AGE INCREASES RATE OF Aß AND ε4 RELATED MEMORY DECLINE IN PRECLINICAL ALZHEIMER'S DISEASE

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Introduction

Older age, high amyloid (Aβ+) and the apolipoprotein E (APOE) ε4 allele are risk factors for Alzheimer's disease (AD). However, the extent to which increasing age is related to memory decline in the presence of Aβ+ and ε4 is not understood fully. We aimed to determine the effect of age, Aβ+ and ε4 on memory decline in a large group of older adults who did not meet clinical criteria for AD dementia.

Methods

Sample: Non-demented older adults (n=485) underwent Aβ imaging, and APOE genotyping at a single timepoint, and completed memory assessments at baseline 18-, 36-, 54- and 72- month assessments

Table 1: Demographic characteristics of CN older adults

	Aβ- (n=345)	Aβ+ ε4- (n=60)	Aβ+ ε4 (n=80)	p
N (%) female	190 (55%)	27 (45%)	47 (59%)	.245
Age	70.40 (6.33)	77.69 (7.30)	74.08 (6.99)	.000
Premorbid IQ	108.22 (7.11)	110.60 (7.46)	108.18 (8.02)	.062
GDS	0.97 (1.42)	0.77 (1.17)	1.11 (1.25)	.377
BeCKeT	1.22 (0.28)	2.05 (0.38)	1.80 (0.45)	.000
Scan time	2.16 (1.78)	1.68 (2.09)	1.03 (1.83)	.000
CDR	0.05 (0.16)	0.17 (0.25)	0.19 (0.25)	.000
CDR SOB	0.09 (0.29)	0.23 (0.41)	0.44 (0.76)	.000
MMSE	28.86 (1.35)	28.42 (1.78)	28.00 (1.87)	.000

Biomarkers

Aβ imaging with positron emission tomography (PET) was conducted using one of three radioligands - Pittsburgh Compound B (PiB), florbetapir or flutemetamol. A linear regression transformation was applied to the standardized uptake value ratio (SUVR) for each Aβ tracer to transform it into a "PiB-referenced" SUVR unit.8 These were termed BeCKeT (Before the Centiloid Kernel Transformation).8 A BeCKeT threshold of ≥1.5 was used to classify Aβ+. An 80ml blood sample was taken from each participant at baseline, a sample of which was forwarded for APOE genotyping.

Cognitive endpoint

An episodic memory composite score was computed by averaging standardized scores of the California Verbal Learning Test, Second Edition delayed recall, Logical Memory delayed recall and Cogstate One Card Learning Task.

Methods (continued)

Data analyses

The extent to which age accelerated memory decline in each Aβ/ε4 group was determined using a mixed effects model with an unstructured covariance matrix. In this model, age was defined as a continuous time-dependent variable and group (Aβ-, Aβ+ε4+, Aβ+ ε4-) defined as a fixed factor. Following Caselli and colleagues,6 the relationship between memory decline and age was fitted to a quadratic model although goodness of fit for this model was challenged by determining whether linear or cubic models improved variance explained (Table 2). Clinical or demographic measures that differed between groups were added to the model (Table 1). For each group, model-estimated equations were plotted to obtain curves of best fit.

Table 2: Comparison of model fits for AB related change over time in episodic memory (note lower -2LL values are better)

Model	-2 LL	df	Model Fit
Linear	3278.4	19	$\chi^2 = 64.3$, $p < .0001$
Quadratic	3214.1	20	
Cubic	3257.9	21	

Curve fitting analysis indicated that the quadratic function provided the best fit of relationships between Aβ, ApoE4 and episodic memory when age was taken into account. The quadratic function is shown in Table 3. This function was then applied to data for each study group to allow estimation of characteristics of each function (Table 3).

Table 3: Characteristics of functions derived from quadratic model for study groups

Group	β1	β2	c(intercept)	Quadratic equation
Aβ-	0.197	-0.00125	-7.573	c + (b1*age) + (b2(age*age))
Aβ+ ε4-	0.4064	-0.00293	-14.0473	
Aβ+ ε4+	0.4211	-0.00324	-13.7926	

Results

Modelled curves were developed for the quadratic function describing the relationship between age and episodic memory for each of the study groups. These are shown in Figure 1.

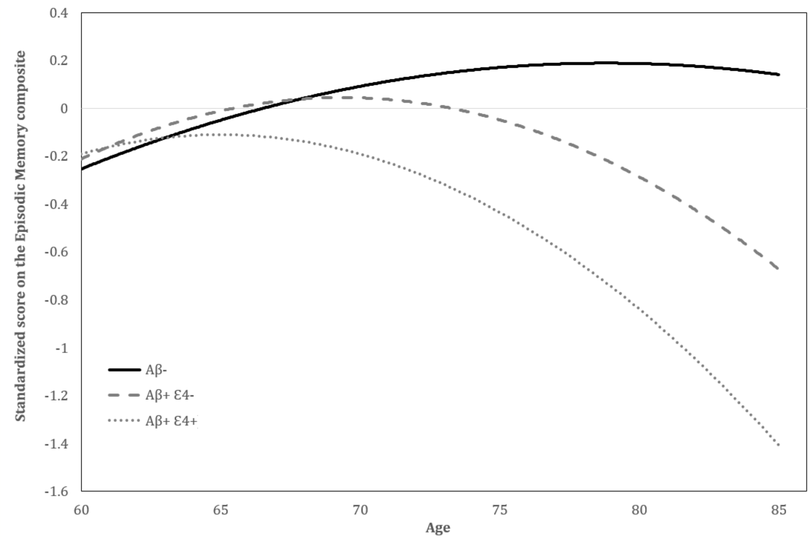

Fig 1: Curves describing rate of decline in episodic memory in amyloid positive (Aβ+) and amyloid negative (Aβ-) cognitively normal older adults who do (E4+) and not (E4-) carry ApoE4.

Conclusion

The longitudinal effect of age on memory was greater in Aβ+ ε4 carriers than in Aβ+ ε4 non-carriers, which was in turn greater than in Aβ- individuals. Estimates of infection points indicated that decline in episodic memory began at an earlier age in Aβ+ ε4 carriers (65 years) than in Aβ+ ε4 non-carriers (70 years) and Aβ- individuals (79 years).

The results of this study are consistent with those from previous studies showing that in cognitively normal older adults Aβ+ and ε4 combine to influence memory decline. The current results extend these findings by showing that show that Aβ+ related memory decline accelerates with increasing age and that the age and Aβ related acceleration in episodic decline is moderated further by carriage of the ApoeE4 allele. The estimates provided can be used to determine the risk of memory decline from Aβ+ and ε4 at each age.