in language performance ($p_{uncorrected} < .05$), of which only the posterior cingulate cortex survived the correction for multiple comparisons. Additionally, a few cortical regions showed that thicker cortex was associated with a steeper decline in executive functioning ($p_{\text{uncorrected}} < 0.05$; Fig. 3).

Finally, we examined the interactions of Aβ status and brain structure measures on the rate of cognitive decline (Model 4). Aβ+ individuals with a thinner parahippocampal and a thicker pars triangularis ($\beta \pm SE = 1.90 \pm 0.91$; $\beta \pm SE = 4.04 \pm 1.87$; $p_{uncorrected} < 0.05$; Fig. 3) showed worse language performance. While also thinner postcentral and superior parietal cortex ($\beta \pm SE = 1.01 \pm 0.37$; $\beta \pm SE = 0.94 \pm 0.36$; $p_{uncorrected} < 0.05$) was associated with faster language decline in A$\beta-$ individuals. Furthermore, we observed that thicker cortex in occipital and parietal regions was associated with slower processing speed and steeper decline over time in Aβ+ individuals ($p_{uncorrected} < 0.05$; Fig. 3; see Table S1 for full LMM results). We repeated all analyses excluding n = 12 individuals that passed away before the second neuropsychological assessment took place, and observed overall largely similar results (see Table S2).

Mediation analyses

Next, we investigated whether the effect of Aβ pathology on cognitive performance was mediated by cortical thickness (indirect effect) or not (independent effect) for cortical regions that were associated with abnormal Aβ (i.e., parahippocampal gyrus and medial orbitofrontal cortex). Memory decline associated with Aβ+ was fully mediated by parahippocampal thinning (36.4%; $P < 0.05$; Fig. 4). Decline in language performance associated with Aβ+ was partially mediated by parahippocampal thinning (21.6%; $P < 0.05$), and partially independent (78.4% $P < 0.05$) after controlling for the presence of parahippocampal atrophy. The effect of Aβ on decline in processing speed, and executive functioning were independent of parahippocampal thickness. Moreover Aβ associated cognitive decline was independent of medial orbitofrontal thickness for all cognitive domains ($P < 0.05$; Fig. 4).

Discussion

In this study of oldest-old with initially intact cognition, we found that abnormal Aβ was associated with steeper decline in memory and processing speed performance over 1.5 years. Our findings support the notion that both Aβ pathology and brain atrophy have detrimental effects on cognitive functioning among cognitively normal individuals that are separate from normal ageing. These

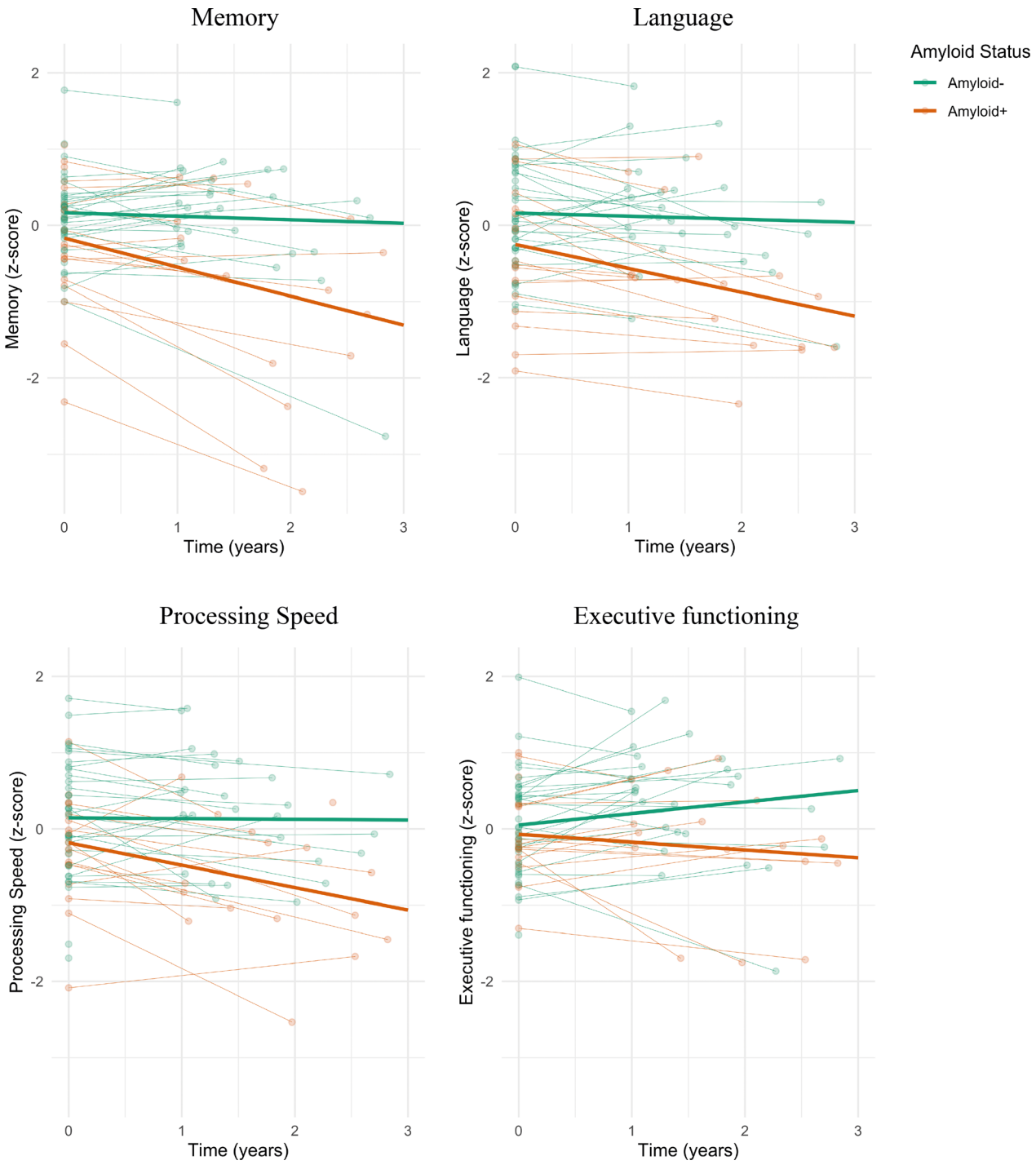

Figure 1. Cognitive performance over time in relation to Aβ status. Spaghetti plots showing individual longitudinal change on memory, language, processing speed, and executive performance according to Aβ status (Amyloid- is normal Aβ; Amyloid+ is abnormal Aβ). All scores were *z*-scored and for processing speed and executive functioning inversed such that lower scores indicate worse impairment.

results suggest that Aβ abnormality is indicative of an neurodegenerative process, that also in the oldest-old with apparent high reserve and maintenance mechanisms lead to cognitive decline. In addition, non-Aβ pathologies may also contribute to decline in the oldest-old as a thinner medial and lateral temporal cortex was related to

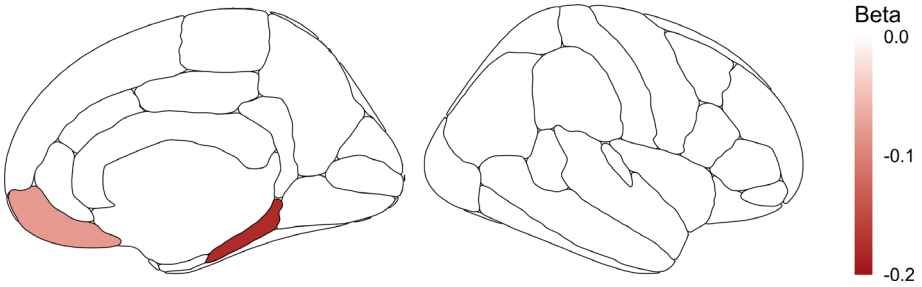

Figure 2. Amyloid associations with regional cortical thickness. Beta's are provided for regions with thinner cortex in abnormal Aβ individuals compared to normal Aβ individuals at $p_{uncorrected} < 0.05$.

subsequent decline in memory and language irrespective of Aβ pathology, indicating that other, possibly Aβ independent pathological processes might also be involved in cognitive decline in the oldest-old.

Numerous studies have reported on the role of Aβ pathology in very early cognitive decline,[37–39] and we further extend on those findings by showing that the detrimental effect of Aβ is also present in nonagenarians with initially intact cognition. Our baseline results are in line with other cross-sectional data showing only a subtle effect of Aβ pathology in preclinical AD on cognition,[6,7,40] consistent with the hypothesis that changes in cognition occur relatively late in the AD pathophysiological cascade. Over time, the differences between Aβ+ and Aβ− individuals became larger, as the Aβ+ subjects showed steeper decline on memory as reported previously,[41,42] and also in the processing speed domain.

Furthermore, at baseline Aβ+ individuals showed thinner cortex in parahippocampal and orbitofrontal regions compared to Aβ−, consistent with other work in CN individuals demonstrating a relationship between Aβ and reduced grey matter.[43–46] However, while previously hippocampal atrophy has been closely related to memory functioning and shown to be a strong and early predictor of conversion to dementia,[47–49] we observed no differences between Aβ+ and Aβ− individuals in hippocampal volume. Possibly, other pathological factors, such as hippocampal sclerosis, TDP-43 pathology, ARTAG, argyrophilic grain disease (AGD), primary age-related tauopathy (PART), and cerebrovascular disease, may contribute to atrophy in these regions, which at old ages become increasingly more common.[15,16,50] Such pathologies may also explain our observation that thinner medial and lateral temporal cortex was associated with subsequent decline in memory and language regardless of Aβ status. Associations of decreased gray matter volume in temporal, frontal, and parietal regions with progression to dementia have been demonstrated in individuals without Aβ.[51,52] Selective sparing of these cortical regions, most notably the anterior cingulate cortex and medial temporal lobe, is frequently reported in superagers compared to age-matched controls and has been associated with resilience to cognitive decline.[53–55] Whether the oldest-old with good cognitive health in the present study are protected by relatively preserved cortical regions is unknown from the present analyses without a control group, however the anterior cingulate and medial temporal thickness were still negatively associated with cognition.

Mediation analyses indicated that cortical regions that were associated with abnormal Aβ (i.e., parahippocampal gyrus and medial orbitofrontal cortex) partly mediated the effects of Aβ on downstream memory and language decline. Aβ no longer had a significant association with memory performance over time when parahippocampal thickness was included in the mediation model, supporting that the structural integrity of the parahippocampal gyrus is important for memory functioning.[56,57] A finding that might be related to the commonly observed neurofibrillary tangle pathology in the medial temporal lobe in CN adults.[58] No significant mediation of cortical thickness was observed for the other cognitive domains, indicative of a direct effect of Aβ pathology on cognitive decline.

Another finding we observed, which did not survive correction for multiple comparisons, was that thicker parietal cortices in Aβ+ individuals were associated steeper decline in processing speed. This finding was unexpected, as usually cortical thinning is a sign of neuronal loss. It is unclear what such thicker cortex may reflect. Possibly, as this effect was only observed in abnormal Aβ, it might reflect a tissue reactive response to Aβ pathology, as previous studies have shown a positive correlation of microglial activation and Aβ deposition.[59] Microglial activation in preclinical disease stages has been associated with initially preserved or increased brain volume.[60,61] Still, it has to be noted that the number of Aβ+ subjects in this study was small, and requires replication in larger samples. Further repeated MRI studies are needed to investigate whether these brain areas may show thinning at a later point in time.

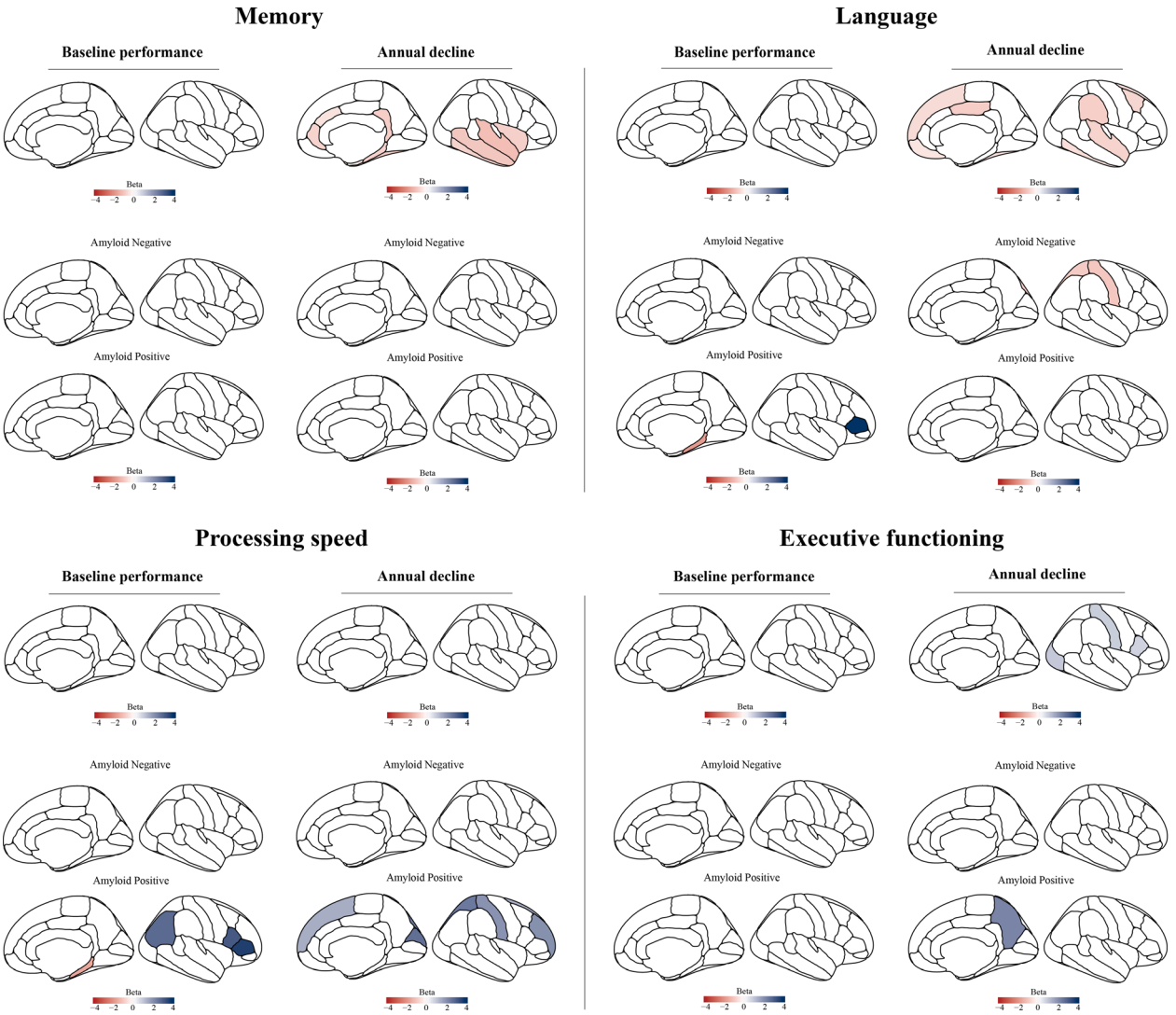

Figure 3. Associations of cortical thickness with baseline and decline in cognitive functioning, by Aβ status. Effect of cortical thickness on baseline (left) and annual change (right) on memory, language, processing speed, and executive functioning across all subjects and by Aβ status. Top left: thinner caudal* and rostral* anterior cingulate, entorhinal*, fusiform*, inferior, superior* and middle* temporal, insula*, isthmus cingulate, parahippocampal*, and temporal pole* was associated with a faster decline in memory. Top right: thinner caudal middle frontal, entorhinal, fusiform, inferior and superior temporal, medial orbitofrontal, posterior cingulate*, superior frontal, and supramarginal cortex was associated with faster decline in language. Aβ+ individuals with thinner pars triangularis and parahippocampal cortex showed worse language performance compared to Aβ− individuals. Aβ− individuals with thinner postcentral and a superior parietal cortex showed faster decline in language performance compared to Aβ+ individuals. Bottom left: Aβ+ individuals with thinner parahippocampal and a thicker inferior parietal, pars triangularis, pars opercularis showed worse processing speed performance compared to Aβ− individuals. Aβ+ individuals with thicker cuneus, frontal pole, postcentral, rostral middle frontal, superior frontal, and superior parietal cortex showed a faster decline on processing speed compared to Aβ− individuals. Bottom right: thicker lateral occipital, pars opercularis, and postcentral regions were associated with faster decline in executive functioning. Aβ+ individuals with thicker precuneus showed a faster decline in executive functioning compared to Aβ− individuals. Beta estimates in red indicate thinner cortex is associated with steeper decline on cognitive test score, blue indicates a thicker cortex is associated with steeper decline on cognitive test score. Data are presented for regions significant with an uncorrected *P*-value < 0.05. *Indicates region significant at $p_{FDR} < 0.05$.

Furthermore, we investigated the influence of APOE genotype on cognitive decline, which is considered the major genetic risk factor for sporadic AD.[62] Carriership of the ε4 allele has been associated with the presence and lower age of onset of Aβ deposits, and Aβ−associated cognitive decline.[3,63] The underrepresentation of ε4-

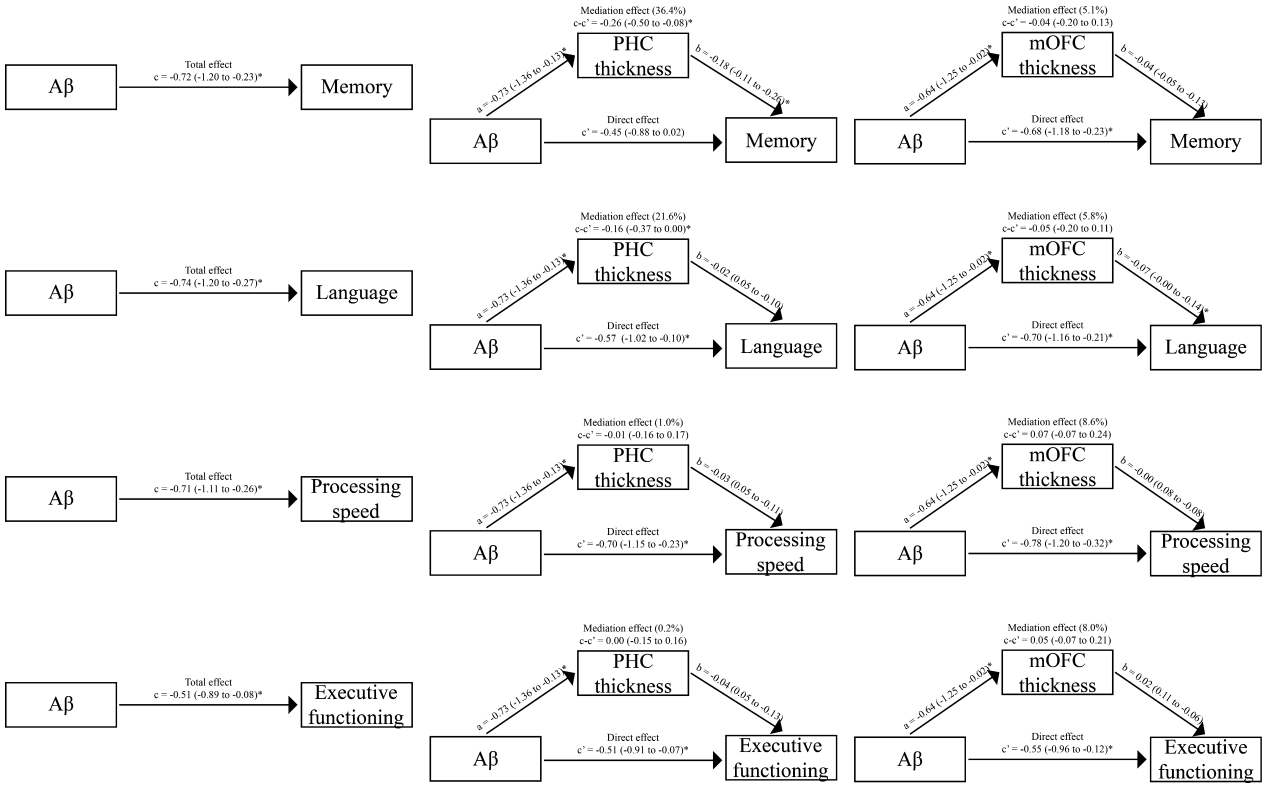

Figure 4. Mediation analysis showing how cortical thinning mediates the effect of Aβ on longitudinal decline in cognitive functioning. The total effect of Aβ on memory, language, processing speed, and executive functioning over time (left). Mediation effect of Aβ trough PHC thickness on memory, language, processing speed, and executive functioning over time (middle). Mediation effect of Aβ trough mOFC thickness on memory, language, processing speed, and executive functioning over time (right). The figure shows regression coefficients with a 95% confidence interval. (A) the effect of Aβ on cortical thickness; (B) the effect of cortical thickness on cognitive decline when controlling for Aβ; c, the total effect of Aβ on cognitive decline (without controlling for mediation effects); C', the direct effect of Aβ on cognitive decline when adjusting for mediation; C-C', the mediation effect. *$P < 0.05$; Aβ, amyloid-beta; PHC, parahippocampal cortex; mOFC, medial orbitofrontal cortex.

carriers in our sample (9.4%), might have contributed to the intact cognition at a very high age in these individuals, and to the absence of an association between APOEε4 carriership and cognitive decline as well. An interesting next step may lie in investigating factors associated with cognitive resilience among the oldest-old who are APOE ε4 carriers.

There are some limitations to our study. Subjects only underwent an MRI and PET scan at baseline, and cognitive decline was based on cognitive assessments at two time points on average 1.5 years apart. Future studies with longer follow-up will aid in determining the temporal ordering of the changes in brain structure and cognitive impairments. Also, the relatively small number of individuals with abnormal amyloid might have resulted in limited statistical power to detect differences that are expected to be subtle in individuals who have initially intact cognition, which is also reflected by the notion that only a few relationships survived correction for multiple testing, and uncorrected results should be interpreted with caution. Furthermore, information on tau levels was unavailable in our sample, and so, it remains unknown to what extent effects of Aβ on cortical thinning and cognitive decline was influenced by tau pathology. Previous studies suggest that the presence of abnormal tau biomarkers, the other pathological hallmark of AD, is related to worse cognitive functioning in the presence of Aβ,[8] and increases with age.[4,64] Therefore, future studies measuring tau pathology using CSF or PET in this age group could contribute to a better understanding of the complex Aβ and tau interaction, and their associations with cognition. Strengths of our study include the extensive phenotyping of a longitudinal cohort of oldest-old individuals with maintained cognitive health.

In conclusion, our findings contribute to our understanding of the role of Aβ deposition on cognitive decline in the oldest-old, and suggest that also at very high ages Aβ abnormality is not benign.

Acknowledgments

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Conflict of Interest

Nothing to report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1A. Baseline and annual change effect of Aβ status on cognitive functioning.
Table S1B. Cortical thickness (mm) according to amyloid status.
Table S1C. Hippocampal volume according to amyloid status.
Table S1D. Associations of cortical thickness with baseline and decline on memory performance by Aβ status.
Table S1E. Associations of hippocampal volume with baseline and decline on memory performance by Aβ status.
Table S1F. Associations of cortical thickness with baseline and decline on language performance by Aβ status.
Table S1G. Associations of hippocampal volume with baseline and decline on language performance by Aβ status.
Table S1H. Associations of cortical thickness with baseline and decline on processing speed performance by Aβ status.
Table S1I. Associations of hippocampal volume with baseline and decline on processing speed performance by Aβ status.
Table S1J. Associations of cortical thickness with baseline and decline on executive functioning performance by Aβ status.
Table S1K. Associations of hippocampal volume with baseline and decline on executive functioning performance by Aβ status.
Table S2A. Baseline and annual change effect of Aβ status on cognitive functioning in a subset without terminal decline.
Table S2B. Cortical thickness (mm) according to amyloid status in a subset without terminal decline.
Table S2C. Hippocampal volume according to amyloid status in a subset without terminal decline.
Table S2D. Associations of cortical thickness with baseline and decline on memory performance by Aβ status in a subset without terminal decline.
Table S2E. Associations of hippocampal volume with baseline and decline on memory performance by Aβ status in a subset without terminal decline.
Table S2F. Associations of cortical thickness with baseline and decline on language performance by Aβ status in a subset without terminal decline.
Table S2G. Associations of hippocampal volume with baseline and decline on language performance by Aβ status in a subset without terminal decline.
Table S2H. Associations of cortical thickness with baseline and decline on processing speed performance by Aβ status in a subset without terminal decline.
Table S2I. Associations of hippocampal volume with baseline and decline on processing speed performance by Aβ status in a subset without terminal decline.
Table S2J. Associations of cortical thickness with baseline and decline on executive functioning performance by Aβ status in a subset without terminal decline.
Table S2K. Associations of hippocampal volume with baseline and decline on executive functioning performance by Aβ status in a subset without terminal decline.
Table S3. Baseline and annual change of other effects on cognitive functioning.

