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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 non-episodic cognitive abilities. Up to 20 waves of longitudinal cognitive data were collected from 858 autopsied participants in two ongoing clinical-pathologic cohort studies of aging. Neuropathologic examinations quantified measures of beta amyloid plaque ($A\beta$), 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 non-episodic cognition. Path analysis examined the relation of age, *APOE* and the six 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, as well as macroscopic infarcts; age on decline in non-episodic 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, as well as neocortical Lewy bodies; *APOE* on non-episodic 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.

Keywords

Age; *APOE*; Neuropathologies; Alzheimer's disease; Cognitive decline; Path analysis

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DISCLOSURES

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

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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 plaque (A β) deposition and PHF-tau immunoreactive neuronal neurofibrillary tangle (tau tangle) formation), cerebrovascular disease (i.e. macroscopic and microscopic infarcts) and neocortical Lewy body disease (i.e. alpha-synuclein immunoreactive neocortical Lewy bodies (LB)) (Medical Research Council Cognitive Function and Aging Study 2001, Sonnen et al 2007, Launer et al 2008, Troncoso et al 2008, Nelson et al 2010, Wilson et al 2012, Royall and Palmer 2012). A general consensus on neurodegeneration in AD places tau tangle formation downstream of A β deposition (Sperling et al 2011, Jack et al 2011). This hypothesis is supported by the fact that mutations in all three causal genes of familial AD (i.e. APP, PS1 and PS2) lead to the accumulation of A β and tau tangles, whereas mutations in the tau gene do not result in A β accumulation (Hardy and Selkoe 2002, Hutton et al 1998). Clinical-pathologic studies have also shown that the association of A β 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 β 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 (Hyman et al 1984, Braak and Braak 1995). Thus, it has been argued that tau tangles, frequently seen in the mesial temporal lobe in the absence of A β , may represent a separate age-related pathologic process (Yamada 2003, Jellinger and Attems 2007, Nelson et al 2009). Further, while 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 (Medical Research Council Cognitive Function and Aging Study 2001, Sonnen et al 2007, Launer et al 2008, Troncoso et al 2008).

Older age and Apolipoprotein E (*APOE*) are the two most robust risk factors for late life cognitive decline, MCI and dementia (Evans et al 1989, Karlamangla et al 2009, Lipnicki et al 2013, Corder et al 1993, Dubé 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 three diseases but the relationships are more complex. *APOE* is strongly related to amyloid deposition and slightly less so with tau tangle pathology (Mortimer et al 2009, Morris et al 2010). We are not aware of prior studies that have disentangled the effect of *APOE* on mesial temporal versus neocortical tangles. On the other hand, *APOE* is only weakly associated with infarcts and LB (Schneider et al 2005, Tsuang et al 2013).

In prior 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 two 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 non-plaque age-related process leads to mesial temporal tangles (Mungas et al 2013). Here, we extend our prior work and expand this two-process model in four 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 Lewy bodies. Third, whereas our prior model used neuropathologies as the endpoint, here, we linked the neuropathologies to the downstream phenotype of cognitive decline using repeated measures of cognitive function over up to 20 years prior to 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 non-episodic 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 (Wilson et al 2002, Barral et al 2012, Wikgren et al 2012). Third, AD pathology may have a selective effect on episodic memory compared to cerebrovascular disease which may be relatively selective for measures of executive function and Lewy bodies for measures of visuospatial ability (Reed et al 2007, Johnson et al 2011, Schneider et al 2012, Yang et al 2013, Cholerton et al 2013).

METHODS

Participants

Participants came from two 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 enrolls older religious clergy from over 40 groups across the United States. MAP started in 1997 and enrolls 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 2012, Bennett et al 2012). 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, 1,131 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, Min=65.9, Max=108.3).

Cognitive evaluations

Seventeen cognitive tests were administered to each participant every year. In order to distinguish episodic memory and other cognitive abilities and to reduce floor and ceiling effects, we created two composite scores. The composite of episodic memory consists 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 non-episodic 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).

Neuropathology assessments

Post-mortem 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 (BA6/8), mid frontal cortex (BA46/9), inferior temporal cortex (BA20), angular gyrus cortex (BA39/40), cingulate cortex (BA32/33), and calcarine cortex (BA17). 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 by microscopy, were identified by examining at least 9 sections stained for hematoxylin and eosin (Arvanitakis et al 2011). Only presence versus absence of chronic infarcts was considered in the analysis. Neocortical Lewy body pathology required presence of alpha-synuclein immunoreactive Lewy bodies in either midfrontal, middle temporal, or inferior parietal cortex, together with either nigral or limbic positivity (Schneider et al 2012).

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 one copy of $\epsilon 4$ allele were considered carriers, and the rest were considered non-carriers.

Statistical Analysis

We hypothesized a structural model for the relationship of age, *APOE* and neuropathologies with late life cognitive decline. Figure 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 non-episodic 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 non-episodic 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] and Mplus, Version 7.0 [Muthen & Muthen, 1998–2012].

RESULTS

Participants (N=858) in the analyses were on average 88.5 years of age at the time of death (SD=6.5, Min=65.9, Max=108.3), and 224 (26.1%) were *APOE* $\epsilon 4$ carriers. Over up to 19 years of follow-up, episodic memory declined a mean of 0.110 unit per year ($p<0.001$) and non-episodic 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. Over 13% (115 out of 858) of participants 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 Lewy bodies. 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 non-episodic cognition (Estimate = -0.043 , $p<0.001$). Similarly, the presence of $\epsilon 4$ allele also led to faster rates of decline in episodic memory (Estimate = -0.064 , $p<0.001$) and non-episodic cognition (Estimate = -0.061 , $p<0.001$). On the other hand, after adjusting for A β ,

mesial temporal and neocortical tau tangles, macro- and microscopic infarcts and cortical Lewy bodies, age and *APOE* were no longer associated with decline in either domain (Figure 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 non-episodic cognition was also greatly reduced (Estimate = -0.038 , $p=0.001$).

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

Neuropathologies on cognitive decline

We examined the relation of the six pathologies to cognitive decline. Neocortical tau tangle pathology, macroscopic infarcts and neocortical Lewy bodies were associated with decline in both episodic memory and non-episodic cognition, while 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 non-episodic 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 , $p=0.121$).

Age, *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 $A\beta$. Both 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 which more than 60% went through $A\beta$ (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 $A\beta$ (Estimate = 0.062, $p<0.001$). This result supports a non-amyloid 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 $A\beta$. Thirty percent of the total effect of *APOE* on mesial temporal tau tangles was mediated by $A\beta$.

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 Figure 3). A substantial proportion of the age effect on decline in episodic memory worked through mesial temporal tau tangles (direct effect 30%, and indirect effect through $A\beta$ 8%). In addition, a comparable proportion was attributable to $A\beta$ and neocortical tau tangles (43%), and macroscopic infarcts explained the remaining 20%. On decline in non-episodic cognition, the effect through mesial temporal tau tangles was attenuated and no longer significant. As a result, the effect of age on decline in non-episodic cognition was shared by $A\beta$ and neocortical tau tangle pathology (71%), as well as macroscopic infarcts (29%).

Only 20% of the *APOE* effect on episodic decline was explained by A β and mesial temporal tau tangle pathology, while 59% was due to the effect of neocortical tau tangle pathology, either directly or indirectly through A β . The presence of neocortical Lewy bodies accounted for the rest of *APOE* effect on decline in episodic memory (21%). On the other hand, the effect of *APOE* on non-episodic cognitive decline was primarily driven by A β and neocortical tau tangles. Forty-five percent of the total effect of *APOE* on decline in non-episodic cognition was explained by 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 Lewy bodies. The contribution of infarcts to the relationship of *APOE* on decline in both domains was minimal.

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 about 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 LBD. Overall, our data suggest that common neuropathologies are significantly associated with declines in both episodic and non-episodic cognition. This finding explains the recent observation that mixed pathologies are the most common cause of AD dementia and a common cause of both amnesic and non-amnesic MCI (Sonner et al 2007, Schneider et al 2009, White 2009). Further, there was a little to no decline in both episodic memory and non-episodic 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, while the effect of *APOE* on cognitive decline was primarily due to A β , tangle pathology and neocortical Lewy bodies. 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 both *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 effect on episodic memory than non-episodic cognition. Our data suggest that mesial temporal tangle pathology is indeed a result of two separate processes and it is exclusively associated with decline in episodic memory. Thus, in complement to the amyloid cascade hypothesis where tangle formation only occurs downstream of amyloid, the results render further support that there may 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 may well wish to prioritize neocortical pathology rather than the hippocampus as 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 (Lim et al 2009; Carey et al 2009). In this study we confirmed that macroscopic infarcts were associated with declines in both episodic memory and non-episodic 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.

Prior 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). One the one hand, apoE isoforms play differential roles in regulating Amyloid β clearance such that apoE4 inhibits A β clearance and/or stimulates A β deposition (Castellano et al 2011; Arold et al 2012). Separately, apoE 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 apoE induce intracellular NFT-like inclusions in neurons containing PHTau, and apoE4 isoform is more susceptible to such truncation than apoE3 (Huang et al 2001, Ljungberg et al 2002, Harris et al 2003).

Our results also reveal an intriguing finding, namely that neocortical Lewy body disease relates *APOE* to cognitive decline. The findings in the literature addressing this association have been mixed. Several studies reported that apoE4 increased risk of dementia due to pure synucleinopathies (Tsuang et al 2013, Kobayashi et al 2011), suggesting a separate neurodegenerative mechanism by the apoE4 isoform. Another study, however, showed no evidence of association of *APOE* with Lewy body counts in four brain regions of mid frontal, superior temporal, inferior parietal, and cingulate gyrus (Wider et al 2012). In a secondary analysis, we tested whether there may be additional pathways that link *APOE* to neocortical Lewy bodies through amyloid beta and tau tangle pathologies. The result did not support indirect effects of *APOE* on neocortical Lewy bodies through these pathologies, suggesting that further investigation is needed to examine the potential mechanism that links *APOE* to neocortical Lewy body pathology.

This study has strengths and limitations. Both the ROS and MAP cohorts had over 90% follow-up rates among survivors and over 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 TDP-43 (Tremblay et al 2011), hippocampal sclerosis (Corey-Bloom et al 1997, Nelson et al 2012), 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, Saava et al 2009). It will be important to consider these complex associations in future analyses. Third, our data were collected from volunteer cohorts.

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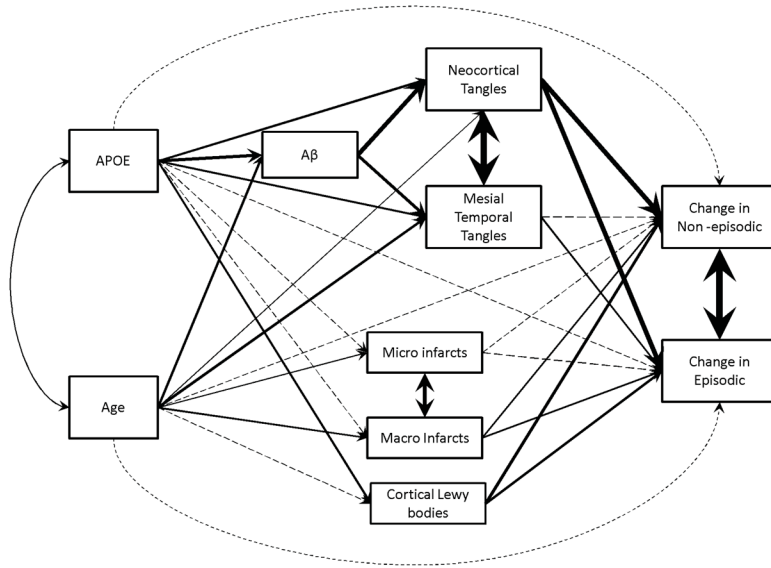


Figure 1. Graphical representation of the model structure. Nonsignificant coefficients were presented as dotted lines; thickness of solid lines corresponds to the relative effect size of the coefficients.

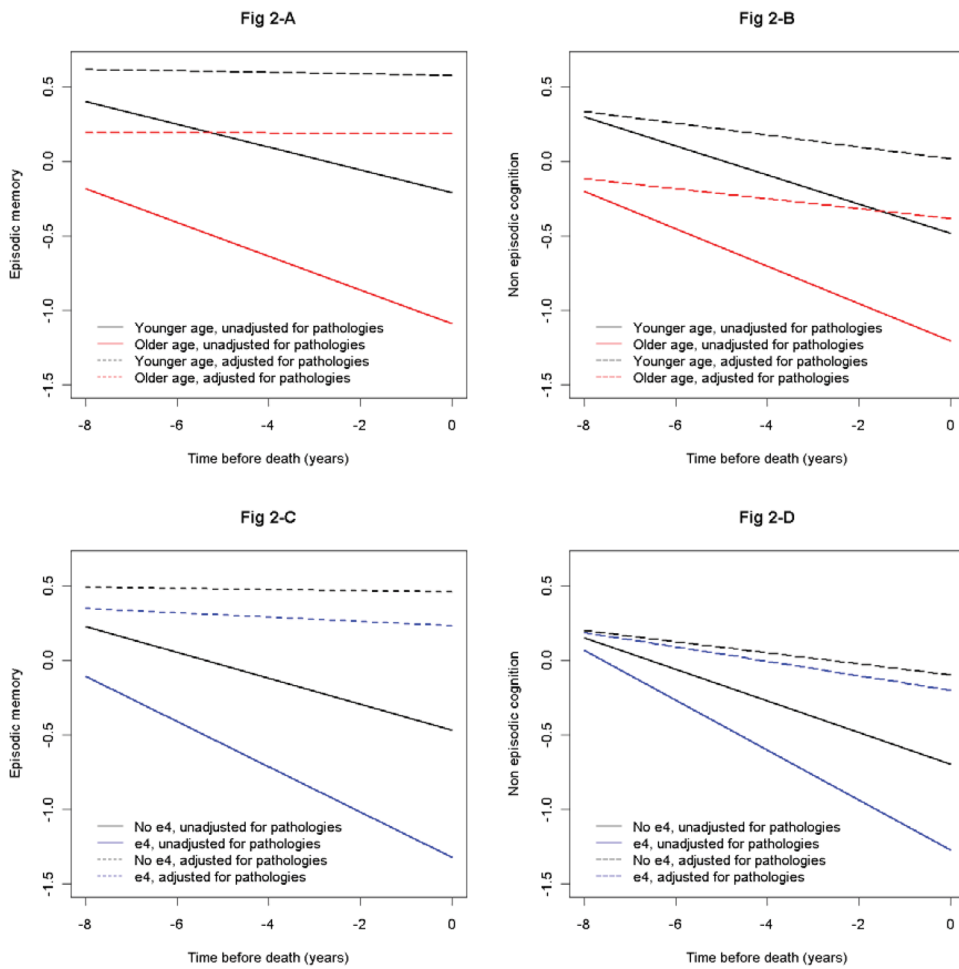


Figure 2.
 Fig 2-A and B. Association of age with declines in episodic memory and non-episodic cognition.
 Fig 2-C and D: Association of *APOE* with the declines in episodic memory and non-episodic cognition.

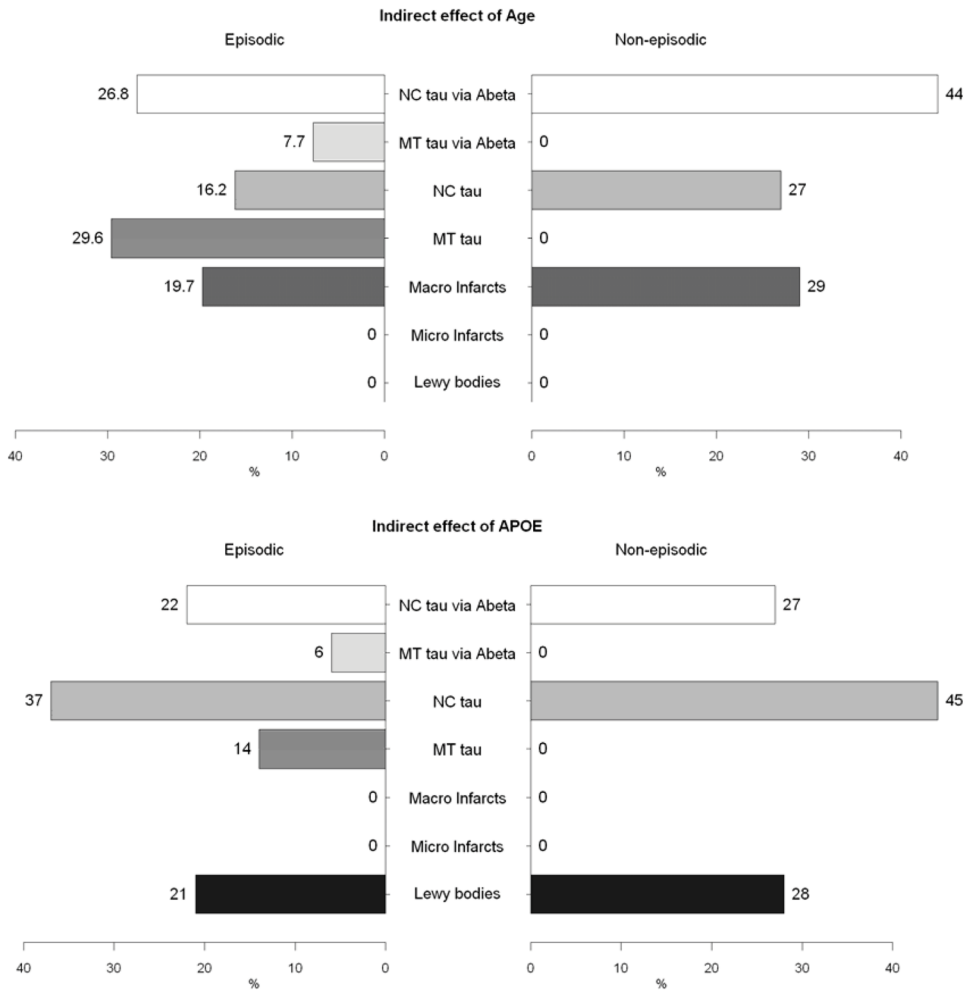


Figure 3. Percent contributions of indirect effect of age (upper panel) and *APOE* (lower panel) through common neuropathologies on declines in episodic memory and non-episodic cognition.

Table 1

Descriptive characteristics (N=858)

Variable	Mean, SD, range (or # and percent)
Age at death	88.5, 6.5, 66–108
Female	556 (64.8%)
A β load	4.06, 4.23, 0 – 22.94
Neocortical PHFtau tangle density	2.82, 6.61, 0 – 80.10
Mesial temporal PHFtau 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%

Table 2

Model path coefficients

Effects	Std Coeff	P-value
A β (regressed on)		
Age	0.223	<0.001
<i>APOE</i>	0.278	<0.001
Mesial temporal tangles (regressed on)		
Age	0.246	<0.001
<i>APOE</i>	0.179	<0.001
A β	0.280	<0.001
Neocortical tangles (regressed on)		
Age	0.054	0.030
<i>APOE</i>	0.190	<0.001
A β	0.409	<0.001
Macroscopic infarcts (regressed on)		
Age	0.176	<0.001
<i>APOE</i>	0.067	0.156
Microinfarcts (regressed on)		
Age	0.112	0.013
<i>APOE</i>	0.021	0.675
Neocortical Lewy bodies (regressed on)		
Age	0.077	0.243
<i>APOE</i>	0.195	0.001
Episodic decline (regressed on)		
Age	-0.034	0.296
<i>APOE</i>	-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
Non-episodic decline (regressed on)		
Age	-0.032	0.318
<i>APOE</i>	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

Std Coeff: standardized coefficient

Table 3Effect partition of age and *APOE* on tangles pathologies

Pathway	Mesial temporal tangles		Neocortical tangles	
	Std Coeff	p-value	Std Coeff	p-value
<i>APOE</i> →A β →tangles	0.078	<0.001	0.114	<0.001
<i>APOE</i> →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

Std Coeff: standardized coefficient

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

Pathway	Episodic		Non-episodic	
	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
<i>APOE</i> →Decline	-0.019	0.544	0.009	0.791
<i>APOE</i> →Neocortical Lewy bodies→Decline	-0.045	0.015	-0.052	0.009
<i>APOE</i> → Microinfarcts→Decline	-0.001	0.741	-0.001	0.704
<i>APOE</i> → Macroscopic infarcts→Decline	-0.011	0.205	-0.010	0.202
<i>APOE</i> → Mesial temporal tangles→Decline	-0.031	<0.001	-0.011	0.132
<i>APOE</i> → Neocortical tangles→Decline	-0.079	<0.001	-0.083	<0.001
<i>APOE</i> →A β →Mesial temporal tangles→Decline	-0.013	<0.001	-0.005	0.126
<i>APOE</i> →A β →Neocortical tangles→Decline	-0.048	<0.001	-0.050	<0.001

* Nonsignificant path coefficients were set to zero in estimating the percent contribution

Std Coeff: standardized coefficient