



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

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