How cognitive markers of Alzheimer’s Disease are influenced by, and ultimately predict, brain pathology: A forward looking approach.

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Target journals:

1. **Annals of Neurology:** (structured abstract max 250 words (Objective,Methods, Results,Interpretation); body max ~3,000 words, (Intro, Subjects/Materials/Methods, Results, Discussion)
2. **Journal of Neurology:** (unstructured abstract 150-250words, MS or Latex(if math), not to exceed 8 pages (20 type-written pages of 32 lines each).

**To Do:**

ABSTRACT (structured, max 250 words)

**Objective:** To assess the risk of Alzheimer’s disease (AD) related neuropathology burden given current cognitive state and rate of cognitive change among older adults.

**Methods:** Participants included 1,303 individuals enrolled in the Religious Orders Study (ROS) and 1,789 individuals enrolled in the Rush Memory and Aging Project (MAP); roughly 50% were deceased. Using multi-state Cox proportional hazard models, we compared the cognitive status of all subjects alive at a given age and assigned future risk of dying with different AD related neuropathologies. Endpoints under consideration are Braak Stages (0-2,3-4,5-6), CERAD(0,1,2,3) and TDP (0,1,2,3).

**Results:** For all three pathological groupings (Braak, CERAD, TDP), we found that a cognitive test score 1 standard deviation below average put individuals at about 3 times the risk for being diagnosed with late stage AD at autopsy according to pathological designations. The effect remained significant after adjusting for gender, APOE4 status, smoking status, education level and vascular health scores. Risk of death at later stages in all three groups increased with age as well.

**Interpretation:** These results provide support for previous hypotheses on how underlying neuropathologies affect cognitive function and change, by validating temporal ordering of this process (REF). The ability to predict the likelihood that an individual will be diagnosed with a pathology at autopsy also presents new possibilities in clinical settings for diagnosis and treatment development programs.

Keywords: cognitive decline, Alzheimer’s disease, survival analysis, multi-state models

INTRODUCTION:

Understanding how the underlying pathology of individuals with possible or probable Alzheimer’s disease (AD) affects current cognitive state as well as future cognitive decline, remains an open area of research. Though much progress has been made, there still exists a gap between precise identification of antemortem diagnosis of probable AD and postmortem findings1. Utilizing postmortem data, greater levels of pathology assessed at autopsy tend to be associated with lower average cognitive function and steeper cognitive decline, regardless of whether the patient had been diagnosed with AD or not2–7. Of great empirical and clinical interest, however, is to understand how underlying brain pathology may be affecting cognitive function and decline in living individuals in order to increase diagnostic precision8 and develop effective treatment plans. Using longitudinal cognitive data and postmortem pathological outcomes, we employ a multi-state modeling approach in the current study to predict the likelihood that a certain neuropathological outcome will result given an individual’s current cognitive function profile during study participation.

Multiple landmark aging studies have gathered rich measures of brain pathology but due to the nature of the assessment procedures, such data can only be obtained when participants have undergone autopsies. This implies that any inference about the forward relationship of pathology on cognition must be indirect and result in a reversal of temporal ordering. A method commonly used, for example, is to categorize individuals by their final pathology and then ‘look backwards’ at each of those subjects’ cognitive trajectories. A modeling approach would then be to treat cognition as an outcome, with age and pathology as predictors though these variables were collected in the reverse order. The primary assumption of such an approach is that the pathology observed at the end, at autopsy, was operative earlier in each subject’s life, which, although feasible, may not be the case (REF). In the present study, we avoid this reversal of temporal ordering by implementing a multi-state modeling approach.

To our knowledge studies have yet to examine how cognitive trajectories measured during study participation may put a person at risk of exhibiting a specific pathology at autopsy. Using a multi-state modeling technique, we can examine how an individual’s current cognitive state and/or rate of cognitive decline predict risk of AD related neuropathology found postmortem. This ‘forward looking’ approach has some key advantages. First, this approach utilizes information from all available subjects, both living and deceased compared to a ‘looking back’ approach that only uses data from deceased and autopsied individuals. Second, and most importantly, results from this analysis can be useful for individual patient prediction in clinical settings, implementation of relevant preventative treatments, and helpful for study planning. Such an approach would thus allow for a forward prediction line of reasoning that goes in line with theoretical accounts9 and may be clinically informative.

**Subjects and Methods:**

**Subjects**

Subjects were part of two large longitudinal clinical-pathologic cohort studies of dementia, the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) 10,11. ROS participants are older Catholic nuns, priests, and brothers who agreed to participate in annual clinical evaluations and brain donation at death. This study was approved by the Institutional Review Board of Rush—Presbyterian—St. Luke’s Medical Center. The ROS sample consisted of 1,303 individuals, 70.83% of whom were female and were 75.92 (SD = 7.44, range = 55-103) years old at baseline. ROS incorporated cognitive assessments for up to 20 years. MAP consists of older community-dwelling adults who agreed to participate in annual clinical evaluations and brain donations at death. The study was approved by the Institutional Review Board of Rush University Medical Center. MAP participants consisted of 1,789 individuals 73.39% of whom were female and who were 79.94 (SD = 7.64, range = 53 - 101) years old on average at baseline. The MAP study incorporated annual cognitive assessments for up to 17 years.

The total sample for our current analysis consisted of 3,092 individuals with an average of 6.82 (SD = 5.37, range = 0 - 22) years of annual assessments. As of September 16th, 2015 roughly 50 percent (N = 1,492) of participants were deceased and were 88.4 (SD = 6.6, range = 65-108) years of age on average. Table 1 presents additional descriptive data.

**Pathologic Outcome Categories**

We examined three types of pathological endpoints that are associated with AD pathology; Braak staging, Consortium to Establish a Registry for Alzheimer’s disease (CERAD) protocol12 scoring, and a transactive response DNA binding protein (TDP-43) score. Recently, the transactive response DNA binding protein (TDP-43) gained traction as a postmortem marker of AD, both through ABeta dependent and AB independent pathways13.

**Braak Stages.** Briefly, Braak and Braak described a staging scheme neurofibrillary tangles (NFTs)14, which proposes six stages that can be reduced to four with improved inter-rater reliability15 : 1) No NFTs; 2) Braak stages I/II - NFTs predominantly in entorhinal cortex and closely related areas; 3) Braak stages III/IV - NFTs more abundant in hippocampus and amygdala while extending slightly into association cortex; 4) and Braak stages V/VI with NFTs widely distributed throughout the neocortex and ultimately involving primary motor and sensory areas. For our purposes, we combined the first two of these stages, as both No NFTs and Braak stages I/II represent little to no AD pathology.

**CERAD.** The CERAD scoring is a semi-quantitative measure of the neuritic plaques in the brain. The CERAD score we used converts the standard CERAD score to an assessment of AD diagnosis post mortem16,17, with a score of 0 indicating no AD, a score of 1 indicating possible AD, 2 indicating probable AD and a score of 3 indicating definite AD.

**TDP-43.** The final endpoint we considered was the TDP-43 score with a score of 0 representing no TDP pathology, and Stage 1, Stage 2, and Stage 3 representing increasing levels of TDP pathology respectively18.

**Cognitive Performance Assessments**

Participants in both studies underwent annual cognitive testing. Both studies had 19 common cognitive performance tests reported in previous publications10,11. The present analysis employs measures of episodic memory and a global measure of cognition. The composite episodic memory score was created based on scores from immediate and delayed recall performance from Logical Memory and of the East Boston Story, and Word List Memory, Recall, and Recognition from the Consortium to Establish a Registry for AD (CERAD). Raw scores on each of the tests were z scored, using the baseline mean and standard deviation from the full cohort, and subsequently averaging the z scores that yielded a composite score. To create a global cognition indicator, scores from 17 of the 19 tests were similarly converted to z scores using the baseline mean and standard deviations and averaged to form a measure of global cognition.

**Statistical Analyses**

In order to assess how cognitive performance (episodic and global) influences the risk of specific neuro-pathological outcomes, we fit a series of three multi-state models; one for each end-stage category listed above (i.e., Braak, CERAD, and TDP score). Aside from cognitive status, the only time varying covariate was age. The demographic variables we controlled for were gender, APOe4 status, education level, vascular risk, and smoking status. In addition, we controlled for follow up year and vascular health. For each pathological outcome category, an individual was considered censored if they were still alive at the end of the study time frame.

**Results:**

**Descriptive Data**

Descriptive summaries of the study sample report continuous variables’ as mean and standard deviation; frequencies and percentages are presented for the categorical variables (see Table 1). Descriptive summaries of autopsied participants are presented in Table 2. At autopsy, 228 (15%) persons had no evidence of neurofibrillary tangles according to Braak staging procedures and 310 (22%) had evidence of most severe pathology. Two-hundred and ninety-six (19%) persons had no AD according to CERAD scoring and 402 (27%) were classified as definite AD. Five-hundred and twenty-two persons (35%) had no TDP pathology and 140 (9.4%) were classified in the third stage of TDP.

**Multi-State Model Results**

Three separate multi-state models were run; one for each of the pathological outcome categories (i.e., Braak, CERAD, and TDP-43). We used Kaplan-Meier type estimators within each pathological outcome category to estimate time-to-outcome curves for each pathological outcome level, as well as for the total group. Estimated coefficients from the multi-state models for the main covariates, global cognitive score and episodic memory score, are reported. All reported p-values were those of two-sided tests; significance was defined as p < 0.05. All analyses were performed using R version 3.1.2 [19] and the ‘survival’ package [REF].

Liz’s attempt to put findings into words:

Across the three pathology outcomes, the coefficient for a one unit decrease in global cognitive scores or episodic memory scores was associated with a hazard ratio of one or close to one in the adjusted models. The coefficient for a 1 point change in Braak 5–6 death is 0.26 + 0.83, a 2.98 fold increase in risk for each 1 point loss.

This shows that at any one time point, a one unit drop in cognitive scores from a participant’s previous score is related to about a three-fold risk of being categorized as having the highest level of neurofibrillary tangles (Braak V/VI), definite AD (CERAD 3), and TDP pathology.

AND THEN WE’LL ADD SOMETHING HERE ABOUT THE MIXED PATHOLOGIES

DISCUSSION:

This study employed multi-state Cox proportional hazard models to determine the extent to which changes in cognitive profiles increase risk of exhibiting AD pathology at autopsy. We found that individuals with a decrease in their cognitive score compared to their prior score, may have up to a three-fold risk of exhibiting severe AD-related pathology at autopsy. ADD MORE DETAILS HERE…

To our knowledge, no studies have evaluated the concurrent risk of having AD pathology based on a cognitive score. Nonetheless, multiple studies have shown that those who receive an AD diagnosis or have AD-related pathology at autopsy perform more poorly on cognitive tests at baseline (e.g., Andel et al., 2001; Small et al., 1997) and show steeper declines in performance longitudinally (Boyle et al., 2013; Wilson et la., 2010). However, these studies employ modeling techniques that incorporates a reverse causality such that analysis are conducted after an AD diagnosis is already made or autopsies have been conducted. In this study, we make use of all available longitudinal data and make predictions based on individuals who have undergone autopsy and those who remain in this study. One previous study incorporated a similar approach by investigating the risk of having dementia based on baseline and longitudinal change in cognitive scores using a joint survival and growth model (McCardle et al., 2015). The authors found that lower baseline, not change in, episodic memory was associated with AD onset (McCardle et al., 2015). Our study extends previous studies by demonstrating that lower global cognition and episodic memory also elevates the risk of having AD pathology at autopsy.

We observed parallel results between a composite of global cognition and episodic memory; we evaluate the independent effect of episodic memory since it is speculated to be a precursor to AD (Bäckman & Small, 2007). The apparent equivalent effects of global cognition and episodic memory suggest the viability of using a single cognitive task to predict possible pathology. Nonetheless, we cannot rule out the possibility that other specific tasks will have an equal or even greater predictive power. For example, some studies have shown that tasks of executive function may also be predictive of AD (e.g., Mungas et al., 2010). Future studies testing similar or differential predictability of specific cognitive scores will be informative to uncovering the cognitive measures most sensitive to detecting likelihood of having specific pathologies at autopsy.

Our results have diagnostic and methodological implications. First, these findings suggest that neuropsychologists can improve the precision in which they make a diagnosis or shift treatment regiments for patients. For example, a patient who appears to decrease one standard deviation from their mean across visits is likely to have a X% chance of having AD pathology. In this case, a clinician may decide to more closely monitor the patient or suggests a more stringent treatment plan.

Further, these results may be useful in the identification and selection of candidate individuals for development of trial ready cohorts. That is, clinicians would know which subjects to recruit for relevant trials, especially trials that would involve autopsies in their conclusion

There are strengths and limitations to this study. One strength lies in the use of multi-state proportional hazard models that make use of all available data and do not exclude any individuals who do not undergo autopsy or who are still alive…..

MAYBE ADD LIMITATIONS ABOUT THE SAMPLE?: Findings are from a select cohort that cannot be generalized….

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Table Descriptive Summary for all participants. Continuous variables are expressed as mean(sd), factors are expressed as count(%)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Total | MAP | ROS |
| N | 3092 | 1789 | 1303 |
| Age | 78.25 (7.8) | 79.94 (7.6) | 75.92 (7.4) |
| Female(%) | 2236 (72.32) | 1313 (73.39) | 923 (70.84) |
| APOe4 (%) | 690 (22.32) | 386 (21.58) | 304 (23.33) |
| Smoker (%) | 1065 (34.44) | 797 (44.55) | 268 (20.57) |
| Global Cognition | 0.02 (0.7) | -0.03 (0.7) | 0.09 (0.6) |
| Vascular Score | 0.94 (0.8) | 1.08 (0.8) | 0.76 (0.7) |
| Education | 16.12 (3.8) | 14.56 (3.3) | 18.26 (3.3) |
| <HS (%) | 186 (6.02) | 155 (8.66) | 31 (2.38) |
| HS (%) | 970 (31.37) | 853 (47.68) | 117 (8.98) |
| College (%) | 1607 (51.97) | 720 (40.25) | 887 (68.07) |
| Grad (%) | 329 (10.64) | 61 (3.41) | 268 (20.57) |

Table . Descriptive summary of autopsied participants’ pathology indices, cognitive scores, and demographic covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| End Stage | N | Age | Female(%) | APOe4 (%) | Smoker (%) | Global Cognition | Vascular Score | Education |
| **Braak** |  |  |  |  |  |  |  |  |
| 0-II | 228 | 77.3 (7.2) | 116 (50.88) | 154 (67.54) | 83 (36.4) | -0.32 (1) | 1.16 (0.8) | 16.91 (3.8) |
| III/IV | 715 | 81.67 (6.9) | 469 (65.59) | 151 (21.12) | 222 (31.05) | -0.74 (1) | 1.01 (0.9) | 16.25 (3.6) |
| V/VI | 310 | 81.44 (5.7) | 229 (73.87) | 171 (55.16) | 96 (30.97) | -1.89 (1.2) | 1.03 (0.8) | 16.1 (3.6) |
| Braak Missing | 239 | 81.1 (6.7) | 161 (67.36) | 54 (22.59) | 97 (40.59) | -0.86 (1) | 1.25 (0.9) | 15.04 (4) |
| **CERAD** |  |  |  |  |  |  |  |  |
| 0 | 296 | 79.09 (7.5) | 175 (59.12) | 31 (10.47) | 103 (34.8) | -0.36 (1) | 1.1 (0.9) | 16.44 (3.8) |
| 1 | 124 | 80.72 (6.8) | 73 (58.87) | 22 (17.74) | 34 (27.42) | -0.49 (0.9) | 1.05 (0.8) | 16.47 (3.5) |
| 2 | 431 | 81.79 (7) | 268 (62.18) | 105 (24.36) | 142 (32.95) | -0.93 (1.1) | 1.03 (0.9) | 16.29 (3.7) |
| 3 | 402 | 81.08 (6.2) | 298 (74.13) | 220 (54.73) | 122 (30.35) | -1.54 (1.3) | 1.02 (0.8) | 16.25 (3.6) |
| CERAD Missing | 239 | 81.1 (6.7) | 161 (67.36) | 54 (22.59) | 97 (40.59) | -0.86 (1) | 1.25 (0.9) | 15.04 (4) |
| **TDP** |  |  |  |  |  |  |  |  |
| TDP 0 | 522 | 79.51 (7.1) | 331 (63.41) | 107 (20.5) | 170 (32.57) | -0.72 (1.1) | 1.08 (0.9) | 16.16 (3.8) |
| TDP 1 | 166 | 81.45 (6.9) | 115 (69.28) | 35 (21.08) | 51 (30.72) | -0.72 (1.1) | 1.15 (0.9) | 15.76 (3) |
| TDP 2 | 203 | 81.76 (6.5) | 148 (72.91) | 66 (32.51) | 71 (34.98) | -1.27 (1.2) | 1.07 (0.9) | 16.15 (3.5) |
| TDP 3 | 140 | 82.05 (6.5) | 95 (67.86) | 52 (37.14) | 43 (30.71) | -1.71 (1.2) | 1.03 (0.8) | 15.84 (3.5) |
| TDP Missing | 461 | 81.43 (6.6) | 286 (62.04) | 123 (26.68) | 163 (35.36) | -0.87 (1.1) | 1.06 (0.9) | 16.29 (4.1) |

