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AD pathology and cerebral infarctions are associated with memory and executive functioning one and five-years before death

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Abstract

We provide rigorous psychometric evidence for distinct patterns of cognitive impairment for Alzheimer's disease (AD) and cerebral infarctions using 440 participants from the Religious Order

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Study. Latent variable models were used to decompose the effects of AD pathology and cerebral infarctions assessed at autopsy on overall cognition and specific neuropsychological tests at one and five-years prior to death. Results support clinical and univariate psychometric analyses that memory impairment is more pronounced in AD, and executive impairment more pronounced in the presence of cerebral infarctions. These specific effects are subtle relative to the stronger associations of both AD neuropathology and cerebral infarctions with overall level of cognitive impairment.

Keywords

Neuropathology; Alzheimer's disease; cerebrovascular disease; neuropsychological measures; latent variable models

INTRODUCTION

Alzheimer's disease (AD) and cerebral infarctions are the two most common pathological causes of dementia in older adults (Bennett et al., 2006; Bennett, Schneider, Bienias, Evans, & Wilson, 2005; Schneider, Boyle, Arvanitakis, Bienias, & Bennett, 2007; Schneider, Wilson, Bienias, Evans, & Bennett, 2004; Schneider et al., 2003; Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010). Some prior work suggests that AD pathology and cerebral infarctions may have synergistic effects on the likelihood of dementia (Snowdon et al., 1997) although most studies suggest that they have independent (i.e., additive) contributions (Petrovitch et al., 2005; Sonnen et al., 2007; Troncoso et al., 2008). Understanding the clinical implications of these two types of pathological changes remains a major challenge.

In this paper, we evaluate the effects of AD pathology and cerebral infarctions on overall cognition in the Religious Orders Study (ROS). We examine the effects of AD pathology and cerebral infarctions simultaneously. That is, the effects of both types of injury are considered additive, and we evaluate their impact on specific neuropsychological tests above and beyond their effects on overall cognition.

Previous studies from this cohort have modeled the effects of AD pathology and cerebral infarctions on specific cognitive tests and on a composite measure of overall cognitive functioning and found both AD pathology and cerebral infarctions were associated with a wide range of cognitive abilities prior to death including episodic memory and perceptual speed (Wilson, et al., 2010). Specifically, neurofibrillary tangles in AD pathology were associated with the greatest declines in episodic, semantic, and perceptual speed, compared to working memory (Wilson, et al., 2010). Poor episodic memory has been found in a number of studies (Baudic et al., 2006; Nestor, Scheltens, & Hodges, 2004; Tierney et al., 2001) to be associated with AD, which is possibly due to the degeneration of neurofibrillary tangles. Cerebrovascular dysfunction was found to be more associated with reduced attention, executive dysfunction, and decreased information processing speed (Cohen et al., 2009).

Here, we extend that work by introducing statistical control for the effect of neuropathological signs on overall cognition before describing effects on specific tests. We hypothesized that, beyond their effects on cognitive impairment, AD pathology would be associated with poorer performance on tests of episodic memory, while cerebral infarctions would be associated with poorer performance on tests of working memory and perceptual speed, even several years prior to death.

METHODS

Study Participants

We used data collected in the Religious Order Study (ROS). ROS began enrollment in 1994. At the time of these analyses, the study had enrolled 1,160 older nuns, priests, and brothers from about 40 groups across the US. Participants consented to annual cognitive testing and signed an Anatomical Gift Act for brain donation at the time of death. The study has impressive rates of follow-up of living participants (in excess of 95%) and of autopsies among participants who died (also in excess of 95%), leading to excellent internal validity. Among the 506 decedents eligible for this study, we excluded those who at the time of analysis had incomplete data for AD pathology and/or cerebral infarctions ($N=32$), and were missing all neuropsychological tests within one-year (between 0.5 to 1.5 years) prior to death and within five-years (between 4.5 and 5.5 years) prior to death ($N=34$). Thus our final analytic sample included 440 participants, all of whom had neuropathological and neuropsychological performance data one-year prior to death (mean years prior to death=1, standard deviation (SD) = 0.28, range 0.5 - 1.5 years). Of these, 356 participants had neuropsychological data five-years prior to death (mean years prior to death = 5, SD = 0.27, range 4.5 - 5.5 years).

The orders were selected by convenience, both in terms of geographic location, and by personal contacts leading to introductions. Recruitment began with orders in the Chicago area, some of which had other facilities around the country. Then branched out of the Chicago area for groups of men, African Americans, and Hispanics. Overall, the goal was to develop a large cohort that would ensure the high follow-up and autopsy rates required for good internal validity. Details concerning the names of the participating orders, and a map with cities, and states can be found in reference for Bennett and colleagues (2012). The ROS study was approved by the Rush University Medical Center Institutional Review Board.

Assessment of cognitive function

The ROS neuropsychological battery consists of 21 neuropsychological tests (Wilson et al., 2002). We evaluated data from 17 of these that address a wide range of cognitive abilities including episodic memory, working memory, processing speed, semantic memory, and visuospatial abilities. Measures of episodic memory included: Logical Memory Story A (Immediate and Delayed Recall) (Wechsler, 1989), East Boston Story (Immediate and Delayed Recall) (Albert et al., 1991), and Word List Learning (total recall across trials, delayed recall, and recognition) (Morris et al., 1989). Measures of semantic memory included: Boston Naming Test (Goodglass & Kaplan, 1983) and Verbal Category Fluency (Wilson, et al., 2002). Measures of working memory included Digit Span Forward and Backward (Wechsler, 1989), Digit Ordering (Cooper et al., 1992; Wilson, et al., 2002), and Alphabetical Span (Craik, 1986). Measures of visuospatial abilities included Judgment of Line Orientation (Benton, Sivan, Hamsher, Varney, & Spreen, 1994) and Raven's Progressive Matrices (Raven, Court, & J., 1992). Measures of perceptual speed included Number Comparison (Ekstrom, French, Harman, & Derman, 1976) and Symbol Digit Modalities Test (Smith, 1982). In each test, higher scores indicated better performance. We excluded three tests from the ROS battery from our analyses because they are measures of reading ability: Extended Range Vocabulary Test (Ekstrom, et al., 1976), National Adult Reading Test (Nelson, 1982), and Complex Ideational Material (Goodglass & Kaplan, 1983). We excluded the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) because we wanted to evaluate the effects of AD pathology and cerebral infarctions on specific cognitive domains. Details regarding the cognitive tests have been described elsewhere (Wilson, et al., 2002; Wilson, Krueger, Boyle, & Bennett, 2011). We used the Blom transformation to address skew in the distribution of test scores. The Blom

transformation replaces raw scores with the normal equivalent deviate of the raw score percentile rank. We derived ranks for the Blom transformation by calibrating relatively young (age 65-69) ROS participants returning for their second assessment, the sub-group of participants likely to have the highest scores. Details are provided in *Supplementary Data: Detailed Statistical Methods*.

Neuropathology variables

Brain autopsies were performed using standard techniques (Bennett et al., 2003). The mean postmortem interval was 8.1 hours. Brains were weighed and examined for atrophy, infarctions, atherosclerosis, and other abnormalities such as subdural hematomas or brain tumors. They were then placed in a calibrated plexiglass jig and sliced in the coronal plane at 1 cm intervals and the slabs were photographed. The number and location of gross cerebral infarctions were recorded based on evaluations of these slabs (Arvanitakis, Leurgans, Barnes, Bennett, & Schneider, 2011); chronicity was confirmed by microscopic review of hematoxylin and eosin-stained sections, as previously reported (Bennett, et al., 2003). Cerebral infarction pathology was defined as the presence of any chronic macroscopic cerebral infarctions and coded as a dichotomous variable for use in the analysis. The macro cerebral infarctions are inclusive of white and grey matter infarctions visible to the naked eye. We also examined the percentage of lacunar infarctions that were defined by less than 1 cm in diameter on the x-axis, y-axis, and z-axis, which was found in 65% of the autopsy cases with any cerebral infarcts.

In our analyses we use Bennett et al's index of *global pathology* to summarize the burden of AD pathology. Details regarding the creation of the global pathology measure have been described elsewhere (Bennett, et al., 2003). Briefly, the global pathology index is the average of three facets of neuropathological findings of AD: neuritic plaques, neurofibrillary tangles, and diffuse plaques. Each facet is the sum of standardized counts of the particular neuropathological finding in four cortical regions: the midfrontal gyrus, superior temporal gyrus, inferior parietal gyrus, and entorhinal cortex. Plaque and tangle counts were obtained by a board-certified neuropathologist or a trained technician blinded to all clinical data. Bennett and colleagues describe this measure in a sample of 128 ROS participants who had come to autopsy (Bennett, et al., 2003), among whom the mean (SD) of the global pathology index was 0.79 (0.67) units. Decedents with probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (McKhann et al., 1984) had a mean (SD) global pathology score of 1.19 (0.74), while decedents without dementia had a mean (SD) global pathology score of 0.54 (0.48). These results correspond to an effect size of 1.07 (Bennett, et al., 2003). In this paper we will refer to the index of global pathology as "AD pathology".

Data Analysis

We used latent variable modeling to identify an underlying overall cognitive performance dimension that accounted for the relationships among the 17 neuropsychological tests. We then used structural equation modeling to simultaneously regress performance on neuropsychological tests and underlying general cognitive ability on the index of AD pathology and cerebral infarcts. Regressions of test performance on neuropathology measures—after controlling for differences in overall cognitive performance across levels of neuropathology and the dependence of test performance on overall cognitive ability—capture a direct effect of neuropathology on specific test performance and are tests of the hypothesis of distinct neuropsychological profiles in the presence of particular kinds of neuropathology. The direct effects could show that, net of the effect of the pathology marker on overall cognitive impairment, performance on a specific neuropsychological test is

selectively impaired. If a higher value on the specific test implies better performance, and a higher value on the pathology marker indicates more of the marker present, then selective impairment will be reflected by a negative sign for the regression coefficient (κ). The interpretation of such an effect is that, per unit increase in the pathology marker, there is a κ -magnitude decrease in performance on the test, net of any influence of the marker on underlying ability. The direct effect could also be positive reflected by a positive sign for the regression coefficient κ , indicating selective preservation. Selective preservation means that performance on the specific test is better than what would be expected in the presence of the pathological marker and its influence on cognition globally.

The data analysis required several steps. First, we specified a latent variable measurement model for the neuropsychological tests. Second, we modeled the association between cognitive ability and both AD pathology and cerebral infarctions. Third, we determined whether there was an association between AD pathology or cerebral infarctions and specific cognitive tests after controlling for the effect of these pathologies on cognitive ability (Gallo, Anthony, & Muthén, 1994; Jöreskog & Goldberger, 1975). We conducted all analyses using Stata version 10.0 (StataCorp LP, 1984-2011) and Mplus version 6.0 using the maximum likelihood estimator (Muthén & Muthén, 1998-2011). We assessed model fit with the root mean square error of approximation (RMSEA) (Browne & Cudeck, 1993) and the comparative fit index (CFI) (Bentler, 1990). The RMSEA (Browne & Cudeck, 1993) approaches zero as model fit improves; thresholds of 0.10 (Browne & Cudeck, 1993) and 0.06 (Hu & Bentler, 1998) have been recommended as indicators of adequate model fit. The CFI approaches 1.00 as model fit improves; values greater than 0.95 indicate adequate model fit (Bentler, 1990). Detailed statistical methods are provided in Appendix A.

RESULTS

Sample Characteristics

Table 1 provides participant characteristics for the two data samples: ROS participants at one or five-years prior to autopsy. Most participants were female, white, and had at least a college education.

Of the 356 participants with data five-years prior to death, 137 (39%) had cerebral infarctions. Of the 440 participants with data one-year prior to death, 161 (37%) had cerebral infarctions.

The index for AD pathology ranged from 0 to 2.9 with a mean of 0.7 (SD, 0.6) at both five-years and one-year prior to death. In our regression models, coefficients associated with the index for AD pathology describe the difference in the outcome per unit difference in the index for AD pathology. A unit difference in the index for AD pathology could, for example, describe differences between persons with a value in the range 0 to 0.1 units versus persons with a value in the range 1.0 to 1.1 units. In our sample, at five-years prior to death, persons with a value for the AD pathology index in the range 0 to 0.1 units had a mean MMSE score of 28 points ($SD \pm 2.2$) prior to death and 1% met NIA/Reagan neuropathological criteria (Hyman, 1998) for intermediate to high likelihood of AD at autopsy. In contrast, persons in this sample with an index for AD pathology value in the range 1.0 to 1.1 units had a mean MMSE score of 25 points ($SD \pm 5.3$) at five years prior to death and 94% met NIA/Reagan criteria for low to intermediate likelihood of AD at autopsy. At one-year prior to death, persons with an index value for AD pathology between 0 to 0.1 units had a mean MMSE score of 25.6 points ($SD \pm 5.8$) with 2% meeting NIA/Reagan neuropathological criteria, while those with a value in the range between 1 to 1.1 units had a mean MMSE score of 19 ($SD \pm 9.9$) with 95% meeting NIA/Reagan criteria.

Multivariate Results: Indirect Effects of Neuropathology

We describe the results of the latent variable model in terms of direct and indirect effects. Direct effects are regressions of test performance on predictors (AD pathology, cerebral infarcts). Indirect effects refer to regressions of overall cognitive performance on predictors. Parameter estimates for the models are displayed in Tables 2 and 3. At five-years prior to death for every unit of the index for AD pathology there was a decrement of 0.82 units in overall cognitive performance. The presence of one or more cerebral infarctions was associated with a decrement of 0.44 units in overall cognitive performance (Table 2, *Supplementary Data Figure 2*). At one-year prior to death, one unit of the index for AD pathology had a somewhat greater effect on overall cognitive performance than the same level of AD pathology five-years prior to death (Table 3, *Supplementary Data Figure 3*). With each one unit higher of the index for AD pathology, there was a 0.93 unit greater decrement in overall cognitive performance. The effect of cerebral infarctions on overall cognitive performance was about the same one year and five years prior to death, which was almost half a standard deviation unit for all the tests. However the impairment in these tests due to cerebral infarctions were less pronounced than the effects of AD pathology.

Multivariate Results: Direct Effects of Neuropathology

We describe the direct effects in terms of *selective impairment* and *selective preservation*. Selective preservation means that the level of performance on a specific test was better on average than what would be expected given the level of overall cognitive performance. Selective impairment means that performance was worse on average than what would be expected given the overall cognitive performance.

Cerebral infarctions were associated with neither selective preservation nor impairment at five-years prior to death. In contrast, we found selective preservation and selective impairment for certain tests within five-years prior to death attributable to AD. A different pattern of selective impairments and survival was found in the one-year prior to death models.

At five-years prior to death, we found selective preservation of digit ordering in the presence of more AD pathology. The parameter estimate associated with this effect is $\kappa = 0.31$ ($p < 0.001$).

Because the parameter estimate is positive, but the effect of AD pathology on overall cognitive performance is negative, this is a selective preservation effect. The parameter estimate provides the shift in the expected score on the Blom transformation of digit ordering per unit difference in the index for AD pathology. The expected score for a test item for a person with the overall mean level of overall cognitive performance ($\eta = 0$) is given with the equation:

$$E(y_i) = \nu_i + \lambda_i \gamma x_j + \kappa_i x_j$$

where y is a Blom-transformed test score (e.g., digit ordering), ν is the test intercept, λ is the factor loading (the regression of test performance on overall performance, modeled as a latent trait, η), γ is the indirect effect, x is the index for AD pathology, and κ is the direct effect. For a hypothetical person with a value of 0 on the index for AD pathology ($x = 0$) and the overall mean level of overall cognitive performance ($\eta = 0$), the expected score is $E(y_i) = \nu = -0.68$. Because the scores are Blom transformed, we can express this as an expected percentile score using the normal distribution transformation: $\Phi(E(y)) = 0.25$. Therefore, relative to a calibration sample of young-old (ages 65-69) ROS participants, persons within five-years of death and an index for AD pathology of 0 are expected to

perform at the 25th percentile on the digit ordering test on average. Given the indirect effect of the index for AD pathology on overall cognitive performance at 5 years prior to death, the model implies that performance will be at the 15th percentile ($\Phi(-0.68 + 0.70 \times -0.82)$), but the direct effect reveals that the expected score is actually at the 20th percentile ($\Phi(-0.68 + (0.70 \times -0.82) + (0.31 \times -0.82))$). Thus, on average, the level of impairment on overall general cognitive performance attributable to having a value of 1.0 on the index for AD pathology variable over-estimates the decrement in the level of performance on the digit ordering test. In other words, digit ordering is selectively preserved in the presence of AD pathology five-years prior to death.

We also see selective impairment associated with AD pathology on select neuropsychological tests at five-years prior to death (Table 2, Figure 1). Performance on word list recognition ($\kappa_{AD} = -0.27$, $p < 0.01$), word list recall ($\kappa_{AD} = -0.19$, $p < 0.01$), Story A delayed ($\kappa_{AD} = -0.10$, $p < 0.05$), and East Boston delayed ($\kappa_{AD} = -0.10$, $p < 0.09$) all show signs of selective impairment. In the presence of AD pathology performance on tasks associated with episodic memory are selectively impaired above and beyond the effect of AD pathology on overall cognitive performance.

In the one-year prior to death model, only one of the specific impairments found in the five-years prior to death model was similarly identified: performance on word list recognition ($\kappa_{AD} = -0.29$, $p < 0.01$, Table 3). At one-year prior to death we also found selective impairment in Boston Naming performance ($\kappa_{AD} = -0.19$, $p < 0.05$) and a suggestion of a specific impairment in East Boston immediate performance ($\kappa_{AD} = -0.11$, $p < 0.09$). At one-year prior to death, cerebral infarctions were associated with selective impairment of perceptual speed (number comparisons, $\kappa_{CI} = -0.28$, $p < 0.001$, symbol digit modalities, $\kappa_{CI} = -0.21$, $p < 0.05$).

DISCUSSION

We examined the relationship between AD pathology and cerebral infarctions on specific cognitive impairments using a large and well characterized sample of older adults who underwent longitudinal cognitive testing and eventual neuropathological examination. Results of the current study broadly support the hypothesis that there are dissociable effects of AD pathology and cerebral infarctions on different cognitive abilities. One interesting finding was that there was little selective impairment associated with vascular pathology on tests considered to measure executive functioning, such as category fluency, digits backwards, and digit ordering. More sensitive tests of executive functioning may have been able to detect such selective impairment. Another possibility is that even with more sensitive tests we would still not identify selective impairment associated with vascular pathology. It should be recalled that the analyses we did were of average effects across groups of people. Vascular pathology in some individuals may be associated with isolated deficits in executive functioning, in others vascular pathology may be associated with isolated deficits in other domains such as memory, and in others vascular pathology may be associated with deficits across all cognitive domains. Our analyses suggest that on average across the entire study population there was no specific impairment associated with vascular pathology on the tests of executive functioning beyond an overall effect on global cognition.

The findings from this study suggest that there is a pattern of selective preservation and impairment for certain tests five-years prior to death associated with AD pathology and a pattern of selective impairment for certain tests one-year prior to death associated with both AD pathology and cerebral infarctions. Our modeling approach allows us to parcel out the effects of pathology on overall cognitive performance. Dowling and colleagues (2010), in the ROS and Memory and Aging Project found multiple neuropathology determinants that

differed by cognitive domain using the MIMIC model. This study is novel and different from Dowling and colleagues (2010) in that the deficits are estimated above and beyond overall (global) cognitive impairment in AD and cerebral infarctions, with relative decrements in specific neuropsychological tests that fit prior knowledge. The findings support a widely held hypothesis (Schneider, et al., 2007; Schneider, et al., 2003) and often reported finding that beyond the effects on overall cognition there are additional specific effects of AD pathology on episodic memory performance and additional specific effects of infarcts on executive functioning (Bondi et al., 2008; Reed et al., 2007; Villardita, 1993). A particular strength of our analysis is that signs of AD and cerebral infarctions are based on rigorous neuropathological examination, and that our statistical model enabled us to control for the effect of pathology on overall cognitive performance while testing hypotheses regarding specific neuropsychological tasks.

We examined the relationship between cognition and the pathological findings using cognitive data collected at one-year and five-years prior to death because we anticipated that the relationships between neuropathology and cognition might be different due to distinct natural histories of these two disease processes. For many participants, disease severity (certainly AD pathology and possibly cerebral infarctions) will be worse one-year proximal to death as compared to five-years prior to death. We had anticipated *a priori* that there may be less differential effects of pathology on cognitive function when the disease is more severe. This is confirmed to some degree for AD neuropathology, as the number of selective impairments diminishes in the one-year prior to death model versus the five-years prior to death model. When disease is very severe, all cognitive domains are de-compensated and large indirect effects are found and few selective impairments are found. The opposite pattern is seen for cerebral infarctions, where the selective impairments are not apparent five-years prior to death but are apparent at one-year prior to death. A limitation of our analysis is we do not know the age of the infarctions, but this pattern would suggest that some may have occurred between one- and five-years prior to death. Nevertheless, even five years prior to death, persons with one or more cerebral infarctions at autopsy had overall cognitive performance about half a standard deviation lower than persons without a cerebral infarction.

A major strength of this study is the large number of people enrolled without dementia at baseline and followed to autopsy. The participants had comparable lifestyles as nuns, priests, and brothers. ROS contains high rates of follow-up participation and autopsy. The limitations include that the cohort is not representative of older adults living in the US. The cohort is one of convenience and the generalizability of the findings will need to come from replication. The truncated variance of lifestyle factors limits our ability to investigate the relationships between these factors and our study variables. The analyses were performed on samples available at one and five years prior to death, which unknown prospectively during life. Our results have limited clinical relevance. While we had access to several well-used measures of episodic memory, the measurement of executive functioning was limited in this study. Previous authors have used the symbol digit modalities test as a measure of aspects of executive functioning (Smith, 1982), but it is heavily dependent on general or more global aspects of motor and mental speed. Additionally, systems important for working memory and known to be widely distributed and heavily dependent on frontal-subcortical circuitry (Stern et al., 2007). Another limitation is the measurement of cerebral infarctions, as these are gross measures, we may be missing infarctions that are less than 0.5 cm in diameter, on average. We also were limited to considering pathology data; it is well established that hyperintense signals from magnetic resonance imaging in white matter is associated with decrements in executive functioning (could provide references here though this is certainly well established). Imaging results were not available to us for these analyses.”

The findings at one-year and five-years prior to death from this study warrant further analysis for examining longitudinal trajectories of cognition in this same sample. The findings are clinically useful for identifying the distinct patterns of neuropsychological impairment due to Alzheimer's like brain changes and brain changes that are vascular in origin, though the effects were small. Overall, the results of this current study suggest that patterns of neuropsychological deficits may help to understand the differential contributions of AD and cerebral infarctions, and support previous neuropsychological conceptualizations of specific effects of AD and cerebral infarctions. AD pathology is associated with worse overall cognition, with relatively preserved performance on working memory at five-years prior to death and selectively impaired episodic memory at one-year and five-years prior to death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

- Albert M, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *International Journal of Neuroscience*. 1991; 57(3-4):167–178. [PubMed: 1938160]
- Arvanitakis Z, Leurgans S, Barnes L, Bennett D, Schneider J. Microinfarct pathology, dementia, and cognitive systems. *Stroke*. 2011; 42:722–727. [PubMed: 21212395]
- Baudic S, Barba GD, Thibaudet MC, Smaghe A, Remy P, Traykov L. Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of Clinical Neuropsychology*. 2006; 21(1):15–21. [PubMed: 16125364]
- Bennett D, Schneider J, Arvanitakis Z, Kelly J, Aggarwal N, Shah R, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006; 66(12):1837–1844. doi: 66/12/1837 [pii] 10.1212/01.wnl.0000219668.47116.e6. [PubMed: 16801647]
- Bennett D, Schneider J, Arvanitakis Z, Wilson R. Overview and findings from the Religious Orders Study. *Current Alzheimer's Research*. 2012; 9:630–647.
- Bennett D, Schneider J, Bienias J, Evans D, Wilson R. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology*. 2005; 64(5):834–841. doi: 64/5/834 [pii] 10.1212/01.WNL.0000152982.47274.9E. [PubMed: 15753419]
- Bennett D, Wilson R, Schneider J, Evans D, Aggarwal N, Arnold S, et al. Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. *Neurology*. 2003; 60(2): 246–252. [PubMed: 12552039]
- Bentler PM. Comparative fit indexes in structural models. *Psychological Bulletin*. 1990; 107(2):238–246. [PubMed: 2320703]
- Benton, AL.; Sivan, AB.; Hamsher, K.; Varney, NR.; Spreen, O. Contributions to neuropsychological assessment. 2nd ed.. Oxford University Press; New York: 1994.
- Blom, G. Statistical Estimates and Transformed Beta Variables. John Wiley & Sons, Inc.; New York: 1958.
- Bondi MW, Jak AJ, Delano-Wood L, Jacobson MW, Delis DC, Salmon DP. Neuropsychological contributions to the early identification of Alzheimer's disease. *Neuropsychology Review*. 2008; 18(1):73–90. doi: 10.1007/s11065-008-9054-1. [PubMed: 18347989]

- Browne, M.; Cudeck, R. Alternative ways of assessing model fit.. In: Bollen, K.; Long, J., editors. Testing structural equation models. Sage; Thousand Oaks, CA: 1993. p. 136-162.
- Cohen RA, Poppas A, Forman DE, Hoth KF, Haley AP, Gunstad J, et al. Vascular and cognitive functions associated with cardiovascular disease in the elderly. *Journal of Clinical and Experimental Neuropsychology*. 2009; 31(1):96–110. [PubMed: 18608677]
- Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. *Brain*. 1992; 115(Pt 6):1701–1725. [PubMed: 1486457]
- Craik, FIM. A functional account of age differences in memory.. In: Klix, E.; Hagendorf, H., editors. Human memory and cognitive capabilities: Mechanisms and performances. Elsevier Science; Amsterdam: 1986.
- Dowling N, Tomaszewski Farias S, Reed B, Sonnen J, Strauss M, Schneider J, et al. Neuropathological Associates of Multiple Cognitive Functions in Two Community-Based Cohorts of Older Adults. *J Int Neuropsychol Soc*. 2010:1–13. doi: S1355617710001426 [pii] 10.1017/S1355617710001426.
- Ekstrom, R.; French, J.; Harman, H.; Derman, D. Kit of factor-referenced cognitive tests. revised ed.. Educational Testing Service; Princeton, N.J.: 1976.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189–198. [PubMed: 1202204]
- Gallo JJ, Anthony JC, Muthén BO. Age differences in the symptoms of depression: a latent trait analysis. *Journals of Gerontology*. 1994; 49(6):251–264.
- Goodglass, H.; Kaplan, D. The assessment of aphasia and related disorders. 2nd edition. Lea & Febiger; Philadelphia: 1983.
- Hu L, Bentler P. Fit indices in covariance structure analysis: Sensitivity to underparameterized model misspecifications. *Psychological Methods*. 1998; 4:424–453.
- Hyman BT. New neuropathological criteria for Alzheimer disease. *Arch Neurol*. 1998; 55(9):1174–1176. [PubMed: 9740109]
- Jöreskog K, Goldberger A. Estimation of a model of multiple indicators and multiple causes of a single latent variable. *Journal of the American Statistical Association*. 1975; 10:631–639.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34(7):939–944. [PubMed: 6610841]
- Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989; 39(9):1159–1165. [PubMed: 2771064]
- Muthén, LK.; Muthén, BO. Mplus Version 6.0. Muthén & Muthén; Los Angeles: 1998-2011.
- Nelson, HE. National Adult Reading Test (NART): Test manual. NFER Nelson; Windsor, England: 1982.
- Nestor, PJ.; Scheltens, P.; Hodges, JR. Advances in the early detection of Alzheimer's disease.. 2004.
- Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, et al. AD lesions and infarcts in demented and non-demented Japanese-American men. *Ann Neurol*. 2005; 57(1):98–103. [PubMed: 15562458]
- Raven, JC.; Court, JH.; J., R. Manual for Raven's progressive matrices and vocabulary: Standard Progressive Matrices. Oxford Psychologists Press; Oxford, England: 1992.
- Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, et al. Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain*. 2007; 130(Pt 3):731–739. [PubMed: 17267522]
- Schneider J, Boyle P, Arvanitakis Z, Bienias J, Bennett D. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Ann Neurol*. 2007; 62(1):59–66. [PubMed: 17503514]

- Schneider J, Wilson R, Bienias J, Evans D, Bennett D. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology*. 2004; 62(7):1148–1155. [PubMed: 15079015]
- Schneider J, Wilson R, Cochran E, Bienias J, Arnold S, Evans D, et al. Relation of cerebral infarctions to dementia and cognitive function in older persons. *Neurology*. 2003; 60(7):1082–1088. [PubMed: 12682310]
- Smith, A. Symbol Digit Modalities Test manual—revised. Western Psychological Services; Los Angeles: 1982.
- Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *Jama*. 1997; 277(10):813–817. [PubMed: 9052711]
- Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol*. 2007; 62(4):406–413. [PubMed: 17879383]
- StataCorp LP. Stata (Version 11.0). StataCorp.; College Station, Texas: 1984-2011.
- Stern Y, Zarahn E, Habeck C, Holtzer R, Rakitin BC, Kumar A, et al. A Common Neural Network for Cognitive Reserve in Verbal and Object Working Memory in Young but not Old. *Cereb Cortex*. 2007
- Tierney MC, Black SE, Szalai JP, Snow WG, Fisher RH, Nadon G, et al. Recognition Memory and Verbal Fluency Differentiate Probable Alzheimer Disease From Subcortical Ischemic Vascular Dementia. *Arch Neurol*. 2001; 58(10):1654–1659. doi: 10.1001/archneur.58.10.1654. [PubMed: 11594925]
- Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. *Ann Neurol*. 2008; 64(2):168–176. [PubMed: 18496870]
- Villardita C. Alzheimer's disease compared with cerebrovascular dementia. Neuropsychological similarities and differences. *Acta Neurol Scand*. 1993; 87(4):299–308. [PubMed: 8503260]
- Wechsler, D. Wechsler Adult Intelligence Scale-Revised Manual. Psychological Corporation, A Harcourt Assessment Company; New York: 1989.
- Wilson R, Beckett L, Barnes L, Schneider J, Bach J, Evans D, et al. Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging*. 2002; 17(2):179–193. [PubMed: 12061405]
- Wilson R, Krueger K, Boyle P, Bennett D. Loss of basic lexical knowledge in old age. *J Neurol Neurosurg Psychiatry*. 2011; 82(4):369–372. doi: jnnp.2010.212589 [pii] 10.1136/jnnp.2010.212589. [PubMed: 20802026]
- Wilson R, Leurgans S, Boyle P, Schneider J, Bennett D. Neurodegenerative basis of age-related cognitive decline. *Neurology*. 2010; 75(12):1070–1078. doi: WNL.0b013e3181f39adc [pii] 10.1212/WNL.0b013e3181f39adc. [PubMed: 20844243]

Figure 1.

Profile plot of neuropsychological test performance by neuropathology at five-years and one-year prior to death.

Figure 1 depicts the path diagram of the latent variable model, with differential effects of CVD and AD pathology predicting neuropsychological test performance at 1 year prior to death with standardized parameter estimates (N=440).

Table 1

Participant characteristics within five-years and one-year proximate to death in the Religious Orders Study.

Characteristic	Five-years prior to death			One-year prior to death		
	Mean or n	(SD) or (%)	Observed range	Mean or n	(SD) or (%)	Observed range
Total [n (%)]	356	(100)		440	(100)	
Age at baseline [M (SD)]	78.4	(6.8)	[63.0–102.1]	79.5	(6.9)	[64.8–102.1]
Sex [n (%)]						
Male	128	(36.0)		167	(38.0)	
Female	228	(64.0)		273	(62.8)	
Age Groups [years, n (%)]						
65 to 69	11	(3.1)		2	(0.5)	
70 to 74	30	(8.4)		23	(5.2)	
75 to 79	70	(19.7)		48	(10.9)	
80 to 84	103	(28.9)		110	(25.0)	
85 to 89	82	(23.0)		124	(28.2)	
90 and older	60	(16.9)		133	(30.2)	
Education Level [M (SD)]	17.8	(3.4)	[5.0–26.0]	18.0	(3.5)	[3.0–30.0]
Race [n (%)]						
White	346	(97.2)		424	(96.4)	
Black	8	(2.2)		13	(3.0)	
Asian or Pacific Islander	2	(0.6)		3	(0.7)	
Hispanic origin [n (%)]						
No	348	(97.8)		431	(98.0)	
Yes	8	(2.2)		9	(2.0)	
Mini-Mental State [M (SD)]	26.2	(4.7)	[1.0–30.0]	22.3	(8.1)	[0.0–30.0]
Global AD pathology [M (SD)]	0.7	(0.6)	[0.0–2.9]	0.7	(0.6)	[0.0–2.9]
Macroscopic Cerebral Infarctions [n (%)]						
No	219	(61.5)		279	(63.4)	
Yes	137	(38.5)		161	(36.6)	

Table 1 is a tabulation of the demographic and cognitive characteristics at baseline for total cohort and subjects with cerebral infarctions and AD pathology data.

Table 2

Factor loadings and individual item effect associated with neuropathology in the Religious Orders Study at five-years prior to death (N=356).

Tests	Factor Loadings	Individual Test Effect Associated With AD Pathology	Individual Test Effect Associated With Cerebral Infarctions
Story A Immediate	0.80	0.00	0.00
Story A Delayed	0.82	-0.10 ⁺	0.00
Word List Memory	0.80	0.00	0.00
Word List Recall	0.75	-0.19 ^{**}	0.00
Word List Recognition	0.47	-0.27 ^{**}	0.00
Symbol Digit	0.69	0.00	0.00
Number Comparison	0.44	0.00	0.00
Progressive Matrices	0.48	0.00	0.00
Categorical Fluency	0.69	0.00	0.00
Boston Naming	0.60	0.00	0.00
Alphabetical Span	0.61	0.00	0.00
Line Orientation	0.36	0.00	0.00
Digit Forward	0.42	0.00	0.00
Digit Backward	0.48	0.00	0.00
Digit Ordering	0.70	0.31 ^{***}	0.00
East Boston Immediate	0.67	0.00	0.00
East Boston Delayed	0.68	-0.10 ⁺	0.00
Indirect Effect		-0.82 ^{***}	-0.44 ^{***}
Chi-square (df)	327.518 (136)		
CFI	0.946		
RMSEA	0.063		

‡standardized parameter estimates with positive sign indicates selective preservation; negative sign indicates selective impairment.

Table 2 presents the parameter estimates for the factor loadings and the individual test effects on neuropathology in the Religious Orders Study at five-years prior to death (N=356).

⁺
p<0.09

^{*}
p<0.05

^{**}
p<0.01

^{***}
p<0.001

Table 3

Factor loadings and individual test effect associated with neuropathology in the Religious Orders Study at one-year prior to death (N=440).

Tests	Factor Loadings	Individual Test Effect Associated With AD Pathology	Individual Test Effect Associated With Cerebral Infarctions
Story A Immediate	0.94	0.00	0.00
Story A Delayed	0.97	0.00	0.00
Word List Memory	0.80	0.00	0.00
Word List Recall	0.81	0.00	0.00
Word List Recognition	0.66	-0.29 ***	0.00
Symbol Digit	0.86	0.00	-0.21 *
Number Comparison	0.54	0.00	-0.28 ***
Progressive Matrices	0.61	0.00	0.00
Categorical Fluency	0.70	0.00	0.00
Boston Naming	0.80	-0.19 *	0.00
Alphabetical Span	0.67	0.00	0.00
Line Orientation	0.52	0.00	0.00
Digit Forward	0.62	0.00	0.00
Digit Backward	0.69	0.00	0.00
Digit Ordering	0.73	0.00	0.00
East Boston Immediate	0.73	-0.11 +	0.00
East Boston Delayed	0.80	0.00	0.00
Indirect Effect		-0.93 ***	-0.48 ***
Chi-square (df)	342.032 (136)		
CFI	0.960		
RMSEA	0.059		

**p<0.01

‡standardized parameter estimates with positive sign indicates selective preservation; negative sign indicates selective impairment.

Table 3 presents the parameter estimates for the factor loadings and the individual test effects on neuropathology in the Religious Orders Study at one-year prior to death (N=440).

+p<0.09

*p<0.05

***p<0.001