Apolipoprotein E ϵ4 Allele: Associations with Hippocampal Volumetrics and Verbal Episodic Memory Performance across Alzheimer's, Lewy Body and Mixed Dementias

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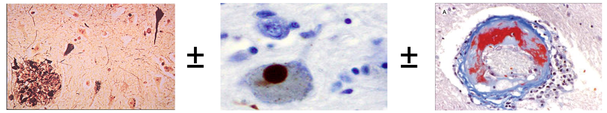
INTRODUCTION

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are two of the most common types of neurodegenerative dementias. [1, 2] In Canada, about 750,000 individuals currently suffer from dementia with an estimated annual economic cost of $33 billion, which is expected to increase ten-fold in a generation.[3] Hence, there is an urgent need to develop disease-modifying agents to prevent, delay or slow progression of these dementias at early stages. However, the development of any such intervention is challenged by:

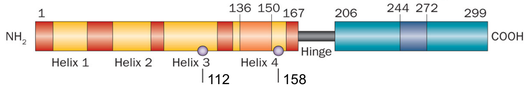
- **Clinical Heterogeneity**
  - Not all patients meet full clinical criteria for a particular diagnostic group, with many meeting criteria across different groups.
  - Clinical diagnosis does not always match with neuropathological diagnosis on autopsy and may reveal mixed pathologies.
- **Pathological Comorbidity**



Pure AD ± **Pure DLB** ± **SVD**

Figure 1. The co-occurrence of two or more pathologies in the same demented patient may result in mixed dementia.

Mixed pathologies, the co-occurrence of two or more pathologies in the same demented patient, are common.[4] The reason for this clinical heterogeneity and pathological comorbidity, in part, resides in genetic factors. Apolipoprotein E (*APOE*) is one such gene known to influence the risk of AD, DLB and mixed AD/DLB: [5, 6]



APOE ϵ2	*APOE* ϵ3	*APOE* ϵ4
Cys-112, *Cys*-158	*Cys*-112, *Arg*-158	*Arg*-112, *Arg*-158
Protective	**Neutral**	**Risk Factor**

Figure 2. Schematic diagram of *APOE* gene with its three variants that differ from each other at one or two amino acid positions upon protein translation: ϵ2, ϵ3 and ϵ4.

Apolipoprotein E ϵ4 allele is consistently associated with smaller hippocampal volumes among AD patients.[7, 8] To our knowledge, however, this association has not been studied in DLB and mixed dementias.

AIM & OBJECTIVES

Overall aim of this study is to investigate if *APOE* ϵ4 allele associates with hippocampal volumetric and memory measures across different dementias, irrespective of the clinical diagnosis.

Objectives: Association of *APOE* ϵ4 with hippocampal volumetrics:

- In a dose-dependent manner ("– / –" vs. "– / +" vs. "+ / +")
- Based on an extreme subgroup approach ("– / –" vs. "+ / +")
- With verbal episodic memory performance

METHODS

261 patients with a clinical diagnosis of dementia:

160 AD, 46 AD with SVD, 35 mixed AD/DLB, and 20 pure DLB

Recruited from Cognitive Neurology and Geriatric Psychiatry Clinics, Sunnybrook Research Institute

Consenting participants underwent detailed standardized assessments. For this study, the following measures were utilized:

Neuroimaging	**Neuropsychology**	**Genetics**
T1 and T2/PD	MMSE, DRS, CVLT	APOE Status

MRI Pre-Processing:

Performed using the Semi-Automated Brain Region Extraction (SABRE) processing pipeline.

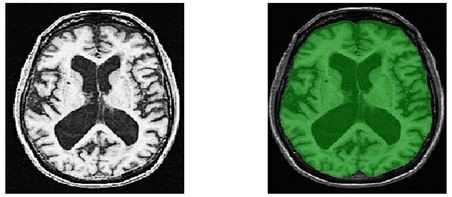


Figure 3. The corrected mask (green, right) was applied to each patient's T1 image (left) to obtain an accurate estimation of supra-tentorial total intracranial volume (ST-TIV).

MMSE: Mini-Mental State Examination; DRS: Dementia Rating Scale; CVLT: California Verbal Learning Test; SVD: Small vessel disease

Hippocampal Segmentation:

Performed using Sunnybrook Hippocampal Volumetry (SBHV) tools.

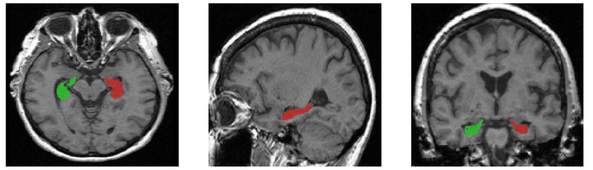


Figure 4. Hippocampus segmentation mask overlayed on its T1 image and displayed in axial (left), sagittal (middle) and coronal (right) views

RESULTS

Table 1. Demographic, neuropsychological and hippocampal volumetric (HV) data.

	ϵ4 – / –	ϵ4 + / –	ϵ4 + / +
Gender, *n* (M / F)	48 / 56	63 / 56	20 / 18
Formal Education, years	14.3 (3.7)	14.1 (3.4)	12.9 (3.9)
MMSE /30	23.5 (4.3)	23.8 (4.1)	22.1 (5.5)
DRS Total /144	119.1 (13.5)	118.8 (12.6)	119.8 (12.5)
HV Total, mm^3	4761.1 (723.4)	4752.0 (699.9)	4612.7 (854.5)
HV Right, mm^3	2432.7 (365.3)	2409.9 (382.8)	2350.1 (461.8)
HV Left, mm^3	2328.4 (405.0)	2342.1 (355.0)	2262.6 (422.7)

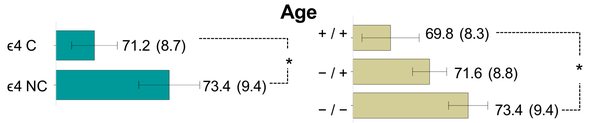


Figure 5. The "carriers" (C) of ϵ4 allele were statistically **younger** in age than "non-carriers" (NC) (left); the homozygous ϵ4 carriers were even younger (right); * $p < 0.05$

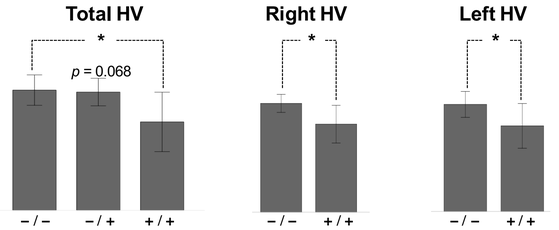


Figure 6. There was a trend ($p = 0.068$) for the total bilateral hippocampal volume (HV) to be **smaller** in a dose-dependent fashion (ϵ4 "–/–" < ϵ4 "–/+" < ϵ4 "+/+"). The total bilateral HV, and individual left and right HVs were significantly **smaller** in "+/+" vs. "–/–" extreme ϵ4 subgroups; * $p < 0.05$

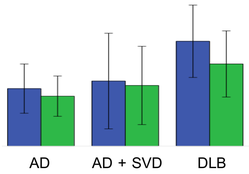


Figure 7. The total bilateral HVs were also found to be **smaller** in ϵ4 "carriers" (C) vs. "non-carriers" (NC), within each of the clinical diagnostic groups.

Table 2. Linear regression analysis shows that total hippocampal volume statistically co-varies with CVLT indices and DRS memory sub-score in ϵ4 "carriers" as compared to "non-carriers"; *** $p < 0.005$; ** $p < 0.01$; * $p < 0.05$; NS, not significant ($p > 0.05$)

Tests	Indices	ϵ4 – Carriers	ϵ4 – Non-Carriers
CVLT	List A Total Recall	***	NS
	Short Delay Free Recall	**	*
	Short Delay Cue Recall	**	NS
	Long Delay Free Recall	***	NS
	Long Delay Cue Recall	**	NS
DRS	Memory Sub-score	***	NS

DISCUSSION

These results suggest that *APOE* ϵ4 allele consistently predicts smaller hippocampal volumes and episodic memory impairments across a sample of heterogeneous dementia patients, irrespective of the clinical diagnosis. This hippocampal-memory association may serve as a reliable **endophenotype** of *APOE* ϵ4 allele across dementia patients.

ACKNOWLEDGEMENTS

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