Multiple imputation of random covariates to assess the brain structural correlates of cognitive trajectories in HIV disease

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Objective

Our **primary objective** in this study was to **investigate** the **relationship between** trajectory membership weights ("**closeness**") and **brain structural integrity**, and **identify** which brain regions exhibited the **strongest association**.

Usually, one would **input the observed/measured data** and fit the model in their software of choice, such as SPM or FSL. However, because the **membership weights** we are including in our model are **not observable quantities but** are, instead, **random variables**, we could not simply input their point estimates without biasing the results. Therefore we decided to **approach** this **as a missing data problem** and **employ multiple imputation** in our investigation.

Abstract

Background: Molsberry et al. (2015) have described trajectories to cognitive impairment among participants in the Multicenter AIDS Cohort Study (MACS) (**see adjacent poster**). This analysis builds on the findings of Molsberry et al. with the goal to determine the relationship between patterns of brain volume and the individual trajectories to impairment.

Methods: 302 (167 HIV-infected; mean age = 55.7 yrs.; mean education: 16.2 yrs.) of the men enrolled in the MACS MRI study contributed data to this analysis. We used voxel-based morphometry to segment the brain images to analyze gray matter.

The **Mixed Membership Trajectory Model (MMTM)** had identified a "**normal aging**" profile, a "**premature aging**" profile and, an "**unhealthy**". Each study participant had a membership weight for each of these trajectories.

We estimated model parameters for 100 imputations, manually performed the post-hoc contrasts, and pooled the results accounting for between– and within–imputation variability.

Results: The unhealthy profile is linked to areas associated with cognitive decline, including the posterior cingulate/precuneus, the inferior frontal cortex, and insula. Premature aging membership weights are independently associated with the integrity of a portion of the precuneus.

Background

HIV-mediated neural damage results in neurobehavioral disturbances and **HIV-associated neurocognitive disorders (HAND)**, which consists of asymptomatic neurocognitive impairment (ANI), mild neurocognitive impairment (MND), and HIV-associated dementia (HAD). The **Multicenter AIDS Cohort Study (MACS)** is a four-center study of the natural and treated history of **HIV infection among gay/bisexual men**.

Materials & Methods

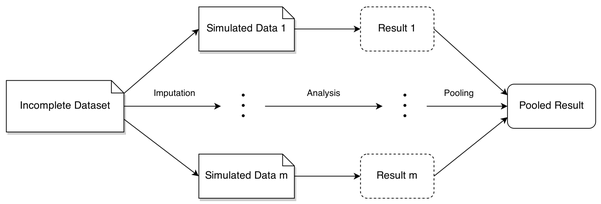


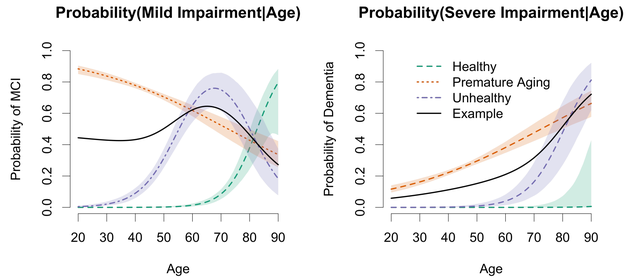
Diagram of Multiple Imputation (MI)

This research was reviewed and approved by the Institutional Review Boards at all four MACS clinic sites – Baltimore, Maryland-Washington DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania.

A total of **302 men** had undergone **high-resolution anatomical brain** imaging (**MP-RAGE at 3T** field strength). Images were **pre-processed with N3** software and **processed** (affine registered, segmented, and normalized) **with voxel-based morphometry** (VBM8) in SPM12 in MATLAB. Our analysis focused on **smoothed** (8x8x8mm FWHM), **log-transformed** (to adjust for the skewed distribution), **modulated normalized gray matter** (GM) images.

Multiple imputation (MI) is a method to obtain **valid inferences from imputed data**; naïve imputation methods bias estimates and distort standard errors. We **simulated multiple versions** of a complete dataset, using **MCMC draws** of the **membership weights** from their posterior distribution. We **analyzed each simulated complete dataset** using SPM12 and then **pooled the results together** using formulas that account for between– and within–imputation variability, producing **statistical parametric maps** that **incorporate missing data uncertainty**.

Results and Discussion



Example trajectory is a weighted mixture of the three extreme profiles (2% Healthy, 50% Premature Aging, 48% Unhealthy).

	Closest to…		
	Healthy Profile	**Unhealthy Profile**	**Premature Aging Profile**
	231 (76.49%)	57 (18.87%)	14 (4.64%)
Age at scan	57.09 (6.05)	56.04 (5.72)	57.43 (7.57)
Race (Caucasian)	173 (74.89%)	35 (61.40%)	9 (64.29%)
Education	16.68 (5.91)	15.09 (2.80)	16.29 (3.60)
AIDS	18 (7.79%)	7 (12.28%)	2 (14.29%)
Depressed (Ever)	173 (74.89%)	43 (75.44%)	10 (71.43%)
HCV	20 (8.66%)	18 (31.58%)	2 (14.29%)
Alive	2 (0.87%)	2 (3.51%)	2 (14.29%)

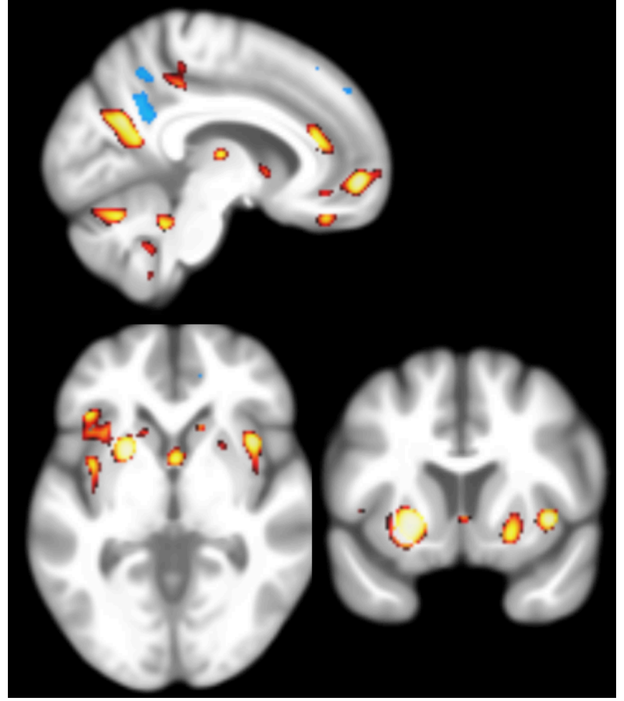
Values are the mean (standard deviation) or n (%).

Figure 1 shows the regions associated with the Unhealthy profile (yellow/red) and the Premature Aging profile (blue) projected onto a mean image created from the MACS MRI database. Closeness to both profiles is associated with the integrity of the posterior cingulate/precuneus. However, closeness to the Unhealthy profile is also associated with the volume of the putamen, insula, inferior frontal cortex, and the caudate nucleus.

Conclusions

Trajectories to cognitive impairment in HIV disease are the result, in part, of atrophy in brain regions linked to HIV disease (basal ganglia), as well as cortical regions linked with normal and pathological aging. These data suggest the possibility of predicting cognitive morbidity based on patterns of CNS atrophy.

Brain Regions Whose Volume is Correlated with Closeness to the MMTM "Unhealthy" Trajectory (**Hot**) and "Premature Aging" Trajectory (**Cool**)



For the "**premature aging**" profile closeness, the **blue**-highlighted **regions** are **p-values < .01**. For the "**unhealthy**" profile closeness, the **yellow/red**-highlighted **regions** are **p-values < .005**.

References

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