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Beyond Alzheimer's Disease: *APOE ε4* and the Aging Brain

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Abstract

The majority of individuals who carry the apolipoprotein ε4 allele will not develop dementia in their lifetime. Previous literature documents the elevated risk for Alzheimer's Disease (AD) among ε4 carriers. However, more recent evidence from longitudinal studies suggests that these risks may be overestimated. Nonetheless, many cross-sectional studies indicate that older ε4 carriers may experience poorer performance on tests of episodic memory compared to noncarriers. By themselves, these studies cannot disentangle ε4's influence on brain structure and function from the effects of AD neuropathology. In this brief review, we discuss several ways in which ε4 can impact brain aging informed by animal models. We emphasize the importance of taking an individualized approach in future studies by incorporating blood and CSF biomarkers as well as novel neuroimaging pulse sequences that can help differentiate ε4's role in cognitive aging from its impact on AD pathology.

Keywords: Cognitive aging; Alzheimer's risk; Inflammation; Blood brain barrier; Neuronal dysfunction

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Introduction

Beyond risk for Alzheimer's diseases

Age-Related Cognitive Impairment (ARCI) contributes to decreased quality of life, increased risk for hospitalization, loss of independence, and higher overall mortality [1,2]. While the majority of older adults – more than 85% will not develop Alzheimer's Disease (AD) in their lifetime, one in three older adults without dementia will experience declines in memory, visual-spatial abilities and executive functions ranging from mild to severe [2,3]. Understanding the risks for cognitive impairment, as well as potential resilience factors, is a critical first step in developing interventions to prevent and treat ARCI [1]. In this article, we provide a brief update on the risks for ARCI associated with the apolipoprotein ε4 allele (*APOE ε4*). Based on recent animal models, we now recognize that ε4 impacts brain structure and function in multiple ways that are independent from AD pathology. In contrast to the prevailing view, cognitive impairments among *APOE ε4* carriers are inconsistent and are not reliably related to preclinical AD. We highlight the importance of taking a "precision aging" approach to research, focusing on individual differences in profiles of risk in order to better predict the trajectory of cognitive change [1].

Literature Review

E4 mechanisms impacting brain aging

The exacerbating influence of the apolipoprotein-E lipid transport protein isoform (ApoE4) on AD pathology is well documented [4-6]. ApoE4 increases accumulation of Aβ and tau aggregation and interferes with normal clearance of Aβ by decreasing resident microglia's migration toward amyloid plaques and reducing Aβ phagocytosis [4,5,7-9]. However, recent longitudinal studies suggest that the risk for developing AD associated with *APOE ε4* may be lower than originally thought. Compared to early studies estimating 3 to 4-fold risk for carrying one ε4 allele and as high as 15-fold risk for two ε4 alleles, more recent studies report hazard ratios ranging from 1.2 to 1.8 [10-13]. Two recent large-scale population studies in the United Kingdom and Denmark found that more than 95% of ε4-positive older adults did not develop dementia over 12- and 10-year follow-up periods, respectively [14,15].

Independent of AD neuropathologies, other mechanisms have emerged from knock-in human ApoE4 mouse models that have the potential to negatively impact the aging brain. ApoE4 has been shown to predispose the rain to heightened

inflammation and excessive cytokine production in response to pro-inflammatory insults such as head injury [16]. Transcriptomic analyses have revealed over activation of microglia-based inflammation and phagocytic programs in both normal aging and the AD brain [6,17]. *In vitro* induced Pluripotent Stem Cell (iPSC) models have illustrated that ApoE4 microglia exhibit heightened proinflammatory responses, altered morphology, reduced Aβ phagocytosis, and diminished capacity for lipid uptake, all of which can negatively impact neuronal activity and network coordination [18,19].

Additionally, the ApoE4 isoform disrupts cholesterol transport to astrocytes [20], thereby affecting their metabolic and immune/inflammatory signaling support to neurons and exacerbating maladaptive responses to pathology. In human iPSCs derived from cognitively normal individuals, ApoE4 homozygous astrocytes exhibit reduced efficiency in neurotrophic actions in neuron co-cultures [21]. Neurons exposed to conditioned media from ApoE4 astrocytes show increased basal mitochondrial and glycolytic metabolic rates when challenged with Aβ in ApoE4 astrocyte-derived media, but not in media from ε3 astrocytes [22]. Glial Fibrillary Acidic Protein (GFAP), a potential biomarker of cytoskeletal damage in astrocytes, and myo-inositol, a metabolic marker for astrocytes, have both been linked to higher Aβ positivity in cognitively unimpaired older adults, as measured by positron emission tomography [23,24].

ApoE4 knock-in mice show synaptic dysfunction and reductions in dendritic arborization and spine density leading to poor spatial learning and memory [25-27]. Similar results were noted in a different ApoE4 mouse model generated by targeted replacement [28]. Dendritic spine morphological alterations are known to occur in older adults with ApoE4 with no evidence of dementia [29].

ApoE4 is associated with neurovascular dysfunction and loss of integrity of the Blood-Brain Barrier (BBB) [30,31]. ApoE4 targeted replacement mice exhibit decrease in vascular density and resting cerebral perfusion without concurrent alterations in blood pressure. Additionally, changes to homeostatic mechanisms responsible for regulating sufficient blood supply during brain activity, such as neurovascular coupling and endothelium-initiated microvascular response, have been linked to heightened white matter damage and cognitive decline in these mice compared to those carrying ApoE3 alleles or wild-type mice [30]. These same alterations might also undermine the integrity of the BBB. The anatomical foundation of the BBB is the cerebral microvascular endothelium, which, along with astrocytes, pericytes, neurons, and the extracellular matrix, constitute the "neurovascular unit". Tight Junctions (TJ) between endothelial cells of the BBB regulate diffusion of water-soluble substances from the blood into the brain. Multi-omics analysis (RNA, proteome, and phosphoproteome) of young ApoE4 knock-in mice indicates an early disruption of the transcriptome, followed by an impact on signaling networks related to BBB health in brain endothelium and pericytes, preceding behavioral changes [32]. Other factors, like diet and biological sex, may interact with ApoE4 to influence BBB function and contribute to changes noted in cognitive performance in animal models [33].

Taken together, these findings highlight the need to understand the impacts of *APOE ε4* on brain structure and function that may contribute ARCI, rather than focusing solely on risk for AD pathology [34].

APOE ε4 and cognitive aging

It is commonly assumed that prodromal AD pathology results in poorer cognitive performance among *APOE ε4* carriers, particularly verbal memory. However, a recent comprehensive review found that only 25% of studies of older adults reported poorer verbal memory for ε4 carriers compared to noncarriers, and even fewer reported differences in working memory, executive functions, or processing speed [35]. Longitudinal studies are equally inconsistent, with some reporting more rapid cognitive decline among ε4 carriers relative to noncarriers even after controlling for the presence of AD and other neuropathologies, while others have reported no changes over time [36-47]. Studies of episodic memory, however, provide a more consistent picture, suggesting that *APOE ε4* carriers rely on holistic or familiarity-based information during the retrieval of memory details. For example, when recalling autobiographical memories, older ε4 carriers generate fewer spatial, temporal, and perceptual episodic details and have more difficulty generating examples of unique personal events compared to noncarriers [48,49]. Studies of object memory demonstrate that ε4 carriers and noncarriers are equally good at recognizing 'old' objects, but ε4 carriers are impaired when identifying the location of the object within an array and more likely to commit false alarms of similar objects [50,51]. *APOE ε4* carriers either have more difficulty encoding spatial-temporal details into memory representations, or they rely on gist-like representations to a greater degree during memory recall.

Whether poor episodic memory performance results from pre-clinical AD pathology and/or ε4's other impacts on brain function remains unclear. Some studies have taken a post-hoc approach, reporting that episodic memory differences between ε4 carriers and noncarriers disappeared after removing individuals from the original analyses who developed AD years later, implicating a more prominent role of preclinical AD pathology on memory function in these studies [52]. However, other studies have found continued evidence of poor performance among ε4 carriers on tests of memory and other cognitive tasks. These results persisted even after excluding individuals who were diagnosed with dementia, with Corley and colleagues using a follow-up period lasting 12 years and Gharbi-Meliani and colleagues using more than 20 years, suggesting that influences beyond AD pathology were responsible for poor memory performance [12,53]. Taken together, these approaches by themselves are not sufficient to clarify ε4's potential effect on cognitive functioning independent of AD pathology.

Memory and other cognitive changes likely reflect a combination of phenotypic effects and, for some, prodromal pathology, as well as protective factors that may ameliorate both of these influences. No studies to date have obtained biomarkers from a

sufficiently large sample of ε4 carriers that could disentangle the various contributions of ApoE4 on ARCI.

Taking a precision aging approach

Separating the impacts of the *APOE ε4* allele on brain structure and function from AD pathology is a current challenge in cognitive aging research. We have argued elsewhere that future research must take an individualized approach to understand this complexity [1,54]. This would involve investigating multiple potential impacts of ApoE4 on brain structure and function simultaneously rather than focusing solely on cognitive outcomes.

Prodromal AD pathology cannot be evaluated sufficiently with cognitive screening with instruments such as the MMSE or MoCA, nor is the diagnosis of MCI, since most of these individuals will not develop AD [55]. PET measurement of Aβ and phosphorylated tau (p-tau) provides localization of pathology, but is invasive and expensive, with limited availability. The reliability of emerging blood markers of Aβ and p-tau is increasing, providing a cost-effective way to measure overall burden of AD brain pathology [56]. It is important to note, however, that the presence of Aβ is not a guarantee of impending dementia. Carriers of ε4 can show elevated levels of Aβ compared to noncarriers without evidence of cognitive impairment or dementia, even beyond age 100 [57-65].

Other biomarkers obtained from blood and CSF may be particularly helpful in detecting brain dysfunction attributed to mechanisms other than AD neuropathology. Age-related inflammation can be measured by the soluble form of the Triggering Receptor Expressed on Myeloid cells 2 (sTREM2), which was shown to be elevated in aging irrespective of ε4, amyloid levels, and sex [66,67]. Neurofilament Light chain protein (NfL), a well-established blood biomarker associated with brain injury in neurogenerative diseases, stroke, brain trauma, cardiovascular disease, can provide insight into the structural integrity of axons [68-70]. Neuronal pentraxin 2 (*NPTX2*), also known as Neuronal Activity-Regulated Pentraxin (*NARP*), is an immediate-early gene involved in guiding synaptic plasticity and a potential biomarker of synaptic damage and early neurodegeneration [71]. Finally, assessing synaptic integrity in studies of AD and other neurologic conditions revealed lower levels of neurogranin in the CSF, a protein expressed in pyramidal cells of the hippocampus and cortex [72-75]. These burgeoning biomarkers, among others, may provide valuable insight into the influence of additional mechanisms on brain structure and function. Incorporating them in future studies with ε4 carriers will be a critical step toward understanding its impact on the brain in a more holistic way.

Various neuroimaging modalities can also provide insight into other potential impacts of ApoE4 on brain structure and function. MRI spectroscopy may be particularly helpful in disentangling cell loss from neuroinflammation, through measurement of the glial marker myo-inositol, which is elevated in the presence of astrocytes and microglia, and N-Acetylasparate (NAA) and glutamate, which decrease as a result of neuronal loss [76,77]. Other PET measures of brain inflammation include Translocator Protein (TSPO), an outer mitochondrial membrane protein expressed in activated microglia, and Monoamine Oxidase-B (MAO-B), a PET biomarker associated with reactive astrogliosis [77-79]. Synaptic Vesical protein 2A (SV2A) PET imaging is another novel technique that may reflect decreases in synaptic density [80]. Changes in neurovascular function can be assessed using quantitative Arterial Spin Labelling (ASL) MRI, which has been shown to be moderated by *APOE ε4* status, and Cerebral Metabolic Rate of glucose (CMRgl) measured by FDG-PET imaging [81,82]. Dynamic Contrast-Enhanced MRI and ASL can be used to measure BBB permeability [83,84]. Thus far, studies of cognitively normal ε4 carriers using DCE-MRI are inconsistent, with some finding increased BBB permeability within the hippocampus among older carriers compared to noncarriers, while another found a trend toward enhanced permeability among middle-aged carriers compared to noncarriers [31,85]. On the other hand, several studies of older ε4 carriers using ASL appear to be more consistent, indicating that higher cerebral blood flow is associated with poorer performance on verbal memory and pattern separation [81,86]. Further implementation of these imaging techniques will continue to solidify ε4's role with the neurovasculature.

Conclusion

This brief review extends our understanding of ε4's impact on the aging brain. Expanding the use of novel biomarkers and neuroimaging methods that are informed by animal studies may help disentangle *APOE ε4*'s potential phenotypic contributions to ARCI from risk for AD. Future studies taking an individualized approach by assessing multiple risk factors may help clarify the various ways *APOE ε4* can potentially contribute to ARCI and, for some individuals, conversion to dementia later in life.

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