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Review

Neuropsychiatric symptoms and apolipoprotein E genotypes in neurocognitive disorders

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From the Contents

Abstract

Complex genetic relationships between neurodegenerative disorders and neuropsychiatric symptoms have been shown, suggesting shared pathogenic mechanisms and emphasizing the potential for developing common therapeutic targets. Apolipoprotein E (*APOE*) genotypes and their corresponding protein (ApoE) isoforms may influence the biophysical properties of the cell membrane lipid bilayer. However, the role of *APOE* in central nervous system pathophysiology extended beyond its lipid transport function. In the present review article, we analyzed the links existing between *APOE* genotypes and the neurobiology of neuropsychiatric symptoms in neurodegenerative and vascular diseases. *APOE* genotypes (*APOE* ε2, *APOE* ε3, and *APOE* ε4) were implicated in common mechanisms underlying a wide spectrum of neurodegenerative diseases, including sporadic Alzheimer's disease, synucleinopathies such as Parkinson's disease and Lewy body disease, stroke, and traumatic brain injury. These shared pathways often involved neuroinflammation, abnormal protein accumulation, or responses to acute detrimental events. Across these conditions, *APOE* variants are believed to contribute to the modulation of inflammatory responses, the regulation of amyloid and tau pathology, as well as the clearance of proteins such as α-synuclein. The bidirectional interactions among ApoE, amyloid and mitochondrial metabolism, immunomodulatory effects, neuronal repair, and remodeling underscored the complexity of ApoE's role in neuropsychiatric symptoms associated with these conditions since from early phases of cognitive impairment such as mild cognitive impairment and mild behavioral impairment. Besides ApoE-specific isoforms' link to increased neuropsychiatric symptoms in Alzheimer's disease (depression, psychosis, aberrant motor behaviors, and anxiety, not apathy), the *APOE* ε4 genotype was also considered a significant genetic risk factor for Lewy body disease and its worse cognitive outcomes. Conversely, the *APOE* ε2 variant has been observed not to exert a protective effect equally in all neurodegenerative diseases. Specifically, in Lewy body disease, this variant may delay disease onset, paralleling its protective role in Alzheimer's disease, although its role in frontotemporal dementia is uncertain. The *APOE* ε4 genotype has been associated with adverse cognitive outcomes across other various neurodegenerative conditions. In Parkinson's disease, the *APOE* ε4 allele significantly impacted cognitive performance, increasing the risk of developing dementia, even in cases of pure synucleinopathies with minimal co-pathology from Alzheimer's disease. Similarly, in traumatic brain injury, recovery rates varied, with *APOE* ε4 carriers demonstrating a greater risk of poor long-term cognitive outcomes and elevated levels of neuropsychiatric symptoms. Furthermore, *APOE* ε4 influenced the age of onset and severity of stroke, as well as the likelihood of developing stroke-associated dementia, potentially due to its role in compromising endothelial integrity and promoting blood–brain barrier dysfunction.

Key Words: Alzheimer's disease; ApoE isoforms; apolipoprotein E gene; depression; Lewy body disease; mild cognitive impairment; neuroinflammation; neuropsychiatric symptoms; Parkinson's disease; stroke; traumatic brain injury

Introduction

Despite their diversity, neurodegenerative diseases share common features such as abnormal protein accumulation, neuroinflammation, neuronal death, and activation of the innate immune system, primarily mediated by glial cells, especially microglia (Krasemann et al., 2017). A focal point of recent research was the role of the apolipoprotein E gene (*APOE*) and its protein (ApoE) isoforms in neurodegeneration in different conditions (Lozupone and Panza, 2024). Human ApoE is a 299-amino acid-secreted glycoprotein that binds cholesterol and phospholipids. It is encoded by the *APOE* gene located at locus 19q13.32 and exists in three common isoforms: *APOE* ε2, *APOE* ε3, and *APOE* ε4 (Weisgraber, 1994). In neurodegenerative and vascular conditions and acute traumatic brain injuries (TBI), abnormal protein accumulation in neurons can alter ApoE functions, particularly in lysosome activity or autophagy. Conversely, conditions such as stroke or TBI primarily involve an inflammatory response driven by microglia (Fernández-Calle et al., 2022). Understanding ApoE's multiple roles in immune regulation and neuronal metabolism is challenging, suggesting potential common mechanisms across various neurodegenerative and vascular diseases and acute TBI involving protein accumulation or acute damage (Fernández-Calle et al., 2022).

A complex genetic relationship exists among neurodegenerative diseases and neuropsychiatric symptoms (NPS). Among putative pleiotropic genomic regions, *APOE* could play a key role (Reynolds et al., 2023). Two studies have

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hypothesized an association between the *APOE* ε4 allele and the presence of NPS, but the results were contrasting (Wise et al., 2019; Yoro-Zohoun et al., 2021). One underlying hypothesis explaining its association with NPS is that *APOE* ε4 may influence the link between cardiovascular risk biomarkers and systemic inflammation (Treiber et al., 2008). Certain studies have identified a significant link between NPS and the *APOE* ε4 allele in older adults without dementia. Specifically, ε4-carriers showed higher scores for appetite and eating disorders and lower scores for aberrant motor disturbances compared with non-carriers (Stella et al., 2024). It is important to underline that there are very clear limits to link the *APOE* ε2-linked neuroprotection to proteinopathies other than Alzheimer's disease (AD) (alpha-synuclein and tauopathies) (Goldberg et al., 2020a). Therefore, in the present review article, we explored the association between *APOE* genotypes and NPS in neurodegenerative and vascular conditions for understanding the potential interaction of cognitive dysfunctions associated with NPS in individuals with different *APOE* alleles. While much of the research on *APOE* and NPS focused on individuals with AD, such symptoms were also observed in older adults with mild cognitive impairment (MCI) and mild behavioral impairment (MBI), synucleinopathies such as Parkinson's disease (PD) and Lewy body disease (LBD), stroke, multiple sclerosis, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and TBI.

Search Strategy

The literature cited in this review were identified through separate searches conducted in the US National Library of Medicine (PubMed), Medical Literature Analysis and Retrieval System Online (Medline), EMBASE, Scopus, Ovid, and Google Scholar databases. Articles published from inception to December 10, 2024, were included to explore potential associations between the exposure (ApoE/*APOE* isoforms/genotypes) and the neurodegenerative and vascular diseases NPS outcome(s) (AD /PD/LBD/FTD/stroke/TIA/TBI-neuropsychiatric symptoms) using selected key words/descriptors, i.e., (apolipoprotein E[tiab]) OR (ApoE[tiab]) OR (*APOE*[tiab]) OR (isoforms[tiab]) OR (genotypes[tiab] AND (Alzheimer's disease[tiab]) OR (AD[tiab]) OR (pathophysiology[tiab]) OR (LBD[tiab]) OR (PD[tiab]) OR (TIA[tiab]) OR (stroke[tiab]) OR (TBI[tiab]) AND (neuropsychiatric symptoms[tiab]) OR (NPS[tiab]). The search strategy was applied to PubMed and Medline and adapted to the other four electronic databases. No language restrictions were imposed. Two investigators (ML and FP) independently conducted the searches, screened the titles and abstracts of retrieved articles in duplicate, reviewed the full texts, and selected records for inclusion.

Mediating Role of Apolipoprotein E on Neurodegenerative and Vascular Diseases

ApoE, identified as the most abundant lipoprotein in the brain through mass spectrometry (Roher et al., 2009), is primarily synthesized by hepatocytes and circulates in plasma within peripheral tissues (Mahley, 1999). In the central nervous system (CNS), however, its expression is predominantly localized to glial cells. Astrocytes, which play a crucial role in neuronal communication and metabolic support, are the main source of ApoE in the CNS, with microglia—the brain's resident immune cells—contributing to a lesser extent (Lanfranco et al., 2021). Additionally, cells such as oligodendrocytes and pericytes in the CNS, as well as macrophages and adipocytes in peripheral tissues, contribute to ApoE production (Yang et al., 2023; Blumenfeld et al., 2024). Although neurons typically produce minimal ApoE under normal conditions, its expression can be induced by neuronal stress and injury (Boschert et al., 1999; Xu et al., 2006; Zalocusky et al., 2021).

Humans possess three major *APOE* alleles, *APOE* ε2, *APOE* ε3, and *APOE* ε4, which are distinguished by single amino acid substitutions at positions 112 and 158 (Zhao et al., 2018). *APOE* ε3, the most common allele, occurring in 78% of Caucasians, is largely considered neutral in relation to the risk of neurodegenerative diseases (Corder et al., 1993; Koutsodendris et al., 2022). In contrast, *APOE* ε4, found in 14% of Caucasians, is the most important genetic risk factor for sporadic AD, with risk increasing with each additional *APOE* ε4 allele (Troutwine et al., 2022). Conversely, *APOE* ε2, present in nearly 8% of the population, was linked to a reduced risk of sporadic AD (Farrer et al., 1997, Panza et al., 1999). These *APOE* variants were also strongly associated with key pathological hallmarks of sporadic AD, including amyloid-β (Aβ) and phosphorylated tau (Roda et al., 2019; Saunders et al., 2022; Hou et al., 2020; Xia et al., 2024).

The impact of *APOE* ε4 extended beyond sporadic AD to diseases such as PD and LBD (Paul et al. 2016), poor recovery from TBI (Chamelian et al., 2004; Olivecrona et al., 2017), cerebral amyloid angiopathy (Premkumar et al., 1996; Ringman et al., 2014; Yu et al., 2015; Shinohara et al., 2016), chronic traumatic encephalopathy (Atherton et al., 2022), and chemotherapy-induced cognitive impairment (Fernandez et al., 2020; Van Dyk et al., 2021; Hsiao et al., 2024). Additionally, *APOE* ε4 was linked to non-neurological conditions such as dyslipidemia, cardiovascular disease, and serious COVID-19 (Bennet et al., 2007; Carvalho-Wells et al., 2012; Gkouskou et al., 2021; Safdari Lord et al., 2022; Shao et al., 2022; Chen et al., 2023). The *APOE* ε4 genotype has been widely suggested to have a synergistic relationship with hypertension, amplifying the manifestations of cerebral small vessel disease. However, this association is complex and may be modulated by factors such as age and the use of vascular treatments (Rodrigue et al., 2013). Furthermore, *APOE* ε2 was associated with longevity, though it also raised the risk of hypercholesterolemia, cardiovascular diseases, macular degeneration, and several kinds of tumors (Brewer et al., 1983; Mahley, 1999; Huang et al., 2014; Levy et al., 2015; Shinohara et al., 2020; Rasmussen et al., 2023). A UK Biobank study has shown that *APOE* alleles affected a wide range of disorders, including obesity, liver disease, chronic airway obstruction, and type 2 diabetes (Chen et al., 2019; Lumsden et al., 2020).

The broad association of *APOE* alleles with multiple diseases points to its involvement in fundamental cellular processes. Recent findings suggested that different *APOE* variants may influence biological pathways such as lipid and glucose metabolism (Farmer et al., 2021), inflammation (Lin et al., 2018; Kloske et al., 2020; Parhizkar et al., 2022), cellular trafficking (Narayan et al., 2020; de Leeuw et al., 2022), and mitochondrial function (Chen et al., 2011). *APOE* ε4 astrocytes exhibited reduced glucose uptake and isoform-specific effects on glucose utilization compared with *APOE* ε2 and *APOE* ε3 astrocytes, along with specific disruptions in central carbon metabolism (Williams et al., 2020). These disruptions across diverse cell types highlight the widespread effects of *APOE* isoforms on cell biology.

As the second most lipid-rich organ in the body (Hamilton et al., 2007; Dawson, 2015), the brain is particularly vulnerable to disruptions in lipid homeostasis, a factor that plays a pivotal role in the pathogenesis of neurodegenerative diseases. Several genes linked to lipid metabolism beyond *APOE* such as *CLU, INPP5D, ABCA7, TREM2, PLCG2*, and *GBA*, were recognized as genetic risk factors for prevalent neurodegenerative conditions, including AD, PD, and LBD (Paul et al., 2016; Nalls et al., 2019; Bellenguez et al., 2022). One mechanism through which ApoE affects neurodegenerative disease risk may involve lipid metabolism. ApoE plays a central role in transporting lipids such as cholesterol, phospholipids, and triglycerides into cells via receptors such as the low-density lipoprotein receptor (Huang et al., 2014). Recent studies have also identified new ApoE receptors (Yeh et al., 2016; Zhou et al., 2023).

While the role of ApoE isoforms in protein aggregation and deposition has been extensively studied, the hypothesis that lipid metabolism may integrate the diverse phenotypic effects of ApoE is gaining attention and warrants further research to clarify its primary mechanisms and to determine its causal impact on disease risk. Given the extensive impact of lipid metabolism on cellular health, targeting these pathways offers a promising strategy for mitigating ApoE-mediated disease risk. ApoE isoforms have distinct effects on lipid metabolism, resulting in variations in brain lipid composition. ApoE4 is less efficient at lipid transport and binds more strongly to very low-density lipoproteins than ApoE3 or ApoE2 (Sienski et al., 2021). This variance in binding affinity alters the lipidation of ApoE-containing particles, impairing their ability to transport cholesterol and phospholipids, which contributes to changes in synaptic plasticity and neuronal function, thereby promoting neurodegeneration (Zhao et al., 2018). Thus, the receptor-binding and lipid-binding regions within ApoE4 fragments synergized to promote neurotoxicity and mitochondrial dysfunction, potentially playing a pivotal role in the pathogenesis of AD (Chang et al., 2005; Lo Vecchio et al, 2022).

Beyond its role in lipid metabolism, ApoE influenced the composition of cellular membranes, affecting membrane fluidity and the function of membrane-bound proteins such as receptors and ion channels. This can profoundly impact cell signaling pathways and synaptic function,

particularly in neurons. For example, the presence of ApoE4 has been associated with changes in the composition of phospholipids and cholesterol in synaptic membranes, leading to disruptions in synaptic signaling and plasticity (Fan et al., 2016). Furthermore, a key process influenced by ApoE isoforms is the metabolism of amyloid precursor protein and the production of Aβ, a hallmark of AD (Lozupone et al., 2023). ApoE4 promoted Aβ aggregation and deposition, while ApoE2 appeared to protect by enhancing Aβ clearance (Xia et al., 2024). These isoform-specific effects on Aβ metabolism were linked to differences in lipid-binding properties and interactions with cellular receptors that mediate Aβ clearance (Mahley, 1999).

Initially, *APOE* was causally linked to Aβ peptide aggregation and clearance. However, over the last years, our understanding of *APOE*-mediated AD pathogenesis has expanded to encompass mechanisms beyond Aβ, including tau/neurofibrillary tangle degeneration, microglial and astrocytic responses, and blood–brain barrier (BBB) dysfunction (Bu, 2022). ApoE plays a critical role in tau pathogenesis, neuroinflammation, and tau-driven neurodegeneration, independent of Aβ pathology. ApoE4 confers a toxic function, while its absence has a protective effect (Shi et al., 2017). Remarkably, removing astrocytic ApoE4 has been shown to mitigate tau-induced synaptic loss and reduce microglial phagocytosis of synaptic elements, underscoring the central role of astrocytic ApoE in synaptic degeneration (Wang et al., 2021). The *APOE* ε4 allele appeared to prime microglia toward a phagocytic and proinflammatory state through the *APOE*-triggering receptor expressed on myeloid cells 2 gene (TREM2) axis, affecting both normal aging and AD progression (Hasel and Liddelow, 2021). Conversely, the influence of *APOE* alleles on the astrocyte transcriptome is less pronounced, mainly reflecting disruptions in lipid metabolism and extracellular matrix regulation.

Lipid metabolism disruptions were closely associated with neuroinflammation, a core feature of many neurodegenerative diseases (Estes et al., 2021; Yang et al., 2022). ApoE is also involved in the regulation of inflammation, which is tightly connected to lipid homeostasis. ApoE4 significantly altered pathways involved in cholesterol homeostasis and transport. Moreover, ApoE4 astrocytes exhibited impaired clearance of toxic fatty acids from the extracellular space, as ApoE4 rerouted these lipids back into secretion (Lindner et al., 2022). Lipid mediators such as eicosanoids and sphingolipids are key regulators of inflammation, and disruptions in their metabolism are linked to chronic inflammation in neurodegenerative diseases (Di Paolo and Kim, 2011). ApoE4 was associated with a pro-inflammatory profile, marked by higher levels of inflammatory cytokines and altered immune cell activation, which further exacerbates neurodegenerative mechanisms (Parhizkar et al., 2022; Lee et al., 2023; **Figure 1**).

The *APOE* ε4 allele was associated with small vascular damage as well as mitochondrial dysfunction. From genetic to epigenetic mechanisms, such as the epigenomic factor of activated microglia (EFAM), *APOE* ε4 initiated an inflammatory cascade leading to small vessel rupture and the leakage of blood-derived toxic proteins into the brain (Ma et al., 2021). *APOE* ε4 also promoted the formation of lipid rafts, which serve as physical platforms for amyloid precursor protein neuronal localization and subsequent Aβ synthesis. While *APOE* normally facilitated Aβ clearance through its interaction with low-density lipoprotein receptor-related protein 1 (LRP1), the ε4 isoform impaired this process, resulting in Aβ accumulation and plaque formation. Furthermore, the interaction between *APOE* and the translocase of the outer mitochondrial membrane 40 homolog (TOMM40) gene on the outer mitochondrial membrane drove mitochondrial dysfunction, reducing cytochrome oxidase activity and increasing Aβ production (Caselli et al., 2012).

APOE ε4 was also linked to an elevated risk of atherosclerosis, whereas the *APOE* ε2 and *APOE* ε3-Jacksonville (*APOE* ε3/Jac) genotypes lowered this risk by reducing Aβ deposition. Interestingly, EFAM has been shown to mitigate the increased risk of AD associated with *APOE* ε4 by altering the neocortical transcriptome, which reduces microglial activation and tau pathology. *APOE* ε3 homozygotes exhibited a potentially sustained inflammatory response to AD pathology, characterized by enhanced microglial migration toward Aβ deposits and increased Aβ uptake, thereby mitigating cognitive deficits (Medway et al., 2019).

The interaction between *APOE* and α-synuclein (α-syn) influenced PD pathology, with *APOE* genotypes, particularly *APOE* ε4, enhancing α-syn aggregation (Emamzadeh et al., 2016). While no studies have directly linked *APOE* ε4 to oligodendrocytic synucleinopathy or multiple system atrophy, astrocyte-secreted *APOE* ε4 has been found to reduce α-syn uptake in oligodendrocyte cultures (Ogaki et al., 2018). The implications of *APOE* ε4 in synucleinopathies continue to be explored. Recent researches suggested that *APOE* regulates α-syn brain pathology independently of its effects on AD-related Aβ and tau pathology, with *APOE* ε4 specifically worsening α-syn pathology (Davis et al., 2020; Zhao et al., 2020). *APOE* ε4, in contrast to *APOE* ε2 or *APOE* ε3, aggravated α-syn pathology, amplified neuronal and synaptic loss, and heightened astrogliosis by nine months of age. Transcriptomic analysis of α-syn mice expressing *APOE* ε4 revealed alterations in lipid metabolism, energy pathways, and synapse-related functions. Furthermore, *APOE* ε4 was associated with increased α-syn pathology in human postmortem brains with LBD and minimal amyloid pathology (Zhao et al., 2020).

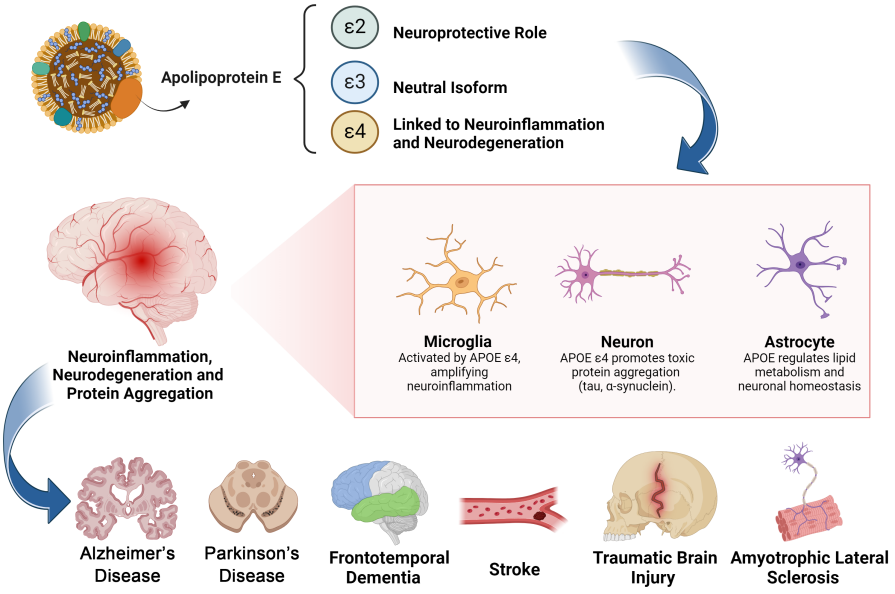

Figure 1 | **The mediating role of the apolipoprotein E gene in neurodegenerative and vascular disorders.**
The image illustrates the key role of the apolipoprotein E gene (*APOE*), particularly the ε4 variant, in neuroinflammation, neurodegeneration, and protein aggregation. The interactions between microglia, astrocytes, and neurons highlight how *APOE* ε4 may amplify inflammation and promote the accumulation of toxic proteins, contributing to the progression of various diseases. Alzheimer's disease (represented by brain atrophy), Parkinson's disease (loss of dopaminergic neurons in the substantia nigra), frontotemporal dementia, stroke, traumatic brain injury, and amyotrophic lateral sclerosis (motor neuron degeneration). Created with BioRender.com.

Apolipoprotein E Gene and Neuropsychiatric Symptoms of Specific Neurodegenerative Diseases

Alzheimer's disease

NPS are widespread in AD, accounting for up to 90% of patients at some point during the illness. These issues can arise early in the disease progression, even preceding noticeable cognitive impairment, and are associated with a faster progression of AD, greater caregiver strain, and elevated medical costs (Siafarikas et al., 2018; Bomasang-Layno et al., 2021; Tahami et al., 2023). The effects of *APOE* ε4 on cognitive decline may depend on a "threshold" of amyloid or tau burden, emphasizing that genetic predisposition interacts dynamically with the presence and extent of

pathology because it does not independently guarantee AD development without pathological markers (Lozupone and Panza, 2024).

According to recent studies, some of the most commonly reported NPS in AD were apathy, depression, anxiety, agitation, aggression, and psychosis. Additionally, a significant number of patients have been reported to experience issues such as disrupted sleep, irritability, and altered appetite, although these are less prevalent (Hajjo et al., 2022). Patients with AD already face a significantly elevated mortality risk, but certain types of NPS may have a greater impact on survival. For example, evidence suggested that individuals with MCI who presented mood-related NPS may also face an elevated risk of mortality (Huang et al., 2022). Different *APOE* genotypes could impact NPS in AD differently (Panza et al., 2011). The *APOE* ε4 allele stands out as the most significant genetic risk factor for sporadic AD, although the precise mechanisms underlying this risk are still not completely clear. Specifically, the *APOE* ε4 allele may influence each NPS in a distinct and specific manner when considered individually, rather than as a collective group (Serrano-Pozo et al., 2021; Yoro-Zohoun et al., 2021; **Figure 2**).

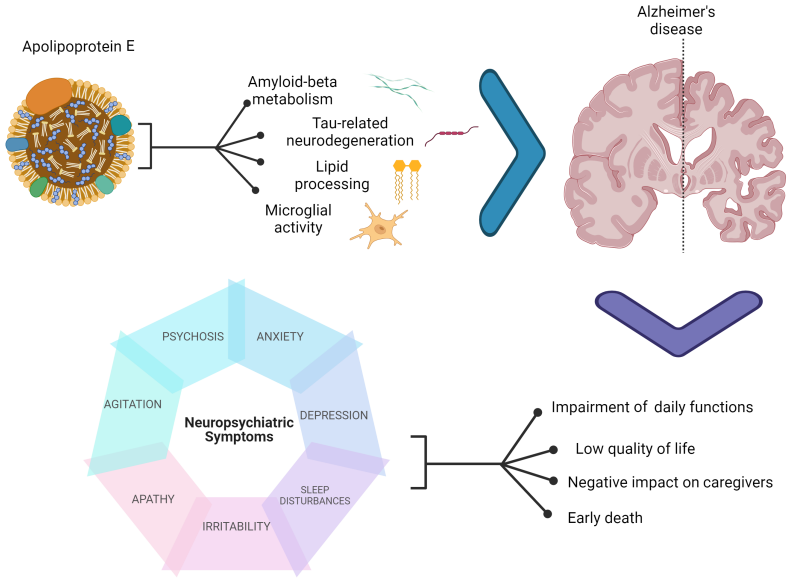

Figure 2 | **Neuropsychiatric symptoms in AD and the role of the apolipoprotein E gene.**
AD can lead to neuropsychiatric symptoms such as apathy, agitation, aggression, depression, psychosis, sleep disturbances, irritability, and appetite changes also through the mediating role of the apolipoprotein E gene on AD pathophysiology. They may lead to impaired daily functioning, increased caregiver burden, and premature death. Created with BioRender.com. AD: Alzheimer's disease.

Psychosis

Psychosis affected a notable percentage of patients with AD, manifesting primarily through delusions and hallucinations. The most common delusions present in AD patients may involve misinterpretations of reality, such as believing that caregivers are stealing from them, while hallucinations often manifest as seeing or hearing things that are not present (Benmelouka et al. 2022). Psychosis was more present in the latter stages of the disease (in approximately 45% of patients with advanced AD), while the presence of psychosis in the early stages of AD was relatively rare. However, recent studies have demonstrated a lack of proper diagnostic tools for early psychosis detection in AD patients, which makes a precise determination of the prevalence of this NPS somewhat difficult compounded by recent challenges and proposed strategies for improving AD psychosis trial methodologies (Devanand et al., 2022; Ballard et al., 2024).

The presence of psychotic symptoms in AD patients was associated with more rapid cognitive decline, increased rates of institutionalization, and heightened mortality risk (Naasan et al., 2021). Psychosis in AD has been associated with specific neuropathological changes, including alterations in tau protein levels and synaptic dysfunctions, suggesting a complex interplay among neurodegeneration and psychiatric manifestations (Ismail et al., 2022). Moreover, recent research has highlighted a correlation between psychosis and different *APOE* genotypes. More specifically, in carriers of at least one *APOE* ε4 allele, psychosis was associated with an increased risk of cognitive decline. A significant interaction was also identified between psychosis and *APOE* allele status, further highlighting the interplay between genetic predisposition and NPS in disease progression since from prodromal phases (Creese et al., 2023).

The *APOE* ε4 allele has been shown to increase the risk of psychotic symptoms in AD, particularly delusions and hallucinations (Harwood et al., 1999). Among AD patients carrying the *APOE* ε4 allele, this elevated risk for psychosis was observed even after controlling for factors such as age, gender, education, and the level of cognitive impairment, especially at severe stages of cognitive decline (Harwood et al., 1999). While the exact mechanism by which the *APOE* ε4 allele increases the risk for psychotic symptoms remains unclear, it is hypothesized that the ε4 allele amplifies key neuropathological features of AD, including Aβ deposition, neurofibrillary tangle formation, cerebral amyloid angiopathy, and Lewy body (LB) inclusions (Goldberg et al., 2024).

Evidence also suggested that the link between the *APOE* genotype and psychotic symptoms, particularly delusions, may stem from neuropathological changes concentrated in the temporal lobe (Basso et al., 1978; Lehtovirta et al., 1996; Hashimoto et al., 2001). For example, single-photon emission computed tomography studies have identified reduced blood flow (hypoperfusion) in the temporal lobes of *APOE* ε4-carriers with delusions (Lehtovirta et al., 1996). Complementary structural MRI analyses have consistently demonstrated greater medial temporal lobe atrophy in AD patients carrying the *APOE* ε4 allele. These findings suggest a robust relationship between the presence of the *APOE* ε4 allele and degeneration in specific brain regions, highlighting the allele's influence on both the progression and intensity of psychotic symptoms.

Interestingly, distinct psychotic clinical phenotypes, such as delusions and hallucinations, may have differential associations with *APOE* alleles. Hallucinations were found to occur more frequently in individuals without *APOE* ε4 alleles compared with double *APOE* ε4-carriers. In contrast, delusions were more strongly associated with the presence of the *APOE* ε4 allele. However, in AD patients, the *APOE* ε4 allele demonstrated a differential association with delusions and hallucinations collectively, but not with delusions in isolation (Chriestie et al., 2012). These findings underscored the complex relationship between *APOE* alleles and the manifestation of psychotic symptoms, warranting further investigation into the interplay of genetic, neuropathological, and clinical factors in AD psychosis.

Depression

Mood disturbances, such as psychosis, represented common clinical manifestations associated with AD that significantly may affect their quality of life and that of their caregivers (Porsteinsson et al., 1997). Currently, depression is considered one of the most prevalent mood disturbances, affecting up to 80% of patients with AD, and occurring practically regardless of the stage or advancement of the disease. Depression manifestations in AD were mainly characterized by loss of interest in previously enjoyed activities, social withdrawal, and persistent sadness. Patients often express feelings of hopelessness or worthlessness, which can be exacerbated by the cognitive decline associated with the disease (Burke et al., 2019). Other NPS belonging to mood disturbances inherent to AD were represented by sleep and eating disorders which often lead to episodes of irritability or anger (Nobis et al., 2018).

Neuroimaging studies have shown that mood-related symptoms in the context of AD correlated with specific brain regions involved in emotional processing and regulation, such as the prefrontal cortex and limbic system. For instance, patients with depression exhibited reduced metabolic activity in the left cingulate gyrus and bilateral frontal lobes, areas critical for mood regulation and cognitive function. Structural changes such as cortical atrophy and white matter degeneration in these regions have been linked to the severity of depressive symptoms, suggesting that

neurodegeneration, neuroinflammation, and neurotransmitter alterations may directly influence mood disturbances (Li et al., 2024).

In AD patients exhibiting NPS, carrying the *APOE* ε4 allele has been associated with an increased risk of affective and apathetic syndromes (D'Onofrio et al., 2010). Notably, a potential link between the *APOE* gene and various vascular risk factors emerging in later life has been identified, which may further correlate with depressive disorders. The presence of the *APOE* ε4 allele, in particular, has been suggested as a genetic predisposition marker for the development of ischemic cerebrovascular diseases (McCarron et al., 1999). This aligns with current etiological models of late-life depression and cognitive decline, which emphasize the role of vascular risk factors as central contributors. These models underscore the potential for devising prevention and intervention strategies tailored specifically for populations at high risk, highlighting the importance of understanding genetic influences, such as the *APOE* ε4 allele, in mitigating these conditions (de Leeuw et al., 2004).

The *APOE* ε4 allele not only may predispose carriers to vascular diseases but may also amplify the detrimental effects of vascular risk factors. This genetic marker is associated with exacerbated consequences of vascular damage, potentially resulting in more severe clinical conditions (de Leeuw et al., 2004). Additionally, the *APOE* ε4 allele has been linked to a reduced capacity for brain injury recovery and a limited ability for neuronal repair, which may contribute to the onset and progression of depression in older adults carrying this allele (Crawford et al., 2002).

The *APOE* gene, especially the ε4 allele, also regulates neurobiological processes implicated in appetite and food preferences (Hajjo et al., 2022). Individuals with the ε4 allele may experience altered neuropeptide signaling, resulting in shifts in hunger signals and satiety responses (Marin et al., 2023). These changes can lead to weight loss or shifts in dietary patterns, complicating nutritional management for this population. Moreover, sleep disorders were common among individuals with AD and they had a substantial impact on their overall quality of life. Findings indicated that sleep issues associated with depressive symptoms and with the presence of the *APOE* ε4 allele were linked to AD in follow-up assessments of individuals who were originally cognitively healthy (Burke et al., 2016). Evidence indicated that *APOE* ε4-carriers tended to experience more pronounced sleep fragmentation and alterations in sleep patterns (Kuang et al., 2021; Ming et al., 2023). The worsening of sleep quality may contribute to the build-up of Aβ plaques, and disrupted sleep has been related to increased Aβ accumulation, oxidative stress, and tau hyperphosphorylation (Lv et al., 2022; Xiong et al., 2022).

Apathy

Apathy, characterized by diminished motivation and emotional disengagement, is the most frequently observed NPS in AD, exerting a substantial impact on caregiver distress (Mehak et al., 2023). The association between apathy and incident dementia appeared to be influenced by both cognitive status and *APOE* genotype, suggesting these factors may serve as key moderators in understanding how apathy contributes to dementia risk (Lozupone et al., 2024). Evidence suggested that apathy may act as a preclinical or prodromal symptom of dementia, with its relationship to dementia risk particularly affected by the *APOE* ε3 genotype. Further exploration is required to uncover the precise mechanisms underlying this link and to identify effective interventions targeting apathy within the broader context of dementia risk (Dolphin et al., 2023). Interestingly, the risk of dementia associated with apathy appeared to be lower in *APOE* ε4-carriers, possibly because *APOE* ε4-related pathways play a more dominant role in driving neurodegeneration, thereby diminishing the relative contribution of apathy to dementia progression (Nobis et al., 2018; Dolphin et al., 2023).

Anxiety

Anxiety was increasingly acknowledged as a notable NPS affecting around 40% of patients with AD, since from the early phases of cognitive decline, particularly among those with MCI (Mendez et al., 2021). A correlation existed between anxiety and specific neurobiological alterations, such as heightened amyloid accumulation and shrinkage in the entorhinal region, which are indicative of AD pathology. Notably, studies suggested that anxiety can accelerate the transition from MCI to dementia, underscoring its potential significance as an early marker of the disease (Mendez et al., 2021; Botto et al., 2022). Anxiety was associated with a quicker progression from MCI to AD, with longitudinal studies indicating that individuals with higher anxiety levels may experience more rapid cognitive decline, particularly affecting memory capabilities (Gracia-Garcia et al., 2023).

The *APOE* ε4 genotype has been linked to increased anxiety levels in older adults without dementia, highlighting its potential role in emotional regulation and neuropsychiatric vulnerability (Mosca et al., 2018). Preclinical studies further supported this association, demonstrating that the *APOE* gene influenced anxiety-related behaviors through alterations in brain structure and function. For example, mice carrying the *APOE* ε4 allele exhibited pathological changes in the central nucleus of the amygdala, a critical region for anxiety regulation (Raber, 2007).

In studies using genetically modified mice expressing human *APOE* genotypes, the impact of the gene was found to be both isoform-specific and age-dependent. Male *APOE*-/- (gene knockout) and ApoE4-expressing mice displayed elevated anxiety behaviors, while mice expressing the ApoE3 isoform showed behaviors comparable to those of normal controls. Importantly, these differences were not observed in younger animals, suggesting that the anxiety phenotype emerged with age or with the progression of underlying neurodegenerative changes (Robertson et al., 2005). Furthermore, the expression of *APOE* in different cell types, neurons (via the neuron-specific enolase promoter) versus astrocytes (via the glial fibrillary acidic protein promoter), also influenced anxiety levels, underscoring the cell-type-specific roles of *APOE* in regulating emotional behaviors.

In studies using animal models, it has been observed that *APOE* ε4-carrier mice performed better on cognitive tasks but exhibited greater anxiety levels than their ε2 and ε3 counterparts, highlighting a complex interplay between *APOE* variants, anxiety, and cognitive abilities (Siegel et al., 2010; Boutros et al., 2023). Additionally, the ε2 allele was considered protective against behavioral responses to stress, suggesting its potential role in moderating anxiety symptoms also in AD (Raulin et al., 2022; Torres et al., 2022). The *APOE* ε4 allele may contribute to heightened levels of anxiety in individuals with AD, particularly among those with early-onset AD (onset before 65 years of age) (Porter et al., 2003). This association aligns with evidence from mouse models, which highlight the isoform-dependent effects of *APOE* on anxiety-related behaviors. In a study of probable AD patients, the specific *APOE* genotype carried influenced anxiety severity, mirroring findings in preclinical models (Robertson et al., 2005).

Role of the apolipoprotein E gene on caregiver stress in sporadic Alzheimer's disease

APOE variants also played a relevant role in the development of abnormal motor behavior (AMB) in AD, one of the most distressing NPS for caregivers. Studies indicated that individuals with the *APOE* ε4 allele experienced a greater frequency and intensity of AMB, which included activities such as pacing and wandering (Garcia-Segura et al., 2019). This relationship was likely linked to the isoform effects on Aβ pathology and neuroinflammatory processes. Specifically, the *APOE* ε4 allele was known to hinder the functioning of microglia, resulting in decreased clearance of Aβ and worsening neurodegeneration, which can present as AMB (Garcia-Segura et al., 2019).

Caregivers for AD patients with symptoms such as hallucinations, delusions, depression, and AMB faced higher stress compared with caregivers of older adults without NPS. Caregiver stress can lead to different negative outcomes, including declines in physical and mental health, reduced quality of life, and increased financial burdens, making it a significant public health concern (Broxson et al., 2020). A study investigating the impact of psychological stress on the relationship between *APOE* genetic variants and metabolic traits found that stress exacerbates adverse metabolic outcomes associated with specific *APOE* genotypes, particularly in caregivers who often experience elevated stress levels (Kring et al., 2011). Interventions such as psychoeducation, support groups, and respite care can notably decrease caregiver stress and enhance overall well-being. These findings highlighted the importance of healthcare systems adopting such measures to bolster caregiver support, ultimately leading to better care for dementia patients (Rodríguez-Alcázar et al., 2024).

Therapeutic opportunities

These reviewed findings highlighted the multifaceted impact of the *APOE* ε4 allele, from its role in increasing vascular and neurological vulnerability to its potential influence on

the emergence of affective and depressive syndromes in aging populations. Understanding these pathways may provide critical insights for developing targeted therapies and preventive measures for individuals at higher risk due to their genetic makeup. This nuanced relationship between *APOE* variants and NPS emphasizes the isoform-specific and age-dependent effects of ApoE on the brain. The complex interplay between genetic factors, cognitive status, and NPS in shaping dementia trajectories, highlighted the need for personalized strategies to address NPS and its implications in neurodegenerative diseases. Therapeutic strategies targeting *APOE* genotypes, particularly *APOE* ε4, in AD, focused on mitigating the pathogenic effects of *APOE* ε4 while enhancing the protective functions of *APOE* ε2 and ε3 (Lozupone et al., 2023). Most of these are in clinical trials. Briefly, they could be grouped in: (1) Reducing *APOE* ε4 pathogenicity. Therapies aiming at neutralizing the harmful effects of the *APOE* ε4 genotype included: *APOE* ε4 structural modulators; small molecule stabilizers; *APOE* ε4-specific antisense oligonucleotides; to reduce *APOE* ε4-driven amyloid aggregation. (2) Enhancing *APOE* function across genotypes. Even in non-ε4 carriers, *APOE* plays a critical role in lipid transport, synaptic repair, and neuronal health. Strategies to enhance *APOE* beneficial functions include: *APOE*-mimetic peptides and lipidation enhancers. (3) Gene therapy for *APOE* modification. Gene therapy approaches aimed to modify *APOE* expression or deliver protective isoforms with *APOE* ε2 delivery and CRISPR/Cas9 genome editing (Wang et al., 2108). (4) Modulating *APOE*-mediated inflammation. Anti-inflammatory strategies targeting *APOE* ε4 included microglial modulation and anti-inflammatory small molecules.

Huperzine A (Hup A), an alkaloid derived from club moss (Huperzia serrata) (Cao et al., 2021), has been shown to modulate *APOE* expression while preventing excessive autophagy and apoptosis. Chen et al. (2024a) indicated that Hup A primarily influences the transcriptional regulation of key genes involved in lipid metabolism, including *APOE*. These findings highlighted Hup A's potential as a therapeutic agent in conditions characterized by dysregulated *APOE* expression and lipid metabolism, such as AD. By modulating pathways related to cell survival and lipid homeostasis, Hup A may offer a multifaceted approach to mitigate neurodegenerative processes. Further research is needed to fully elucidate its mechanisms and optimize its therapeutic application.

Mild cognitive impairment and mild behavioral impairment

The progression from MCI to dementia could be linked to the presence of NPS such as depression, apathy, anxiety, and sleep disturbances. Depression, particularly in its severe form, has been associated with a higher risk of amnestic MCI, while apathy has been strongly correlated with the development of non-amnestic MCI (Hu et al., 2020). It was reported that long-term depression can lead to brain atrophy, whereas intermittent or past depression may not increase MCI risk if cognitive function remains intact (Hu et al., 2020).

MBI is a neurobehavioral construct encompassing five core NPS domains before or contemporary with the presence of MCI: affective dysregulation, impulse dyscontrol, social inappropriateness, psychotic symptoms, and apathy (Ismail et al., 2016). Apathy, characterized by reduced interest, initiative, and emotional reactivity, was particularly common and persistent (Lozupone et al., 2024). Apathy posed a greater risk for incident dementia in individuals with normal cognition compared with those with MCI, underscoring the importance of considering baseline cognitive status when assessing behavioral risks for dementia (Vellone et al., 2022). Furthermore, MBI is commonly observed in individuals with amnestic MCI and is associated with more severe affective symptoms, apathy, and impulse dyscontrol. Recent studies have investigated the genetic underpinnings of MBI severity. Although *APOE* and brain-derived neurotrophic factor (*BDNF*) polymorphisms were not individually linked to MBI severity, their combined impact suggested potential interactions that warrant further exploration (Matuskova et al., 2024).

Understanding the role of NPS and their interaction with genetic factors such as the *APOE* genotype may be crucial for enhancing early detection and intervention strategies for MCI, as well as in individuals without dementia (Stella et al., 2024). Furthermore, synergistic interactions between NPS and *APOE* ε4 allele were identified among individuals with MCI, significantly enhancing the predictive accuracy for incident dementia (Valero et al., 2020). The *APOE* genotype influenced the relationship between depression and MCI (Hu et al., 2020). The combined presence of depression and the ε3/ε4 or ε4/ε4 genotype has been associated with a notably higher risk for MCI development. Additionally, age (particularly over 70 years) and gender influenced this association, with women showing a higher risk of MCI linked to depression, potentially moderated by psychological resilience (Hu et al., 2020).

Integrate *APOE* genotype and NPS assessments could refine risk predictions and enhance early detection and could potentially delay or prevent the progression to dementia, thereby altering disease outcomes for individuals with MCI and other cognitive conditions such as MBI and subjective cognitive decline (Vellone et al., 2022). This last dementia at-risk group included a condition characterized by self-reported cognitive symptoms in the absence of objective cognitive impairment. Preliminary studies in older adults with subjective cognitive decline revealed that *APOE* ε4 homozygosity was more prevalent in individuals with MBI (Nathan et al., 2020). Additionally, specific genetic and affective factors, such as the *APOE* ε4 allele and subclinical anxiety symptoms, were identified as risk factors for early-stage AD. These factors may modulate the expression of brain structural markers in individuals with subjective cognitive decline, highlighting their potential role in the preclinical stages of neurodegeneration (Sun et al., 2019).

Synucleinopathies: Parkinson's disease and Lewy body disease

The role of *APOE* variants has also been highlighted in α-synucleinopathies, such as PD and LBD, neurodegenerative disorders that exhibited significant overlap in their clinical presentations and pathophysiological mechanisms. PD, affecting over 6 million people worldwide, was characterized by the progressive damage of dopaminergic neurons in the substantia nigra and the inclusion of LB within surviving neurons, abundant at presynaptic terminals (García-Sanz et al., 2021). The accumulation of α-syn protein in LBs is central to the pathology of PD and LBD, with different brain localizations. The inner structure of LBs often comprises lipid-rich material rather than solely aggregated proteins, suggesting a complex interplay between lipids and α-syn in the early stages of the disease (Fares et al., 2021; García-Sanz et al., 2021). α-Syn is a 140-amino acid protein characterized by three distinct domains: a C-terminal acidic region, a central hydrophobic region that drives aggregation, and an N-terminal domain responsible for lipid binding, similar to *APOE* (Villar-Piqué, 2016). Notably, the six known mutations in the SNCA gene linked to familial PD are all confined to the N-terminal domain (Ruf et al., 2019). This domain contains unique hexameric 11-amino-acid repeats, typical of apolipoproteins, which endow α-syn with its lipid-binding capacity (Hsiao, 2017).

In contrast, LBD presents with a similar neuropathological feature but with distinct clinical manifestations, including early NPS such as pronounced cognitive fluctuations, visual hallucinations, REM sleep behavior disorder, and apathy (McKeith et al., 2017). The role of *APOE* variants in PD has garnered increasing attention due to their role in lipid metabolism and neuronal degeneration. Although *APOE*'s role in AD is well-documented, its function in PD was less explored but equally significant. While some studies have found no significant association between *APOE* alleles and the overall risk of developing PD, genome-wide association studies have suggested that the *APOE* ε4 allele contributed to progressive cognitive decline in PD. This highlighted its role in modulating cognitive symptoms rather than influencing the initial risk of the disease (Federoff et al., 2012; Tan et al., 2021). ApoE fragments were found in neurons and LBs within the substantia nigra of patients with PD and in the neocortex of incidental LBD (a precursor of PD). Its amino-terminal fragments located in LBs were specifically associated with cognitive impairments related to PD (Rohn and Mack, 2018).

Although studies suggested that the *APOE* ε4 allele was associated with an increased risk of AD, its interaction with cholesterol metabolism did not produce the same effect in DLB. This implied potentially distinct pathogenic pathways in the two disorders (Borroni et al., 2006; Hallett et al., 2019). Recent findings suggest that the AD polygenic risk score did not drive dementia in LBD, indicating that the *APOE* ε4 allele may contribute to dementia in LBD through AD pathology-independent mechanisms, potentially involving neuroinflammation (Wu et al., 2024). Furthermore, alterations of *APOE* interactions with its receptor, low-density lipoprotein receptor LRP1, which normally prevents neuronal apoptosis and contributes to lipoprotein homeostasis, may contribute to the pathogenesis of PD. The deletion of *APOE* reduced α-syn aggregation in transgenic mice. Conversely, elevated ApoE levels, especially in

the presence of aggregated α-syn, may worsen the progression of PD (Gallardo et al., 2008). The impact of different *APOE* genotypes (*APOE* 2, *APOE* 3, and *APOE* 4) on α-syn aggregation was also investigated *in vitro* (Emamzadeh et al., 2016). Indeed, *APOE* ε4-carriers have been linked to increased α-syn aggregation, which is associated with a higher risk of developing PD and earlier onset of symptoms, although studies were contrasting (Gao et al., 2011). Recent studies have confirmed that the *APOE* ε4 genotype, unlike ε2 or ε3, exacerbated or accelerated dementia in PD, increased α-syn pathology, impaired behavioral performance, exacerbated neuronal and synaptic loss, and enhanced astrogliosis, highlighting disruptions in lipid and energy metabolism as well as synaptic pathways (Davis et al., 2020; Zhao et al., 2020). Recent findings in animal models added evidence of a potential protective role of the *APOE* ε2 allele against α-syn aggregation and confirmed that *APOE* ε2 and *APOE* ε3 did not appear to alter the risk of progression in dementia (Davis et al., 2020).

Neuroinflammation plays a critical role in PD progression (Poewe, 2021), although no definitive microglial phenotype has been linked to the disease (Krasemann, 2017). While the *APOE* gene was well-known for its involvement in neurodegenerative microglial phenotypes, limited data existed on its variants in PD-related microglia. Recent studies have identified a microglial phenotype involved in α-syn clearance, which shared characteristics with other neurodegenerative phenotypes (Choi, 2020). Further exploration of *APOE* variants and their impact on microglial phenotypes could shed light on their role in the onset of PD, the progression to dementia, and the clearance of α-syn. The frequent coexistence of synucleinopathies and amyloidopathies in the brains of patients with PD and AD complicates the interpretation of *APOE* involvement in synucleinopathies. Interestingly, in AD patients, the *APOE* ε4 allele has been associated with higher cerebrospinal fluid (CSF) α-syn levels, particularly in those with MCI who later progressed to AD, showing a dose-dependent effect of the *APOE* ε4 allele (Twohig, 2018). Moreover, elevated CSF α-syn levels were associated with increased brain Aβ burden in carriers of autosomal-dominant AD mutations that also possessed the *APOE* ε4 variant. This finding suggests that α-syn may contribute to the pathophysiology of both synucleinopathies and AD, highlighting a potential intersection of these neurodegenerative processes (Twohig, 2019).

Reduced levels of $A\beta_{1-42}$ and elevated concentrations of phosphorylated tau in CSF have been linked to accelerated cognitive decline in PD. However, the association between the *APOE* ε4 allele and cognitive decline appears to be independent of these biomarkers, suggesting a direct role for *APOE* in influencing α-syn pathology (Davis et al., 2020). A previous study has also shown significantly increased ApoE levels in the CSF of PD patients compared with controls, highlighting its potential as a biomarker for disease progression (Paslawski et al., 2019). Moreover, *APOE* genetic variants may elevate the risk of dementia across all synucleinopathy subtypes, including PD, though they do not necessarily affect the onset of PD itself (Pang et al., 2018). Dickson et al. (2018) found that LB pathology severity was associated with the *APOE* ε4 allele, independent of concurrent AD pathology, although this analysis was limited to cortical regions. Goldberg et al. (2020a) proposed that the *APOE* ε4 allele might play a role in the spread and severity of LB pathology from the midbrain to other brain regions, whereas *APOE* ε2 or *APOE* ε3 variants appeared to be more confined to the midbrain in mouse models.

Lee et al. (2023) explored the relationship between NPS profiles and cognitive impairment in patients with PD and MCI, suggesting that higher scores in mood-related symptoms were linked to poorer verbal memory and executive functions. Increased hyperactivity-related symptoms correlated with diminished naming abilities, visuospatial functions, and verbal memory while psychotic symptoms were associated with lower visuospatial abilities. Notably, elevated scores in mood-related, hyperactivity-related, and psychotic symptoms significantly increased the risk of progressing to dementia, even after adjusting for age, sex, education, disease duration, and levodopa treatment (Lee et al., 2023). Furthermore, Meng et al. (2023) confirmed that NPS, such as depression, anxiety, apathy, and psychosis, were longitudinally associated with cognitive impairment in PD patients, leading to accelerated cognitive decline, a phenomenon potentially explained by dysfunctions in frontostriatal circuits and the HPA axis, although the underlying mechanisms require further investigation.

Patients with PD carrying the *APOE* ε4 allele and experiencing late-onset PD (> 55 years old) tended higher rates of depression, as well as fewer delusions and euphoria. However, these findings may be influenced by the greater use of antiparkinsonian medications among *APOE* ε4 allele carriers (Pavlova et al., 2014). Accurate phenotyping of motor, cognitive, and behavioral symptoms remains essential for characterizing a patient's clinical profile (Béreau et al., 2023). Moreover, genetic factors, such as *APOE* variants, hold the potential for enhancing clinical-genetic models aimed at predicting the risk of developing conditions such as motivational apathy or cognitive apathy, further linking *APOE* not only to cognitive decline, but also to NPS in PD (Szwedo et al., 2022; Wise and Alcalay, 2022; Béreau et al., 2023).

Therapeutic opportunities

Among *APOE*-based therapeutics opportunities, an ApoE peptide-based protein nanosystem demonstrated significant potential as a delivery platform for RNA therapeutics targeting the brain. This innovative approach holds promise not only for overcoming the challenges of transporting therapeutics across the BBB, but also for achieving neuron protection in the treatment of PD. By leveraging the brain-targeting capabilities of ApoE peptides, this nanosystem could contribute to the development of more effective therapeutic strategies for PD, addressing both neurodegeneration and underlying molecular mechanisms (Zhang et al., 2024).

Frontotemporal lobar degeneration and amyotrophic lateral sclerosis

FTLD encompasses a broad spectrum of genetically mediated neurodegenerative conditions, ranging from ALS to AD phenotypes. This spectrum also includes disorders such as progressive supranuclear palsy, PD, and corticobasal syndrome (Koretsky et al., 2023). The *APOE* locus has been involved in some forms of FTLD (Manzoni et al., 2024). The influence of *APOE* alleles on other proteinopathies than AD including FTLD-related 3R and 4R tau inclusion bodies, TAR DNA-binding protein 43 (TDP-43) cytosolic inclusion bodies, and argyrophilic grain disease was also evaluated (Goldberg et al., 2020a). The *APOE* ε2 allele generally does not confer protection against several other proteinopathies, including synucleinopathies and FTLD/tauopathies. This lack of protective effect extends to both 3R and 4R tau forms and TDP-43 pathologies, indicating that the neuroprotective advantage of the *APOE* ε2 allele is highly limited in scope.

While *APOE* ε4 is well-known for its strong association with AD, a meta-analysis suggested it was also implicated in FTLD. The approximately twofold increased risk for ε4-carriers in FTLD suggested a moderate genetic effect. However, the influence of *APOE* polymorphisms in FTLD is generally considered weaker than in AD (Rubino et al., 2013). The ε4 allele may contribute to neuroinflammation, lipid dysregulation, or neuronal repair deficits, which are shared pathological features of FTLD and AD. However, FTLD pathology typically lacks amyloid plaques and tau tangles, which are central to AD. Instead, FTLD is associated with tau or TDP-43 and other proteinopathies, suggesting different pathways through which *APOE* ε4 might exert its influence. *APOE* ε4 likely interacts with neuroinflammation and tau phosphorylation to drive disease progression in both AD and FTLD, albeit through overlapping but distinct pathways (Rubino et al., 2013).

The evidence from transgenic and knock-in mouse models confirmed that *APOE* ε4 exaggerates tau pathology compared with *APOE* ε3. This suggests that *APOE* ε4 plays a direct role in amplifying neurodegeneration, potentially through its impact on microtubule stability and neuronal metabolism (Inbar et al., 2010). Middle-aged ε4-carriers exhibited cortical thinning, particularly in the superior frontal and midfrontal regions. This means that *APOE* ε4 may contribute to a specific anatomical and symptomatic pattern of degeneration. FTLD patients with ε4 showed greater atrophy in the bilateral parietal cortex and hippocampus, regions tied to memory and visuospatial skills (Fennema-Notestine et al., 2011). These findings suggested that ε4 may exacerbate regional vulnerability in FTLD. The ε4 allele specifically increases atrophy in frontal, insular, and right-hemisphere regions, which aligns with the clinical symptoms of the behavioral variant of frontotemporal dementia (bvFTD (e.g., behavioral disinhibition, emotional blunting, and executive dysfunction). *APOE* ε4 showed a dose-dependent effect on behavioral symptoms in bvFTD, indicating that individuals with more ε4 alleles (i.e., homozygous carriers) are likely to exhibit more severe behavioral and personality changes (Engelborghs et al., 2006). This suggested that *APOE* ε4 not only may drive neurodegeneration but also may modulate clinical

expression, potentially by influencing the regions that govern emotional regulation and social behavior.

ALS is a rare and progressive neurodegenerative disease marked by the rapid degeneration of motor neurons, resulting in severe muscle weakness, complete paralysis, and ultimately death. Classified as an orphan disease, ALS affected approximately 9.9 per 100,000 individuals, a number that globally is projected to rise to 222,801 by 2040, underlining the urgent need to understand this devastating condition (Mehta et al., 2023; Bradford and Rodgers, 2024). ALS pathogenesis involves several proteins, including superoxide dismutase 1 and TDP-43 (Jeon et al., 2019). Additional factors such as defective energy metabolism, disruption in iron homeostasis, and neuroinflammation also contributed to the disease progression (Cheng et al., 2021). The impact of the *APOE* gene on ALS remained unclear. Some studies indicated that the *APOE* ε2 allele may offer protection while the *APOE* ε4 allele could be detrimental to ALS onset. However, other studies found no influence of *APOE* genotypes on the clinical course of ALS (Li et al., 2004; Jawaid et al., 2011). More recent reports suggested that the *APOE* ε2 allele correlated with hypometabolism in the brain's motor areas affected by frontotemporal dementia (FTD), although no direct link has been found between *APOE* genotypes and the risk of developing ALS (Govone et al., 2014; Canosa et al., 2019).

Alterations in receptors associated with ApoE have been implicated in the ALS phenotype. For instance, a significant change in the expression of ATP-binding cassette (ABC) A1 and other ABC transporters has been identified in the cortex of ALS patients (Andres-Benito et al., 2017). Moreover, defects in cholesterol metabolism were reported in the brains of ALS patients (Abdel-Khalik et al., 2017). Lipidomic analyses in ALS animal models revealed abnormal lipid droplet collection in dysfunctional astrocytes, as well as mitochondrial dysfunction (Chaves-Filho et al., 2019). Advancements in experimental techniques may enable future studies to further explore the role of the *APOE* genotype in lipid dysregulation and ALS pathology.

Defective cholesterol metabolism, influenced by the *APOE* alleles, may contribute to motor neuron degeneration. Specifically, the low affinity of the *APOE* ε2 allele for low-density lipoprotein receptors can impair cholesterol transport from astrocytes to neurons, potentially altering its metabolism and decreasing the availability of liver X receptor β, a crucial factor in motor neuron survival and neuroinflammation (Jawaid et al., 2011). This impaired cholesterol metabolism could increase neuronal vulnerability and accelerate ALS progression, while this disrupted cholesterol transport may impair neuron function, increasing their vulnerability to degeneration, and potentially accelerating the progression of both motor and cognitive symptoms in ALS (Goldstein and Abrahams, 2013).

A recent study has suggested that the *APOE* ε2 allele was associated with an increased risk of cognitive decline in ALS, particularly impacting frontal brain regions such as the prefrontal and orbitofrontal cortices crucial for executive functions and emotional regulation, which may predispose ALS patients to FTD (Canosa et al., 2019). However, findings from studies investigating the role of the *APOE* ε2 allele in the onset of the disease remained conflicting (Li et al., 2004; Jawaid et al., 2011). Overall, the relationship between the *APOE* locus and ALS remained complex, with ongoing research needed to clarify the underlying mechanisms and explore potential therapeutic strategies targeting cholesterol metabolism and neuroinflammation. These insights suggested that therapies targeting these pathways may hold promise for managing ALS.

ALS often occurs with significant NPS, such as cognitive impairment, behavioral changes, and affective disorders such as depression and anxiety. Up to 15% of ALS patients also presented with FTD, and approximately 35% exhibited milder frontotemporal syndromes (Bradford and Rodgers, 2024). Depression and anxiety were also common, impacting the quality of life and complicating the management of the disease (Zucchi et al., 2019). The impaired cholesterol metabolism associated with the *APOE* ε2 allele could exacerbate these NPS by affecting neuronal integrity and promoting neuroinflammation (Goldstein and Abrahams, 2013). A recent analysis revealed that the cognitive and behavioral profiles of patients with ALS closely resembled those observed in the bvFTD. This overlap underscored the spectrum nature of ALS and FTD, both of which share underlying TDP-43 proteinopathy in many cases. Patients with ALS often exhibit executive dysfunction, apathy, and social disinhibition, which are hallmark features of bvFTD (Lillo et al., 2012).

Therapeutic opportunities

Understanding how *APOE* may contribute to tau pathology and regional vulnerability could lead to targeted therapies that mitigate its effects (e.g., tau inhibitors or anti-inflammatory approaches). Understanding the role of the *APOE* locus in these processes may be crucial for developing comprehensive treatment strategies addressing both the motor symptoms and NPS of FTLD by targeting cholesterol metabolism and neuroinflammation to mitigate i.e. the impact of the *APOE* ε2 allele on ALS patients. Additionally exploring therapeutic strategies targeting these pathways, such as modulating ApoE function or restoring ABC transporter expression, may offer new avenues for intervention (Andres-Benito et al., 2017).

Traumatic brain injury

TBI is recognized as a significant risk factor for developing AD and has been associated with an earlier onset of dementia (Grasset et al., 2020). Recovery outcomes post-TBI are highly variable among individuals, with emerging evidence suggesting a genetic basis for this variability. Notably, multiple meta-analyses have demonstrated a connection between the *APOE* ε4 genotype and an elevated risk of poor long-term outcomes following TBI (McFadyen et al., 2021). The relationship between the *APOE* locus and TBI has been widely studied. RNA sequencing and bioinformatics analyses have connected TBI to neuroinflammation and neurodegeneration, identifying *APOE*, microtubule-associated protein tau, and TREM 2 as differentially expressed genes, with astrocytes and microglia playing key roles in these processes (Zhao et al., 2018). Giarratana et al. (2020) demonstrated that activation of protein kinase C epsilon (PKCε) in *APOE* ε4 knock-in mice following TBI led to a reduction in inflammation and microglial activation. This effect was attributed to the associated increase in BDNF levels.

One key pathophysiological consequence of TBI is BBB dysfunction, which has been observed in TBI patients (Wu et al., 2020). *APOE* plays a critical role in maintaining BBB integrity, but its impact varies by different variants. Studies in *APOE* ε4 knock-in mice showed higher BBB permeability compared with *APOE* ε3 mice (Lochhead et al., 2020). Although both *APOE* ε3 and *APOE* ε4 mice exhibited similar responses to TBI, *APOE* ε3 mice demonstrated better BBB recovery post-injury (Main et al., 2018). In humans, individuals who are homozygous or heterozygous for *APOE* ε4 exhibited increased BBB breakdown, particularly in regions such as the hippocampus and medial temporal lobe. This disruption in BBB integrity has been linked to the acceleration of cognitive decline. *APOE* ε4-carriers experienced accelerated BBB degradation (Montagne et al., 2021). Early TBI research revealed increased tau levels in CSF and intraneuronal $A\beta_{1-42}$ accumulation in damaged axons. However, the role of intraneuronal Aβ in TBI remained unclear. A study by Abu Hamdeh et al. (2018) found elevated levels of amyloid oligomers/protofibrils and $A\beta_{1-42}$ in postmortem cerebral tissue of TBI patients carrying the *APOE* ε4 allele, suggesting that soluble amyloid intermediates may accumulate faster in the presence of *APOE* ε4 after TBI. In contrast, Montagne et al. (2021) found no association between BBB breakdown and Aβ or tau levels in CSF from *APOE* ε4-carriers, although a previous study reported increased phosphorylated tau in the CSF and hippocampal region of *APOE* ε4 mice post-TBI (Cao et al., 2017).

Chronic traumatic encephalopathy, historically known as dementia pugilistica, first described in 1928 as a condition predominantly affecting boxers, can result from repeated TBIs and is associated with cerebrovascular dysfunction (Ramos-Cejudo et al., 2018). Over time, its clinical and pathological spectrum has expanded beyond boxers to include athletes in other contact sports, military personnel, and individuals with a history of repetitive mild TBI. Neuropathologically, chronic traumatic encephalopathy shares characteristics with AD, including neurofibrillary tangles and diffuse Aβ plaques, especially in *APOE* ε4-carriers (Ling et al., 2015). A postmortem study of 1275 brains investigated the relationship between the *APOE* genotype and cerebrovascular disease, revealing notable findings. The *APOE* ε2 genotype, though not protective, was associated with an increased risk of hemorrhages in cases of cerebral amyloid angiopathy. This condition is characterized by the deposition of amyloid plaques on the walls of cerebral arteries and capillaries, which can compromise vascular integrity and contribute to hemorrhagic events (Goldberg et al., 2020b).

Considering its involvement in worse neuronal maintenance, growth, and repair, research has increasingly focused on the genetic influences of the *APOE* ε4 allele with TBI outcomes, including increased mortality, impaired functional

recovery, and adverse neuropsychological effects (McFadyen et al., 2021). Conversely, the *APOE* ε2 allele might offer neuroprotection, although its low prevalence limits its study (Goldberg et al., 2020b). The neurochemical mechanisms of *APOE* ε4 toxic effects involved the release of neurotoxic fragments, mitochondrial dysfunction, and increased neuroinflammation, leading to more severe TBI and diminished recovery (Muza et al., 2019; McFadyen et al., 2021). Despite evidence linking *APOE* ε4 with worse outcomes in severe TBIs, meta-analyses have yielded mixed results on its impact on cognitive functions post-TBI (Muza et al., 2019). Mild TBI, common in contact sports and military settings, can lead to neurodegenerative conditions such as AD and chronic traumatic encephalopathy, with the *APOE* ε4 allele being a significant risk factor (McFadyen et al., 2021).

TBI frequently results in NPS and cognitive symptoms, which can significantly impact recovery and overall quality of life. While most patients recovered quickly, a notable minority continued to experience persistent symptoms (Rabinowitz et al., 2020). Research regarding clinical outcomes after TBI has grown rapidly, emphasizing its frequent association with elevated levels of NPS. Various theories have been proposed to clarify the increased amount of NPS in veterans who have experienced a TBI (Merrit et al., 2018), accounting for both environmental and biological contributions. Among these, the *APOE* genotype has emerged as a critical factor, with findings suggesting that it may provide a biological basis for the vulnerability underlying complex NPS observed in veterans. Recent studies have highlighted that being an *APOE* ε4 allele carrier increased the risk of developing NPS—including depression, anxiety, and post-traumatic stress disorder, even long after the acute phase of injury. This underscores the enduring impact of *APOE* ε4 on mental health outcomes post-TBI, suggesting a persistent and genetic predisposition to neuropsychiatric complications in this population (Merrit et al., 2018).

NPS such as depression, anxiety, and agitation were common and affected a substantial number of TBI survivors, with prevalence rates varying depending on injury severity and individual factors. Depression was prevalent among TBI patients, often exacerbated by the complex interplay of neurological damage and psychological stress (Feiger et al., 2022). TBI can lead to a range of neurobehavioral symptoms, including both somatic (headache, fatigue, dizziness/nausea, sleep disturbance, seizures) and neuropsychiatric effects. NPS were classified into cognitive deficits, such as impaired attention, memory, and executive function, and behavioral disorders, which may involve aggression, impulsivity, or personality changes. These symptoms were not confined to concussion but can be observed across all TBI severities. 30% to 80% of patients with mild to moderate TBI experienced neurobehavioral symptoms for up to three months, with a subset showing persistent issues beyond this period. Factors such as female gender, advanced age, and pre-existing psychological conditions can exacerbate these outcomes. Early identification and targeted interventions for cognitive and behavioral issues are crucial for improving recovery and mitigating long-term impact (Riggio and Wong, 2009).

Therapeutic opportunities

This underscores the importance of identifying *APOE* ε4-carriers early, which could help inform personalized treatment strategies and post-injury rehabilitation plans. Recent findings suggested that targeting PKCε activation could represent a potential therapeutic approach to mitigate neuroinflammation and promote recovery in individuals carrying the *APOE* ε4 allele, who were otherwise at higher risk for adverse outcomes post-TBI (Giarratana et al., 2020). Furthermore, the previous findings underscore the importance of maintaining BBB function as a potential target for therapeutic intervention in *APOE* ε4-carriers at risk for cognitive impairments.

Apolipoprotein E Gene and Neuropsychiatric Symptoms in Vascular Diseases

Stroke and transient ischemic attack

Stroke and transient ischemic attack (TIA) are major public health concerns, with stroke ranking as the second leading cause of death and disability, presenting significant health challenges with variable outcomes, only partially explained by known covariates. Effective long-term management of stroke, including lifestyle changes, pharmacotherapy, and attention to factors such as social support and patient education, is essential for preventing recurrence (Helbach et al., 2024). The *APOE* gene, known for its role in lipid metabolism and predisposition to neurodegenerative diseases, also has a significant impact on ischemic stroke. The *APOE* ε4 allele has been implicated in poorer outcomes following ischemic stroke. Specifically, it was associated with delayed recovery of verbal memory and reduced entorhinal cortex volume one year post-stroke (Werden et al., 2019). Moreover, the ε4 allele was found to increase the risk of stroke-associated dementia, a link that is likely mediated through its effects on BBB dysfunction (Pendlebury et al., 2020). In the largest meta-analysis conducted by the Swedish Heart and Lung Foundation, which accounted for variables such as *APOE* alleles, sex, age of onset, stroke severity, and outcomes, the ε4 allele was associated with a younger age of ischemic stroke onset. This finding underscored the potential role of *APOE* ε4 in modulating not only the risk of stroke but also its progression and longer-term neurological sequelae, although it did not directly influence stroke outcomes (Lagging et al., 2019). Additionally, the *APOE* ε2 allele has been linked to poorer outcomes in men, potentially related to a higher prevalence of white matter disease.

Furthermore, a Chinese meta-analysis identified the *APOE* ε4 genotype as a potential predictor for various types of strokes, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (Chen et al., 2016). The *APOE* ε4 allele has a strong association with pre- and post-stroke dementia, negatively impacting cerebral reserve and accelerating cognitive decline, in patients who have experienced a TIA or stroke. This relationship persisted even after accounting for factors such as stroke severity and white matter disease, indicating that the effect of the *APOE* ε4 genotype was not solely mediated by cerebrovascular burden (Pendlebury et al., 2020).

Endothelial cells and astrocytes may play critical roles in the post-stroke environment. A study by Xiang et al. (2020) using an oxygen and glucose deprivation-reoxygenation model demonstrated that astrocyte-derived ApoE activated the PI3K/eNOS pathway in endothelial cells, offering a protective mechanism. Ischemic strokes, which can damage both white and gray matter, disrupt essential neural repair processes such as axonal regeneration and remyelination. Over time, these impairments may escalate, contributing to the development of vascular dementia or even AD (Wang et al., 2016). Interestingly, both the *APOE* ε2 and *APOE* ε4 genotypes have been linked to white matter disease in ischemic stroke patients (Wang et al., 2015). In a study using E4FAD mice, Hayden et al. (2020) investigated the relationship between white matter ischemic lesions, the *APOE* ε4 genotype, and amyloid pathology in AD. The results revealed that while the presence of the 5xFAD transgene did not influence stroke lesions or cortical amyloid deposition, increased microglial activity and cortical neuron damage were observed in stroke-induced E4FAD mice. These findings suggest that heightened microglial reactivity may play a role in promoting Aβ clearance. However, the study had notable limitations, including its focus on early time points (7–14 days post-stroke) and the use of young mice, which may not fully capture the long-term and age-dependent interactions between ischemic injury, *APOE* genotype, and AD pathology. Further research involving extended time points and older animals is needed to better understand the complex interplay between these factors (Hayden et al., 2020).

NPS, such as depression, anxiety, and agitation, were common among stroke survivors and represented a significant unmet clinical need, given their close association with cognitive deficits and functional disability. Studies have shown that up to 56% of young stroke survivors exhibited NPS within 2 years post-stroke. Depression was particularly prevalent, with a frequency of 47.3%, often associated with dementia and multiple infarcts. Among patients with aphasia, post-stroke depression affected 52%–62% and anxiety around 44%, significantly impacting daily functionality. Additionally, agitation, aggression, and post-stroke psychosis, although less common, posed significant challenges and required further research for effective treatment (Edelkraut et al., 2022). Post-stroke epilepsy was significantly correlated with these symptoms, suggesting a complex interaction between post-stroke neurological conditions (Priya et al., 2021). Post-stroke emotional disturbances can significantly impact survival, functional independence, and quality of life, yet these complications are often underreported. Effective management is crucial for improving stroke outcomes, with therapies aimed at emotional regulation and quality of life enhancement, such as cognitive-behavioral therapy and mindfulness-based interventions, proving to be effective in reducing worry and supporting functional independence and other

neuropsychiatric consequences of stroke (Vitturi et al., 2021; Oestreich et al., 2024).

Therapeutic opportunities

ApoE mimetic peptides have demonstrated the ability to down-regulate the inflammatory response and alleviate secondary neuronal damage following intracerebral hemorrhage. Building on this concept, researchers designed a novel ApoE receptor mimetic peptide, known as 6KApoEp, which consists of the low-density LRP1 receptor-binding domain of ApoE combined with six lysines. This peptide is sufficiently small to penetrate the BBB and modulate the inflammatory response associated with CNS damage. Mechanistically, LRP1 plays a crucial role in inhibiting the CypA/MMP-9 pathway, thereby reducing BBB damage. Studies have shown that 6KApoEp interacted with LRP1, and their interaction co-localized within pericytes, cells essential for maintaining BBB integrity. These findings, as reported by Chen et al. (2024b), highlighted the potential therapeutic application of 6KApoEp in mitigating inflammation and protecting the BBB during CNS damage. Further research could explore its clinical efficacy in conditions such as intracerebral hemorrhage and other neurodegenerative diseases.

Conclusions

In addition to its well-established role in lipid metabolism (**Figure 3**), *APOE* variants may affect mitochondrial function, as lipids are crucial to mitochondrial membranes and energy production. Disruptions in lipid metabolism can impair mitochondrial activity, leading to oxidative stress and energy deficits, both of which are hallmarks of many neurodegenerative and vascular diseases (Chen et al., 2011). Specifically, the *APOE* ε4 allele has been implicated in neurobiological compromises, potentially contributing to its harmful effects on neuronal survival and cognitive function (Farmer et al., 2021). Additionally, the *APOE* ε4 variant has been independently associated with LB inclusions in limbic regions such as the amygdala and neocortex, irrespective of AD pathologies (Dickson et al., 2018). Furthermore, the *APOE* locus emerged as a pivotal factor in modulating NPS across a spectrum of neurodegenerative diseases. The *APOE* ε4 allele specifically has been identified as a significant determinant of the risk and severity of NPS in these conditions. Furthermore, there is evidence of a synergistic interaction between NPS and the *APOE* locus observable even in the early phases of the disease and throughout its progression. NPS influenced not only neurodegenerative disorders course, but also may represent prognostic markers. Among prevalent MCI cases, specific NPS such as depression or apathy interacted with the *APOE* ε4 allele to further elevate the risk of incident dementia (Pink et al., 2015). Identifying factors that contribute to NPS development may allow for earlier interventions and targeted treatments.

Despite these insights, the present review article underscored that current data remained fragmented and, at times, conflicting, pointing to the necessity for further investigation. Future research should prioritize elucidating the precise mechanisms through which the *APOE* locus may influence NPS, exploring the potential mediating role of cognition, and evaluating the effectiveness of *APOE*-modulating therapeutic interventions. An integrated approach considering *APOE*'s role across neurodegenerative diseases could lead to novel prevention and treatment strategies, significantly enhancing clinical management and patient support. Emerging technologies such as gene therapy and genome-editing techniques offer promising avenues for mitigating the effects of *APOE* ε4. These approaches aim to correct or modify the *APOE* gene, potentially reducing the risk of neurodegenerative diseases and their neuropsychiatric correlates (Roberts et al., 2024). Continued research into these innovative strategies is essential to translate findings into effective treatments and improve patient outcomes.

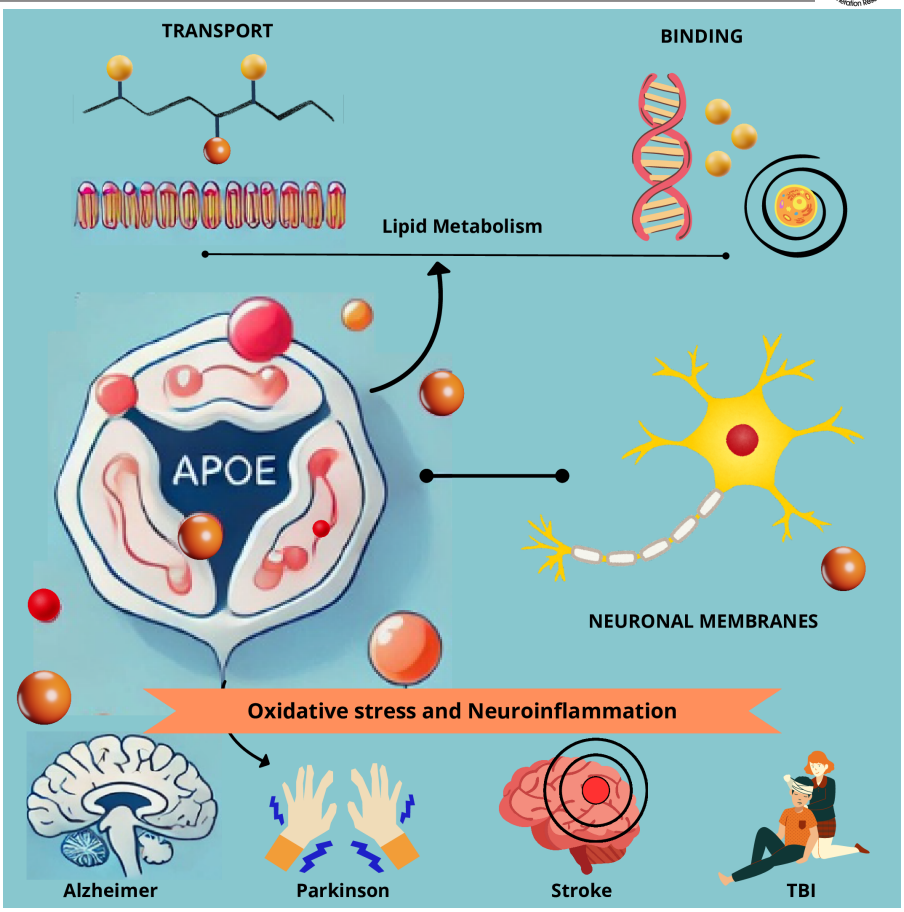

Figure 3 | **APOE function on lipid metabolism.**
APOE gene plays a central role in lipid metabolism, particularly in the binding and transport of lipids such as cholesterol and phospholipids to neuronal membranes, contributing to neuronal plasticity. ApoE function is influenced by oxidative stress, neuroinflammation, and mitochondrial dysfunction, which contribute to the development of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, stroke, and TBI. Created with Canva. APOE: Apolipoprotein E gene; TBI: traumatic brain injury.

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