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Featured Article

APOE-ε4 associates with hippocampal volume, learning, and memory across the spectrum of Alzheimer's disease and dementia with Lewy bodies

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Abstract

Introduction: Although the apolipoprotein E ε4-allele (*APOE*-ε4) is a susceptibility factor for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), its relationship with imaging and cognitive measures across the AD/DLB spectrum remains unexplored.

Methods: We studied 298 patients (AD = 250, DLB = 48; 38 autopsy confirmed; NCT01800214) using neuropsychological testing, volumetric magnetic resonance imaging, and *APOE* genotyping to investigate the association of *APOE*-ε4 with hippocampal volume and learning/memory phenotypes, irrespective of diagnosis.

Results: Across the AD/DLB spectrum: (1) hippocampal volumes were smaller with increasing *APOE*-ε4 dosage (no genotype × diagnosis interaction observed), (2) learning performance as assessed by total recall scores was associated with hippocampal volumes only among *APOE*-ε4 carriers, and (3) *APOE*-ε4 carriers performed worse on long-delay free word recall.

Discussion: These findings provide evidence that *APOE*-ε4 is linked to hippocampal atrophy and learning/memory phenotypes across the AD/DLB spectrum, which could be useful as biomarkers of disease progression in therapeutic trials of mixed disease.

Keywords: *APOE*; MRI; Hippocampus; Alzheimer's disease; Dementia with Lewy bodies; Learning; Memory; Endophenotype

The authors have declared that no conflict of interest exists.
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1. Introduction

Pathologic hallmarks of Alzheimer's disease (AD) are extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). Dementia with Lewy bodies (DLBs) are characterized by intraneuronal α-synuclein inclusions of Lewy bodies (LBs) and Lewy neurites [1,2]. Clinically, AD and DLB are diagnosed almost exclusively using their respective international consensus diagnostic criteria [1,3,4]. While clinical criteria are generally adequate for providing an initial diagnosis and to inform the use of symptomatic therapies, several issues are noteworthy. First, the hallmark proteinopathies of AD and DLB frequently coexist, even among patients diagnosed with a single specific form of dementia in life [5–7]. Second, clinical diagnoses do not always match with autopsy results, often revealing additional incidental co-pathologies, e.g., small vessel disease [8,9]. Third, concomitant pathologies contribute to substantial heterogeneity in disease presentation and progression [7]. These findings serve to challenge the classic neurodegenerative disease distinctions when relying on clinical diagnosis alone. Thus, the identification of common genotype-phenotype (endophenotypic) relationships across the AD/DLB spectrum may offer an objective approach to address these limitations [10]. Indeed, genotype in combination with morphometric measurements derived from structural imaging have emerged as important biomarkers in dementia, which have the potential to advance diagnostic accuracy and improve therapeutic end points in disease-modifying trials (including mixed disease).

Apolipoprotein E (*APOE*) is an important gene that may influence the expression of dementia across the AD to Parkinson's disease spectrum (Supplementary Fig. 1) [11,12]. Human *APOE* has three allelic variants, resulting from two single nucleotide polymorphisms, which differ at one or two amino acid positions: ε2 (Cys-112/Cys-158), ε3 (Cys-112/Arg-158), and ε4 (Arg-112/Arg-158) [13]. Apolipoprotein E ε4-allele (*APOE*-ε4) is a well-recognized susceptibility factor for late-onset AD, whereas *APOE*-ε2 is considered protective against AD. Recent neuropathological studies demonstrate an overrepresentation of *APOE*-ε4 not only in AD but also in α-synucleinopathies, specifically among patients showing LB pathology with coexisting "high-level" AD (mixed AD/DLB) and none/"low-level" AD ("pure" DLB or Parkinson's disease dementia) [11,12]. In addition, the associations between *APOE*-ε4 and cerebrovascular pathologies, including cerebral small vessel disease and amyloid angiopathy, have been reported in AD [14]. Given that *APOE*-ε4 is a shared susceptibility factor across the AD/DLB spectrum, its association with imaging and cognitive endophenotypes irrespective of specific clinical diagnosis may clarify its role in shared mechanisms of neurodegeneration.

One important brain structure that can be measured through imaging is the hippocampus, which undergoes early neurodegenerative changes in AD, while it is relatively preserved early in the course of DLB [1,3,15]. Hippocampal degeneration in DLB is typically related to the severity of NFT pathology, possibly via mechanisms similar to AD [16,17]. Deficits in learning and memory, which are linked independently to hippocampal integrity and neurogenesis, are also common features of both AD and DLB dementias [18]. No study to date has assessed the interrelationships among *APOE*-ε4, hippocampal volumes, and cognition across the AD/DLB spectrum.

Herein, we investigated the hypothesis that *APOE*-ε4 may be associated with magnetic resonance imaging (MRI)–derived hippocampal volumes, learning, and memory performance, across the AD/DLB spectrum.

2. Methods

2.1. Participants

We included 298 participants (AD = 250 and DLB = 48), recruited from the Cognitive Neurology and Geriatric Psychiatry clinics and enrolled in the prospective Sunnybrook Dementia Study ([19]; ClinicalTrials.gov: NCT01800214) at the Sunnybrook Health Sciences Centre, University of Toronto. The details of this study have been previously reported [19]. All participants underwent a detailed neurological evaluation, including standardized MRI, comprehensive neuropsychological battery [20], and *APOE* genotyping [21]. On recruitment, AD was diagnosed using the Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [22], whereas DLBs were diagnosed using the Third Report of DLB Consortium criteria [1]. All cases were retrospectively reassessed using the current diagnostic criteria for possible/probable AD [3] and possible/probable DLB [4]. Probable AD included those with amnestic (N = 174) and nonamnestic (N = 16) presentations, whereas possible AD allowed for the inclusion of those with a high burden of white matter hyperintensities (WMHs) of presumed vascular origin (>10 cm^3) (N = 60) [3]. Probable DLBs were diagnosed if two or more of the core clinical features of cognitive fluctuations, visual hallucinations, parkinsonism, or REM behavior disorder were present (N = 32), whereas possible DLBs were diagnosed when only one of these core features was present (N = 16). Diagnostic consensus was achieved through review by at least two physicians (M.M., N.H., and S.E.B.) with expertise in dementia diagnosis. Neuropathologic confirmation was available on 38 patients, assessed using standardized techniques. The study was approved by the Sunnybrook Research Ethics Board. All participants (or surrogate caregivers) provided informed consent as per the Declaration of Helsinki.

Details of participant selection and categorization are shown in Fig. 1.