The effect of APOE ε4 status on subregional basal forebrain atrophy in Alzheimer's disease

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Objective **To investigate the effects of APOE ε4 carriage on rates of volume loss in basal forebrain (BF) subregions among older individuals.**

Dysfunction of the cholinergic BF system and deposition of amyloid-β (Aβ) are early pathological features in Alzheimer's disease (AD). The Apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor for late-onset AD and exacerbates Aβ accumulation and cognitive decline.

Methods

The BF subregional and hippocampal volumes were quantified from MRIs of **516 participants from the Australian Imaging, Biomarker and Lifestyle (AIBL) study** (age = 73.0 ± 6.2, 53.9% female, 33.7% ε4 carriers), who completed Aβ PET imaging and longitudinal structural MRI (follow-up over 5.0 ± 3.1 years). Aβ load was quantified in Centiloid (CL) on PET using CapAIBL [1] and Aβ+ was defined as CL > 20.

Participants were grouped according to the presence of cognitive impairment (CU, CI) and Aβ status (Aβ-, Aβ+) as summarised in Table 1. The CI Aβ- group (N = 41) was excluded from the analysis.

Linear mixed-effects models (LMM) were used to assess the differences of longitudinal volumetric changes in the BF subregions (Ch4p: the posterior nucleus basalis of Meynert, Ch1/Ch2: the medial septum and vertical limb of the diagonal band) and hippocampus between non-ε4 and ε4 carriers across different groups.

Table 1: Baseline cohort characteristics.

	CU Aβ-		CU Aβ+		CI Aβ+	
	Non-ε4	ε4	Non-ε4	ε4	Non-ε4	ε4
No. of participants	231	57	50	51	27	59
Baseline age (years)	72.3 ± 5.7	68.5 ± 4.6	76.5 ± 6.1	73.8 ± 6.2	73.8 ± 7.3	75.0 ± 5.8
Follow-up (years)	5.5 ± 3.1	6.5 ± 2.9	4.4 ± 2.8	4.7 ± 3.3	3.5 ± 2.3	3.1 ± 2.0
Sex (F [%])	138 [59.7]	33 [57.9]	26 [52.0]	25 [49.0]	14 [51.9]	30 [50.9]
Education (≥ 12 yrs [%])	131 [56.7]	29 [50.9]	30 [60.0]	29 [56.9]	11 [40.7]	29 [49.2]
MMSE	28.9 ± 1.2	28.9 ± 1.0	28.6 ± 1.3	28.7 ± 1.5	24.0 ± 5.3	25.0 ± 3.3
Aβ burden (Centiloid)	0.7 ± 7.2	1.1 ± 7.4	50.9 ± 24.3	64.1 ± 26.7	85.3 ± 33.3	87.2 ± 25.7

CU = cognitively unimpaired (CDR = 0), CI = cognitively impaired (CDR = 0.5 – 1), MMSE = mini-mental state examination.

Table 2: Linear mixed effects models examining the rates of volume loss between non-ε4 and ε4 carriers in the CU Aβ-, CU Aβ+, and CI Aβ+ groups for BF subregions of Ch4p and Ch1/Ch2 as well as hippocamps.

Brain Region	Estimate	Standard Error	*p*-value	Cohen's *d*
Contrast: non-ε4 vs ε4 in CU Aβ-				
BF Ch4p	-0.010	0.013	0.444	0.12
BF Ch1/Ch2	-0.0002	0.012	0.989	< 0.001
Hippocampus	-0.002	0.012	0.854	0.03
Contrast: non-ε4 vs ε4 in CU Aβ+				
BF Ch4p	-0.012	0.026	0.644	0.15
BF Ch1/Ch2	-0.021	0.027	0.443	0.25
Hippocampus	-0.079	0.033	0.019 *	0.47
Contrast: non-ε4 vs ε4 in CI Aβ+				
BF Ch4p	-0.070	0.034	0.041 *	1.05
BF Ch1/Ch2	-0.021	0.044	0.640	0.26
Hippocampus	-0.133	0.050	0.009 **	0.94

BF = basal forebrain, CU = cognitively unimpaired (CDR = 0), CI = cognitively impaired (CDR = 0.5 – 1). Note the positive effect sizes indicate greater loss in ε4 carriers compared to non-carriers.

Results

The APOE ε4 status did not influence rates of volume loss in BF subregions of Ch4p and Ch1/Ch2 among CU individuals, while, in CU Aβ+ group, ε4 carriers had greater volume loss in hippocampus.

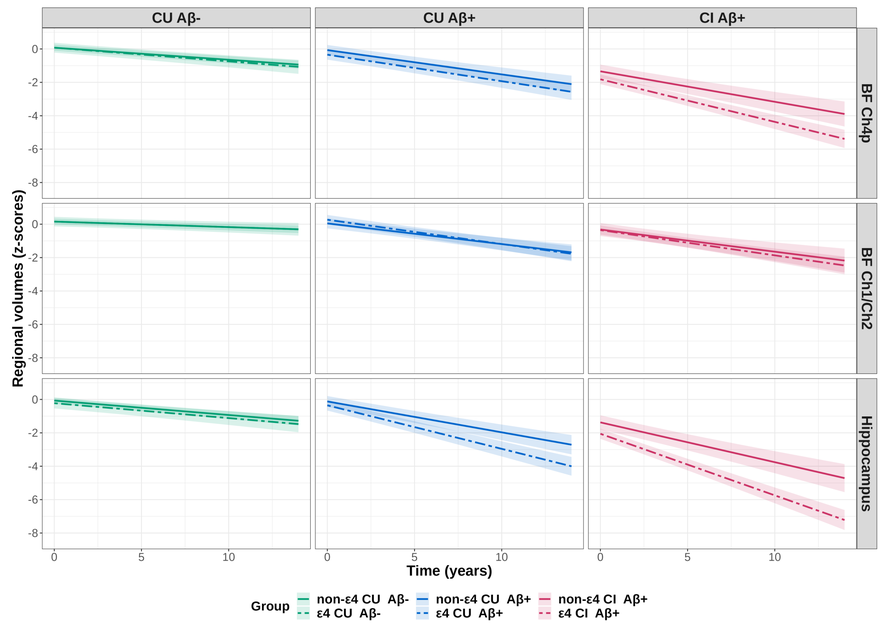

Figure 1: Longitudinal trajectories of regional volume for BF subregions (Ch4p and Ch1/Ch2) and hippocampus stratified by group and APOE ε4 status.

Shaded regions show 95% confidence intervals. The y-axis was normalized using the mean and standard deviation of the baseline volumetric measures in non-ε4 carriers of the CU Aβ group.

In CI Aβ+ adults, the presence of APOE ε4 allele was associated with a large rate of volume loss in Ch4p and hippocampus (Cohen's d > 0.9), but showed no influence on change in Ch1/Ch2 volumes (Figure 1).

Conclusion

These findings demonstrated **differential effects of APOE ε4 on volume loss of BF subregions**. The effect of APOE ε4 carriage on Ch4p volume loss becomes apparent in the symptomatic stage of AD (i.e., CI Aβ+), which might happen through the exacerbated Aβ and tau accumulation, whereas no effect on Ch1/Ch2 was noted across different AD stages.

FOR FURTHER INFORMATION

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REFERENCES

1. Bourgeat, Pierrick, et al. "Comparison of MR-less PiB SUVR quantification methods." *Neurobiology of aging* 36 (2015): S159-S166.

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