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A 2-process model for neuropathology of Alzheimer's disease

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ABSTRACT

This study examined relations among neuritic and diffuse plaques, neurofibrillary tangles, age, and apolipoprotein E *(APOE)* in 2 large samples of neuropathology cases, the Religious Orders Study and the Memory and Aging Project. Cognitive status ranged from normal to demented and AD neuropathology ranged from none to severe. Confirmatory factor analysis identified a best-fitting 4-factor solution to describe interrelationships among plaques and tangles: a global neuritic plaque factor; a global diffuse plaque factor; a factor defined by medial temporal neurofibrillary tangles; and a neocortical tangle factor. Results supported a hypothesis that neuritic plaques mediate the association of age and APOE with neocortical tangles, and similarly mediate the effect of APOE on medial temporal tangles. However, medial temporal tangles were related to age independent of neuritic plaques. These results support a primary amyloid-based AD process that accounts for neocortical tangles and makes the largest contribution to medial temporal tangles. A second, age-related but non-amyloid process likely contributes to medial temporal lobe tangles.

1. Introduction

Alzheimer's disease (AD) has been defined by neuropathological features of neuritic plaques and neurofibrillary tangles since it was first identified in 1906 and these 2 types of neuropathology continue to constitute the basis for the neuropathological diagnosis of AD (Hyman, 1997; Hyman et al., 2012; Montine et al., 2012). There is an extensive literature on the relationship of these neuropathological features to clinical status (Bennett et al., 2004; Gomez-Isla et al., 2008; Nelson et al., 2009b). A widely accepted model of neuropathological and clinical progression of AD posits that neurofibrillary tangles initially appear in the entorhinal cortex and hippocampus and later spread to the neocortex. This forms the basis for the widely used Braak and Braak staging of AD pathology (Braak and Braak, 1991; Braak et al., 1993; Thal et al., 2008) and provides an anatomical explanation for the progression of clinical symptoms. Because the hippocampus is a critical anatomical substrate of episodic memory, the early presence of neurofibrillary tangles in the hippocampus helps to explain the amnesia associated with early AD. Neurofibrillary tangle pathology in neocortical areas in later stages of AD corresponds to broader cognitive impairment, affecting non-memory domains and resulting in clinical dementia. Regional and spatial patterns of neuritic plaques do not show the same characteristic pattern as for neurofibrillary tangles (Longstreth et al., 2009; Sonnen et al., 2008; Thal et al., 2008); specifically, neuritic plaques are likely to be distributed throughout neocortical regions in the earliest stages of plaque development (Thal et al., 2008).

At the level of molecular biology, the "amyloid cascade hypothesis" has emerged as the leading theory to explain the development of AD neuropathology (Hardy and Allsop, 1991; Hardy and Higgins, 1992; Selkoe, 1991). This hypothesis posits that the formation and deposition of amyloid-β peptide (Aβ), the primary constituent of neuritic plaques, is the first step in a sequence of events that ultimately leads to impaired cell function, the formation of neurofibrillary tangles, cell death, cognitive decline, and clinical dementia (Jack et al., 2010). It is supported by the observation that all 3 genetic mutations associated with early onset AD and the apolipoprotein E polymorphism (*APOE*) alter the metabolism of amyloid, are associated with development of neuritic plaques composed of Aβ, and manifest tangle formation. Furthermore, preclinical data support a linkage between Aβ processing and tangle formation (Klein et al., 2004; Oddo et al., 2006).

A comprehensive explanation of the genesis of AD should incorporate neurobiology, neuropathology, and clinical characteristics. The amyloid cascade hypothesis explains many of the findings related to AD, but is problematic in some respects. Notably, this hypothesis would suggest that the presence of neurofibrillary

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tangles should mirror the presence of amyloid plaques (Longstreth et al., 2009). However, repeated observations indicate that this is not the case; neurofibrillary tangles are commonly observed in medial temporal lobes in the absence of amyloid plaques (Jellinger and Bancher, 1998; Murray et al., 2011; Nelson et al., 2009a).

An alternatative explanation for the observation of medial temporal neurofibrillary tangles in the absence of amyloid plaques is that medial temporal tangles could result from a second, non-AD process (Nelson et al., 2009a). We hypothesize that 2 independent processes may better explain the complex relation of amyloid and tangles to aging, AD, and cognition. Process 1 is prototypical AD, and leads to amyloid deposition throughout the neocortex and medial temporal lobes and to widespread tangle formation and impairment in multiple cognitive domains. Process 2 is a different age-related process, is associated with tangle formation in the medial temporal lobes, and presumably contributes to episodic memory deficits. It is well known that mixed pathologies commonly contribute to cognitive impairment in old age (Petrovitch et al., 2005; Schneider et al., 2007; Sonnen et al., 2007; Troncoso et al., 2008). It is also well accepted that other diseases, such as fronto-temporal lobe dementia, can manifest pathologically with tangles in the absence of amyloid (Dickson, 2009; Nelson et al., 2009a). The 1- and 2-process explanations of tangle formation generate different predictions about relations of major risk factors such as age and APOE with plaques and tangles. In the 1-process formulation, age and *APOE* relate to tangles via mediating effects of plaques. In the 2-process account, medial temporal tangles would have an additional relationship with age that could not be explained by plaques.

The goal of this study was to evaluate competing hypotheses from 1- and 2-process models to account for relationships among age, *APOE*, and regional measures of the characteristic neuropathological features of AD, neuritic plaques, diffuse plaques, and neurofibrillary tangles. One hypothesis is that these features all are manifestations of a unitary AD process. In this case, neurofibrillary pathology throughout the brain would be related to age and *APOE* via the mediating effects of neuritic plaques and would not be related to these risk factors after controlling for neuritic plaques. An alternative hypothesis would posit a typical AD process that would explain much of the observed neuropathology, but also an additional process that would provide incremental explanation of neurofibrillary tangles in the medial temporal lobes. This explanation would predict that the relation of age with medial temporal neurofibrillary tangles would fall outside the primary AD pathway and would not be entirely explained by neuritic plaques, whereas in contrast, *APOE* effects would be AD related and mediated by neuritic plaques.

This study took advantage of a relatively large neuropathology sample with well-characterized and broadly variable AD neuropathology. We used latent variable modeling to characterize the plaque and tangle neuropathology of AD and to test competing hypotheses about how neuropathology indices relate to one another and to age and *APOE*. Latent variables are statistical representations of conceptual constructs that are not directly measurable. They are empirically derived to explain covariance among observable but imperfect indicators of the constructs of interest, and in so doing, may help to define, measure, and clarify these constructs and how they relate to directly observed external variables.

2. Methods

2.1. Participants

The Religious Orders Study (ROS) and the Memory and Aging Project (MAP) are both community-based, prospective cohort studies of risk factors for incident AD and other chronic conditions of aging conducted by the Rush Alzheimer's Disease Center. Recruitment and inclusion criteria for these studies and subject evaluations have been previously described in detail (Wilson et al., 2003; Wilson et al., 2002a; Wilson et al., 2002b). Briefly, both studies recruit older individuals without known dementia who agree to receive clinical and psychological evaluation each year and to donate their brains for post mortem examination. The annual attrition rate in both cohorts is less than 1% among survivors, and the autopsy rate exceeds 80% in both cohorts. These studies share similar clinical and neuropathology protocol (Bennett et al., 2006b). All individuals from these 2 samples who had available neuropathology data were included in this study; individuals with and without AD pathology were included, and individuals with other neuropathologies, such as Lewy bodies and vascular brain injury, also were included.

2.2. Clinical methods

Clinical diagnosis of dementia and AD followed National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCD-ADRDA) criteria and were implemented in a 3-step process as described previously (Bennett et al., 2006a). Mild cognitive impairment (MCI) referred to persons with cognitive impairment based on neuropsychological test performance in the absence of dementia as described previously (Bennett et al., 2002; Boyle et al., 2006). These criteria are similar to cognitive impairment no dementia (CIND). Persons without dementia or MCI were characterized as no cognitive impairment (NCI). *APOE* genotyping was performed by Agencourt Bioscience Corporation as previously described (Buchman et al., 2009).

Table 1 presents a summary of the sample characteristics by clinical diagnosis before death. The analytical sample for the present study consisted of 591 subjects with complete data on most of the neuropathology variables included in the analysis (sample sizes for individual variables ranged from 496 to 591). The sample was predominantly white, non-Hispanic (96%), and was 59% female with a mean age at death of 87 years and an average education level of about 17 years. Approximately 30% of the participants were carriers of at least 1 *APOE* ε4 allele. In the last clinical evaluation, about one third of the sample had NCI, 25% had MCI, and the remaining 43% had AD or other form of dementia. The mean interval from last psychological evaluation to brain autopsy was 6.5 months (standard deviation [SD] = 3.9, range 0–20 months). Overall, sample characteristics were very similar across ROS and MAP.

2.3. Neuropathology methods

AD neuropathology indices were obtained from a standard neuropathology protocol as previously described (Bennett et al., 2006c; Bennett et al., 2003). AD neuropathology variables of interest in this study included counts in a 1-mm^2 area of greatest density of neuritic plaques (NP), diffuse plaques (DP), and neurofibrillary tangles (NFT) from 5 brain regions: hippocampal CA1 sector, entorhinal cortex, and midfrontal, middle temporal, and inferior parietal cortices. Becaues of the skewness of the distributions of these AD neuropathology measures, we recoded the values into deciles. The potential loss of information resulting from the discretization of these measures into deciles was offset by gains in meeting distributional assumptions of latent variable models and improvements in overall model fit. Table 1 shows summary statistics for raw plaque and tangle counts.

2.4. Data analysis

2.4.1. Overview

Latent variable modeling methods were used to identify latent variables to characterize and explain the regional distribution of AD