Mixed Membership Trajectory Model of Cognitive Impairment in the MACS

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Abstract

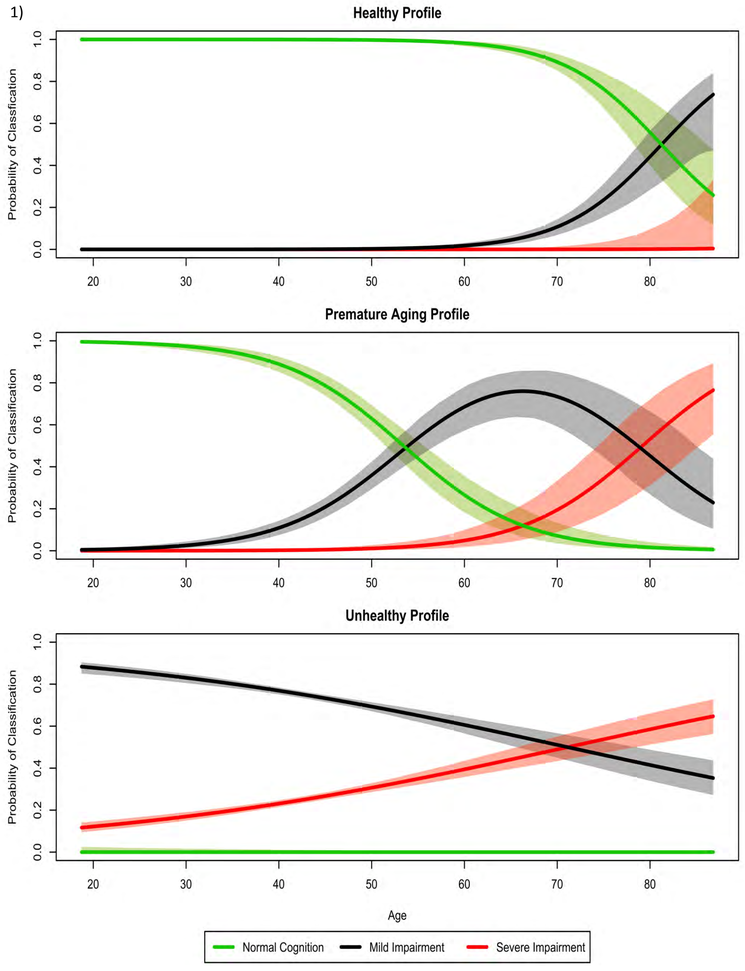
Cognitive decline is one of the many deficits associated with HIV disease. HIV-associated Neurocognitive Disorder, or HAND, is influenced by a variety of factors and differs from other forms of conigitive impairment in that the symptoms can fluctuate in severity. The Multicenter AIDS Cohort Study (MACS) is a four-site longitudinal study of the natural and treated history of HIV Disease among gay and bisexual men. Using data from 3,892 men (both HIV-infected and uninfected) enrolled in the neuropsychology substudy of the MACS, a Mixed Membership Trajectory Model (MMTM) was applied to capture the pathways from normal cognitive function to mild impairment to severe impairment. MMTMs allow the data to identify canonical pathways and to model the effects of risk factors on an individual's "closeness" to these trajectories. With the MMTM, we identified three canonical trajectories - a "normal aging" profile with relatively low probability of even mild impairment until well into middle age (60% of sample), a "premature aging" profile with a probability of mild impairment climbing at age 45-50 (21% of sample); and, an "unhealthy" profile with a high probability of mild impairment even at a very young age (19% of sample). The premature aging profile was characterized as including men who were from the original study cohort (1984-1991), had HIV Disease and had AIDS, with 11% with HCV infection. The unhealthy profile was characterized by men from the latest enrollment cohort (2001-2003), HCV infection, and other medical confounds. We tested the effects of seven time invariant predictors on the “closeness” of individuals to each of these profiles. HCV infection, HIV, AIDS, recruitment cohort, confounding conditions, depression, and the interaction between cohort and race have a significant effect on the closeness of individuals to these profiles. We have invoked, for the first time, a novel, data driven method for identifying trajectories to cognitive impairment in men with, or at-risk for HIV infection. These results provide new insights into the natural and treated history of HIV/AIDS and suggest that premature cognitive impairment remains a concern, particularly for those individuals infected with HIV who develop AIDS.

Methods

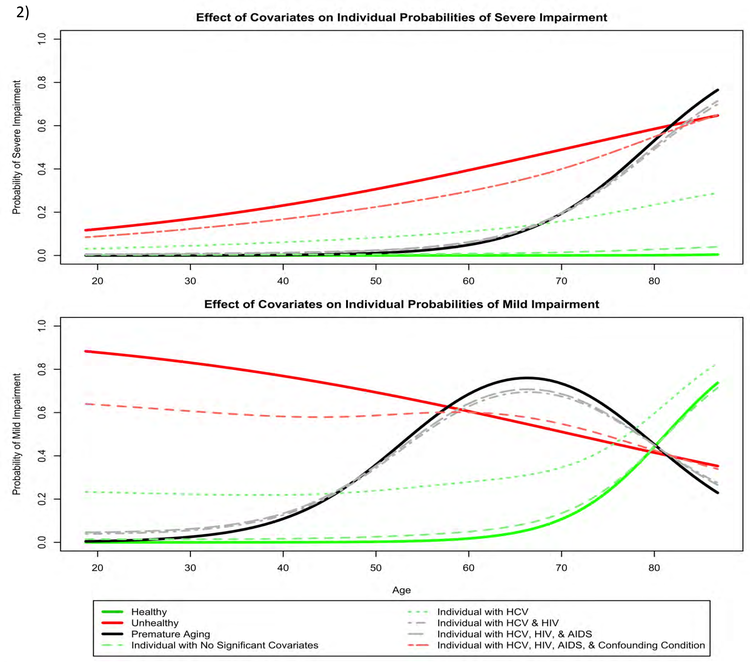
We report here an MMTM with three canonical trajectories describing the progression from normal to mildly impaired to severely impaired cognition. In this study, we use 25,641 observations from 3,892 MACS participants, an average of 6.5 per individual, who completed enough neuropsychological testing at a given observation to be assigned a cognitive classification. Within each canonical profile, the probability of each cognitive classification is modeled using multinomial logistic regression. Additionally, an individual’s trajectory is then modeled as a weighted combination of these canonical trajectories, and these weights can be used to determine which profile an individual identifies most closely with. Because impaired cognition is thought to be linked with mortality as well as a number of other factors, we enter data on survivorship into the model and allow the distribution of the membership vectors to depend on eight time-invariant predictors. The difference between the coefficient for a given predictor for each component of the membership vector is analogous to the effect of that predictor on the log odds of an individual identifying with one profile more closely than the other. In this study, if the estimate of a predictor’s impact is positive, the predictor increases the log odds that an individual is closer to the “healthy” profile than the “unhealthy” profile”.

Results

1)



2)



3)

Covariate	Estimate [95% CI] for Effect on Log Odds of Closeness to Unhealthy Profile Relative to the Healthy Profile	Estimate [95% CI] for Effect on Log Odds of Closeness to Premature Aging Profile Relative to the Healthy Profile	Estimate [95% CI] for Effect on Log Odds of Closeness to Premature Aging Profile Relative to the Unhealthy Profile
Cohort	-0.805 (-1.131,-0.484)*	0.738 (0.317,1.269)*	1.588 (1.124, 2.127)*
Race (White)	-0.046 (-0.364, 0.277)	-0.318 (-0.688, 0.096)	-0.272 (-0.644, 0.171)
Confounding Conditions	-0.154 (-0.030, -0.014)*	0.592 (0.390, 0.798)*	0.746 (0.533, 0.959)*
Hepatitis C Virus Infection	-0.321 (-0.575, -0.058)*	-0.344 (-0.656,-0.020)*	-0.024 (-0.346, 0.287)
Depression	-0.433 (-0.606, -0.262)*	0.196 (-0.032, 0.402)	0.629 (0.365, 0.874)*
HIV	-1.267 (-1.569, -0.977)*	-3.795 (-4.176, -3.458)*	-2.529 (-2.963, -2.173)*
AIDS	-0.194 (-0.351, -0.034)*	-2.57 (-2.863,-2.253)*	-2.370 (-2.733, -1.994)*
HIV & Race Interaction	0.549 (0.167, 0.943)*	0.523 (-0.149, 1.119)	-0.026 (-0.744, 0.597)

Figure 1: The probability of each cognitive classification as a function of age for each of the three canonical profiles identified. The top plot illustrates the “normal” profile, where the green curve represents the probability of normal cognition, the black curve represents the probability of mild cognitive impairment, and the red curve represents the probability of severe cognitive impairment. The bands around each curve represent 95% pointwise-posterior credibility bands. The middle and bottom plots depict the probability of each cognitive classification for the “premature aging” and “unhealthy” profiles respectively. Approximately 60% of participants identified most closely with the normal profile, 21% with the premature aging profile, and 19% with the unhealthy profile.

Figure 2: Individual trajectories to severe (top) and mild (bottom) cognitive impairment. The canonical trajectories are shown in thick, solid lines for the “healthy”, “premature aging”, and “unhealthy” profiles in green, black, and red respectively. Individuals with specific combinations of covariates were randomly sampled and their trajectories are displayed in thin, patterned lines to demonstrate the idea of mixed membership. The light green colored lines represent individuals who identify most closely with the “healthy” profile, the light gray colored lines represent individuals who identify most closely with the “premature aging” profile, and the light red lines indicate individuals who identify most closely with the “unhealthy profile”.

Figure 3: The time invariant predictors included in the full model and the estimates of their effect. Predictors with positive values increase the log odds that an individual will identify more the reference profile. For instance, the estimate of -0.805 for the effect of cohort between the “healthy” and “unhealthy” profiles indicates that individuals in the later cohort are more likely to identify with the unhealthy profile than the healthy profile when all other factors are held constant. A predictor has a significant effect if the confidence interval for it’s estimate does not include zero.

Discussion

- We report here a MMTM with three canonical trajectories, demonstrating evidence of three distinct pathways within the MACS to cognitive impairment as a function of age in men both with and without HIV disease. While the determination of these trajectories is data-driven, the choice of three profiles is a modeling decision made on the basis of the interpretability of results. Note that this model should not be thought of as a “true” model, but rather the best solution for a three profile model.
- HIV, AIDS, HCV, cohort, the presence of confounding medical conditions, depression, and the interaction between race and cohort have a significant effect on the closeness of individuals to these profiles.
- Other factors may also have an effect on the log odds of an individual’s proximity to one profile over the other. Such factors might include the ApoeE4 gene, access to combination antiretroviral therapies, and recreational drug use. At this time, we cannot include1 such information in the model because we do not have data on enough individuals (ApoeE4) or because the model is currently limited to time invariant predictors (combination antiretroviral therapy access and recreational drug use).
- In order to improve the efficacy of the model, we will need to continue collecting data as the subjects age, particularly from older MACS participants. Moreover, as there are currently no comparable longitudinal studies conducting neuropsychiatric evaluations data among women or young substance users.