Project 3, BIOS 6623

Trajectories of Onset of Memory and Other Cognitive Loss

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**Introduction**

The goal of this project is to identify trajectories of onset of memory and other cognitive loss in a population of healthy, community dwelling, and cognitively intact elders at risk of developing mild cognitive impairment (MCI) or dementia. 216 individuals entered the study, and 187 of these were included in the descriptive statistics and analysis because they had at least three measurements of the outcome of interest over the course of the study. This cognitive test of interest that was measured over time in these individuals was category fluency for animals. We were interested in determining the rate of memory decline in healthy individuals over the course of the aging process, as well as the rate of memory decline in those individuals who would be diagnosed with MCI or dementia during the course of the study. Finally, we wanted to determine the period of time before MCI or dementia diagnosis in which the rate of memory decline either changes or accelerates.

**Methods**

There were 216 individuals included at the start of the study. Only those with at least three outcomes measurements for animal category fluency were included in the analytic cohort, so 29 individuals were removed from the data set and 187 remained. The baseline demographic information at baseline for this population is reported in Table 1, with counts and percentages reported for categorical variables and means and standard deviations reported for continuous variables. The baseline values for other cognitive tests are also noted, to allow for a more detailed comparison of the two subpopulations in which individuals were and were not diagnosed with dementia during the study.

To prepare for interpretation of the models that were to be run, new variables were created. First, a new age variable was create in which the minimum age in the study, 59, was subtracted from all other ages to make the intercept more interpretable in the models. Second, a variable was created to show the difference between age at an observation and age at dementia/MCI diagnosis, which was used to plot the animal category fluency score in time leading up to diagnosis.

The time-before-diagnosis variable was also used in finding the change-point for the model—the point in time before diagnosis at which memory/cognitive scores begin to decline or change at a different pace. A model was to be fit that accounted for individuals’ age, dementia status at the end of the study, socioeconomic status as measured by the Hollingshead scale, and gender in explaining their category fluency for animals score, as well as including a term that would allow linear trends to change at some point prior to diagnosis.

To be able to allow these terms to change, a change-point was determined for this model through likelihood-based methods. Maximum likelihood methods with Gaussian assumptions fit a variety of change points that ranged from 6 years before diagnosis to 2 years after diagnosis. The model being used to fit the change point was modeled the outcome—category fluency for animals—and adjusted for dementia status, age adjusted for minimum age of 59, the interaction between dementia status and age, socioeconomic status, gender, and the maximum of 0 and the difference between age at visit and dementia onset—if applicable—and the tested change point. To account for the repeated measures on individuals, a random intercept was fitted for each individual to account for their different starting points. Furthermore, a spatial power covariance structure was applied to the errors in the model to account for the repeated measures that occurred at differently spaced time points for individuals throughout the study.

From these methods, one change point was determined, and a final variable was created which selected the maximum of the age of onset subtracted from the age of the individual minus the change point. Then, this mixed model that was run in the bootstrap was fitted outside the bootstrap to determine the estimates for each variable based on the original data set of individuals with at least three observations.

To determine a confidence interval for the change point, 1000 iterations of a bootstrap were run that sampled with replacement from the 187 individuals in the analysis cohort, calculated the change point based on this new data set, and estimated the slope before and after the change point, as well as estimating the parameters of the model. The change-point 95% confidence interval was calculated by selecting the 2.5th and 97.5th percentiles of the bootstrap means.

These bootstrapped results were also utilized to determine more correct standard errors compared to those in the model, which were too small because they could not account for the uncertainty of the change point. These bootstrapped standard errors were found by calculating the standard deviation of the distribution of each bootstrapped estimate. Then, p-values for each estimate were recalculated by dividing the coefficient by the recalculated standard error and then determining the probability of this value with the normal approximation.

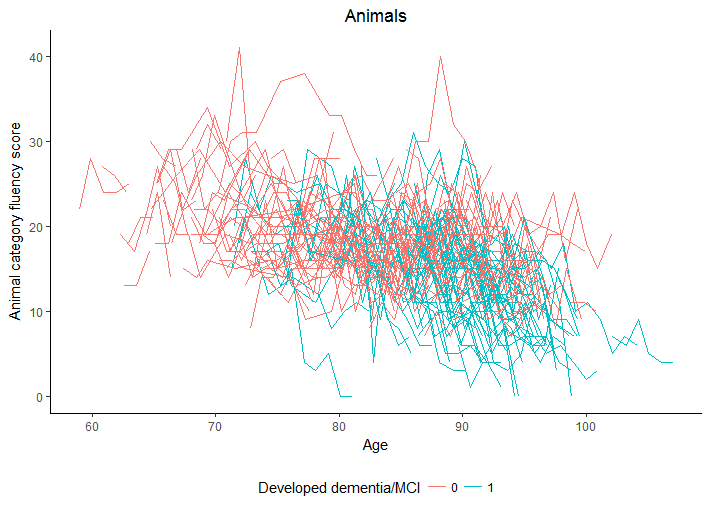
**Results**

The baseline demographics for the 187 individuals included in the study are displayed in Table 1. Overall, individuals entered the study at a mean age of 80.10, and were followed for an average of approximately 17.5 visits in which the category fluency score for animals was measured over the next 8.82 years. There were more women included in the study, but a much lower proportion of women were diagnosed with dementia over the course of the study. Socioeconomic scores were fairly evenly distributed between those who were and were not diagnosed with dementia/MCI in the study. Those who were diagnosed with dementia entered the study, on average, 8 years older than those were not diagnosed, and they had lower average baseline scores in all four memory and cognitive tests that were measured at their visits, including animal category fluency.

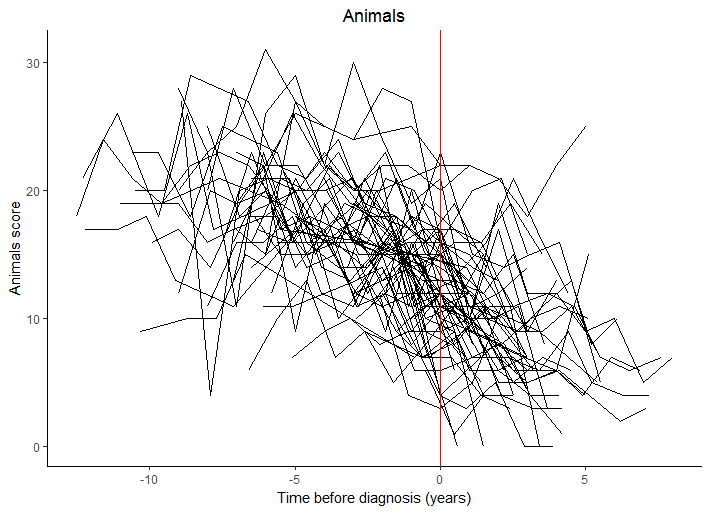
**Table 1.** This table displays the baseline demographic information of the 187 individuals who had at least 3 measurements on the animal category fluency outcome over the course of the study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Overall** | **Did not develop dementia/MCI during study** | **Developed dementia/MCI during study** |
| **n** |  | 187 | 119 | 68 |
| **Number observations (mean (sd))** | | 17.49 (7.48) | 16.42 (8.22) | 19.35 (5.54) |
| **Years of follow-up (mean (sd))** | | 8.82 (4.05) | 8.23 (4.41) | 9.87 (3.08) |
| **Gender (%)** | Male | 82 (43.9) | 59 (49.6) | 23 (33.8) |
|  | Female | 105 (56.1) | 60 (50.4) | 45 (66.2) |
| **SES (mean (sd))** |  | 49.32 (11.68) | 49.66 (10.86) | 48.74 (13.07) |
| **Age (mean (sd))** |  | 80.10 (8.87) | 77.16 (8.92) | 85.24 (6.01) |
| **BlockR (mean (sd))** |  | 24.56 (9.36) | 26.52 (9.43) | 21.12 (8.22) |
| **Animals (mean (sd))** |  | 17.33 (5.11) | 18.30 (4.99) | 15.62 (4.91) |
| **LogMemI (mean (sd))** |  | 13.48 (4.36) | 14.60 (4.02) | 11.53 (4.28) |
| **LogMemII (mean (sd))** |  | 11.13 (5.00) | 12.55 (4.51) | 8.65 (4.88) |

**Figure 1.** This figure displays the trajectories of individuals with at least three animal category fluency measurements in the study, colored by dementia status.



**Figure 2.** This figure displays the trajectories of animal category fluency scores leading up to dementia/MCI diagnosis for individuals who were diagnosed with dementia/MCI at some point in the study.



**Table 2.** This table displays the estimates from the mixed modelwith the bootstrapped standard errors and p-values calculated from these bootstrapped errors.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Model Estimate** | **Bootstrapped Standard Error** | **p-value** |
| Intercept | 24.59 | 2.9 | <0.0001 |
| Change Point | -0.93 | 0.15 | <0.0001 |
| Gender | -0.56 | 0.57 | 0.3311 |
| SES | 0.04 | 0.02 | 0.0811 |
| Age - 59 | -0.18 | 0.03 | <0.0001 |
| Dementia | -4.39 | 2.81 | 0.1187 |
| Interaction | 0.01 | 0.09 | 0.9493 |

**Table 3.** This table displays the change point determined by maximum likelihood methods and bootstrapped change point mean and confidence interval.

|  |  |  |
| --- | --- | --- |
| **Change Point (likelihood)** | **Change point (bootstrap)** | **Bootstrapped 95% CI** |
| -3.9 | -4.05 | -5.5, -2.6 |

**Table 4.** This table displays the bootstrapped mean and 95% confidence interval of the slopes before and after the change point.

|  |  |  |
| --- | --- | --- |
|  | **Bootstrapped mean** | **Bootstrapped 95% CI** |
| Slope before change-point | -1.48 | -2.63, -0.32 |
| Slope after change-point | -0.94 | -1.25, -0.64 |

* Results: Present results for analyses described in the methods (~1-1.5 pages). Use Tables and Figures as appropriate, including in the text the full interpretation of statistical results for the main findings (i.e. point estimates, confidence bounds, p-values, interpretation of results of test).
* Conclusions: Interpret your results (~.5 to 1 page) in context of scientific question(s). Also discuss any limitations to your analysis that may affect interpretation or that require additional consideration by the investigator.

**Conclusions**

* What is the rate of memory decline based on these measures over the aging process in healthy individuals?
* What is the rate of memory decline based on these measures over the aging process in those diagnosed with MCI/dementia during the study?
* Is there a period of time before the diagnosis of MCI/dementia in which the rate of the memory decline changes (or accelerates)?

**Code**

The code for this project can be found at <https://github.com/BIOS6623-UCD/bios6623-johnsra3/tree/master/Project3/Code>.