Review Article

The Apolipoprotein E Antagonistic Pleiotropy Hypothesis: Review and Recommendations

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Research on apolipoprotein E (APOE) has consistently revealed a relationship between the gene's $\varepsilon4$ allele and risk for development of Alzheimer's disease (AD). However, research with younger populations of $\varepsilon4$ carriers has suggested that the APOE $\varepsilon4$ allele may in fact be beneficial in earlier ages and may only confer risk of cognitive decline later in life. Accordingly, we and others have proposed that APOE may represent an example of antagonistic pleiotropy. Antagonistic pleiotropy is an evolutionary biology concept that proposes certain genes or alleles that may differentially impact fitness during different life stages. We critically review this hypothesis in light of new research of the impact of APOE on cognition and neural integrity across the lifespan. We provide recommendations for the revision of the antagonistic pleiotropy hypothesis of APOE and suggest important avenues for future research in this area.

1. Introduction

Apolipoprotein E (APOE) is a protein coded by a gene located on chromosome 19 and plays an important role in cholesterol metabolism and synaptogenesis in the brain [1, 2]. The APOE gene has three variants, or alleles: $\varepsilon2$, $\varepsilon3$, and $\varepsilon4$. The $\varepsilon4$ allele has been consistently associated with a higher risk of developing late-onset or sporadic Alzheimer's disease (AD) and a faster rate of disease progression (e.g., [3]), and as such is perhaps the most frequently studied genetic risk factor for AD. Studies of nondemented older adults utilizing event-related fMRI paradigms have also suggested that $\varepsilon4$ carriers may more strongly recruit task-related brain regions or may recruit additional brain regions beyond task-related areas in order to compensate for preclinical AD changes to achieve the same performance as noncarriers (e.g., [4]). Preferentially recruited areas beyond task-related regions have frequently been found to include frontal regions with a possible predilection for the right hemisphere [1]. While $\varepsilon4$ carriers may initially maintain cognitive performance through these compensatory recruitment processes, once AD disease burden increases, compensatory recruitment processes cannot sustain premorbid cognitive performance levels and cognitive decline ensues [1].

Although APOE has been extensively studied in older populations, its impact on cognition in younger ages has been seldom considered. Interestingly, the few studies that have investigated APOE's impact in early life have frequently reported that $\varepsilon4$ carriers may cognitively outperform noncarriers. For instance, Yu et al. [5] found young $\varepsilon4$ carriers to have higher IQs than noncarriers, Alexander et al. [6] found $\varepsilon4$ carriers as young as six to have higher verbal fluency scores than noncarriers, and Wright et al. [7] found $\varepsilon4$ infants to produce higher scores on the 24-month Mental Development Index of the Bayley Scale.

As we proposed previously in our review on this topic [1], these seemingly contradictory patterns of results may be reconciled through the antagonistic pleiotropy concept. Antagonistic pleiotropy is a concept from evolutionary biology purporting that certain genes may impact fitness (i.e., survival and reproduction) differently during different life stages. Utilizing the concept of antagonistic pleiotropy,

we [1] suggested a model of the impact of APOE on cognition across the lifespan. According to this model, we have the following.

(a) Young ε4 carriers outperform noncarriers on tests of memory and other cognitive domains.

(b) They may also recruit additional right hemisphere frontal regions in order to achieve this advantage.

(c) By middle age, there are slight if any neurocognitive differences between ε4 carriers and noncarriers.

(d) In more advanced ages, ε4 carriers may begin to preferentially recruit right frontal brain regions in order to maintain cognitive performance comparable to noncarriers.

Finally, the model proposes that once AD disease burden sufficiently accrues, ε4 carriers' compensatory recruitment will begin to fail, marking the beginning of cognitive decline.

Much research investigating APOE across the lifespan has been conducted since the antagonistic pleiotropy hypothesis of APOE was proposed. We aim to review our model in light of this most recent research. We provide recommendations for revisions of this model to include recent findings and suggest important areas for future research to evaluate and expand the antagonistic pleiotropy hypothesis of APOE.

We utilized the PubMed database in searching the literature for this review. All searches were limited to those articles published in the last three years because of our intent to focus on research published following our proposal [1] of the antagonistic pleiotropy hypothesis of APOE in 2008. Search terms included "APOE and brain imaging," "APOE and cognition," and "APOE and neuropsychology." The abstracts of articles returned through these searches were examined and relevant articles were gathered. Articles were considered relevant if they examined APOE genotype in relation to cognitive performance or functional imaging in any age group. The reference lists of obtained articles were also searched by hand for additional relevant literature. The articles discussed in this review as well as their sample size, focus, and relevant findings are listed in Table 1.

2. APOE and Cognition in Early Life

Fortunately, research on the impact of APOE in early life has become more prevalent in recent years. However, this work has yielded inconsistent conclusions regarding the impact of APOE on cognition early in the lifespan. Consistent with the model of antagonistic pleiotropy, some studies have reported an ε4 advantage in early life. Bloss et al. [8] found that school-age children with the ε4 APOE allele performed better than children with the ε2 allele on the Rey Complex Figure Test (RCFT) copy trial. Children with the ε2 allele were also more likely than carriers of other alleles to be left-handed, a possible sign of abnormal neural development. Because of ε4 carriers' apparent benefits and ε2 carriers' deficits in this young sample, a reversal of

typical findings in older age groups, the authors suggested that these results are consistent with antagonistic pleiotropy. Also in support, Mondadori [46] reported young adult ε4 carriers to outperform noncarriers on the delayed recall portion of an episodic memory task, although no other differences by genotype were found in working memory, visuospatial processing, or executive functioning. Marchant et al. [9] reported that 18 to 30-year-old APOE ε4 carriers showed an advantage over noncarriers on tests of frontal lobe functioning. Noé et al. [10] studied a sample with moderate to severe traumatic brain injury (TBI) and found that while ε4 carriers were more severe at baseline, they also exhibited a steeper rate of improvement in working memory compared to noncarriers. This work is consistent with our model [1], suggesting an advantage in cognition and head injury outcome for young ε4 carriers.

Nevertheless, studies reporting the opposite findings are equally as prevalent. Gozal et al. [47] found that the APOE ε4 allele was associated with cognitive impairment in 5- to 7-year-old children with obstructive sleep apnea. Dennis et al. [11] and Filbey et al. [12] both failed to find cognitive differences between ε4 carriers and noncarriers in their 20's and 30's and Liu et al. [48] failed to find differences by APOE genotype in those younger than age 50. Hiekkanen et al. [13] also reported that APOE genotype was unassociated with one-year outcome of mild TBI in adults aged 18 to 70. Luciano et al. [14], studying a sample of 70-year olds in the Lothian Birth Cohort, failed to find differences by APOE genotype in IQ measured at age 11. It is noteworthy that several studies finding reduced cognition in ε4 carriers only did so when carriers also had other risk factors for AD. For instance, Ruiz et al. [15] reported finding no differences in cognition by APOE status in a sample of adolescents. However, the authors discovered that ε4 carriers who also carried the MTHFR 677TT allele, a gene possibly detrimental to cognition, displayed significantly worse cognitive performance than adolescents with other allelic combinations. Bloss et al. [16] found that school-age children with the APOE ε4 allele as well as a family history of AD performed more poorly on standardized achievement tests of reading and language and the RCFT copy. Importantly, there was no main effect of APOE genotype; children with the ε4 allele were only found to exhibit depressed scores when they also had a family history of AD, suggesting that these two risk factors interact to influence cognition. Acevedo et al. [17] found that 7 to 10-year-old ε4 carriers were more likely to have been placed in an intensive care unit after birth, achieved lower spatial memory retention, and, among girls only, ε4 carriers achieved lower visual recall scores on the Family Pictures Test. The authors conceptualized the latter finding as representing an interaction between the potentially gendered risk of AD, which is more prevalent in women, with the APOE ε4 risk factor. It is important to note that while the authors indicated that participants' birth complications were unlikely to have impacted cognition, the presence of birth complications was not controlled for in analyses. Because ε4 carriers were more likely to experience birth complications, this fact could explain the association between ε4 status and cognition in this sample.

TABLE 1: Samples, methods, and relevant findings of reviewed articles.

Article	Sample	Methods used	Relevant findings
Bloss et al. [8]	147 youth, age 11–16	Assessment of verbal cognition and visuospatial processing	APOE ε4 carriers performed better than ε2 carriers on a test of visuospatial processing
Marchant et al. [9]	156 college students, age 18–30	Assessment of spatial working memory, estimated IQ, immediate verbal memory, verbal fluency, sustained attention, and decision-making ability	APOE ε4 carriers showed an advantage over noncarriers on tests of verbal fluency and decision-making
Noé et al. [10]	82 patients currently with post-traumatic amnesia (PTA; mean age = 31.5) and 107 patients without PTA (mean age = 29.5)	Assessment of PTA severity, verbal memory, and working memory	APOE ε4 carriers were more severe at baseline but exhibited a steeper rate of improvement in working memory over time than noncarriers
Dennis et al. [11]	24 young adults (mean age = 21.3)	Functional MRI during the encoding portion of an object memory task followed by a recall session 24 hours later, and an assessment of memory, processing speed, attention, and executive functioning	APOE ε4 carriers and noncarriers performed similarly on all cognitive tests, while ε4 carriers showed more bilateral MTL activity and functional connectivity of MTL and posterior cingulate and perilimbic structures during memory encoding
Filbey et al. [12]	36 healthy adults, age 50–75 and 16 adults, age 19–32	Functional MRI during a visual working memory task and an assessment of global cognition	APOE ε4 carriers and noncarriers did not differ in cognitive performance, while ε4 carriers showed more medial frontal and MTL activity compared to noncarriers during the working memory task. Older ε4 carriers also showed decreased activation compared to noncarriers in several frontal, parietal, temporal, and cingulate cortices
Hiekkanen et al. [13]	33 mild TBI patients (mean age = 44.2)	Structural MRI, assessment of PTA, and Glasgow Coma Scale ratings over a one year follow-up period	While MRI findings and PTA severity predicted TBI outcome after one year, APOE genotype was unassociated with TBI outcome
Luciano et al. [14]	1,091 participants in the Lothian Birth Cohort	Assessment of IQ at age 11 and measures of global cognition, working memory, nonverbal reasoning, construction, verbal fluency, and processing speed at age 70	APOE genotype was unrelated to IQ at age 11, yet the ε4 allele was associated with lower processing speed, nonverbal reasoning, and general cognition measured at age 70
Ruiz et al. [15]	412 participants, age 13–18	Assessment of verbal and quantitative skills and problem solving ability	APOE genotype was not associated with cognition, but ε4 carriers who also had the MTHFR 677TT allele had lower quantitative and reasoning abilities
Bloss et al. [16]	109 youth, age 11–16	Assessment of verbal cognition and visuospatial processing	APOE genotype was not associated with cognition, but ε4 carriers who also had a family history of AD had lower verbal and visuospatial abilities
Acevedo et al. [17]	50 youth, age 7–10	Assessment of general intelligence, memory, attention, executive functioning, and visuospatial processing	APOE ε4 carriers were more likely to have been placed in intensive care after birth and had lower spatial memory abilities, especially among girls
Filippini et al. [18]	36 adults, age 20–35	Structural MRI, perfusion MRI at rest, and functional MRI at rest and during a memory encoding task	APOE ε4 carriers showed more connectivity among default-mode network regions and more hippocampal activation during the memory task than noncarriers
Kukolja et al. [4]	18 healthy older adults (mean age = 60.5)	Functional MRI during a spatial contextual memory task	APOE ε4 carriers had poorer memory performance than noncarriers. ε4 carriers also more strongly activated prefrontal, temporal, and parietal regions during encoding than did noncarriers but showed less activation in prefrontal cortex during retrieval
Trivedi et al. [19]	155 healthy adults, age 18–84	Functional MRI during episodic encoding and metacognitive self-appraisal tasks	APOE ε4 carriers showed increasing hippocampal activation with age during the memory task, while noncarriers showed age-related reductions in hippocampal activity
Wierenga et al. [20]	22 healthy older adults (mean age = 78.10)	Functional MRI during an object naming task	APOE genotype was unrelated to naming ability, yet ε4 carriers exhibited greater activity in the left fusiform, right perisylvian cortex, and bilateral medial prefrontal cortex than noncarriers

TABLE 1: Continued.

Article	Sample	Methods used	Relevant findings
Seidenberg et al. [21]	69 healthy older adults, age 65–85	Functional MRI during a semantic memory task	Those with an ε4 allele and family history of AD showed greater activations in bilateral cingulate, temporoparietal, and prefrontal regions than those without risk factors. ε4 carriers also showed greater recruitment of right middle frontal regions
Woodard et al. [22]	57 older adults, age 65–85 with or without amnestic MCI	Functional MRI during a semantic memory task	Those with an ε4 allele and family history of AD displayed increased activation in temporoparietal, hippocampal, and posterior cingulate regions than those without risk factors. MCI patients showed similar patterns along with enhanced frontal recruitment
Bartrés-Faz et al. [23]	32 older adults with mild memory impairments (mean age = 66.83)	Functional MRI during a face-name learning task	APOE ε4 carriers showed increased connectivity of the hippocampus with anterior cingulate, postcentral gyrus, and caudate nucleus during encoding compared to noncarriers
Borghesani et al. [24]	14 healthy older adults	Functional MRI during a visuospatial memory task	APOE ε4 carriers showed less MTL activation during encoding than noncarriers despite equal performance
Xu et al. [25]	74 healthy adults, age 50–65	Functional MRI during an episodic face recognition task	APOE ε4 carriers showed reduced activation in posterior and anterior cingulate and precuneus than noncarriers during recall
Suthana et al. [26]	32 healthy older adults (mean age = 61.1)	Functional MRI during a word memory task	APOE ε4 carriers displayed reduced hippocampal activation during encoding than noncarriers
Welsh-Bohmer et al. [27]	507 healthy older adults, age 66–103	Assessment of object naming, verbal fluency, memory, construction, processing speed, and global cognition	APOE genotype was unrelated to all measures of cognition
Adamson et al. [28]	50 healthy pilots, age 50–76	Structural MRI and assessment of memory	APOE ε4 carriers performed more poorly on visual paired associate recall than noncarriers but showed no structural brain differences
Debette et al. [29]	717 healthy adult offspring from the Framingham cohort (mean age = 59)	Structural MRI, assessment of memory, abstract reasoning, and mental flexibility, and determination of parental dementia	APOE ε4 carriers were more likely to have a parent with dementia. Among ε4 carriers, parental dementia was associated with lower memory performance
Honea et al. [30]	53 healthy older adults age, 60 and older	Structural MRI, diffusion tensor imaging, and an assessment of memory, language, executive functioning, and visuospatial ability	APOE ε4 carriers performed more poorly on measures of memory and working memory and had smaller hippocampi and parahippocampal FA
Caselli et al. [31]	815 healthy adults age, 21–97	A longitudinal assessment of long-term memory, global cognition, verbal fluency, and visuospatial abilities	APOE ε4 carriers were found to experience memory decline in their 50's, while noncarriers did not show decline until their 70's. A dose-dependent effect was found in which ε4 homozygotes displayed earlier memory decline than heterozygotes. ε4 carriers showed steeper decline than noncarriers in memory, global cognition, and visuospatial processing
De Blasi et al. [32]	620 healthy older adults, age 65–85	Assessment of memory and global cognition	While APOE ε4 was associated with memory encoding and recall, it was unrelated to global cognition
Knopman et al. [33]	1130 adults (mean age = 59)	Assessment of memory, verbal fluency, processing speed, and vascular risk factors	APOE ε4 carriers exhibited increased decline in processing speed and memory compared to noncarriers
Mungas et al. [34]	369 older adults (mean age = 74.3)	Assessment of object naming, verbal fluency, memory, and working memory	APOE ε4 carriers exhibited lower episodic memory scores at baseline and increased decline in memory and executive functioning than noncarriers
Walhovd et al. [35]	161 older adults, age 55–90	Structural MRI, FDG-PET, and an assessment of memory	APOE ε4 allele was associated with poorer recognition memory beyond imaging variables

Table 1: Continued.

Article	Sample	Methods used	Relevant findings
Hayden et al. [36]	2957 older adults (mean age = 74)	Longitudinal assessment of global cognition and family history of dementia	APOE ε4 carriers had lower baseline global cognitionand steeper decline in cognition than noncarriers
Whitehair et al. [37]	516 amnestic MCI patients, age 55–90	Longitudinal assessment of global cognition, memory, processing speed, verbal fluency, working memory, naming, and functioning	APOE ε4 carriers had lower baseline scores on nearly every assessment and also showed steeper declines in nearly every domain
Yaffe et al. [38]	2509 healthy older adults, age 70–79	Longitudinal assessment of global cognition and health variables	APOE ε4 allele was associated with likelihood of cognitive decline
Thambisetty et al. [39]	94 healthy older adults (mean age = 69.2)	Longitudinal structural MRI, PET imaging, and assessment of memory, verbal intelligence, verbal fluency, attention, working memory, and executive functioning	APOE ε4 carriers performed more poorly on category fluency and also had greater decline in regional cerebral blood flow, particularly in areas commonly implicated in AD
Raz et al. [40]	189 healthy adults, age 18–82	Assessment of fluid intelligence, memory, executive functioning, and processing speed	APOE ε4 carriers evidenced greater age-related interference effects in a Stroop task than noncarriers
Barabash et al. [41]	89 amnestic MCI patients (mean age = 79) and 90 healthy adults (mean age = 76)	Longitudinal assessment of cognitive diagnosis	APOE ε4 allele was associated with higher risk of developing MCI, but not AD
Wang et al. [42]	20 healthy older adults (mean age = 75) and 58 amnestic MCI patients (mean age = 76.6)	Longitudinal structural MRI and an assessment of global cognition, memory, attention, language, construction, and abstract thinking	APOE ε4 allele was unassociated with rate of decline in cognition or brain volumes
Heun et al. [43]	200 healthy older adults (mean age = 80.3)	Longitudinal assessment of cognitive diagnosis, global cognition, memory, construction, attention, and language	APOE ε4 allele was unassociated with likelihood of conversion to MCI
Carrión-Baralt et al. [44]	87 nonagenarians	Assessment of global cognition, memory, naming, verbal fluency, attention, and processing speed	APOE ε4 carriers displayed higher global cognition, attention, visuospatial processing, naming, praxis, and memory encoding than noncarriers
Kozauer et al. [45]	659 adults (mean age = 58.4)	Longitudinal assessment of global cognition and memory	APOE ε4 carriers in the younger cohort, who were in their 50's, showed increased decline in memory and global cognition compared to noncarriers. However, older ε4 carriers in their 70's showed no cognitive differences from noncarriers

While these studies do not unequivocally support our model of antagonistic pleiotropy and APOE [1], interpretation of the findings of studies in this area is complicated by the nature of the samples studied. When the potential benefit of holding an ε4 allele could be confined to a very narrow window early on in the lifespan, the importance of studying the impact of APOE in specific age ranges and of examining the interaction of age and APOE status in lifespan samples becomes apparent. Moreover, it is likely that APOE status interacts with other genetic and environmental risk factors (e.g., birth complications, MTHFR 677TT allele, family history of AD) to impact cognition [15–17], implying that participants' additional risk factors beyond APOE should also be considered. Taking such measures will greatly clarify the literature in this area and lead to more reliable findings regarding the impact of APOE on cognition in early life.

3. APOE and Compensatory Recruitment in Early Life

Although comparatively less research has examined neural activity than cognition early in the lifespan, fMRI research with children has produced results more consistently supporting our model of antagonistic pleiotropy and APOE. Dennis et al. [11] examined activity in medial temporal lobe (MTL) structures important for memory and functional connectivity between MTL regions and other brain regions using event-related fMRI. Young adult participants were asked to encode visually presented stimuli and were given a surprise recall session 24 hours later. Results revealed that ε4 carriers had more bilateral activity in MTL structures during memory encoding and had more functional connectivity of MTL structures with posterior cingulate and perilimbic

regions than noncarriers. However, ε4 carriers also showed a tendency towards decreased connectivity between anterior and posterior cortices. Dennis et al. [11] suggested that findings of increased functional connectivity between MTL regions and other regions known to be affected by AD (e.g., posterior cingulate) may suggest that APOE begins to be expressed in AD-associated brain regions long before cognitive decline and that these findings may also be consistent with antagonistic pleiotropy. Filbey et al. [12, 49] also found that young adult ε4 carriers showed more medial frontal [12, 49], cingulate [49], and MTL [12] activity compared to noncarriers in a working memory task. In a slightly older sample of 20-to-35-year-olds, Filippini et al. [18] reported ε4 carriers to have more default mode network (DMN) connectivity and more hippocampal activation during a memory encoding task than noncarriers. However, at least one study [46] reported that young adult ε4 carriers exhibited *less* neural activity in bilateral MTL and left frontal regions during the encoding and retrieval portions of an episodic memory task than performance-matched noncarriers. The authors attributed these findings to enhanced neural efficiency of memory networks in young adult ε4 carriers [46].

The majority of these studies appear to support the proposed model of antagonistic pleiotropy in that ε4 carriers tend to recruit task-related regions more intensely than do noncarriers. However, the above studies provide less support for the proposal that ε4 carriers will preferentially recruit more right hemisphere frontal regions during task performance. While it is unclear whether the ε4 carriers studied by Dennis et al. [11] also showed higher activations in frontal regions because the authors focused on activity in MTL structures, Filippini et al. [18] used voxel-based morphometry and did not reveal any involvement of frontal regions by APOE status. Additionally, while Filbey et al. [12] indicated that ε4 carriers recruited medial frontal regions more than noncarriers, this may be due to the nature of the task, as working memory tasks are more frontally-mediated than assessments of episodic or semantic memory.

4. APOE and Compensatory Recruitment in Old Age

As Trachtenberg et al. [50] note in their thorough review, research examining the blood-oxygen-level-dependent (BOLD) response using fMRI has produced inconsistent findings regarding the impact of APOE that are not easily understood even when considering differences in task, family history of AD, and age. While this observation was also borne out in our review of recent research with older adults, the majority of studies provided evidence of compensatory neural recruitment in older APOE ε4 carriers.

Of studies that found evidence of compensatory recruitment in nondemented older adults with the ε4 allele, many found an increase in activation of task-related regions, regions known to be affected by AD (e.g., posterior cingulate), and frontal regions. For instance, Bookheimer et al. [51] found that nondemented middle-aged and older adult ε4 carriers more strongly activated AD-associated brain regions, such as hippocampal, parietal, and prefrontal regions, than ε3 carriers during a paired-associate word learning task. Furthermore, the authors found that the magnitude and extent of neural activation at baseline was predictive of cognitive decline after two years, as would be expected according to the compensatory recruitment hypothesis [51]. Dickerson et al. [52] also reported findings suggestive of compensatory recruitment in a sample of cognitively intact older adults and patients with MCI or AD. Results revealed that APOE ε4 carriers, regardless of diagnosis, showed enhanced hippocampal activity during encoding in a face-name memory task [52]. Similarly, Bondi et al. [53] reported healthy older adult ε4 carriers display more intense and widespread activations in parietal, frontal, and right MTL regions than noncarriers during encoding in a picture learning task. Notably, ε4 carriers exhibited reduced activations in left hippocampal regions compared to ε3 carriers, supportive of our model's [1] prediction of a predilection for compensatory responses in the right hemisphere [53]. A more recent study by Kukolja et al. [4] found that nondemented older ε4 carriers more strongly activated right hippocampal and predominantly right prefrontal, temporal, and parietal regions during the encoding portion of a spatial context memory task than did noncarriers, as would be expected according to antagonistic pleiotropy. However, the authors also reported that ε4 carriers showed less activity in the prefrontal cortex bilaterally during retrieval. Interestingly, the authors noted that hippocampal activity was inversely associated with items remembered for ε4 carriers but positively associated with recall for noncarriers. The opposite relationship was found in bilateral inferior frontal gyrus, right middle frontal gyrus, and left parietal cortex, the activity of which was positively associated with recall among ε4 carriers. In light of these findings, Kukolja et al. [4] suggested that compensation may occur during encoding among ε4 carriers, coinciding with increased frontal activations during this portion of the task. However, they note that activity decreases during the retrieval portion of the task reveal the likelihood of approaching cognitive decline. Filbey et al. [12] also found nondemented older adult ε4 carriers to more strongly recruit medial frontal and temporal regions during a working memory task, although ε4 carriers showed less activity than noncarriers in several other frontal and temporal regions. Trivedi et al. [19] examined a large sample from age 18 to 84 using an episodic encoding task and found that ε4 carriers exhibited increases in hippocampal activity with age, while noncarriers showed age-related decreases in hippocampal activity. Wierenga et al. [20], studying cognitively intact older ε4 carriers with a confrontation naming task, found that ε4 carriers displayed increased activations compared to noncarriers in the left fusiform gyrus, bilateral medial prefrontal cortex, and right perisylvian cortex despite equal performance across the groups. Seidenberg et al. [21] utilized a semantic memory task designed to require low levels of effort and produce high accuracy rates in a cognitively normal sample of older adults. They found that those with the ε4 allele and a family history of AD preferentially recruited bilateral posterior cingulate/precuneus, bilateral

temporoparietal junction, and bilateral prefrontal cortex than participants without any AD risk factors during recall of familiar versus unfamiliar names. Moreover, in comparing participants with both the ε4 allele and family history of AD to those with just a family history, ε4 carriers exhibited more activation in right middle frontal and right supramarginal gyri. Seidenberg et al.'s [21] results suggest that the APOE ε4 allele was uniquely associated with preferential activation of right hemisphere frontal regions, as we have suggested [1]. Woodard et al. [22] also used a low-effort famous name discrimination task and found that participants with an ε4 allele and family history of AD displayed increased activation compared to those without risk factors in lateral temporoparietal regions, left hippocampus, and posterior cingulate/precuneus. Participants with MCI also showed similar increases in activations, but they did not show enhanced recruitment of the hippocampus and instead showed increased activations in frontal regions, suggesting that compensatory recruitment processes may evolve with changes in cognition and neuropathology burden [22]. Finally, Bartrés-Faz et al. [23] studied hippocampal connectivity in older adults with mild memory impairments. They reported that ε4 carriers exhibited increased connectivity of the hippocampus with the anterior cingulate, inferior parietal/postcentral gyrus, and the caudate nucleus during the encoding portion of a face-name memory task. The authors suggested that this may indicate increased cortical-subcortical connections in the episodic memory networks in ε4 carriers.

Overall, these studies uniformly support the presence of compensatory neural recruitment processes in ε4 carriers. Yet, while some studies support our proposal [1] that ε4 carriers would have a predilection for recruiting right hemisphere regions [4, 20, 21], this was not true for all studies reviewed [12, 19, 22, 23]. This could be a factor of type of task, as Kukolja et al. [4], who found the most evidence for a right hemisphere dominant compensatory response, used a spatial context memory task, which may be expected to preferentially activate right hemisphere regions due to the involvement of visuospatial processing. In contrast, several studies that found a predominantly left hemisphere or bilateral compensatory response (e.g., [12, 20–22]) used tasks (e.g., confrontation naming, working memory, and famous name discrimination) that may be more expected to activate left rather than right hemisphere regions due to the emphasis on language.

There were also studies reviewed which did not support the existence of a compensatory recruitment process in older cognitively intact ε4 carriers. Johnson et al. [54] found that APOE genotype alone did not impact neural activity during a self-appraisal task in middle-age adults, although APOE status did interact with a family history of AD to produce greater frontal and posterior cingulate activations in ε4 carriers without a family history of AD. Johnson et al. [55] reported similar results in an earlier study of middle-age adults using an episodic memory task. While APOE ε4 carriers with no family history of AD did show the predicted enhanced recruitment of MTL structures, ε4 carriers with a family history of AD actually showed the lowest levels of MTL recruitment of all participant groups [55]. As noted by the authors, [54, 55], such results suggest that the impact of APOE on brain activity may be moderated by genetic factors underlying a familial history of AD. Lind et al. [56] found that healthy middle aged and older adult ε4 carriers displayed reduced neural activity in left inferior parietal and anterior cingulate cortices than noncarriers during a semantic categorization task. Borghesani et al. [24], studying MTL activation in nondemented older adults with a visuospatial memory task, also found that ε4 carriers exhibited lower MTL activation during encoding. Filbey et al. [12], while simultaneously finding regions more activated in ε4 carriers (as discussed above), also found that ε4 carriers exhibited less activity than noncarriers in lateral frontal, basal ganglia, cingulate, parietal, and temporal regions during a working memory task. Reporting similar findings, Xu et al. [25] found that middle aged ε4 carriers showed reduced activation in left dorsal posterior cingulate, precuneus, and anterior cingulate than noncarriers during the recall portion of an episodic face recognition task. A study by Suthana et al. [26] reported reduced hippocampal activation in nondemented older ε4 carriers compared to noncarriers during the encoding portion of a word memory task. The authors proposed that this decrease in hippocampal activation may in fact allow for compensatory processes in other regions, which would explain findings of decreased activation in MTL regions in ε4 carriers and may also explain Kukolja et al.'s [4] finding of reduced memory retrieval with increasing hippocampal activation among those with the ε4 allele.

While many of these studies support the compensatory recruitment aspect of our model [1] of antagonistic pleiotropy and APOE, some studies did not find evidence of compensatory recruitment processes in ε4 carriers, instead finding lower levels of activation in ε4 carriers than noncarriers. A notable trend is that those studies finding decreased levels of activity in ε4 carriers frequently did so in regions commonly associated with AD (e.g., posterior cingulate, precuneus, and hippocampus), while studies finding increased activity in ε4 carriers commonly did so in regions beyond those typically involved in early AD (e.g., prefrontal cortex). As several authors have pointed out (e.g., [12]), ε4 carriers may exhibit decrements in activity in regions initially impacted in AD due to increased pathology burden in these areas while continuing to compensate for these decrements with increased activity in regions not initially affected by AD pathological processes. Another possible explanation for discrepancies among studies could be due to differences in vascular risk factors present in the samples. Age-related vascular changes have been found to attenuate neurovascular coupling upon which the BOLD response in fMRI is based (e.g., [57, 58]). Such alterations can complicate the interpretation of the BOLD response and lead to erroneous conclusions if vascular changes are not taken into account [57]. This is particularly relevant as the APOE ε4 allele has been associated with vascular risk factors (e.g., [59, 60]). Therefore, careful consideration of vascular changes and clinically silent or prodromal forms of dementia

are required to clarify the existence of compensatory neural recruitment in older adult ε4 carriers.

5. APOE and Declining Cognition in Old Age

Much recent research has considered the implications of APOE genotype for declining cognition in old age, and the majority of this research has supported our proposal [1] of exaggerated cognitive decline in ε4 carriers compared to noncarriers. While not universally the case [12, 21, 27], most studies reporting cross-sectional differences by APOE genotype found that ε4 carriers performed more poorly in tasks of verbal and visual episodic memory [4, 28–35, 59]. Other reported discrepancies were in working memory [30], general cognition [2, 4, 30, 36–38], category fluency [39], the Stroop task [40], matrix reasoning [14], and symbol search [14]. Many studies also considered cognition longitudinally and found ε4 carriers to display an increased risk of developing mild cognitive impairment (MCI) (e.g., [41]), AD (e.g., [3]), or vascular dementia [59], although other studies have failed to find a relationship between the ε4 allele and risk of developing MCI [42, 43]. Furthermore, although less consistent in the literature, some reported finding steeper rates of cognitive decline in ε4 carriers compared to noncarriers [3, 31, 36, 37], with a number reporting evidence of a dose-dependent response [3, 31, 59]. One interesting study by Casselli et al. [31] longitudinally followed patients between 21 and 97 years of age. Growth curve modeling predicted that APOE ε4 carriers begin to decline in their memory around their 50's, while participants without an ε4 allele only begin to experience memory decline in their 70's. Memory decline also evidenced a dose-dependent relationship, so that participants with two ε4 alleles were predicted to experience memory decline before those with only one ε4 allele. Moreover, ε4 carriers had an overall steeper rate of decline in memory, on the MMSE, and on Judgment of Line Orientation than noncarriers. Importantly, the study's longitudinal design allowed authors to remove from analysis those participants who eventually developed MCI or dementia. The authors therefore suggest that APOE detrimentally affects cognition in older adults independent of the influence of dementia. Liu et al. [48] also examined the impact of the APOE ε4 allele on cognition in a lifespan sample and reported that ε4 carriers' cognitive performance was only reduced compared to noncarriers in those 50 and older; APOE ε4 had no effect on cognition in younger age groups.

Carrión-Baralt et al. [44] reported intriguing results with a sample of Puerto Rican oldest-old. They found ε4 carriers in this sample of nonagenarians to exhibit *higher* performance than noncarriers in overall cognition as well as measures of visuospatial abilities, naming, and attention. The authors suggest that this unexpected finding may have two sources. It may be that those who survive into their 90's have genetic protective factors that confer benefit regardless of APOE genotype. Because of the higher risk of dementia and eventual mortality found with ε4 carriers, nonagenarian ε4 carriers who survived beyond the prime ages for AD development may be more likely to have this protective factor and may therefore perform better than noncarriers. A second possibility noted by Carrión-Baralt et al. [44] is that APOE may exhibit antagonistic pleiotropic effects, being detrimental for cognition and survival in young-old age, but being beneficial in old-old age. Reporting similar findings, Kozauer et al. [45] studied a large sample of two age cohorts after a 22-year followup. Differences in cognition by APOE status were only found in the younger cohort, which was in their 50's, in which ε4 carriers displayed worse performance than noncarriers. These differences were not found at other waves of data collection, implying that they developed upon reaching middle and older ages. Interestingly, cognitive differences by APOE status were not observed in the older cohort, which had a mean age in the mid-70's. This also supports the contention that the APOE ε4 allele may not be detrimental to those who survive into later ages without developing dementia. Similarly, Welsh-Bohmer et al. [27], who also studied APOE in oldest-old, found no relationship between APOE and cognition. While these latter findings of cognitive similarity by APOE status in the oldest-old may not be as persuasive as those of Carrión-Baralt et al. [44], they still suggest that the very common finding of cognitive decline in older ε4 carriers may not hold true for the oldest-old and may fail to do so because of antagonistic pleiotropy. This argues for an extension of our model [1] into old-old age, where APOE ε4 may again impart beneficial cognitive effects to its carriers.

As suggested in our [1] model of APOE as an example of antagonistic pleiotropy, much research has found that the APOE ε4 allele is associated with disproportionate cognitive decline in old age [3, 4, 14, 28–41, 59], although it may be that the ε4 allele confers an advantage on its carriers who reach old-old age without developing dementia, suggesting an extension to our model [1, 27, 45, 48]. The association of APOE ε4 with cognitive decline follows from findings suggesting a close relationship of the ε4 allele with amyloid neuropathology, a hallmark of AD [61–65]. Indeed, many individual studies and reviews have reported APOE to be strongly associated with Aβ42, the most insoluble form of the Aβ peptide, which aggregates to form senile plaques in AD (e.g., [61, 64, 65]). Some studies have also demonstrated a dose-dependent relationship between the APOE ε4 allele and amyloid pathology, in which ε4 homozygotes exhibit more amyloid pathology than those with only one ε4 allele (e.g., [64, 65]). However, the demonstrated relationship between the APOE ε4 allele and AD-related amyloid pathology might argue against the ability of APOE to confer protective effects to its old-old nondemented carriers. With respect to this possibility, it is important to note that studies have found that amyloid pathology, while being strongly associated with the development of AD, does not account for all of the cognitive decline found in these patients (e.g., [61, 65, 66]). Other biomarkers, particularly brain atrophy and tau pathology, commonly account for a large portion of variance in cognitive decline found in AD (e.g., [61, 65, 66]). The fact that the APOE ε4 allele has not been as strongly associated with these other AD biomarkers [61, 65, 66] may explain why old-old APOE ε4 carriers may still exhibit cognitive benefits

despite the strong association of the ε4 allele with amyloid pathology.

6. Conclusions and Recommendations

Our model [1] of antagonistic pleiotropy in APOE was critically re-evaluated in light of recent research. Some aspects of the model were strongly supported. Research suggests that younger ε4 carriers do indeed exhibit compensatory neural recruitment, as proposed by our model [1]. However, our prediction of a predilection for right hemisphere frontal regions in this compensatory process was not clearly corroborated. It instead seems that young ε4 carriers invoke compensatory processes in task-related regions. The cognitive decline in older ε4 carriers predicted by the model was also supported in recent literature, revealing a strong effect on memory as well as other cognitive domains. Yet inconsistent evidence was found to support other aspects of the model. For instance, the presence of compensatory neural recruitment in older ε4 carriers was not unanimously supported. Studies with older ε4 carriers also only partially supported our prediction [1] of a higher likelihood of recruitment of right frontal regions. Differences in compensatory regions may be linked to type of task, as those thought to invoke more of a right hemisphere response also found evidence for right hemisphere compensatory processes, while left hemisphere compensatory processes were occasionally observed for tasks emphasizing language that would be thought to rely more heavily on left hemisphere regions. It is also unclear whether young ε4 carriers show better cognitive performance than noncarriers. As discussed, these inconsistent findings may be explained by the need to consider APOE and cognition in narrow age ranges or to statistically test the interaction between APOE genotype and age in predicting cognition for lifespan samples. It also appears important to control for detrimental health comorbidities that may be more prevalent in ε4 carriers in such analyses. However, if it is determined that APOE ε4 carriers do not show a cognitive benefit in early life, this strongly argues against APOE as displaying antagonistic pleiotropic effects. In fact, findings of compensatory recruitment in young ε4 carriers in the presence of similar, instead of enhanced, cognitive performance implies that the ε4 allele may be detrimental even in young ages, as young carriers have to activate more brain regions to produce the same level of performance as noncarriers. Research in this area is vital to further evaluate the antagonistic pleiotropy hypothesis of APOE.

In light of the reviewed research, we suggest certain revisions to our model [1] of antagonistic pleiotropy and APOE. In the absence of conclusive contrary findings, we maintain that APOE ε4 carriers exhibit cognitive benefits early in life. We also propose that compensatory neural recruitment processes occur in task-related regions in young ε4 carriers but transfer to frontal regions among older adults, once task-related regions become overburdened with AD pathology. While compensatory regions may be in the right hemisphere, lateralization of the compensatory response does not seem to be a consistent trend. Second, we propose that cognitive decline will begin much earlier in ε4 carriers and will progress more rapidly. In light of new research [27, 44, 45], we also predict that the APOE ε4 allele again becomes beneficial in the oldest-old, who survive into old-old age without developing dementia. Additional research is needed to test this notion, as functional imaging to examine compensatory recruitment in nonagenarian populations of ε4 carriers would be particularly elucidating.

The finding of cognitive superiority in nondemented ε4 nonagenarians suggests a second hypothesis of gene-gene interaction that may explain the apparent APOE antagonistic pleiotropic effects as well as the inconsistencies in the literature. It may be that the APOE ε4 allele is not antagonistically pleiotropic but instead interacts with other AD risk factors to differentially influence cognition depending on a person's profile of risk. Indeed, APOE has been found by many studies to interact with a family history of AD to influence cognition (e.g., [25, 29]) and also to interact with other risk genes such as APOCI AA, BCHE, and CHRNA4 [59, 67, 68]. Therefore, it may be that among people without AD risk factors, APOE ε4 does not adversely affect cognition and could perhaps be beneficial to its carriers. Some have gone so far as to suggest that APOE has no influence on cognition beyond increasing risk for AD [69]. These authors suggest that APOE, while putting one at risk for prodromal dementia, does not create a specific cognitive phenotype of its own [69]. APOE's interaction with other genetic risk factors to influence cognition would explain why only some young ε4 carriers show enhanced cognition over noncarriers, why only some ε4 carriers show disproportionate cognitive declines with age, and why nondemented oldest-old ε4 carriers show cognitive enhancements. Perhaps those children with APOE ε4 and other AD risk factors are those that show no difference from noncarriers, due to compensatory recruitment processes, or actually show reductions in cognitive abilities compared to noncarriers. Perhaps those children with APOE ε4 and other AD risk factors are the ones to show disproportionate cognitive decline in old age compared to noncarriers, whereas ε4 carriers without other risk factors do not show more cognitive decline than would be expected. This hypothesis of the interaction of APOE with AD-specific risk factors is further supported by the lack of associations between APOE and cognition in other diseases such as multiple sclerosis [70]. Future research in genetics and epigenetics is needed which carefully considers participants' AD risk profiles. Careful, comprehensive studies conducted in this way will help the field determine whether APOE displays antagonistic pleiotropy or gene-gene interactions with other AD risk factors.

This paper suggests several avenues for future research as well as other important factors when considering APOE as an example of antagonistic pleiotropy. Beyond considering neurovascular decoupling with age and participants' AD risk profiles, future research examining the impact of APOE ε4 allele on cognition and neural activity across the lifespan is needed. Continued evaluation of the antagonistic pleiotropy and gene-gene interaction hypotheses of APOE will move the field closer to realizing effective treatments and preventative measures for AD.

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