Introduction

The goal of this analysis is to explore the trajectories of the onset of memory or cognitive loss in a study population at risk of developing mild cognitive impairment (MCI) or dementia. Subjects were healthy, community dwelling, cognitively intact elderly individuals. These subjects were followed annually and were tested on four cognitive responses, including the Wechsler Memory Scale Logical Memory Story A, the Wechsler Memory Scale Logical Memory II Story A, the Wechsler Adult Intelligence Scale Revived Block Design, and category fluency for animals. The analysis of the category fluency for animals is discussed in this report. Data received included information at baseline and follow-up examinations for subject id, category fluency for animals (referred to as Animals for the remainder of the report) , socioeconomic status information using Hollingshead Four-Factor Index of Socioeconomic Status (a continuous measure of SES), age at visit, gender, Clinical Dementia Rating Scale (CDR), age of onset and an indicator variable for subjects who had 2 consecutive CDR scores of greater than or equal to 0.5 during the study signifying diagnosis of MCI/dementia. The data were unbalanced, as not every patient has the same number of visits or outcome values measured at each visit. The three main aims of this study include (1) determining the rate of memory decline based on our measures over the aging process in healthy individuals, (2) determining the rate of memory decline based on our measures over the aging process in those diagnosed with MCI/dementia during the study, and (3) determining if the annual rates of decline accelerate/change 4 years prior to the onset of MCI/dementia and by how much rates accelerate.

Methods

The main software used in this analysis was SAS 3.6 Enterprise Edition. Only subjects who were followed for three or more time points were included in the analysis. Data was subset further to include exclude the other outcome measures other than the Animals measure. The data was received in the “long” format that was appropriate for use with SAS’s PROC MIXED procedure, and minimal manipulation was performed to subset the data. Data were examined to determine the characteristics of the incoming cohort, whose characteristics can be observed in Table 1. A general linear mixed model was used for this analysis to determine the fixed effects of age at visit, MCI/dementia status, gender, and SES. An interaction term was included to account for the effect of age depending on MCI/Dementia status. An additional variable was also created to account for the potential significance of the acceleration in the rate of memory decline four years prior to the onset of MCI/Dementia. This variable, referred to as “changepoint” in the analysis, was calculated by subtracting the age of onset from the age at each visit and adding the time of interest prior to the age of onset, specifically four years. The minimum age of 59 years was subtracted from the age and interaction variables for ease of interpretation of the intercept in the model. This method was modeled after the method used in Hall’s analysis. (Hall et al., 2000) This age was the minimum age of the subjects used in the Animals analysis. The estimation method used for this analysis was restricted maximum likelihood estimation to account for the fact that regression coefficients were estimated from the data that the variance is estimated, and this helps to reduce bias in the variance estimates.

Random effects were included in the model through PROC MIXED using a random effects framework. Because of the longitudinal design, a random intercept and a random slope for age were included as random effects to account for inherent heterogeneity in the study population. This allows the model to account for a subject-specific starting point (intercept) and a subject-specific trajectory (slope). The random intercept and slope are assumed to be correlated. In this model, the correlation for the G matrix was chosen to be unstructured. Although many more parameters are being estimated in an unstructured covariance pattern than in other covariance patterns, it is most likely that the variances of the repeated measures in this study are not constant over time, so a correlation structure that would assume this may not be appropriate. That is, it is unlikely that the random effects at the first visit will have the same variability as the random effects at the second visit, and so on. An unstructured variance-covariance matrix would account for different variation at each visit. Although an unstructured covariance pattern is more complex than other patterns, in this study it is not appropriate to assume uniform variance across measures, and the unstructured G matrix was chosen to account for this variability among the random effects.

The significance of the fixed effects were determined using Type III F tests from the PROC MIXED output to determine if any of the coefficients were different from zero. The rates of change were calculated from the appropriate combinations of parameter estimates and the significance and errors of these estimates were determined in the PROC MIXED procedure.

Results

Convergence criteria of the model using an unstructured variance-covariance matrix was met. The subject to subject variation for intercept is 29.73 and the subject to subject variation of the slope is 0.03. The covariance between the random intercept and slope was estimated to be -0.74. The percent of variation explained by the subject to subject intercept is 77.1% and the prevent of variation explained by the subject to subject slope is 1.92%. This means that the random intercepts and slopes account for approximately 79% of variation in the model.

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| --- | --- | --- | --- | --- | --- | --- |
|  | N | No. Missing | MCI/Dementia Diagnosis with CDR Criteria (Demind = 1) | N | No. Missing | No MCI/Dementia Diagnosis with CDR Criteria (Demind = 0) |
| Animals | 46 | 22 | 16.57 (4.68) | 102 | 17 | 18.80 (4.91) |
| Age, mean (sd) | 68 | 0 | 84.47 (5.94) | 119 | 0 | 76.85 (8.82) |
| Age of Onset | 68 | 0 | 90.54 (4.87) | N/A |  |  |
| SES mean (sd) | 68 | 0 | 48.74 (13.07) | 119 | 0 | 49.66 (10.87) |
| Gender n (%) | 68 (36.36) | 0 |  | 119 (63.64) | 0 |  |
| Male |  |  | 23 (12.30) |  |  | 59 (31.55) |
| Female |  |  | 45 (24.06) |  |  | 60 (32.09) |

The characteristics of the incoming cohort are listed in Table 1. Fewer patients experiences a diagnosis of MCI/dementia compared to patients who did not experience a diagnosis. The missing values for the animals measurement signify unbalanced data in the study, as not every patient had a category fluency for animals score upon entering the study. The data is unbalanced throughout the study, some patients have measurements at certain years while others are missing data for those years. Overall upon entry into the study, patients with MCI/Dementia had a lower category fluency for animals score and a higher age at entry. SES seemed to be fairly similar for those with MCI/dementia compared to those without, and

**Table 1. Characteristics of the subset of the study cohort used in the Animals analysis. Values represent averages and percentages of the cohort upon entering the study.**

there were more females than males the MCI/dementia group while the number of males and females in the group without MCI/Dementia was fairly even.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Effect | Estimate | Standard Error | DF | t Value | p-value |
| Intercept | 20.01 | 1.45 | 183 | 13.83 | <0.0001 |
| Age - 59 | -0.18 | 0.03 | 185 | -5.94 | <0.0001 |
| Gender\* | 0.55 | 0.57 | 1079 | 0.97 | 0.33 |
| SES | 0.05 | 0.02 | 1079 | 2.00 | 0.04 |
| Demind‡ | -1.39 | 2.17 | 1079 | -0.64 | 0.52 |
| Age - 59\*Demind | 0.03 | 0.08 | 1079 | 0.36 | 0.72 |
| Changepoint | -0.96 | 0.10 | 1079 | -9.36 | <0.0001 |
| Rate of memory decline before four years prior to the onset of MCI/Dementia | -0.15 | 0.07 | 1079 | -2.02 | 0.04 |
| Overall rate of memory decline in those with MCI/Dementia | -1.12 | 0.06 | 1079 | -17.92 | <0.0001 |

The results of the parameter estimates for the animals analysis are listed in Table. 2. The rate of memory decline based on the model over the aging process in healthy individuals is estimated to be -0.18 units/ year (aim 1). On average the category fluency for animals in healthy individuals decreased -0.18 units (95% CI: -0.2403 to -0.1205) for every one year increase in age (p<0.0001). With our estimate the rate of memory decline decreases and this

**Table 2. Results from the Proc Mixed Model for parameter estimates.**

is consistent with the fact that cognition may decrease with age in some individuals. The decline of the category fluency for animals can be viewed in Figure 1. When demind =0, that is when MCI/Dementia is absent, the category fluency for animals declines as age at visit increases, but the majority of the values seem to remain between a range of 8 to 30, with some values range between 8 to 40. The rate of memory decline for healthy individuals is significant in the model indicating a significant decline in the trajectory of memory and other cognitive loss as age advances.

The rate of memory decline based on the model over the aging process in those diagnosed with MCI/Dementia during the study is estimated to be -0.15 units/year four years prior to the onset of MCI/dementia. On average the category fluency for animals in individuals diagnosed with MCI/ Dementia decreased -0.15 units (95% CI: -0.2984 to -0.00450) for every one year increase in age (p = 0.04) before four years prior to the onset of dementia.

**Figure 1. Trajectories of memory decline in those without MCI/Dementia (demind = 0) and those with MCI/Dementia (demind = 1).**

This rate of change was determined by adding the parameter estimates for age and the interaction term. Although the effect of age on the category fluency for animals did not differ significantly by MCI/dementia status (ß = 0.03, p = 0.72), the parameter estimate for the rate of decline four years prior to onset was significant in the model, indicating a significant decline in the trajectory of memory and other cognitive loss four years prior to the onset of dementia. The trajectories of cognitive decline for those diagnosed with MCI/dementia are shown in Figure 1 (demind = 1) and Figure 2. The overall rate of decline in those with MCI/ Dementia is discussed after discussion of the change point.

There is an estimated period of time during which the rates of decline accelerate, specifically we were interested in the potential acceleration in decline four years prior to diagnosis. The rate of decline accelerates by 0.96 units/year (95% CI: -1.1623 to -0.7593) four years prior to the onset of dementia (p < 0.0001). This signifies that based on our data and the model, the decline changes four years prior to onset, which is our change point in the model. This means that the rate of memory decline essentially has an initial rate of decline starting from the intercept to the change point and an accelerated rate of decline after the change point to the end of the study. This accelerated rate of decline after the change point is significant in the model. This can be viewed in figure 2. Figure 2 plots all 68 cases and shows the trajectory from the start of the study to four years prior to diagnosis and the decline after this change point. A decline prior to four years before diagnosis is observed but after four years prior to diagnosis the rates of decline rapidly accelerate, with some subjects having a category fluency of animals score of zero after diagnosis. 

**Figure 2. Category Fluency for Animals by Time to Diagnosis. Reference lines at four years prior to diagnosis and at diagnosis.**

The overall rate of decline in those with MCI/ Dementia from the start of the study to the last time point measured is -1.12 units / year (95% CI: -1.2340 to -0.9904). This rate is calculated by adding the rate of change four years prior to onset of MCI/dementia and the accelerated rate of change after four years prior to the onset of MCI/Dementia. This overall rate of change for those with MCI/Dementia shows a significant increased rate of decline in those with MCI/Dementia compared to those without MCI/Dementia.

The Type III test of Fixed effects can be viewed in Table 3. The null for these tests is that the estimates are equal to 0. In Table 3, the effect of age and the effect of the change point are significantly different from 0. Although in this study including adjustments for gender, SES, the interaction term, and MCI/Dementia status were important, in further studies more data may be needed or these variables may need to be dropped from the model to create a more parsimonious model. In this case however, these variables remained in the model because they were essential to answering our research questions about the rate of memory decline in our study population.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Effect | Num DF | Den DF | F Value | p-value |
| Age - 59 | 1 | 185 | 35.32 | <0.0001 |
| Gender | 1 | 1079 | 0.94 | 0.33 |
| SES | 1 | 1079 | 3.98 | 0.05 |
| Demind | 1 | 1079 | 0.41 | 0.52 |
| Age - 59\*Demind | 1 | 1079 | 0.13 | 0.72 |
| Changepoint | 1 | 1079 | 87.53 | <0.0001 |

**Table 3. Type III F tests for the model parameter estimates.**

Conclusion

Overall we can see significant rates of decline in healthy individuals and in those with MCI/dementia. The rate of decline is healthy individuals is estimated to be 0.18 units/ year. The rate of decline before four years prior to onset of MCI/dementia is estimated to be 0.15 units/year. These values are fairly similar indicting that healthy individuals and MCI/dementia individuals have similar trajectories before four years prior to the onset of MCI/dementia. The accelerated rate of change after the change point of four years prior to the onset of MCI/dementia is estimated to be 0.96units/year. This signifies an additional rate of change in those with MCI/Dementia. The overall rate of decline in those with MCI/Dementia from enrollment to the end of the study was estimated to be 1.12 units/ year. This means that on average the rate of decline in those with MCI/demetia is much higher at 1.12units /year compared to the rate of decline in healthy individuals at 0.18 units/year.

Some limitations to this study include missing animals measurements for subjects at different intervals. This is the nature of a longitudinal study because realistically we may not have information on measurements at every time point. However, a balanced study, with data at every time point may result in less biased estimates. Another factor that may contribute to bias in the estimates is selection of the variance-covariance matrix. Here selection was made based on knowledge of the data but there is no way to know that the structure chosen is the correct structure. Advantages of the longitudinal design include gathering information over time which in reality is how disease progresses and this allows us to see the changes over time to potentially intervene at an appropriate time point. Further studies may want to test an intervention at the time point of four years prior to the onset of MCI/dementia and determine if there is still acceleration in the rate of decline after this change point.

Reproducible Research

GIthub Path: bios6623-bbalkaran/Project3/Code

Data file saves in SAS studio: /home/bridgetbalkaran0/my\_courses/BIOS\_6623 Advanced Data Analysis/ Project 3/memorydata.sas7bdat

References

Hall, C., Lipton, R., Sliwinski, M., & Stewart, W. (2000). A change point model for estimating the onset of cognitive decline in preclinical Alzheimer’s disease. *Statistics In Medicine*, *19*, 1555 - 1566.

Fitzmaurice, Garrett M., Nan M. Laird, and James H. Ware. Applied Longitudinal Analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc., 2011. Print.