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Brain Structural Correlates of Trajectories to Cognitive Impairment in Men with and without HIV Disease.

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Abstract

Background: There are distinct trajectories to cognitive impairment among participants in the Multicenter AIDS Cohort Study (MACS). Here we analyzed the relationship between regional brain volumes and the individual trajectories to impairment in a subsample (n = 302) of the cohort.

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 (VBM) to segment the brain images to analyze gray and white matter volume at the voxel-level. A Mixed Membership Trajectory Model had previously identified three distinct profiles, and each study participant had a membership weight for each of these three trajectories.

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Conflict of Interest: None.

Ethical approval: This research was reviewed and approved by the Institutional Review Boards at all four MACS clinic sites – Johns Hopkins University, Northwestern University, University of California Los Angeles, and the University of Pittsburgh.

Informed consent: Each participant signed a written statement of informed consent prior to starting any research-related activities.

We estimated VBM model parameters for 100 imputations, manually performed the post-hoc contrasts, and pooled the results.

Results: We examined the associations between brain volume at the voxel level and the MMTM membership weights for two profiles: one considered “unhealthy” and the other considered “Premature aging.” The unhealthy profile was linked to the volume of the posterior cingulate gyrus/precuneus, the inferior frontal cortex, and the insula, whereas the premature aging profile was independently associated with the integrity of a portion of the precuneus.

Conclusions: Trajectories to cognitive impairment are the result, in part, of atrophy in cortical regions linked to normal and pathological aging. These data suggest the possibility of predicting cognitive morbidity based on patterns of CNS atrophy.

Keywords

HIV; Dementia; Multiple Imputation; Brain Structure; Mixed Membership Trajectory

Introduction

HIV-mediated neural damage results in neurobehavioral disturbances and HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007), which include asymptomatic neurocognitive impairment, mild neurocognitive impairment, and HIV-associated dementia (Saylor et al., 2016). However, in spite of the success of combination antiretroviral therapy (cART) at reducing the risk of AIDS-defining illnesses and increasing the life span of individuals with HIV disease, the impact of these treatment regimens on neurological and neuropsychological impairments among infected individuals remains unclear. Although HIV associated dementia has all but disappeared among individuals with access to appropriate medical care and management, a milder form of impairment (the “mild cognitive impairment” syndrome) remains prevalent (Sacktor et al., 2002). Understanding the central nervous system (CNS) basis of these impairments remains a high priority research agenda.

One way to study cognition-related syndromes in the context of HIV disease is to analyze trajectories to impairment. That is, what is an individual’s risk of impairment over their lifetime involvement in a longitudinal study, and how do individual factors predict or modify risk of developing impairment? The present study builds on our recent findings (Molsberry et al., 2015) from an analysis using the novel, data-driven Mixed Membership Trajectory Model (MMTM) technique (Manrique-Vallier, 2014) to describe the development of mild and severe cognitive impairment. MMTMs combine features of longitudinal Multivariate Latent Trajectory Models to identify distinct, canonical profiles, with features of cross-sectional Grade of Membership Models (Connor, 2006) to allow individuals to have weighted memberships in each profile(E.A. Erosheva, 2005; E. A. Erosheva, Fienberg, & Joutard, 2007). The utility of this method was shown in an analysis of disability data from the National Long Term Care Survey (NLTCS) (Manrique-Vallier, 2014), finding that most individuals followed a trajectory that implied a late onset of disability; younger cohorts tended to develop disabilities at a later stage in life. An advantage of the MMTMs relative to other trajectory modeling techniques is that the MMTM also expresses each individual participant’s pathway as a weighted combination of the canonical trajectories. In addition to

expressing an individual's closeness to the canonical trajectories (or profiles), the membership weights can also be interpreted as reflecting each individual's health propensities (in this case, cognitive impairment).

Using the neuropsychological data from the MACS participants (both infected and uninfected) Molsberry and colleagues identified three canonical profiles that we descriptively labelled "normal aging," "premature aging," and "unhealthy." The MMTM expressed each individual's trajectory as the weighted combination of the three canonical trajectories. The model used predictor variables previously identified as risk factors for HAND to determine individuals' "closeness" to the canonical profiles. The analysis found that hepatitis-C infection, depression, race, MACS recruitment cohort and confounding conditions all affected individual's closeness to these trajectories. In addition, clinically defined AIDS, and not simply HIV disease, was associated with closeness to the premature aging trajectory. Thus, an individual participant's closeness to one of the canonical trajectories is affected by multiple subject-specific characteristics (See (Molsberry et al., 2015), for details).

In order for these trajectories to have the most meaning in terms of understanding the pathobiology of the development of HAND, there should be some association between each individual's overall (or summary) closeness to each trajectory, and a measure of central nervous system integrity. We took advantage of the fact that there is a subset of individuals (n = 302) within the MACS who are also enrolled in a study involving structural brain imaging and cognition. We utilized these MRI data to determine the extent to which there was an association between brain structural integrity and each individual participant's closeness to the three canonical trajectories identified in our prior report (Molsberry et al., 2015).

Our primary objective in this study was to investigate the relationship between trajectory membership weights ("closeness") and brain structural integrity, in order to identify those brain regions linked to the more abnormal trajectories. In order to accomplish this goal, we would ordinarily input the observed/measured data and fit the model in the software of choice, such as SPM or FSL. However, the membership weights from the MMTM are not observable quantities but are random variables; each membership weight is a mean value with a standard deviation. Thus, we could not simply input their point estimates without biasing the results. Therefore, we approached this analysis as a variation of a missing data problem and used multiple imputation methodologies to overcome the problem.

Methods

This research was reviewed and approved by the Institutional Review Boards at all four MACS clinic sites – Johns Hopkins University, Northwestern University, University of California Los Angeles, and the University of Pittsburgh. Each participant signed a written statement of informed consent prior to starting any research-related activities.

Subjects and Brain Imaging:

The MACS is a four-center study of the natural and treated history of HIV infection among men who have sex with men (Kaslow et al., 1987) that tracks the cognitive test performance of the study volunteers. There were three distinct recruitment stages that focused on groups of infected men with different demographic characteristics, or men at risk for infection. Study participants were enrolled at four sites (Los Angeles, Pittsburgh, Chicago, Baltimore/Washington) in three waves: 1984/85, 1987/90 and 2001/03. The men who enrolled in 1984–85 are Cohort 1, those who enrolled in 1987–91 are Cohort 2 and those who enrolled between 2001 and 2003 are Cohort 3. Cohort 1 was the original sample of 4954 men and Cohort 2 was a 'new recruit cohort' that focused on enrolling minority and special target groups such as the partners of the men in C1. Cohort 3 focused on recruiting racial/ethnic minorities as well as a special target group of uninfected men who had been censored from C1 in 1995. Because the characteristics of the men in Cohorts 1 and 2 were similar, we refer to a combined Cohort 1 (C1) and a separate Cohort 2 (C2, 2001–2003 enrollees only). This dichotomous variable was used in data analyses (see below).

A subset of 302 participants from across the four clinical centers had 3D magnetic resonance (MR) brain images and contributed these MRI data for this analysis (See Tables 1 and 2, and (Becker et al., 2011)) for details of initial MRI study enrollment. These men had undergone high-resolution anatomical brain imaging (MP-RAGE at 3Tesla field strength). There was no association between HIV status and trajectory closeness ($X^2 = 1.22$, df=2, p= .54).

The acquired brain images were preprocessed using a non-parametric correction of intensity nonuniformity (Sled, Zijdenbos, & Evans, 1998). We used a custom-made template of tissue priors, which we had created with the Template-O-Matic (TOM8) toolbox and data from the Information eXtraction from Images (IXI) project. We processed the images with voxel-based morphometry (VBM8) in Statistical Parametric Mapping (SPM12) software running in MATLAB. Brains were affine-registered, segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid volumes (CSF), and then normalized with DARTEL. Our analysis used the smoothed (8 × 8 × 8mm FWHM) modulated, normalized, log-transformed GM and WM images that passed our quality control check.

Mixed Membership Trajectory Model:

MMTMs assume there is a finite, usually small number of distinct patterns that are called "canonical profiles," and individual trajectories are modeled as a weighted mixture of those canonical profiles. Molsberry and colleagues (Molsberry et al., 2015) modeled the canonical profiles of 3,892 men (2,099 infected) in the MACS and estimated the membership weights, all within a hierarchical Bayesian framework (Molsberry et al., 2015). Individuals' cognitive classification (Normal, Mild Impairment, Severe Impairment), recruitment cohort (2001–2003 vs. 1985–1993), AIDS, depression, hepatitis C infection, confounding medical conditions (e.g., hypertension, diabetes, cancer, etc.), race, and death) were used to estimate the parameters of the MMTM. There were three canonical profiles (See Figure 1): we arbitrarily refer to canonical profile 1, for which the probability of normal cognition is initially very high, as the 'normal aging' profile; profile 2, for which the probability of mild impairment begins to climb at age 45–50 years, as the 'premature aging' profile; and profile

3, for which the probability of normal cognition is near zero even at the youngest age, as the 'unhealthy' profile.

Voxel-Level Data Analysis:

Multiple imputation (MI) is a method to obtain valid inferences from imputed data (Rubin, 1986), since naïve imputation methods bias estimates and distort standard errors. MI works by simulating multiple versions of a complete dataset, and in each version the missing values are imputed using some model of data generation. Each simulated complete dataset is analyzed using standard methods and the results are pooled together using special formulas that account for between– and within–imputation variability, producing estimates that incorporate missing data uncertainty. Figure 2 illustrates this process.

We modeled y, the log-transformed tissue volume, at voxel level by multiple regression:

$$\begin{aligned} y &= \beta_{\text{Intercept}} + \beta_{\text{Age}}\text{Age} + \beta_g g + e \\ e &\overset{i.i.d.}{\sim} \text{Normal}\left(0, \sigma^2\right) \end{aligned} \tag{1}$$

where g is the individual's closeness to a profile obtained by the MMTM. We generated m=100 MI datasets containing Monte Carlo Markov Chain draws of the membership weights from the posterior multivariate distribution. Each multiply imputed dataset was then fed into SPM8 for analysis (estimation of β and σ^2). We were interested in performing post-hoc contrasts, which are defined as $c^T\beta$ where c is a column vector of L weights. For example, $c = [0, 0, 1]^T$ (as shown here c may not formally be a contrast vector -- the elements may not sum to zero -- but may be a dummy coding or other coding to isolate parts of β that we are interested in). The estimate has the following distribution (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007):

$$c^T\beta \sim \text{Normal}\left(c^T\beta, \sigma^2 c^T\left(X^T X\right)^{-1} c\right). \tag{2}$$

To apply MI, we let $Q = c^T\beta$ be the quantity of interest estimated by $\hat{Q} = c^T\beta$ and $U\,\sigma^2\, c^T (X^T X)^{-1} c$, where X is a (simulated) complete set of covariates, and then proceeded as described in the Supplemental Materials. SPM was then used to pool the results of 100 separate analyses. Each voxel had a mean and standard deviation from which we calculated F-maps and degrees of freedom at the voxel level. From these we created 3-D maps of p-values –$|P(F_{1,u} \geq F_* | H_0)|$– at the voxel level. This has the consequence that the multiple comparison problem (i.e., tens of thousands of comparisons) doesn't exist in the way that it would in a more standard use of SPM.

Results

The results of the analyses are shown in Figure 3; the regions significantly associated with the Unhealthy profile (yellow/red) and the Premature Aging profile (blue) are projected onto a mean brain image created from the MACS MRI database. The closer that an individual is to either of these profiles was associated with lower volume of the posterior cingulate/

precuneus grey matter. In addition, closeness to the Unhealthy profile is also associated with decreased volume in the putamen, insula, inferior frontal cortex, and caudate nucleus.

Discussion

We show here that we were able to generate a method for associating random variables with a mean and standard deviation (in this case, closeness to a trajectory) with grey matter volume treating the analysis as a variation of a missing data problem. From this novel analysis we found that closeness to the Unhealthy trajectory was associated with the volume of posterior cingulate/precuneus grey matter as well as the putamen, insula, inferior frontal cortex, and caudate nucleus. The former is important because it provides another method for integrating leading edge statistical tools with brain imaging data. The latter is important because it provides concurrent validity to the results of the original MMTM analysis (Molsberry et al., 2015), and because the brain regions involved are associated with cognitive functions.

The trajectories to cognitive impairment in our study sample are associated, in part, with atrophy in brain regions linked to HIV disease (i.e., basal ganglia), as well as cortical regions linked with normal and pathological aging (i.e., precuneus). These data suggest the possibility of predicting cognitive morbidity based on patterns of CNS atrophy. According to this view, given that closeness to the trajectories was affected by HIV and (separately) AIDS (Molsberry et al., 2015), it is not unreasonable to suppose that a brain region linked to HIV Disease is associated with the membership weights (however, see below). Further, as the risk of impairment in the three trajectories was expressed as a function age, it is also not unreasonable to suppose that the closeness to the Unhealthy trajectory is linked to those brain regions that are associated with aging and dementia (e.g., (Bailly et al., 2015; Jones et al., 2006; Karas et al., 2007).

There is consistent evidence among studies of brain structural integrity among individuals with HIV Disease that brain regional atrophy is linked to performance on neuropsychological tests (e.g., (Ances & Hammoud, 2014; Ances, Ortega, Vaida, Heaps, & Paul, 2012; Fennema-Notestine et al., 2013; Kallianpur et al., 2013; Lepore et al., 2008; Paul, Cohen, Navia, & Tashima, 2002; Ragin et al., 2012; Thompson et al., 2006; Thompson et al., 2005; Thurnher & Post, 2008; Towgood et al., 2012; Wang et al., 2009)) as well as HIV Disease (when a seronegative control group was present) and immunological and virological markers of disease status (when a control group was not available). Thus, even with access to cART, HIV is associated with measurable brain atrophy (Cardenas et al., 2009; Cohen & Gongvatana, 2011; Jernigan et al., 2011; Kuper et al., 2011; O'Connor, Jaillard, Renard, & Zeffiro, 2017; O'Connor, Zeffiro, & Zeffiro, 2017; Sanford et al., 2017).

The data presented here complement those findings by showing that regional brain volumes are related to temporal trajectories to cognitive dysfunction which themselves were related to a combination of factors including HIV Disease, AIDS, hepatitis-C infection, depression, race, and MACS recruitment cohort (Molsberry et al., 2015). The multi-factorial nature of the predictors, and the link between trajectory membership and brain structure reinforces the view that a range of comorbidities that occur in the context of risk for HIV infection must be

considered when interpreting analyses of brain structure and cognitive function (see reviews by (Ances & Hammoud, 2014; Masters & Ances, 2014; O'Connor, Jaillard, et al., 2017; O'Connor, Zeffiro, et al., 2017; Saylor et al., 2016).

The prevalence of mild cognitive disorders in the context of HIV Disease remains high, although the prevalence estimates vary widely. One explanation for the "residual" impairment may be a legacy effect or "burnt-out" brain (Manji, Jager, & Winston, 2013). Related to these alternatives is the possibility that enrollment cohort plays a critical role. Individuals who became infected more recently (i.e., many of the men in C2) had the opportunity to receive cART as the first line of therapy, likely had therapy initiated at an earlier point in the natural history of the infection and are less likely to have had clinical AIDS (cf., (Miller, Selnes, & McArthur, 1990)). Alternatively, there may be a low grade, chronic process that alters brain structure even when peripheral measures of viral load and immunocompetence are within acceptable limits; brain metabolic abnormalities in HIV+ patients support this conclusion (e.g., (Chang et al., 2003; Cohen et al., 2010; Cysique et al., 2013; Ernst, Jiang, Nakama, Buchthal, & Chang, 2010; Harezlak et al., 2011; Kallianpur et al., 2013; Valcour et al., 2013; Yiannoutsos et al., 2004)). There is also growing evidence that abnormal cellular inflammation may play a key role in determining CNS structural and functional competence, and ultimately cognitive functions (e.g., (Underwood et al., 2017).

A variety of factors can affect brain structure and cognition in the context of HIV disease. Early in the epidemic, we could reasonably assume that there was but a single trajectory, or pathway to cognitive impairment among individuals with HIV disease. In the current era, this assumption seems much less reasonable. With the variety of factors that can potentially alter brain health and cognition, it seems very likely that there are *multiple* trajectories to impairment and that these trajectories may be represented by different patterns of CNS damage. Here we took advantage of the data from the MACS to demonstrate that there is a biological basis to these previously described trajectories. We have demonstrated that these empirically derived pathways to cognitive impairment – that are related to both HIV- and non-HIV-related factors - are associated with measures of brain regional volume. Thus, these data add to the growing body of evidence that critical risk factors such as hypertension and diabetes not only affect brain structure in HIV-infected individuals (as they do in uninfected individuals), but may (along with other non-medical factors) interact with infection status to produce CNS abnormalities (e.g., (Lake et al., 2017; Spies, Ahmed-Leitao, Fennema-Notestine, Cherner, & Seedat, 2016; Thames et al., 2018; Thames et al., 2017; Underwood et al., 2017)).

A recent meta-analysis (O'Connor, Zeffiro, et al., 2017) identified consistencies in structural brain imaging data, as well as some important qualifiers. The standardized mean for total brain volume, gray matter volume, white matter volume, and for CSF volume were significantly related to HIV Disease. However, in spite of evidence from several structural and functional imaging studies of their sensitivity to the presence of virus, the volume of basal ganglia was not reliable in the meta-analysis. And, perhaps as a consequence of the earlier use of cART, publication year was associated with reductions in the impact of HIV Disease on brain structural (See their Figure 7). However, this meta-analysis was made more difficult by the fact that the estimates of between-study heterogeneity suggested that much of

the observed variance was between studies making many comparisons difficult or impossible.

While the analysis of brain structure such as this one have provided a great deal of information regarding the impact of HIV disease on the brain, “Changes in brain structure are lagging indicators of advancing [neurodegenerative] disease state.”((Rosen, Huang, & Stufflebeam, 2015), pg. 1628). *Functional* brain imaging, and particularly functional connectivity within brain regional networks likely provides information regarding pathological changes in the brain prior to measurable structural change or clinical expression. Thus, as the pathophysiological basis of the milder forms of cognitive dysfunction in HIV disease becomes the focus of new research, we likely need to expand our analysis methods to include sensitive measures of neural function (e.g., (Becker, Bajo, et al., 2012; Becker, Cuesta, et al., 2012; Wilson et al., 2013; Wilson et al., 2015)).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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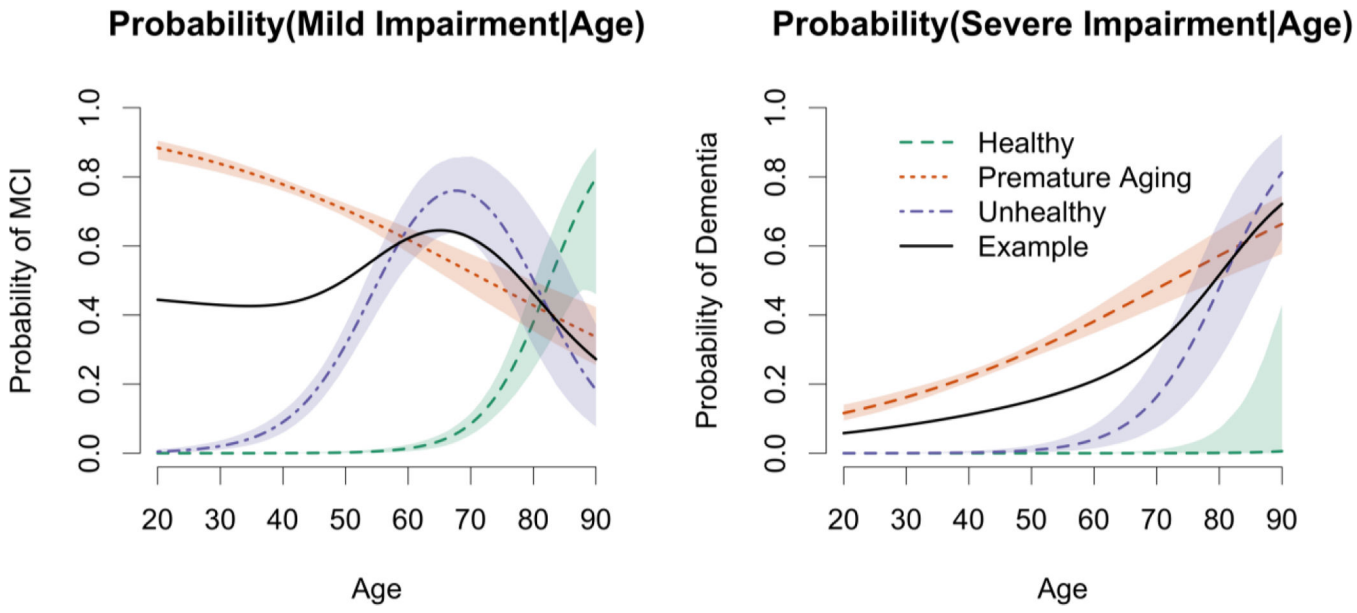

Figure 1:

The example trajectory (black line) from a single individual is a weighted mixture of the three extreme profiles (2% Healthy, 50% Premature Aging, 48% Unhealthy) developed by Molsberry and colleagues (Molsberry, et al., 2015) from 25,471 observations from 3892 MACS participants (an average of 6.54 observations per individual). The dashed lines represent the three canonical profiles with pointwise posterior 95% credible bands for each cognitive classification. The x-axis represents assembled cross-sectional probabilities of the three states (normal, mildly, and severely impaired) across time/age. At any given age, the sum of the three probabilities is equal to 1.00. The y-axis represents the age of the men in the cohort at the time of the examination.

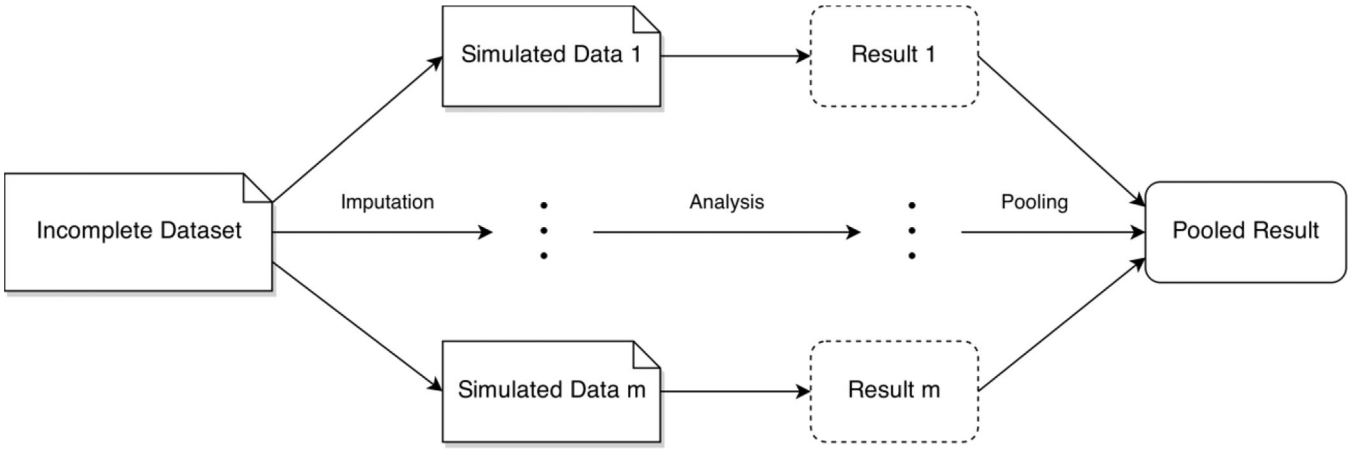

Figure 2:
Overview of Multiple Imputation procedure.

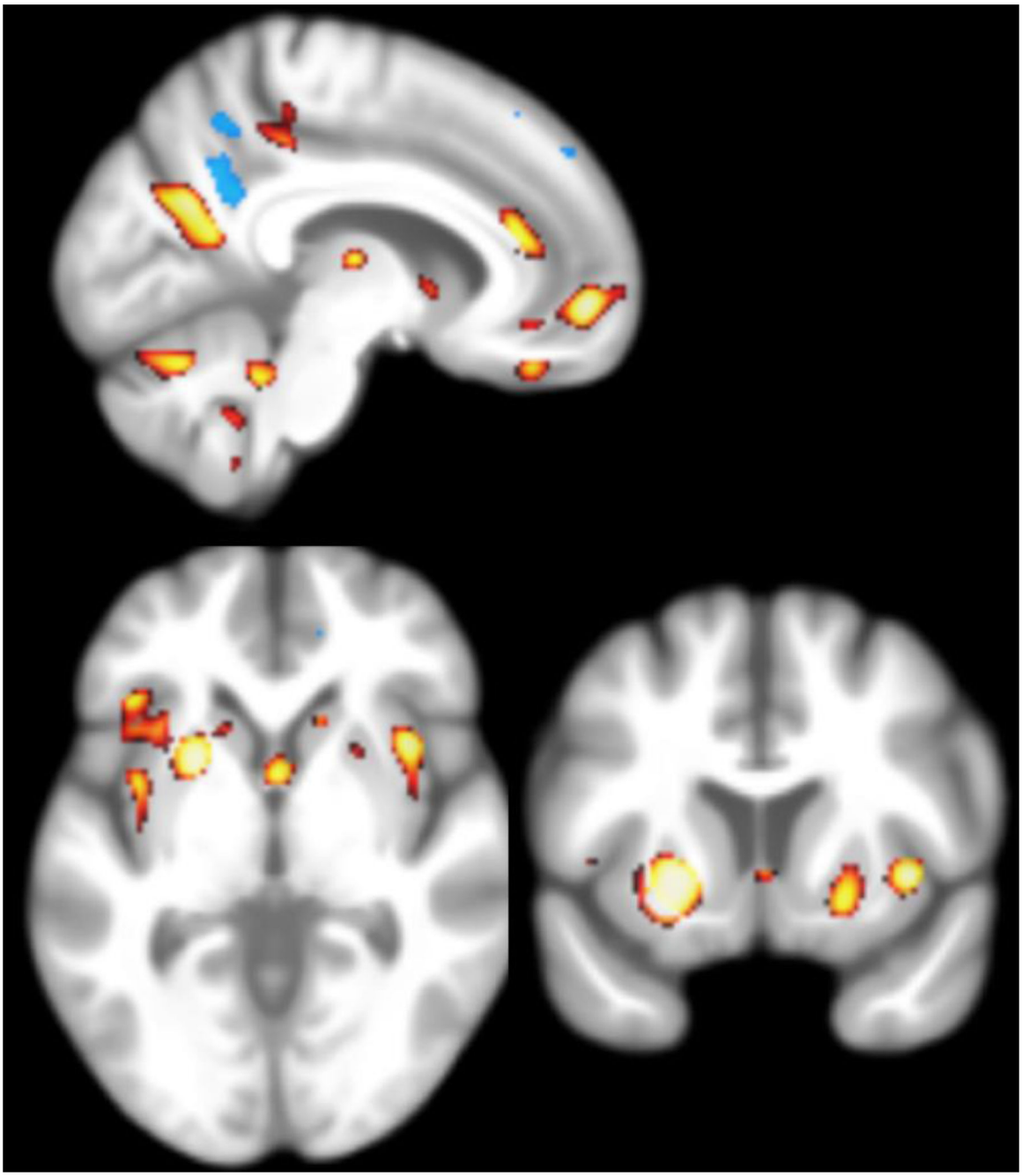

Figure 3:
For the “premature aging” profile closeness, the blue-highlighted regions are *p*-values smaller than 0.01. For the “unhealthy” profile closeness, the yellow/red-highlighted regions are *p*-values smaller than 0.005.

Table 1:

Characteristics of Participants as a Function of MMTM Classification

	Closest to		
	Healthy Profile	**Unhealthy Profile**	**Premature Aging Profile**
N=	231 (76.5)	57 (18.9)	14 (4.6)
Age	57.1 (6.1)	56.0 (5.7)	57.4 (7.8)
Race (Caucasian)	173 (74.9)	35 (61.4)	9 (64.3)
HIV Infected	124 (54.6)	35 (64.3)	9 (64.3)
AIDS[1]	16 (12.9)	7 (20.0)	1 (11.1)
Depressed ever	173 (74.9)	43 (74.4)	10 (71.4)
Hepatitis C Infection	20 (8.7)	18 (32.6)	2 (14.3)

Mean (+ s.d.) for continuous data. Number and percent for categorical data;

[1] expressed as a percent of infected men

Table 2:

Characteristics of Study Sample at the Time of MRI Scan[1]

	Seronegative			Seropositive			Effect Size[2]	
Trajectory	**Normal**	**Premature Aging**	**Abnormal**	**Normal**	**Premature Aging**	**Abnormal**	**Serostatus**	**Trajectory**
Number	103	22	5	124	35	9		
Age[3] (mean, S.D., Range)	59.3 (7.1) (50.3–78.5)	58.9 (5.8) (51.1–76.1)	53.6 (3.0) (51.6–64.5)	56.2 (4.5) (48.3–76.5)	56.0 (5.2) (50.2–76.4)	56.9 (5.8) (52.4–67.0)	.002	.007
Education	16.8 (2.5)	16.9 (2.4)	16.7 (2.3)	15.7 (2.3)	16.5 (4.0)	15.6 (1.7)	.007	.006
Cohort (%(n) Cohort 3)	13.6	27.3	0.0	29.0	48.6	7.0	.16*	.21*
Race (%(n) Caucasian)	87.4	81.8	100	75.0	54.3	66.7	.15*	.20*
Diabetes	9.7	31.8	0.0	14.5	20.0	0.0	.16*	.03
Hypertension	45.6	50.0	60.0	41.9	42.9	55.6	.06	.04
Depressed	14.7	15.0	0.0	24.1	24.2	0.0	.10	.11
Cocaine	9.7	13.6	20.0	25.8	37.1	44.4	.12	.22*
Amphetamines	4.9	0.0	0.0	14.5	14.3	0.0	.07	.17*
AIDS	n/a	n/a	n/a	12.9	20.0	11.1	.10	.11
Detectable Virus	n/a	n/a	n/a	16.4	30.4	37.5	n/a	.09
Current CD4+	n/a	n/a	n/a	691.1 (297)	764.1 (477)	973.1 (420)	n/a	.03*
Nadir CD4+	n/a	n/a	n/a	277.5 (156)	264.1 (188)	294.2 (255)	n/a	.002
Current Viral Load	n/a	n/a	n/a	1.60 (.84)	1.83 (1.1)	2.11 (1.3)	n/a	.03
Peak Viral Load	n/a	n/a	n/a	4.78 (.601)	4.80 (.73)	5.13 (.56)	n/a	.02
CO WAT[3]	55.1 (1.4)	45.7 (3.5)	50.3 (6.7)	53.4 (1.2)	45.0 (2.3)	46.9 (4.4)	.002	.073*
Rey Osterreith Figure-Copy	33.5 (.88)	30.8 (2.3)	29.0 (4.3)	29.8 (.78)	26.9 (1.5)	30.4 (2.8)	.005	.019
Immediate Recall	25.5 (.94)	15.1 (2.4)	17.0 (4.6)	21.6 (.83)	14.4 (1.6)	17.1 (3.0)	.002	.144*
Delayed Recall	25.2 (.94)	14.3 (2.4)	18.2 (4.6)	21.3 (.83)	14.6 (1.6)	16.1 (3.0)	.004	.144*
Stroop Test-Interference	95.8 (4.7)	123.5 (12)	147.3 (23)	94.0 (4.1)	119.2 (7.8)	110.7 (15)	.009	.072*
Grooved Pegboard-Dominant[3]	55.0 (1.8)	42.0 (4.7)	52.7 (9.0)	51.4 (1.6)	39.3 (3.1)	45.1 (5.9)	.006	.076*
Non-Dominant[3]	54.3 (1.8)	43.7 (4.6)	49.3 (8.8)	49.8 (1.6)	40.3 (3.0)	49. (5.8)	.002	.052*
Trailmaking A[3]	64.8 (2.2)	53.9 (5.6)	59.3 (11)	58.3 (1.9)	55.8 (3.6)	58.0 (7.0)	.001	.017*
Trailmaking B[3]	70.8 (2.2)	55.3 (5.6)	58.3 (11)	59.6 (1.9)	54.8 (3.6)	54.0 (7.0)	.006	.042*

1) Continuous (mean + s.d.) and discrete (percent) variables.

[2] Eta_p^2 (for continuous data) or *Phi* (for categorical data)

[3] Mean (± s.d.) and range

* p<.05