

Disentangling the effects of age and *APOE* on neuropathology and late life cognitive decline

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ABSTRACT

Age and *APOE* are the most robust risk factors for dementia and cognitive decline, but the underlying neurobiology remains unclear. We examined the extent to which the hallmark pathologies of Alzheimer's disease, Lewy body disease, and cerebrovascular diseases account for the association of age and *APOE* with decline in episodic memory versus nonepisodic cognitive abilities. Up to 20 waves of longitudinal cognitive data were collected from 858 autopsied participants in 2 ongoing clinical-pathologic cohort studies of aging. Neuropathologic examinations quantified measures of beta amyloid ($A\beta$) plaque, mesial temporal and neocortical neurofibrillary tangles, macro- and microinfarcts, and neocortical Lewy bodies. Random coefficient models estimated person-specific slopes of decline in episodic memory and nonepisodic cognition. Path analysis examined the relation of age, *APOE*, and the 6 pathologic indices to the slopes of cognitive decline. The effect of age on decline in episodic memory was mediated by $A\beta$, mesial temporal and neocortical tau tangles, and macroscopic infarcts; age on decline in nonepisodic cognition was mediated by $A\beta$, neocortical tangles, and macroscopic infarcts. The effect of *APOE* on decline in episodic memory was mediated by $A\beta$, mesial temporal and neocortical tangles, and neocortical Lewy bodies; *APOE* on nonepisodic cognition was mediated by $A\beta$, neocortical tangles, and neocortical Lewy bodies. There were no direct effects of age and *APOE* on decline after accounting for these pathologic pathways.

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1. Introduction

Loss of cognition and the development of mild cognitive impairment (MCI) and dementia in late life are associated with multiple age-related neuropathologies including Alzheimer's disease (AD; i.e., beta amyloid [$A\beta$] plaque deposition and paired helical filament [PHF] tau immunoreactive neuronal neurofibrillary tangle [tau tangle] formation), cerebrovascular disease (CVD; i.e., macroscopic and microscopic infarcts), and neocortical Lewy body (LB) disease (i.e., alpha-synuclein immunoreactive neocortical LBs) (Launer et al., 2008; Nelson et al., 2010; Neuropathology Group, Medical Research Council Cognitive Function and Aging Study, 2001; Royall and Palmer, 2012; Sonnen et al., 2007;

Troncoso et al., 2008; Wilson et al., 2010). A general consensus on neurodegeneration in AD places tau tangle formation downstream of $A\beta$ deposition (Jack et al., 2011; Sperling et al., 2011). This hypothesis is supported by the fact that mutations in all 3 causal genes of familial AD (i.e., Amyloid beta [A4] precursor protein, Presenilin-1, and Presenilin-2) lead to the accumulation of $A\beta$ and tau tangles, whereas mutations in the tau gene do not result in $A\beta$ accumulation (Hardy and Selkoe, 2002; Hutton et al., 1998). Clinical-pathologic studies have also shown that the association of $A\beta$ with cognition is mediated by tau tangle pathology (Bennett et al., 2004; Roberson et al., 2007). The recent revision of neuropathologic criteria for AD requires $A\beta$ deposition (Hyman et al., 2012), which differs from a traditional view that mesial temporal tangles, even in the absence of amyloid, is the earliest manifestation of AD (Braak and Braak, 1995; Hyman et al., 1984). Thus, it has been argued that tau tangles, frequently seen in the mesial temporal lobe in the absence of $A\beta$, might represent a separate age-related pathologic process (Jellinger and Attems,

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2007; Nelson et al., 2009; Yamada, 2003). Further, although there is some evidence of an association between amyloid and cerebrovascular dysfunction (Han et al., 2008) and colocalization of tau and alpha-synuclein (Ishizawa et al., 2003), most clinical pathologic studies suggest infarcts and LB pathologies have relatively independent effects on cognitive impairment and dementia (Launer et al., 2008; Neuropathology Group. Medical Research Council Cognitive Function and Aging Study, 2001; Sonnen et al., 2007; Troncoso et al., 2008).

Older age and apolipoprotein E (APOE) are the 2 most robust risk factors for late life cognitive decline, MCI, and dementia (Corder et al., 1993; Dubé et al., 2013; Evans et al., 1989; Karlamangla et al., 2009; Lipnicki et al., 2013). However, the neurobiologic pathways linking age and APOE with cognition have not been fully elucidated. It is well known that AD, CVD, and LB pathologies accumulate with age. Further, APOE is a risk factor for the pathologies of all 3 diseases but the relationships are more complex. APOE is strongly related to amyloid deposition and slightly less so with tau tangle pathology (Morris et al., 2010; Mortimer et al., 2009). We are not aware of previous studies that have disentangled the effect of APOE on mesial temporal versus neocortical tangles. In contrast, APOE is only weakly associated with infarcts and LBs (Schneider et al., 2005; Tsuang et al., 2013).

In previous studies, we reported that the association of APOE with global cognitive decline was mediated by amyloid and tangles (Yu et al., 2013), and the association of APOE with perceptual speed was partially mediated by macroscopic infarcts (Li et al., 2007). We also reported a 2-process model for AD-related pathologies such that the association of APOE with neocortical tangles and neuritic plaques represents an AD pathway, whereas a separate nonplaque age-related process leads to mesial temporal tangles (Mungas et al., 2013). Here, we extend our previous work and expand this 2-process model in 4 major ways. First, we used molecularly-specific markers of AD including A β load and the density of tau tangles rather than plaques and tangles with silver stain. Second, we added other common age-related pathologies to the model, including macro- and microscopic infarcts and neocortical LBs. Third, whereas our previous model used neuropathologies as the end point, here, we linked the neuropathologies to the downstream phenotype of cognitive decline using repeated measures of cognitive function over up to 20 years before death. Finally, we examined the effects of age, APOE, and neuropathologies on decline in episodic memory and decline in a composite measure of other cognitive abilities. We separated cognition into episodic memory and nonepisodic abilities for several reasons. First, change in episodic memory is the clinical hallmark of AD dementia and amnesic MCI, a precursor to AD dementia. Second, APOE appears to have a relatively selective effect on change in episodic memory (Barral et al., 2012; Wikgren et al., 2012; Wilson et al., 2002). Third, AD pathology might have a selective effect on episodic memory compared with cerebrovascular disease, which might be relatively selective for measures of executive function, and LBs for measures of visuospatial ability (Cholerton et al., 2013; Johnson and Galvin, 2011; Reed et al., 2007; Schneider et al., 2012; Yang et al., 2013).

2. Methods

2.1. Participants

Participants came from 2 ongoing clinical-pathologic cohort studies of aging and AD; the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP). ROS started in 1994 and

enrolled older religious clergy from more than 40 groups across the United States. MAP started in 1997 and enrolled older residents from retirement facilities and subsidized housing across the Chicago metropolitan area. Detailed study design and data collection procedures have been previously reported (Bennett et al., 2012a, 2012b). Both studies were approved by the Institutional Review Board of Rush University Medical Center. All the participants agreed to annual clinical evaluations and brain donation at death.

Uniform ante- and postmortem data collection in ROS and MAP allows us to combine the data from both studies. At the time of these analyses, 1131 persons with at least 2 cognitive evaluations died and were autopsied, of whom 858 (ROS = 459; MAP = 399) had complete data for APOE genotyping and neuropathologies. The average age at death was 88.5 years (SD = 6.5; range, 65.9–108.3).

2.2. Cognitive evaluations

Seventeen cognitive tests were administered to each participant every year. To distinguish episodic memory and other cognitive abilities and to reduce floor and ceiling effects, we created 2 composite scores. The composite of episodic memory consisted of 7 tests, including immediate and delayed recall of story A from logical memory, immediate and delayed recall of the east Boston story, word list memory, word list recall, and word list recognition. A nonepisodic composite was based on standard progressive matrices, verbal fluency, digit span forward and backward, digit ordering, symbol digit modalities, number comparison, reading test, Boston naming, and judgment of line orientation. In both cases, higher scores indicate better cognitive performance. The psychometric properties of the cognitive domains have been described previously (Wilson et al., 2002).

2.3. Neuropathology assessments

Postmortem brains were processed following a standard procedure. One hemisphere was cut coronally into 1-cm slabs and fixed in 4% paraformaldehyde. Using immunohistochemical staining and computer-assisted sampling and image analysis (Bennett et al., 2004), A β and tau tangle pathologies were assessed across 8 cortical regions including entorhinal cortex, hippocampus CA1/subiculum, superior frontal cortex (Brodmann area [BA] 6/8), mid frontal cortex (BA 46/9), inferior temporal cortex (BA 20), angular gyrus cortex (BA 39/40), cingulate cortex (BA 32/33), and calcarine cortex (BA 17). Overall A β load was derived by averaging the mean percentage area per region, across multiple regions. Similarly, mesial temporal and neocortical tangle densities were obtained by averaging PHF tau tangles across corresponding brain regions. Fixed slabs and/or pictures from both hemispheres were examined for macroscopic infarcts, followed by histological confirmation (Schneider et al., 2005). Microinfarcts, defined as infarcts not seen grossly but discovered using microscopy, were identified by examining at least 9 sections stained with hematoxylin and eosin (Arvanitakis et al., 2011). Only presence versus absence of chronic infarcts was considered in the analysis. Neocortical LB pathology required presence of alpha-synuclein immunoreactive LBs in either mid frontal, middle temporal, or inferior parietal cortex, together with either nigral or limbic positivity (Schneider et al., 2012).

2.4. Other variables

Age in years was computed from self-reported date of birth and date of death. DNA was extracted from blood, and in some cases

from frozen brain tissue. *APOE* genotyping was done by sequencing codon 112 and codon 158 of exon 4 of the *APOE* gene (Boyle et al., 2010). Participants with at least 1 copy of the $\epsilon 4$ allele were considered carriers, and the rest were considered noncarriers.

2.5. Statistical analysis

We hypothesized a structural model for the relationship of age, *APOE*, and neuropathologies with late life cognitive decline. Fig. 1 is a graphical representation of the overall model. The primary outcomes for the analyses were person-specific rates of decline (slopes) in episodic memory and nonepisodic cognition, estimated from random coefficient models using all available longitudinal cognitive data. These slopes capture the between-subject deviation from the mean slope of decline. Using path analysis, we examined and compared the effect of individual contributing pathways linking age and *APOE*, through neuropathologies, to the slopes of episodic memory and nonepisodic cognition. Goodness of fit for this structural model was assessed using comparative fit index (CFI), Tucker-Lewis index (TLI), and the root mean square error of approximation (RMSEA). The model is acceptable only if all the indices indicate goodness of fit (i.e., CFI > 0.95, TLI > 0.95, and RMSEA < 0.05). Standardized path coefficients along individual pathways were used to capture the total direct and indirect effects of age, *APOE*, and neuropathologic indices on cognitive decline. We imposed a nominal threshold of $p < 0.05$ for statistical significance. Analyses were performed using SAS/STAT software, version 9.3 (SAS Institute Inc, Cary, NC, USA) and Mplus, version 7.0 (Muthen & Muthen, 1998–2012).

3. Results

Participants ($n = 858$) in the analyses were on average 88.5 years of age at the time of death (SD = 6.5; range, 65.9–108.3), and 224 (26.1%) were *APOE* $\epsilon 4$ carriers. During up to 19 years of follow-up, episodic memory declined a mean of 0.110 unit per year ($p < 0.001$) and

Table 1

Descriptive characteristics ($n = 858$)

Variable	Value
Age at death	88.5, 6.5, 66–108
Female sex	556 (64.8)
A β load	4.06, 4.23, 0–22.94
Neocortical PHF tau tangle density	2.82, 6.61, 0–80.10
Mesial temporal PHF tau tangle density	17.25, 15.32, 0–91.11
Macroscopic infarcts (≥ 1 present)	311 (36.3)
Microinfarcts (≥ 1 present)	250 (29.1)
Neocortical Lewy bodies (present)	100 (11.7)

Data are presented as mean, SD, range, or n (%).

Key: A β , beta amyloid; PHF, paired helical filament.

nonepisodic cognition declined a mean of 0.126 ($p < 0.001$). At autopsy, 743 (86.6%) participants were positive for A β , 824 (96.0%) were positive for neocortical tau tangles, and 856 (99.7%) were positive for mesial temporal tau tangles. More than 13% of participants (115 out of 858) had tau tangle pathology in the absence of A β (including 10 participants who had only mesial temporal tangles). Approximately half of the participants had either macroscopic (36.3%) or micro (29.1%) infarcts, and 12% had neocortical LBs. Additional descriptive statistics are presented in Table 1.

We first examined the associations of age and *APOE* with cognitive decline in a series of random coefficient models using longitudinal cognitive data as the outcome. Older age was associated with faster rates of decline in episodic memory (estimate = -0.052 ; $p < 0.001$) and nonepisodic cognition (estimate = -0.043 ; $p < 0.001$). Similarly, the presence of the $\epsilon 4$ allele also led to faster rates of decline in episodic memory (estimate = -0.064 ; $p < 0.001$) and nonepisodic cognition (estimate = -0.061 ; $p < 0.001$). In contrast, after adjusting for A β , mesial temporal and neocortical tau tangles, macro- and microscopic infarcts, and cortical LBs, age and *APOE* were no longer associated with decline in either domain (Fig. 2). In addition, there was no significant decline in episodic memory when we controlled for the pathologies (estimate = -0.004 ; $p = 0.735$), and the rate of decline in nonepisodic cognition was also greatly reduced (estimate = -0.038 ; $p = 0.001$).

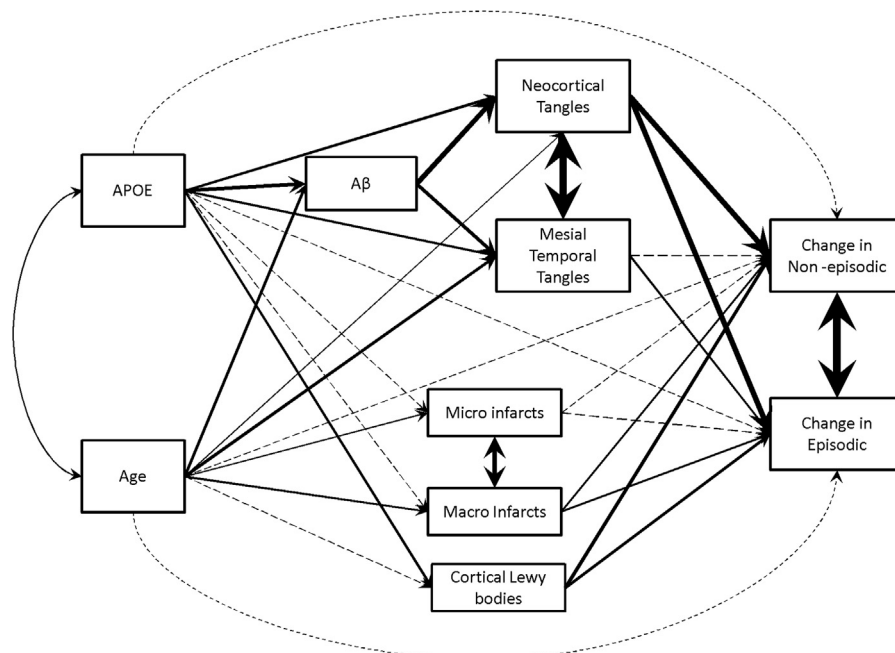


Fig. 1. Graphical representation of the model structure. Nonsignificant coefficients are presented as dotted lines; thickness of solid lines corresponds to the relative effect size of the coefficients. Abbreviations: A β , beta amyloid; *APOE*, *APOE*.

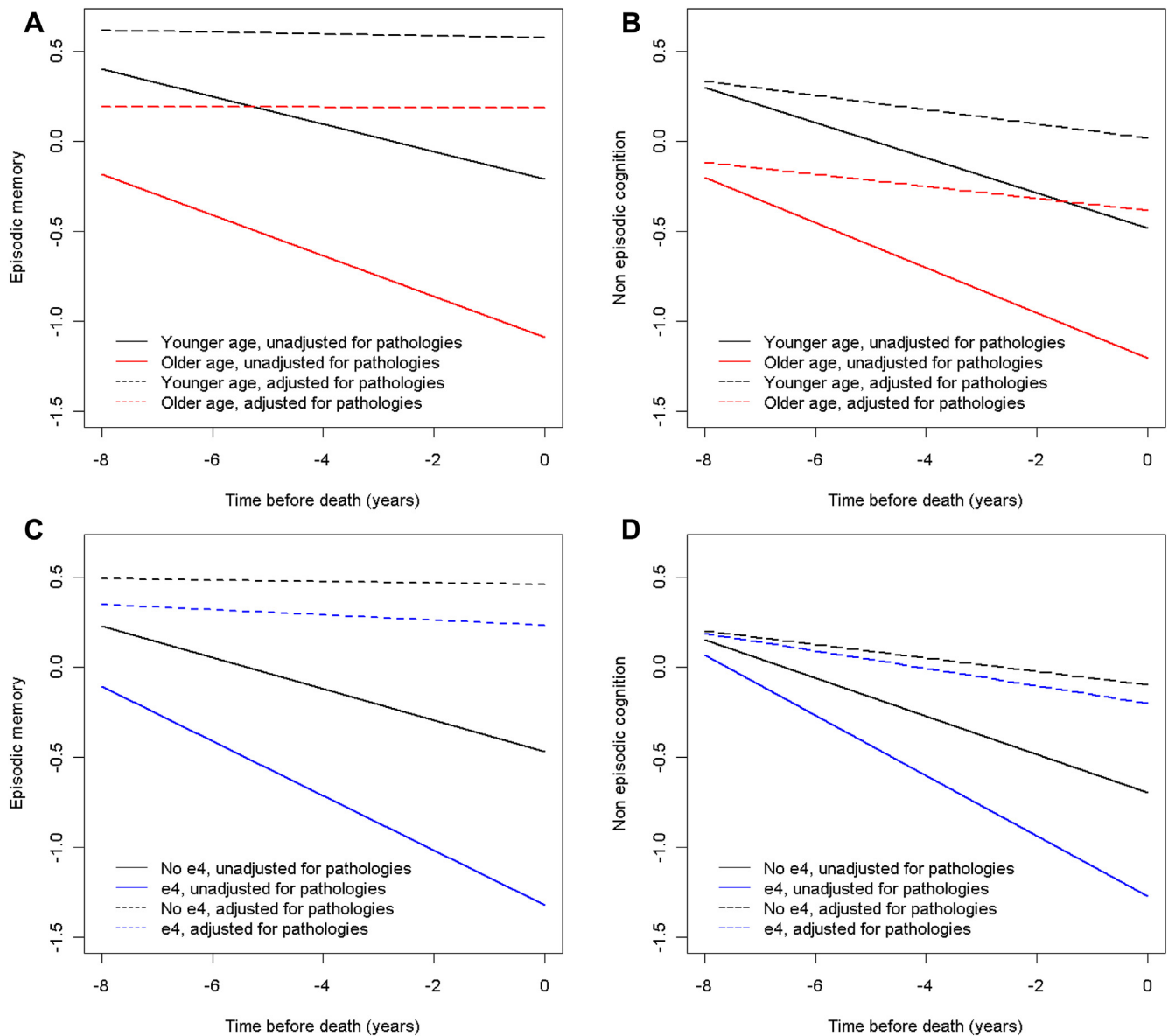


Fig. 2. (A) and (B) Association of age with declines in episodic memory and nonepisodic cognition. (C) and (D) Association of *APOE* with the declines in episodic memory and nonepisodic cognition.

We next applied the path analysis to examine the extent to which the effects of age and *APOE* on cognitive decline are mediated by individual common neuropathologies (Fig. 1). Our model fit the data well (CFI = 0.995, TLI = 0.982, RMSEA = 0.027 [95% confidence interval, 0–0.047]). Individual standardized path coefficients and corresponding *p* values are shown in Table 2. Further, in Fig. 1, nonsignificant coefficients are presented as dotted lines and thickness of solid lines corresponds to the relative effect size of the coefficients.

3.1. Neuropathologies on cognitive decline

We examined the relation of the 6 pathologies to cognitive decline. Neocortical tau tangle pathology, macroscopic infarcts, and neocortical LBs were associated with decline in episodic memory and nonepisodic cognition, and mesial temporal tau tangle pathology was only associated with decline in episodic memory. The effect of $A\beta$ on cognitive decline was largely

mediated by neocortical tau tangle pathology. On decline in episodic memory, 78% of the $A\beta$ effect was mediated by neocortical tau tangles (estimate = -0.171 ; $p < 0.001$), and 22% through mesial temporal tau tangles (estimate = -0.048 ; $p < 0.001$). On decline in nonepisodic cognition, virtually all of the effect of $A\beta$ was mediated by neocortical tau tangles (estimate = -0.179 ; $p < 0.001$), and the indirect effect through mesial temporal tau tangles was not significant (estimate = -0.017 ; $p = 0.121$).

3.2. Relation of age and *APOE* on tau tangle pathology

We also examined the relation of age and *APOE* to tau tangle pathology. In doing so, we allowed in the model links from age and *APOE* to tau tangle pathology with and without $A\beta$. Direct and indirect (through $A\beta$) effects from age and *APOE* to tau tangles were significant (Table 3), suggesting separate pathways that link age and *APOE* to tau tangle pathology. The total estimated effect of age on neocortical tau tangles was 0.145 ($p < 0.001$), of

Table 2
Model path coefficients

Effects	Std Coeff	p
A β (regressed on)		
Age	0.223	<0.001
APOE	0.278	<0.001
Mesial temporal tangles (regressed on)		
Age	0.246	<0.001
APOE	0.179	<0.001
A β	0.280	<0.001
Neocortical tangles (regressed on)		
Age	0.054	0.030
APOE	0.190	<0.001
A β	0.409	<0.001
Macroscopic infarcts (regressed on)		
Age	0.176	<0.001
APOE	0.067	0.156
Microinfarcts (regressed on)		
Age	0.112	0.013
APOE	0.021	0.675
Neocortical Lewy bodies (regressed on)		
Age	0.077	0.243
APOE	0.195	0.001
Episodic decline (regressed on)		
Age	−0.034	0.296
APOE	−0.019	0.544
Mesial temporal tangles	−0.172	<0.001
Neocortical tangles	−0.418	<0.001
Macroscopic infarcts	−0.160	0.001
Microinfarcts	−0.027	0.544
Neocortical Lewy bodies	−0.228	<0.001
Nonepisodic decline (regressed on)		
Age	−0.032	0.318
APOE	0.009	0.791
Mesial temporal tangles	−0.061	0.112
Neocortical tangles	−0.437	<0.001
Macroscopic infarcts	−0.146	<0.001
Microinfarcts	−0.048	0.298
Neocortical Lewy bodies	−0.268	<0.001

Significant coefficients are shown in bold.

Key: A β , beta amyloid; Std Coeff, standardized coefficient.

which more than 60% went through A β (estimate = 0.091; $p < 0.001$). In contrast, approximately 80% of age effect on mesial temporal tau tangles was attributable to a direct effect (estimate = 0.246; $p < 0.001$), and only 20% worked through A β (estimate = 0.062; $p < 0.001$). This result supports a nonamyloid-based process that involves the formation of mesial temporal tau tangles, primarily driven by age. The estimated effect of APOE on neocortical tau tangles was 0.304 ($p < 0.001$), of which 37.5% (estimate = 0.114; $p < 0.001$) was an indirect effect through A β . Thirty percent of the total effect of APOE on mesial temporal tau tangles was mediated by A β .

3.3. Age, APOE, and neuropathologies on cognitive decline

Finally, we examined the product of path coefficients along each pathway, which allows us to assess the relative contributions of the individual pathways that link age and APOE with cognitive decline (Table 4 and Fig. 3). A substantial proportion of

Table 4
Effect partition of age and APOE on declines in cognition^a

Pathway	Episodic		Nonepisodic	
	Std Coeff	p-value	Std Coeff	p-value
Age → decline	−0.034	0.296	−0.032	0.318
Age → neocortical Lewy bodies → decline	−0.018	0.251	−0.021	0.248
Age → microinfarcts → decline	−0.003	0.567	−0.005	0.361
Age → macroscopic infarcts → decline	−0.028	0.013	−0.026	0.015
Age → mesial temporal tangles → decline	−0.042	<0.001	−0.015	0.130
Age → neocortical tangles → decline	−0.023	0.031	−0.024	0.029
Age → A β → mesial temporal tangles → decline	−0.011	<0.001	−0.004	0.128
Age → A β → neocortical tangles → decline	−0.038	<0.001	−0.040	<0.001
APOE → decline	−0.019	0.544	0.009	0.791
APOE → neocortical Lewy bodies → decline	−0.045	0.015	−0.052	0.009
APOE → microinfarcts → decline	−0.001	0.741	−0.001	0.704
APOE → macroscopic infarcts → decline	−0.011	0.205	−0.010	0.202
APOE → mesial temporal tangles → decline	−0.031	<0.001	−0.011	0.132
APOE → neocortical tangles → decline	−0.079	<0.001	−0.083	<0.001
APOE → A β → mesial temporal tangles → decline	−0.013	<0.001	−0.005	0.126
APOE → A β → neocortical tangles → decline	−0.048	<0.001	−0.050	<0.001

Significant coefficients are shown in bold.

Key: A β , beta amyloid; Std Coeff, standardized coefficient.^a Nonsignificant path coefficients were set to 0 in estimating the percent contribution.

the age effect on decline in episodic memory worked through mesial temporal tau tangles (direct effect 30%, and indirect effect through A β , 8%). In addition, a comparable proportion was attributable to A β and neocortical tau tangles (43%), and macroscopic infarcts explained the remaining 20%. On decline in nonepisodic cognition, the effect through mesial temporal tau tangles was attenuated and no longer significant. As a result, the effect of age on decline in nonepisodic cognition was shared by A β and neocortical tau tangle pathology (71%), and macroscopic infarcts (29%).

Only 20% of the APOE effect on episodic decline was explained by A β and mesial temporal tau tangle pathology, and 59% was due to the effect of neocortical tau tangle pathology, either directly or indirectly through A β . The presence of neocortical LBs accounted for the rest of the APOE effect on decline in episodic memory (21%). In contrast, the effect of APOE on nonepisodic cognitive decline was primarily driven by A β and neocortical tau tangles. Forty-five percent of the total effect of APOE on decline in nonepisodic cognition was explained by the direct effect of neocortical tau tangles, and 27% was due to an indirect effect of neocortical tau tangles through A β . The rest (28%) was explained by neocortical LBs. The contribution of infarcts to the relationship of APOE on decline in both domains was minimal.

4. Discussion

In this study, we identified multiple pathways that link age and APOE with common neuropathologies and downstream cognitive decline using clinical and pathologic data from approximately 900 older people who completed up to 20 years of annual cognitive evaluations. It has been shown that specific cognitive domains might be differentially associated with neuropathologic indices (e.g., memory function with AD, executive function with vascular pathology, and visuospatial construction with LB disease). Overall, our data suggest that common neuropathologies are significantly associated with declines in episodic and nonepisodic cognition.

Table 3
Effect partition of age and APOE on tangles pathologies

Pathway	Mesial temporal tangles		Neocortical tangles	
	Std Coeff	p	Std Coeff	p
APOE → A β → tangles	0.078	<0.001	0.114	<0.001
APOE → tangles	0.179	<0.001	0.190	<0.001
Age → A β → tangles	0.062	<0.001	0.091	<0.001
Age → tangles	0.246	<0.001	0.054	0.030

Key: A β , beta amyloid; Std Coeff, standardized coefficient.

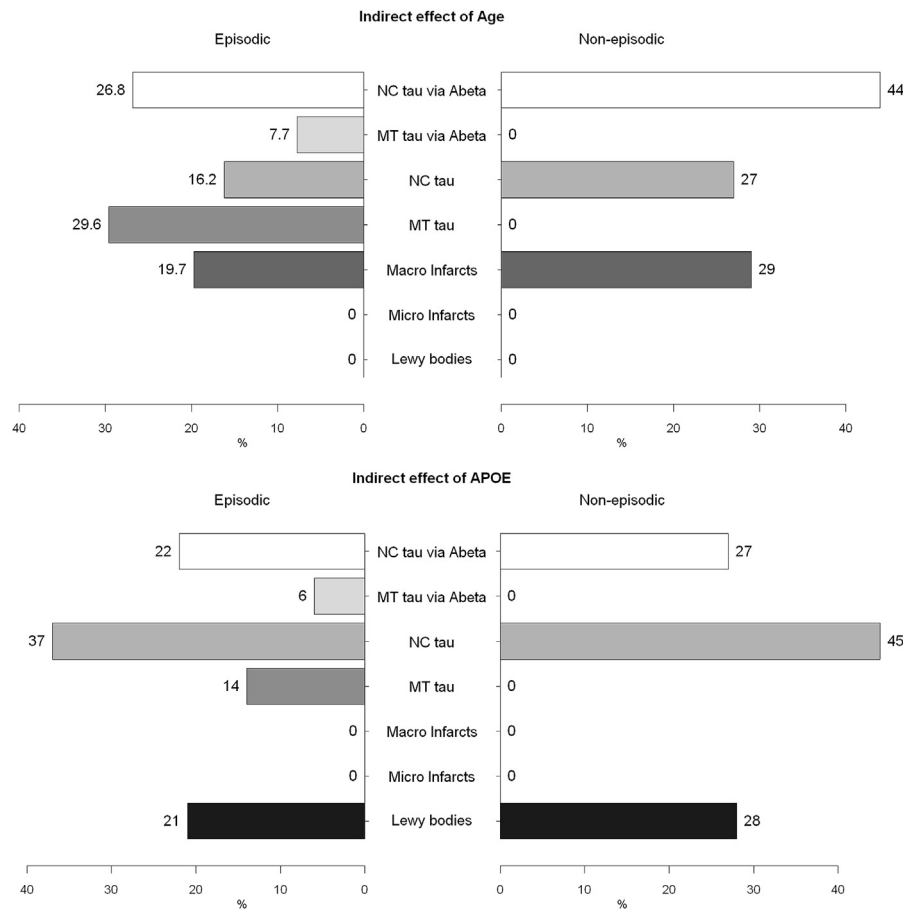


Fig. 3. Percent contributions of indirect effect of age (upper panel) and *APOE* (lower panel) through common neuropathologies on declines in episodic memory and nonepisodic cognition. Abbreviations: *APOE*, *APOE*; MT, mesial temporal; NC, neocortical.

This finding explains the recent observation that mixed pathologies are the most common cause of AD dementia and a common cause of amnesic and nonamnesic MCI (Schneider et al., 2009; Sonnen et al., 2007; White, 2009). Further, there was a little to no decline in episodic memory and nonepisodic cognition after adjusting for neuropathologies, which suggests that mean age-related declines in both aspects of cognition are attributable to common neuropathologies. The effect of age was primarily due to A β , tangle pathology, and macroscopic infarcts, and the effect of *APOE* on cognitive decline was primarily due to A β , tangle pathology, and neocortical LBs. Disentangling these complex relationships among age, *APOE*, AD, and common neuropathologic indices with late life cognitive decline offers crucial insight into the pathophysiological mechanisms that underlie cognitive aging.

A recent finding suggests dual processes for AD pathology whereby mesial temporal lobe tangle pathology represents an *APOE* amyloid-related AD process and a separate age-related process or processes (Mungas et al., 2013). Mesial temporal tangles are thought to have stronger effects on episodic memory than on nonepisodic cognition. Our data suggest that mesial temporal tangle pathology is indeed a result of 2 separate processes and it is exclusively associated with decline in episodic memory. Thus, in complement to the amyloid cascade hypothesis in which tangle formation only occurs downstream of amyloid, the results render further support that there might be other pathogenic processes that stimulate tau phosphorylation and subsequently result in neurofibrillary tangle degeneration. Our finding has important implications for clinical-pathologic studies. Namely, neuropathologic lesions in temporal lobe structures, particularly hippocampus, were thought to be the

earliest sign of AD. However, the new pathologic criteria for AD require amyloid deposition and persons with mesial temporal lobe tangles in the absence of amyloid do not meet AD pathologic criteria. Taken together, this suggests that clinical-pathologic studies might well prioritize neocortical pathology rather than the hippocampus because the latter is populated by a more heterogeneous group of tangles. Our results also showed a small direct effect of age on neocortical tau tangle pathology. Mesial temporal tangles tend to 'spread' into the inferior temporal lobe in aging; and such an extension might explain this small direct effect of aging on neocortical tangles. This hypothesis will be addressed in future work.

The association of macroscopic infarcts with memory impairment and executive dysfunction has been reported previously (Carey et al., 2008; Lim and Alexander, 2009). In this study we confirmed that macroscopic infarcts were associated with declines in episodic memory and nonepisodic cognition. In addition, our results extended these findings and revealed that macroscopic infarcts also operate as a separate pathway that links age to late life cognitive decline.

Previous work has shown that *APOE* is related to cognitive impairment primarily through A β deposition and tangles formation. We confirmed that a large proportion of *APOE* effect on late life cognitive decline depends on A β and tau tangles, regardless of the cognitive domain studied. In part, this effect is mediated through the cascade of *APOE* $\rightarrow$ A β $\rightarrow$ tau tangles $\rightarrow$ cognitive decline, and the rest works directly through neurofibrillary tangle pathology, primarily in the neocortical regions. Several potential mechanisms at the cellular level explain the multiple contributions of *APOE* to the pathogenesis of AD (Huang

et al., 2004). On the one hand, apolipoprotein E isoforms play differential roles in regulating A β clearance such that apolipoprotein E4 inhibits A β clearance and/or stimulates A β deposition (Arold et al., 2012; Castellano et al., 2011). Separately, apolipoprotein E isoforms also differ in their effects on the phosphorylation and aggregation of tau, resulting in formation of neurofibrillary tangles. Transgenic mice models have shown that carboxyl-terminal-truncated forms of apolipoprotein E induce intracellular neurofibrillary tangle-like inclusions in neurons containing phosphorylated tau, and the apolipoprotein E4 isoform is more susceptible to such truncation than apolipoprotein E3 (Harris et al., 2003; Huang et al., 2001; Ljungberg et al., 2002).

Our results also reveal an intriguing finding, namely that neocortical LB disease relates *APOE* to cognitive decline. The findings in the literature addressing this association have been mixed. Several studies reported that apolipoprotein E4 increased risk of dementia because of pure synucleinopathies (Kobayashi et al., 2011; Tsuang et al., 2013), suggesting a separate neurodegenerative mechanism of the apolipoprotein E4 isoform. Another study, however, showed no evidence of association of *APOE* with LB counts in 4 brain regions of mid frontal, superior temporal, inferior parietal, and cingulate gyrus (Wider et al., 2012). In a secondary analysis, we tested whether there might be additional pathways that link *APOE* to neocortical LBs through A β and tau tangle pathologies. The result did not support indirect effects of *APOE* on neocortical LBs through these pathologies, suggesting that further investigation is needed to examine the potential mechanism that links *APOE* to neocortical LB pathology.

This study has strengths and limitations. Both the ROS and MAP cohorts had more than 90% follow-up rates among survivors and more than 80% autopsy rates. Up to 20 years of longitudinal cognitive data were used to measure cognitive decline and all participants underwent standard and blinded neuropathologic assessment. Thus, the potential for bias is reduced and the reliability of clinical and pathologic measures is increased. Limitations should also be noted. First, only the most common neuropathologic indices were included in the analysis. Other age-related neuropathologies such as Transactive response DNA-binding protein 43 (TDP-43) (Tremblay et al., 2011), hippocampal sclerosis (Corey-Bloom et al., 1997; Nelson et al., 2011), and white matter lesions (Inaba et al., 2011) have been shown to be associated with cognitive impairment and AD. We do not yet have sufficient data to fully incorporate these disease markers in our analysis. Second, we and others have reported that the relation of neuropathology to dementia varies by age (James et al., 2012; Nelson et al., 2011; Savva et al., 2009). It will be important to consider these complex associations in future analyses. Third, our data were collected from volunteer cohorts.

Disclosure statement

The authors have no conflicts to disclose that relate to this study.

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