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Differential 5-Year Brain Atrophy Rates in Cognitively Declining and Stable APOE-E4 Elders

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Abstract

Objective: The apolipoprotein E (APOE) $\epsilon 4$ allele is the most important genetic risk factor for late-onset Alzheimer's disease. Many $\epsilon 4$ carriers, however, never develop Alzheimer's disease. The purpose of this study is to characterize the variability in phenotypic expression of the $\epsilon 4$ allele, as measured by the longitudinal trajectory of cognitive test scores and MRI brain volumes, in cognitively intact elders. **Method:** Healthy older adults, ages 65–85, participated in a 5-year longitudinal study that included structural MRI and cognitive testing administered at baseline and at 1.5 and 5 years postenrollment. Participants included 22 $\epsilon 4$ noncarriers, 15 $\epsilon 4$ carriers who experienced a decline in cognition over the 5-year interval, and 11 $\epsilon 4$ carriers who remained cognitively stable. **Results:** No baseline cognitive or volumetric group differences were observed. Compared to noncarriers, declining $\epsilon 4$ carriers had significantly greater rates of atrophy in left ($p = .001$, Cohen's $d = .691$) and right ($p = .003$, $d = .622$) cortical gray matter, left ($p = .003$, $d = .625$) and right ($p = .020$, $d = .492$) hippocampi, and greater expansion of the right inferior lateral ventricle ($p < .001$, $d = .751$) over 5 years. **Conclusions:** This study illustrates the variability in phenotypic expression of the $\epsilon 4$ allele related to neurodegeneration. Specifically, only those individuals who exhibited longitudinal declines in cognitive function experienced concomitant changes in brain volume. Future research is needed to better understand the biological and lifestyle factors that may influence the expression of the $\epsilon 4$ allele. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

Impact Statement

General Scientific Summary—Possession of an APOE $\epsilon 4$ allele significantly increases the risk of developing late-onset Alzheimer's disease (LOAD). This longitudinal study illustrates that cognitively intact $\epsilon 4$ elders exhibit varying rates of brain atrophy as a function of declines in cognition function. This variability in phenotypic expression of the $\epsilon 4$ allele may ultimately lead to the identification of modifiable biological and/or lifestyle factors that mitigate the risk of developing LOAD. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

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The apolipoprotein E (APOE) $\epsilon 4$ allele confers an increased risk for developing late-onset Alzheimer's disease (LOAD; [Corder et al., 1993](#); [Liu et al., 2015](#); [Smith et al., 1998](#)). APOE $\epsilon 4$ homozygotes experience a 13- to 15-fold increased chance of being diagnosed during their lifetime, whereas $\epsilon 4$ heterozygotes experience a 3-fold increase ([Ashford, 2004](#)). Even prior to the diagnosis of mild cognitive impairment or LOAD, older adults possessing an APOE $\epsilon 4$ allele experience greater cognitive deficits in episodic memory, executive functioning, perceptual speed, and global cognition than noncarriers ([Wisdom, Callahan, & Hawkins, 2011](#)). Longitudinal studies of cognitively intact, older $\epsilon 4$ carriers and noncarriers demonstrate greater cognitive decline in the former group over time ([Pietrzak et al., 2015](#); [Rao et al., 2015](#); [Woodard et al., 2010](#)). Likewise,

longitudinal structural MRI studies indicate significantly different trajectories of neurodegeneration in the hippocampus and ventricles between cognitively intact, older $\epsilon 4$ carriers and noncarriers ([Lu et al., 2011](#); [Reiter et al., 2016](#); [Roussotte et al., 2014](#)).

Such studies tend to treat $\epsilon 4$ carriers as a homogeneous group. Yet, many cognitively intact elders with the $\epsilon 4$ allele never develop LOAD during a normal life span ([Relkin, Kwon, Tsai, & Gandy, 1996](#)). A lack of uniform deterioration among $\epsilon 4$ carriers may be explained by biological (e.g., *APOE* $\epsilon 4$ zygosity, comorbid medical illnesses) and/or lifestyle (e.g., education, physical activity) factors that likely modulate the impact of the $\epsilon 4$ allele on the development of Alzheimer's disease (AD; [Schwartz, Rapkin, & Healy, 2016](#); [Small, Rosnick, Fratiglioni, & Bäckman, 2004](#); [Smith et al., 2014](#)).

The primary purpose of this longitudinal study is to examine the variability in phenotypic expression of the $\epsilon 4$ allele in elders who were cognitively intact at study entry. Over the course of the 5-year interval, a subset of $\epsilon 4$ carriers experienced a decline in cognitive status (" $\epsilon 4+$ declining"). We hypothesized that the $\epsilon 4+$ declining group would experience greater volumetric changes as measured by structural MRI than $\epsilon 4$ carriers who experienced no meaningful changes in cognitive performance over the 5-year interval (" $\epsilon 4+$ stable") and $\epsilon 4$ noncarriers (" $\epsilon 4-$ "). A previous study conducted on this sample ([Reiter et al., 2016](#)) identified differences in longitudinal changes in hippocampal volume, global gray matter volume, and ventricular size between $\epsilon 4$ carriers and noncarriers. The present study focused on differences in the rate of volumetric change in these anatomical regions between stable and declining $\epsilon 4$ carriers and noncarriers.

Method

Participants

Healthy, cognitively intact older adults, ages 65–85, were recruited as part of a 5-year longitudinal study ([Rao et al., 2015](#); [Seidenberg et al., 2009](#)) via newspaper advertisements and a telephone screen. An in-person study visit involved *APOE* genotyping based on a polymerase chain reaction method and administration of a cognitive screening battery to determine if the potential participant was cognitively intact. This battery consisted of the Mini Mental State Exam (MMSE; [Folstein, Folstein, & McHugh, 1975](#)), Dementia Rating Scale 2 (DRS-2; [Jurica, Leitten, & Mattis, 2001](#)), and Rey Auditory Verbal Learning Test (RAVLT; [Rey, 1958](#)). Criteria used to define intact cognition in this study have been previously reported ([Seidenberg et al., 2009](#)). All protocols, in full compliance with American Psychological Association ethical standards, were approved by the local institutional review board, and participants received compensation. A total of 72 participants were tested at baseline (T1) with all measures for the current study. Only the 48 participants who returned for both neuropsychological and structural MRI follow-up sessions (1.5 years [T2] and 5 years [T3]) were included in the current study. On this basis, the study attrition rate over 5 years was 33%; three participants had T1 and T3 data but were missing T2 (all were $\epsilon 4+$), and 21 participants (13 $\epsilon 4+$) had T1 and T2 data but were not scanned at T3 due to health decline (6), deceased (5), lost to follow-up (3), refused scan (3), moved away (3), and no longer safe to be scanned (1). No group differences were observed in attrition rates at each of the two follow-up scan sessions.

The 48 participants were subdivided by *APOE* $\epsilon 4$ allele inheritance: 26 $\epsilon 4$ carriers ($\epsilon 4+$) and 22 $\epsilon 4$ noncarriers ($\epsilon 4-$). The $\epsilon 4$ carrier group was further subdivided based on changes in cognitive status over the 5-year study interval. The $\epsilon 4+$ participants were defined as "declining" if a reduction from baseline performance of at least one standard deviation (*SD*) was observed on at least one of the three principal outcome indices ([Woodard et al., 2010](#)). Using these criteria, 15 $\epsilon 4+$ participants (58%) were classified as declining and 11 $\epsilon 4+$ participants (42%) were classified as stable ([Table 1](#)).

Table 1
Baseline Characteristics by Gene and Cognitive Decline Status

Variable	ε4- (n = 22)	ε4+ stable (n = 11)	ε4+ declining (n = 15)	p value	Effect size
Age (years)	73.1 (5.2)	71.9 (4.3)	73.0 (4.3)	.77	.01 ^a
Sex (n, % female)	18, 82%	9, 82%	12, 80%	.99	.02 ^b
Education (years)	14.0 (1.8)	16.8 (3.2)	14.8 (3.1)	.02	.17 ^a
Family history (n, % yes)	0, 0%	7, 64%	12, 80%	.35	.35 ^b

Note. Values are presented as means with standard deviations in parentheses unless otherwise noted. Bolded values are statistically significant at $p < .05$. ε4- = ε4 noncarriers; ε4+ stable = ε4 carriers who remained cognitively stable over 5 years; ε4+ declining = ε4 carriers who cognitively declined over 5 years.

^a Partial eta squared. ^b Cramèr's V.

Table 1. *Baseline Characteristics by Gene and Cognitive Decline Status*

Variable	ε4- (n = 22)	ε4+ stable (n = 11)	ε4+ declining (n = 15)	p value	Effect size
Age (years)	73.1 (5.2)	71.9 (4.3)	73.0 (4.3)	.77	.01 ^a
Sex (n, % female)	18, 82%	9, 82%	12, 80%	.99	.02 ^b
Education (years)	14.0 (1.8)	16.8 (3.2)	14.8 (3.1)	.02	.17 ^a
Family history (n, % yes)	0, 0%	7, 64%	12, 80%	.35	.35 ^b

Note. Values are presented as means with standard deviations in parentheses unless otherwise noted. Bolded values are statistically significant at $p < .05$. ε4- = ε4 noncarriers; ε4+ stable = ε4 carriers who remained cognitively stable over 5 years; ε4+ declining = ε4 carriers who cognitively declined over 5 years.

^a Partial eta squared. ^b Cramèr's V.

No significant differences were observed between the three groups for mean age in years (ε4-: 73.1 years, $SD = 5.2$; ε4+ stable: 71.9 years, $SD = 4.3$; ε4+ declining: 73.0 years, $SD = 4.3$; $p = .768$, $\eta^2 = 0.012$; 95% CIs [71.1, 75.1], [69.0, 74.7], and [70.5, 75.4]) or for number of females (ε4-: 18, 82%; ε4+ stable: 9, 82%; ε4+ declining: 12, 80%; $p = .989$, Cramèr's $V = 0.022$). However, significant group differences, $F(2, 45) = 4.45$, $p = .017$, $\eta^2 = 0.165$, were observed for mean years of education (ε4-: 14.0 years, $SD = 1.8$; ε4+ stable: 16.8 years, $SD = 3.2$; ε4+ declining: 14.8 years, $SD = 3.1$; 95% CIs [12.8, 15.1], [15.2, 18.4], and [13.4, 16.2]), with the ε4+ stable group being significantly more educated than the ε4- group. No significant baseline group differences were observed on the MMSE, DRS-2, or RAVLT, although group differences were observed at 18 months and 5 years on the RAVLT (see [Table 2](#)).

Table 2
Cognitive Performances by Group Across Time

Variable	€4-	€4+ stable	€4+ declining	p value	Effect Size
Baseline					
MMSE	29.3 (0.8)	29.6 (0.8)	28.9 (1.0)	.23	.06
DRS-2 Total	141.1 (2.0)	140.6 (1.6)	140.1 (4.4)	.55	.03
RAVLT Total Trials	49.2 (8.2)	51.7 (7.7)	46.9 (8.0)	.32	.05
RAVLT DR	9.8 (2.1)	10.7 (3.1)	9.1 (2.8)	.31	.05
18 months					
MMSE	29.7 (0.5)	29.3 (0.9)	29.5 (0.8)	.35	.05
DRS-2 Total	139.0 (2.8)	138.9 (2.1)	138.3 (3.5)	.81	.01
RAVLT Total Trials	47.5 (7.6)	54.6 (6.0)	40.4 (7.6)	<.01	.34
RAVLT DR	9.4 (2.6)	11.8 (2.7)	5.8 (2.0)	<.01	.47
5 years					
MMSE	29.7 (0.7)	29.4 (0.7)	28.3 (2.7)	.07	.13
DRS-2 Total	141.7 (2.2)	141.3 (1.9)	138.9 (6.1)	.11	.11
RAVLT Total Trials	48.5 (7.5)	50.6 (6.4)	42.7 (13.5)	.13	.10
RAVLT DR	10.0 (2.5)	11.1 (2.0)	6.2 (4.2)	<.01	.31

Note. Values are presented as means with standard deviations in parentheses. Bolded values are statistically significant at $p < .05$. Effect sizes are partial eta squared values. Sample sizes at baseline: €4- = 22, €4+ stable = 11, €4+ declining = 15; sample sizes at 18 months: €4- = 22, €4+ stable = 11, €4+ declining = 15; sample sizes at 5 years: €4- = 20, €4+ stable = 9, €4+ declining = 13. €4- = €4 noncarriers; €4+ stable = €4 carriers who remained cognitively stable over 5 years; €4+ declining = €4 carriers who cognitively declined over 5 years. MMSE = Mini Mental State Exam; DRS-2 = Dementia Rating Scale–Second Edition; RAVLT = Rey Auditory Verbal Learning Test; DR = Delayed Recall.

Table 2. Cognitive Performances by Group Across Time

Variable	E4-	E4+ stable	E4+ declining	p value	Effect size
Baseline					
MMSE	29.3 (0.8)	29.6 (0.8)	28.9 (1.0)	.23	.06
DRS-2 Total	141.1 (2.0)	140.6 (1.6)	140.1 (4.4)	.55	.03
RAVLT Total Trials	49.2 (8.2)	51.7 (7.7)	46.9 (8.0)	.32	.05
RAVLT DR	9.8 (2.1)	10.7 (3.1)	9.1 (2.8)	.31	.05
18 months					
MMSE	29.7 (0.5)	29.3 (0.9)	29.5 (0.8)	.35	.05
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Note. Values are presented as means with standard deviations in parentheses. Bolded values are statistically significant at $p < .05$. Effect sizes are partial eta squared values. Sample sizes at baseline: E4- = 22, E4+ stable = 11, E4+ declining = 15; sample sizes at 18 months: E4- = 22, E4+ stable = 11, E4+ declining = 15; sample sizes at 5 years: E4- = 20, E4+ stable = 9, E4+ declining = 13. E4- = E4 noncarriers; E4+ stable = E4 carriers who remained cognitively stable over 5 years; E4+ declining = E4 carriers who cognitively declined over 5 years. MMSE = Mini Mental State Exam; DRS-2 = Dementia Rating Scale–Second Edition; RAVLT = Rey Auditory Verbal Learning Test; DR = Delayed Recall.

There were no significant group differences in the number of months between T1 and T2 (€4-: 18.5 months, $SD = 1.7$; €4+ stable: 18.2 months, $SD = 0.6$; €4+ declining: 18.3 months, $SD = 0.8$; $p = .761$, $\eta^2 = 0.012$; 95% CIs [18.0, 19.1], [17.4, 19.0],

and [17.7, 19.0]) or between T1 and T3 ($\epsilon 4-$: 59.0 months, $SD = 2.6$; $\epsilon 4+$ stable: 58.2 months, $SD = 4.5$; $\epsilon 4+$ declining: 56.8 months, $SD = 4.4$; $p = .2091$, $\eta p^2 = 0.067$; 95% CIs [57.4, 60.6], [55.9, 60.4], and [54.9, 57.7]).

MRI Acquisition and Processing

High-resolution, three-dimensional spoiled gradient-recalled at steady-state (SPGR) anatomic images were acquired on a General Electric (Waukesha, WI) Signa Excite 3.0 Tesla short bore scanner equipped with a quad split quadrature transmit/receive head coil (Echo time [TE] = 3.9 ms; repetition time [TR] = 9.5 ms; inversion recovery [IR] preparation time = 450 ms; flip angle = 12°; number of excitations [NEX] = 2; slice thickness = 1.0 mm; field of view [FOV] = 24 cm; resolution = 256 × 224). A scanner upgrade took place near the end of the final retest period. Two $\epsilon 4+$ participants and one $\epsilon 4-$ participant had their third scan conducted on a GE MR750 3.0 Tesla scanner (TE = 3.9 ms; TR = 9.6 ms; IR preparation time = 450 ms; flip angle = 12°; NEX = 1; slice thickness = 1.0 mm; FOV = 24 cm; resolution = 256 × 224). A between-scanner comparison showed no systematic differences. Whole-brain and regional volumes were derived from T1-weighted SPGR images using the longitudinal stream in Freesurfer v.5.1 software (Fischl et al., 2002). A previous study (Reiter et al., 2016) demonstrated longitudinal differences between $\epsilon 4+$ and $\epsilon 4-$ participants primarily in volumes of the hippocampus, inferior lateral and lateral ventricles, and cortical gray matter. To minimize multiple comparisons, we confined the analysis to determine the effect of cognitive decline within the $\epsilon 4+$ group to eight bilateral brain volumes: hippocampi, inferior lateral ventricles, lateral ventricles, and cortical gray matter.

Statistical Analyses

All brain volumes were converted to residualized z scores controlling for intracranial volume and age at baseline. Longitudinal linear mixed-effects (LME) models were used to examine the effects of group and time on anatomical brain volumes (Rao et al., 2015; Reiter et al., 2016). Time was based on the number of days from T1. For our LME models, the $\epsilon 4-$ group served as the reference group. Although years of education differed between groups (see above), education did not significantly correlate with any of the volumetric measurements; as a result, education was not used as a covariate in the LME analyses. To control for inflated Type I error rate due to multiple comparisons, false discovery rate (FDR) correction procedures were applied to all LME analyses.

Results

Table 3 summarizes the results of the LME analyses applied to bilateral volumes derived from the hippocampi, cortical gray matter, lateral ventricles, and inferior lateral ventricles. There were no significant baseline differences between groups for all eight brain volumes. Over the 5-year follow-up interval, the $\epsilon 4+$ declining group had significantly more atrophy than the $\epsilon 4-$ group in the left ($p = .001$, Cohen's $d = .691$) and right ($p = .003$, $d = .622$) cortical gray matter volumes and in the left ($p = .003$, $d = .625$) and right ($p = .020$, $d = .492$) hippocampi. The $\epsilon 4+$ declining group also had significantly greater expansion of the right inferior lateral ventricle than the $\epsilon 4-$ group over the 5-year interval ($p < .001$, $d = .751$). These findings reflect medium to large effect sizes. Figure 1 displays regression lines depicting baseline and predicted annualized rates of change in volumes (in standard score units, adjusted for age and intracranial volume) over the 5-year study period by group. The figure demonstrates that the group separation in volume change becomes more pronounced at 5 years after baseline.

Table 3

Predicted Annual Brain Volume Change Over 5 Years by APOE $\epsilon 4$ and Cognitive Decline Status

Region	Intercept (baseline)			Slope (time)		
	$\epsilon 4^{-a}$	v. $\epsilon 4+$ stable ^b	v. $\epsilon 4+$ declining ^b	$\epsilon 4^{-c}$	v. $\epsilon 4+$ stable ^d	v. $\epsilon 4+$ declining ^d
Left hemisphere						
Lateral ventricle	-.101 (.199)	.494 (.344)	-.003 (.312)	-.025 (.010)	.008 (.017)	.022 (.016)
Inferior lateral ventricle	.060 (.174)	.149 (.302)	-.315 (.274)	-.044 (.019)	.025 (.033)	.062 (.030)
Hippocampus	.190 (.204)	-.154 (.353)	-.160 (.321)	.018 (.017)	-.025 (.031)	-.085 (.028)
Cortical gray matter volume	.045 (.210)	-.202 (.364)	.380 (.330)	.020 (.020)	-.014 (.036)	-.109 (.033)
Right hemisphere						
Lateral ventricle	-.135 (.209)	.645 (.362)	.035 (.328)	-.018 (.009)	-.003 (.016)	.028 (.015)
Inferior lateral ventricle	-.099 (.186)	.378 (.322)	-.190 (.292)	-.039 (.021)	.018 (.036)	.121 (.033)
Hippocampus	.311 (.200)	-.486 (.346)	-.565 (.314)	.025 (.019)	.007 (.033)	-.072 (.030)
Cortical gray matter volume	.022 (.207)	-.057 (.359)	.424 (.325)	.011 (.019)	-.041 (.033)	-.091 (.030)

Note. All values are mean z scores residualized by baseline age and intracranial volume (ICV) with standard errors of the mean in parentheses. Bolded values are statistically significant after controlling for multiple comparisons using the false discovery rate. $\epsilon 4^{-}$ = $\epsilon 4$ allele noncarrier; $\epsilon 4+$ stable = $\epsilon 4$ allele carriers who remained cognitively stable over 5 years; APOE = apolipoprotein E; $\epsilon 4+$ declining = $\epsilon 4$ allele carriers who cognitively declined over 5 years. Intercepts reflect the mean volume at baseline for each region for the $\epsilon 4^{-}$ group alone^a or for each of the $\epsilon 4+$ groups relative to the $\epsilon 4^{-}$ group.^b Slopes reflect the estimated mean annual rate of change from baseline for the $\epsilon 4^{-}$ group alone^c or for each of the $\epsilon 4+$ groups relative to the $\epsilon 4^{-}$ group.^d v. = versus.

Table 3 Predicted Annual Brain Volume Change Over 5 Years by APOE $\epsilon 4$ and Cognitive Decline Status

Region	4 ^a	Intercept (baseline) v. 4 stable ^b	4 declining ^b	v. 4 ^c	Slope (time) v. 4 stable ^d	v. 4 declining ^d
Left hemisphere						
Lateral ventricle	-.101 (.199)	.494 (.344)	-.003 (.312)	-.025 (.010)	.008 (.017)	.022 (.016)
Inferior lateral ventricle	.060 (.174)	.149 (.302)	-.315 (.274)	-.044 (.019)	.025 (.033)	.062 (.030)
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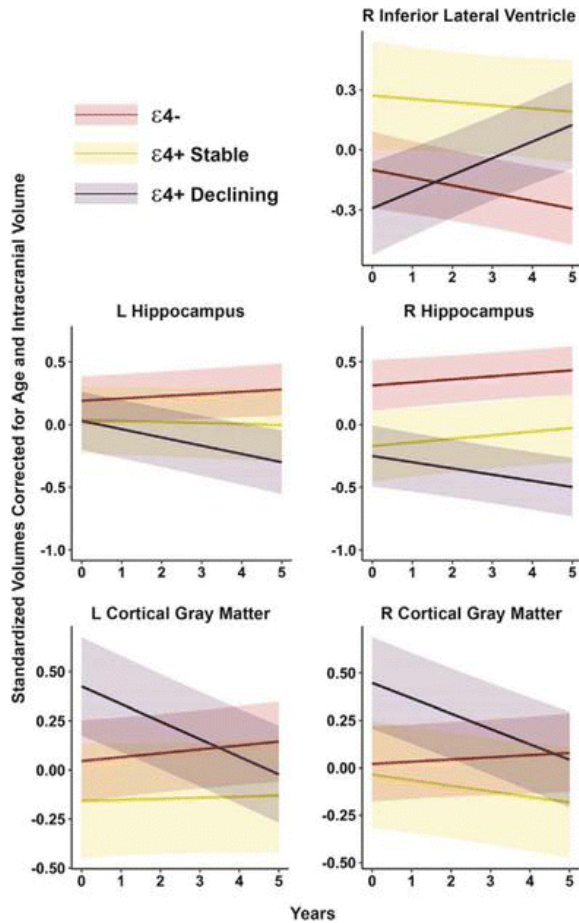


Figure 1. Regression lines depicting baseline and predicted annualized rates of change in volumes (in standard score units, adjusted for age and intracranial volume) over the 5-year study period by group. $\epsilon 4^-$ = $\epsilon 4$ noncarrier; $\epsilon 4^+$ stable = cognitively stable $\epsilon 4$ carrier; $\epsilon 4^+$ declining = cognitively declining $\epsilon 4$ carrier; L = left; R = right.

In a direct comparison of the two $\epsilon 4^+$ groups, the $\epsilon 4^+$ declining group exhibited significantly greater atrophy of the right hippocampus ($p = .030$, $d = .457$) and left cortical gray matter ($p = .017$, $d = .506$) and expansion of the right inferior lateral ventricle ($p = .011$, $d = .541$) than the $\epsilon 4^+$ stable group over the 5-year interval. These findings reflect medium effect sizes. However, these three interaction effects did not survive FDR correction likely due to the small sample size.

Discussion

Results confirmed our hypothesis that the $\epsilon 4$ group that exhibited a decline in verbal episodic memory and global cognitive function over the 5-year retest interval exhibited greater brain atrophy than $\epsilon 4$ noncarriers. In contrast, $\epsilon 4$ carriers who experienced no significant 5-year changes in memory and cognitive test performance exhibited atrophy rates comparable to $\epsilon 4$ noncarriers. The greater atrophy rates in the $\epsilon 4^+$ declining group occurred bilaterally in the hippocampi and global gray matter and in the right inferior lateral ventricle. Importantly, the three groups showed no differences in brain volumes at the baseline examination. Furthermore, all participants were cognitively intact at enrollment as an entry criterion and did not differ from each other on measures of episodic memory or global cognition at baseline.

$\epsilon 4$ carriers exhibit significantly greater rates of hippocampal and cortical gray matter atrophy and ventricular enlargement than $\epsilon 4$ noncarriers (Reiter et al., 2016). Results from the current study indicate that these group differences may be driven by a subset of $\epsilon 4$ carriers who exhibited cognitive decline over the 5-year retest interval. This study demonstrates the

correspondence between longitudinal changes in cognition and brain volumes in a subgroup of $\epsilon 4$ carriers, a finding that has not previously received significant attention in the literature.

Whereas possession of the $\epsilon 4$ allele increases risk of AD, not all $\epsilon 4$ carriers demonstrate AD-related neurodegeneration during their life span ([Relkin et al., 1996](#)). Given the increasing risk of AD with increasing age ([Hebert et al., 1995](#)), it is conceivable that a longer follow-up interval would be needed to see such changes in our stable $\epsilon 4$ carriers. However, our $\epsilon 4+$ declining and stable groups did not differ in mean age. There are also data to suggest that the increased risk of developing AD in the presence of the $\epsilon 4$ allele diminishes after the age of 80 ([Breitner et al., 1999](#)). Thus, it is unlikely that the group differences are simply related to the length of the follow-up interval.

There are several physiological pathways whereby the $\epsilon 4$ allele may exert deleterious effects that lead to neurodegeneration and contribute to loss of cognitive function. The apoE4 isoform expressed by the $\epsilon 4$ allele preferentially binds to low-density lipoprotein receptors, resulting in wide-ranging effects on lipid and cholesterol metabolism, including increased production of very low-density lipoproteins, the release of proinflammatory cytokines, and atherosclerosis ([Zhang, Wu, & Wu, 2011](#)). In nervous tissue, apoE4 is associated with decreased lipoprotein lipase activity and decreased delivery of free fatty acids to brain cells, leading to altered lipid membrane homeostasis, decreased cerebral glucose metabolism, and increased glial activation and inflammation; it impairs the processing and removal of extracellular amyloid-beta peptide, increases the phosphorylation of tau, and impairs cholinergic function ([Lane & Farlow, 2005](#)). Collectively, these processes (among others) may lead to neuronal cell dysfunction and apoptotic processes, leading to cell death. However, susceptibility to the effects of the *APOE* $\epsilon 4$ allele on peripheral and brain lipid metabolism, and ultimately on brain structure and function, varies considerably in the population.

What other factors might influence the variability in the phenotypic expression of the $\epsilon 4$ allele? Physically active $\epsilon 4$ carriers experience significantly less hippocampal atrophy over time compared to inactive $\epsilon 4$ carriers ([Smith et al., 2014](#)). Similarly, physically active $\epsilon 4$ carriers experience increased memory-related brain activation ([Smith et al., 2011](#)) and reduced neurodegeneration of white matter fiber populations within projection and association tracts ([Smith et al., 2016](#)) compared to sedentary $\epsilon 4$ carriers. Importantly, these brain imaging differences were not observed in noncarriers, suggesting that physical activity has a specific neuroprotective effect in $\epsilon 4$ carriers. Moreover, we previously reported that physically inactive $\epsilon 4$ carriers have a greater probability of cognitive decline over 18 months compared to physically active $\epsilon 4$ carriers ([Woodard et al., 2012](#)). In addition, [Schreiber and colleagues \(2016\)](#) found that low vascular risk and lifetime engagement in stimulating cognitive activities served to preserve cognitive abilities in healthy $\epsilon 4$ carriers. [Schwartz and colleagues \(2016\)](#) speculate that greater brain structural integrity, high socioeconomic status, lack of brain injury, high occupational achievement, and perseverance, all indicators of enhanced brain and cognitive reserve, may moderate the effect of the $\epsilon 4$ allele on cognitive decline. Of note, level of educational attainment, an important indicator of cognitive reserve, was 2.0 years greater in the $\epsilon 4+$ stable group than in the $\epsilon 4+$ declining group, although this difference was not significant.

Other possible explanations involve $\epsilon 4$ allele dose and family history of AD. [Martins, Oulhaj, de Jager, and Williams \(2005\)](#) found that $\epsilon 4$ homozygotes displayed a greater rate of cognitive decline than $\epsilon 4$ heterozygotes over a 3-year interval. Our results are unlikely to be influenced by this factor because only two of our $\epsilon 4$ carriers were homozygotes ($\epsilon 4/\epsilon 4$), and both were in the cognitively stable group. Family history of AD has also been examined as an additional risk factor for cognitive decline and neurodegeneration in $\epsilon 4$ carriers. [Donix and colleagues \(2010\)](#) found that family history of AD explained more variance in cortical thickness than *APOE* $\epsilon 4$ status. Family history is unlikely to have influenced our results because there were no statistically significant group differences in family history of AD between the $\epsilon 4+$ stable (64%) and $\epsilon 4+$ declining (80%) groups ($p = .35$).

The $\epsilon 4+$ declining group had significantly greater expansion of the right inferior lateral ventricle than the $\epsilon 4-$ group. In contrast, there were no significant group differences in the volume of the main body of the lateral ventricles. In the absence of hydrocephalus, increased ventricular volume is an indirect estimate of atrophy within periventricular structures ([Tang et](#)

[al., 2015](#)). Not surprisingly, as the hippocampus and other medial temporal lobe structures decrease in volume, the inferior horns of the lateral ventricles expand ([Thompson et al., 2004](#)), which our results appear to typify.

A limitation of this study is the small sample size. Nevertheless, we found medium to large effect sizes in the right inferior lateral ventricle, hippocampi, and cortical gray matter regions. A further limitation, relevant to all longitudinal studies, was attrition. The participants who were missing data at one of the three sessions were excluded from the study. There were no group differences between included and excluded participants at either time point in age, education, or family history and no baseline test score differences between those included or excluded at T2. However, despite all having intact scores at baseline, those unable to be scanned at T3 (Year 5) were more likely to be male ($p = .036$) and had lower baseline scores on the DRS-2 total ($p = .003$) and RAVLT total trials ($p = .012$). Notably, all three participants who missed T2 were $\epsilon 4+$, and 13 of 21 who missed T3 were $\epsilon 4+$. Thus, inclusion of these missing participants would likely have strengthened the present findings.

Another limitation of this study is the absence of data on AD-specific biomarkers, such as can be derived from cerebrospinal fluid analyses of tau and amyloid proteins or positron emission tomography imaging of amyloid deposition. [Lim and colleagues \(2013\)](#) found that $A\beta$ amyloid burden explained 14% of the variance in episodic memory performance in $\epsilon 4$ carriers but had no relationship with memory performance in $\epsilon 4$ noncarriers. Another study found that $\epsilon 4$ carriers with high $A\beta$ levels had greater declines in verbal memory and global cognition over 1.5 years than $\epsilon 4$ carriers with low $A\beta$ levels ([Mormino et al., 2014](#)). If these data were available in the current study, we would hypothesize that AD biomarkers would be more abnormal in $\epsilon 4$ declining than in $\epsilon 4$ stable carriers.

In conclusion, our study demonstrates that the degree of long-term longitudinal changes in episodic memory and global cognition are linked with the severity of changes in brain atrophy in persons who possess the *APOE* $\epsilon 4$ allele. Thus, this study illustrates the variability in phenotypic expression of the $\epsilon 4$ allele, which may be associated with potential lifestyle factors, such as physical activity, and cognitive reserve. Larger scale studies are required to examine these potential influences as a means for understanding modifiable risk and protective factors associated with genetic risk.

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