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Journal
AIDS, 35(6)

ISSN
0269-9370

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Publication Date
2021-05-01

DOI
10.1097/qad.0000000000002827

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

AIDS. 2021 May 01; 35(6): 889–898. doi:10.1097/QAD.0000000000002827.

Longitudinal 5-year prediction of cognitive impairment among men with HIV disease

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Abstract

Background: Although combination antiretroviral therapy reduced the prevalence of HIV-associated dementia, milder syndromes persist. Our goals were to (1) predict cognitive impairment of the Multicenter AIDS Cohort Study (MACS) participants 5 years ahead and (2) from a large pool of factors, select the ones that mostly contributed to our predictions.

Design: Longitudinal, natural and treated history of HIV infection among men who have sex with men.

Methods: The MACS is a longitudinal study of the natural and treated history of HIV disease in men who have sex with men; the neuropsychological substudy aims to characterize cognitive disorders in men with HIV disease.

Results: We modelled on an annual basis the risk of cognitive impairment five years in the future. We were able to predict cognitive impairment at individual-level with high precision and

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overperform default methods. We found that while a diagnosis of AIDS is a critical risk factor, HIV infection *per se* does not necessarily convey additional risk. Other infectious processes, most notably hepatitis B and C, are independently associated with increased risk of impairment. The relative importance of an AIDS diagnosis diminished across calendar time.

Conclusions: Our prediction models are a powerful tool to help clinicians address dementia in early stages for MACS paticipants. The strongest predictors of future cognitive impairment included the presence of clinical AIDS and Hepatitis B or C infection. The fact that the pattern of predictive power differs by calendar year suggests a clinically critical change to the face of the epidemic.

Keywords

HIV; Risk Prediction; LASSO; Cognition

Introduction

The central nervous system (CNS) is a target of HIV; meningitis can follow acute infection [1, 2] and if viral replication remains unchecked, dementia could be an outcome with death following within six months [3, 4]. With the advent of combination antiretroviral therapy (cART), the incidence of dementia has fallen [5], white matter pallor [1, 6] has virtually disappeared, and the prevalence of HIV associated dementia has declined [7]. While cART has slowed the progression of the disease [8] and extended the life expectancy of individuals with HIV infection (e.g., [7, 9]), the long-term effects of this *chronic* condition on the brain and cognition are still not well understood. The prevalence of cognitive dysfunction in HIV disease remains high. Within the Multicenter AIDS Cohort Study (MACS), we found that the frequency of Asymptomatic Neuropsychological Impairment (ANI) increased to 19% in 2011–2012 from 12% in 2007–2008 although there was no increase in the rate of Mild Neuropsychological Disorder (MND) or dementia. Our primary goal is to predict individual risk of cognitive impairment 5 years in the future for MACS participants.

There are a variety of mechanisms that might explain the continued presence of cognitive impairment among infected individuals, and even some of the anti-retroviral therapies may be neurotoxic [10–13]. This leads to the question of what factors are associated with the *development* of cognitive dysfunction among individuals with HIV infection.

In order to address that question, our study had two parts. In the first, we needed to create a model that could accurately predict cognitive impairment for an individual participant five years in the future. Thus, unlike typical neuroepidemiological studies, we are examining subject-level and not group-level outcomes. Our second step was to identify those factors that were important to predicting impairment in each of the cognitive domains, and to provide a “weight” of importance to each of these variables. We did not set out to investigate any and all potential risk factors; we selected those that have been historically important in order to facilitate the development of the model and to measure predictor variable importance. Thus, we have created such empirical prediction models, and have identified specific conditions or biomarkers that indicate that there is an increased (or decreased) risk of cognitive impairment over the next five years at the individual level. Note that this is a

screening process: among a vast pool of risk factors, we are able to select a group of them that is associated with cognitive impairment 5 years in the future. The selected factors are worth being individually investigated in future studies in order to draw strong conclusions.

Methods

Participants

The MACS enrolled a total of 6972 men, irrespective of serostatus, from sites in Baltimore, Washington, Chicago, Los Angeles and Pittsburgh at three separate time points: 4954 men enrolled in 1984–1985 (C1), 668 men enrolled in 1987–1991 (C2) and 1350 men enrolled in 2001–2003 (C3) [14–16]. They return every 6 months for an interview, physical examination and collection of blood for laboratory testing. The interview covers physical health, medical treatments, and sexual and substance use disorders.

Due to the high cost of administering NP examinations, only subsamples of C1 from Baltimore, Chicago, and Pittsburgh were recruited in 1987; all of the men at the Los Angeles site were enrolled. Volunteers were enrolled regardless of their serostatus or symptom status until the target number for that center was reached. All of the participants who became infected with HIV during the course of the study were invited to join the NP study. Recruitment of C2 into the NP substudy followed much the same pattern. Beginning in 2012, all active men in the study were given neuropsychological assessments as well as a measure of activities of daily living [16]. Men over the age of 65 returned for retesting on an annual basis; younger men were tested biannually.

Data description

The data utilized in our analyses can be broadly categorized as baseline (non-longitudinal) and time-varying (longitudinal). At the initial visit a questionnaire was completed which included information regarding: date of birth, education (in years), age at completion of education, native language, race/ethnicity, individual and family medical history, and MACS center. At subsequent visits additional data were collected and these are considered time-varying variables, including emotional well-being, drug use, health condition, comorbidities, medication adherence, and blood-based laboratory measures. Participants completed neuropsychological tests assessing six cognitive domains (see, [15]) as described below.

For the purpose of this analysis we combined C1 and C2 into a single group (C1C2) (n=2850). The men enrolled after 2001 are denoted as C3 (n=1202) were not included in this analysis due to the short duration of follow-up (i.e., <5 years). Moreover, after addressing the missing data and constructing the moving-window datasets (see below), we were left with 804 men in our final sample. The characteristics of the included men are shown in Table 1. Supplemental Table 1 shows the number of observations, number of impaired, and number of seropositive participants in our sample by year. We denoted by “used” the points that were kept in the sample and “dropped” the volunteers that were removed. The total number of visits of “used” participants is in general more than the double of the total number of visits of “dropped” participants. Supplemental Figure 1 compares the two populations with respect to categorical variables and continuous variables, respectively. They

show that participants excluded from our analysis had similar characteristics to those who were included.

Neuropsychological Test Battery: The MACS neuropsychological evaluation includes tests from six cognitive domains: Executive Functioning, Speed of Information Processing, Attention and Working Memory, Learning, Memory and Motor Speed/Coordination [15, 16]. Data from HIV seronegative participants were used to create statistical models to derive T-scores for each participant that were adjusted for age, years of education, ethnicity (white or nonwhite) and number of times the test had been administered. For each cognitive domain, a summary T-score was calculated by averaging all-available T-scores for that domain or, in the case of the Motor domain, using the lowest Grooved Pegboard score. Individuals who completed tests in at least four of the six domains were classified as cognitively normal, mildly impaired or severely impaired. Briefly, an individual was classified as Normal if one or fewer domain T-scores were below 40; Mildly Impaired if two or more domain T-scores were below 40 and the criteria for Severely Impaired were not fulfilled; and Severely Impaired if two or more domain T-scores were below 30 or one domain score less than 25 and another domain less than 40 [15]. These classifications were made for each neuropsychological test visit for each participant. Out of the 4406 participants, 714 (16%) were categorized as severely impaired at least once. Because of the low proportion of severely impaired, we merged the mild and severely impaired categories into one - “impaired”.

Missing data: There were three types of missing data. One was a missed visit - when the participant skips or delays a visit to the center altogether. The second and third types occurred when some variables were not measured; one case is when a *predictor* variable is not recorded, and the other case is when the patient skips the neuropsychological visit and the *outcome* variable is missing. We used different approaches to deal with each type of missing data.

In order to minimize the impact of a missed visit, we optimized the available visits when constructing the dataset for modeling by using a moving window approach. In terms of the missing predictor variables, we recategorized many of these data in order to obtain a lower proportion of missing values: variables that consisted of recent information, such as recent drug us, were transformed in historical use. A missed NP measurement leads to a more complex problem because if outcome variables are missing, there is no imputation or recategorization that can address this issue. The proportion of missing outcomes ranges from 25% up to more than 75%, depending on the year. We will not include in our analysis predictions for the years 2006.5, 2008.5, 2010.5, and 2011 due to the number of available participants with measured NP variables being less than 100 or high proportion of missing when compared to the total sample size. For the other years, we worked under a Missing At Random assumption - having a missing outcome is independent of the true value of that outcome itself (conditionally, within levels of the available predictors). In other words, we assume that two participants with the same predictor values have the same chance of having a missing response. Under this assumption, regression models can be fit using complete cases only. However, test error estimation, as well as model selection and performance

evaluation, are not as straightforward and working only with complete cases results in biased estimators. A consistent and efficient estimator of the prediction error in this setting is given by the doubly robust estimator [17–19]. With such high proportion of missing outcomes, the doubly robust estimator is vital to an accurate assessment of our model's performance. More details on the Missing At Random assumption and the doubly robust estimator can be found on the Supplemental Material.

Prediction Modeling

The analysis plan was motivated by that described by Adhikari and colleagues [20] who developed a multinomial fused LASSO procedure using data from the Cardiovascular Health Study. In that analysis, they studied prediction of cognitive impairment over a 10-year follow-up interval, since the clinical expressions of age-related neurodegenerative conditions tend to develop (relatively) slowly. By contrast, for HIV, historical information [4, 21, 22] suggests cognitive impairment likely develops over a shorter time interval, hence the 5-year time window. In the present study, we did not add a penalty to stabilize the regression coefficients over time with the fused LASSO; we used regular LASSO over the moving windows. *For a fixed moving window, we fitted separate regression models with LASSO penalty for each cognitive domain, which were combined by the neuropsychological criteria into a prediction of cognitive impairment.* Recall that predicting T-scores and later combining them into a cognitive impairment prediction gives our approach the flexibility to apply different criteria. Because of the presence of missing outcome measurements (see above), we used a doubly robust estimator to correctly estimate prediction error both for model selection and model evaluation.

Moving window and predictive modeling: The predictive models were fitted for 6-month time windows from 1988 to 2015; predictors ranged from 1988 to 2010 and outcomes from 1993 to 2015. In an attempt to minimize missing visits and optimize the number of available visits for all participants, we constructed the datasets by fixing minus one-year intervals around the lower desired dates to look for covariates and plus one-year intervals around the upper desired dates to look for the response variable. For example, consider the construction of the dataset from 1992 to predict 1997. To get as many points as possible, we used visits that had the selected predictors anytime between 1991 and 1992 and T-scores between 1997 and 1998. For those men who had at least one visit between 1991 and 1992, we selected nonmissing values for the visit that was closest to 1992. With regard to the outcomes variables (i.e., T-scores) we followed the same logic but looked at all visits in 1997 and 1998, picking the available outcomes in the visit that happened closest to 1997. In order to select which visit to retain, we prioritized the completed visits and among those, we picked the closest to the desired date. This process was repeated for each year that a participant had 5-year follow-up data. The full algorithm for dataset construction is presented in the Supplemental Material.

We modelled each of the domain T-scores (i.e., continuous variables) separately and combined these predictions into a predicted cognitive category. For each time window, we modeled the T-scores using regression models with a LASSO penalty, choosing a tuning

parameter that minimized the corrected, doubly robust Mean Squared Error (MSE) via cross-validation.

It is known that a baseline predictor to future test performance is current test performance. To validate our method's predictive power, we will compare it against this prediction, which we refer to as the push-forward model. It uses as a prediction of cognitive capacity 5 years ahead the most recent cognitive measurement available. In the case our data has no useful information, we expect the two models to perform similarly, but if our model performs better than the push-forward model then we were able to improve on the baseline prediction aggregating information from other factors.

Predictors: All available predictors, nonlongitudinal and time varying, and their first order interactions with HIV serostatus were used. A list of them can be found in the Glossary in th Supplemental Materials. NP test performance, when the most recent NP testing was performed, and their interection was also included. To account for HIV infection, we included for seropositive participants their lowest CD4 cell count and highest Viral Load up to that time. Regarding HIV treatment, we included an binary predictor that indivates if that participant was under some type of HIV treatment. We did not include separate indicators for each type of drug because our models are calendar year based, which works as a proxy for ART era (see Figure 3, Supplemental Material).

Variable importance: Given the high number of predictors and interaction terms, we computed a variable importance (VI) measurement [20] to summarize and identify important factors associated with cognitive impartment. The VI measurements are based on the coefficient sign and magnitude over random subsampling and model refitting. We computed one positive, one negative, and one overall VI measure over all time windows. The positive and negative VI measures indicate positive and negative association between the predictor and cognitive capacity, while the overall VI is the maximum between the two and was used to order the predictors (see Supplemental Materials). The variables were ordered by overall importance, and the top 15 variables for each cognitive domain were presented for the analysis.

The VI measurements are computed over all years. To get a better sense of how the relationship between some predictors and the outcomes change over time, we used a resampling scheme to produce plots of variable importance per year per domain. We ran LASSO models for each year using 75% of the moving-window dataset 50 times, averaging the coefficients of each predictor over the 10 sub-samples and plotting them against time. Given the unstable nature of LASSO coefficients in the context of dependency among features, the average coefficients oscillate over time.

Results

We were able to predict cognitive impairment at individual level with higher accuracy than the baseline push-forward method. The predictive power of the model was compared to the push-forward model using the corrected estimation for MSE and classification error in Figure 1. The LASSO prediction error line (red) is always below the push-forward (blue)

line, indicating that our model performs better than the usual method for the 6 domains and cognitive category, i.e., ours had lower classification error. Our method's accuracy when predicting a man's cognitive impairment 5 years into the future ranges from around 75% to more than 90%, depending on the year. It is consistently greater than the push-forward method by approximately 15%.

In order to identify the most important predictor variables, we analyzed the 15 independent variables with the largest overall VI measure (See Figure 2). Hepatitis C had negative contributions across all domains; in particular, the interactions between HIV and Hepatitis C was consistently negatively correlated with cognitive capacity across most domains. Hepatits B had a similar behavior as Hepatitis C when present; if the participant had a resolved case of Hepatitis B, the importance was lower. For the men with HIV infection, ever having developed AIDS was also an important and negatively associated factor for the predictions of all domain T-scores (recall that a high cognitive domain score means less likely to be impaired). Being classified as "impaired" in the past was negatively associated with Learning 5 years ahead for the infected men only, which means that it increased the likelihood of future impairment. Among seropositives, the use of some type of HIV therapy is correlated with improved Memory domain 5 years in the future. A history of a learning disorder and history of loss of consciousness had a negative contribution in most domains. Physical limitation had a strong positive contribution to the Speed domain, which is likely working as a proxy for some unobserved predictor. Race, native language, and test center likely account for socioeconomic status and other characteristics.

Having identified the important variables, we will briefly discuss how some of these predictors contributions changed over time and how that is aligned with the epidemic. Given the large number of predictors and high oscilation of the coefficients given the nature of the data, we chose to present 3 predictors: 1) Hepatitis C, 2) having previously been diagnosed with AIDS, and 3) the interaction between HIV and age. In Figure 3 the average coefficient for Hepatitis C is generally negative, with greater absolute magnitude for Motor, Executive, and Speed domains. For all domains, the contribution of having previously been diagnosed with AIDS is negative (i.e., the presence of AIDS results in poorer performance). However, this coefficient increases over time until it approaches zero in ~c.y. 2000 (i.e., it no longer has an impact on performance). The interaction between HIV and age contributes negatively to Executeive and Working Memory domains for earlier years, quickly approaching 0; that is, having HIV intensifies the already negative relationship between age and Executive Domain only until 1996, when ART becomes available.

Discussion

The results of these analyses make several important points. First, it is possible to predict the risk of cognitive impairment among a large group of gay and bisexual men five years in the future across the lifespan of a study of the natural and treated history of HIV disease. Second, these data add to the growing body of evidence that while a diagnosis of AIDS is a critical risk factor for the development of cognitive dysfunction, simply being infected with HIV does not necessarily directly convey additional risk. Other infectious processes, most notably Hepatitis, independently increase the risk of cognitive impairment. Although

the presence of HIV infection was not marginally an important factor, its presence combined with other infections such as Hepatitis B and C intensified the negative association of these infections with the outcome. And, third, the relative importance of an AIDS diagnosis diminishes across calendar time.

One of the consistent findings from the MACS is that *symptomatic* HIV disease is the most important predictor of cognitive functions among infected men [16, 23]. This is still true in more recent longitudinal analyses and those involving other methods for classifying impairment [24, 25]. While the nadir CD4+ cell count is certainly an important factor, it is highly – but not perfectly – correlated with AIDS. In this analysis, nadir CD4+ cell counts did add information to the models, suggesting that there may be a unique contribution of the *clinical* event(s) of AIDS, and the response of the body to the severe illness.

For the present analyses we predicted only whether or not an individual was classified as being cognitively impaired, regardless of the severity of that impairment. Because the MACS did not begin routinely obtain activities of daily living data until 2012, we were unable to use the standard HAND classifications [26]. Thus, our focus here and elsewhere [24, 25] necessarily remains on the extent of cognitive dysfunction. It should also be emphasized that there are currently two generally used criteria for cognitive dysfunction in the context of HIV disease, the so-called Frascati [26] and Gisslen [27] criteria. Recently, there has been increasing interest in multivariate normative comparison (MNC) methods. Unlike the more standard “clinical” criteria MNC takes into account the inter-correlations among the cognitive domain scores (e.g., [25, 28]) and, more recently, longitudinal dependency across many visits for the same individual, as well as the correlated cognitive domain scores at any single visit (e.g., [29]). Here we chose to use the Frascati cut-offs for cognitive impairment because unlike the latter two, these generated the highest rate of impairment across the entire study sample, providing the basis for better prediction modeling. However, it must be emphasized that by using this method we have a high rate of impairment in the seronegative men (i.e., high false positive rate) which is also true for virtually all large cohorts such as the MACS. An advantage of our framework is that by first modeling the 6 domain T-scores and then obtaining a prediction of impairment by applying the criteria to the predicted T-score values, we can easily adapt our impairment prediction to different criteria. One interesting question for future analyses would be to compare and contrast different criteria for cognitive dysfunction with respect to predictive power, and use the solution to select which criteria would be best for that dataset. For that task, one might want to use more flexible and less interpretable models than the LASSO, such as a tree boosting algorithm [30].

Our analysis differs from that of other studies in that ours is based on calendar time (i.e., year of assessment) whereas others are usually based on the participant’s age. Due to the constant improvement of HIV treatments comparing participants based solely on age and ignoring calendar year is unreasonable. Given the importance of patient age, this characteristic was taken into account by being incorporated in the statistical model as a predictor. Even though age did not result on high VI measurements for most domains, it consistently presented negative coefficients, indicating it is a factor associated with higher

risk of cognitive that is probably associated with other predictors that present a stronger association with the response variables.

From a technical perspective, we used novel methodologies to address issues that arouse from using the very rich but complex MACS dataset. While some participants stay in the study for a long time and attend all scheduled visits, some drop out, skip visits or skip an NP visit. This leads to a high proportion of missing outcome values, the main difficulty we faced when predicting cognitive impairment. The use of a doubly robust estimator for prediction error is crucial and should be used whenever one desires to evaluate predictive ability and has to deal with missing responses (i.e., the cognitive outcomes). The model developed here produced more accurate predictions than the usual push-forward model, either for T-scores directly or combining these into cognitive categories. Also, our model allows for the computation of a VI measure, which indicates that HIV interacts with hepatitis and other comorbidities. Clinically, the combination of HBV and HIV could be correlated with cognitive impairment. The plots for coefficient values over time indicates that AIDS contributed negatively with predictions but became less important as time went by. This project was able to identify, from a large pool of factors, some that presented a potential interaction with HIV when predicting cognitive capacity.

Predicting the possible decline in cognitive functions has both research and clinical importance. Having identified that factors such as AIDS and Hepatitis co-infection (for example) are critical risk predictors, this should direct investigators to pursue analyses that would lead to an understanding of how these factors may have affected the structure and function of the CNS. Clinically, these data reinforce the idea that non-HIV-related factors need to be addressed as aggressively in their HIV-infected participants as they would be in non-infected individuals.

Neuroepidemiological research, and novel risk prediction modelling such as was done provides critical descriptive information to stimulate and guide additional research. We could not test every possible risk modifier: some were measured only infrequently and some had a high rate of missingness, for example. The findings that HCV and HBV (and interactions with HIV) were important predictors raises questions about the type of therapy used, comorbid alcohol and drug use, and perhaps even hepatic function. These are important questions, and worthy of extensive follow-up; but they were beyond the more limited goals of our study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Preparation of this manuscript was supported in part by funds from the National Institute on Aging to J.T.B. [AG034852]. EK was supported, in part, by funds from the National Science Foundation Division of Mathematical Sciences [Grant 1810979].

The data in this manuscript were collected with the support of the National Institutes of Health by the Multicenter AIDS Cohort Study [MACS) with centers at Baltimore [U01-AI35042]: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (PI), Todd Brown (PI), Jay Bream, Adrian Dobs, Michelle

Estrella, W. David Hardy, Lisette Johnson-Hill, Sean Leng, Anne Monroe, Cynthia Munro, Michael W. Plankey, Wendy Post, Ned Sacktor, Jennifer Schrack, Chloe Thio; Chicago [U01-AI35039]: Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: Steven M. Wolinsky (PI), Sheila Badri, Dana Gabuzda, Frank J. Palella, Jr., Sudhir Penugonda, John P. Phair, Susheel Reddy, Matthew Stephens, Linda Teplin; Los Angeles [U01-AI35040]: University of California, UCLA Schools of Public Health and Medicine: Roger Detels (PI), Otoniel Martínez-Maza (PI), Otto Yang (Co-PI), Peter Anton, Robert Bolan, Elizabeth Breen, Anthony Butch, Shehnaz Hussain, Beth Jamieson, John Oishi, Harry Vinters, Dorothy Wiley, Mallory Witt, Stephen Young, Zuo Feng Zhang; Pittsburgh [U01-AI35041]: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (PI), Lawrence A. Kingsley (PI), Jeremy J. Martinson (PI), James T. Becker, Phalguni Gupta, Kenneth Ho, Susan Koletar, John W. Mellors, Anthony J. Silvestre, Ronald D. Stall; Data Coordinating Center [UM1-AI35043]: The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (PI), Gypsyamber D'Souza (PI), Alison Abraham, Keri Althoff, Michael Collaco, Priya Duggal, Sabina Haberlen, Eithne Keelaghan, Heather McKay, Alvaro Muñoz, Derek Ng, Anne Rostich, Eric C. Seaberg, Sol Su, Pamela Surkan, Nicholas Wada. Institute of Allergy and Infectious Diseases: Robin E. Huebner; National Cancer Institute: Geraldina Dominguez. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR001079 (JHU ICTR) from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH), Johns Hopkins ICTR, or NCATS. The MACS website is located at http://aidscohortstudy.org/.

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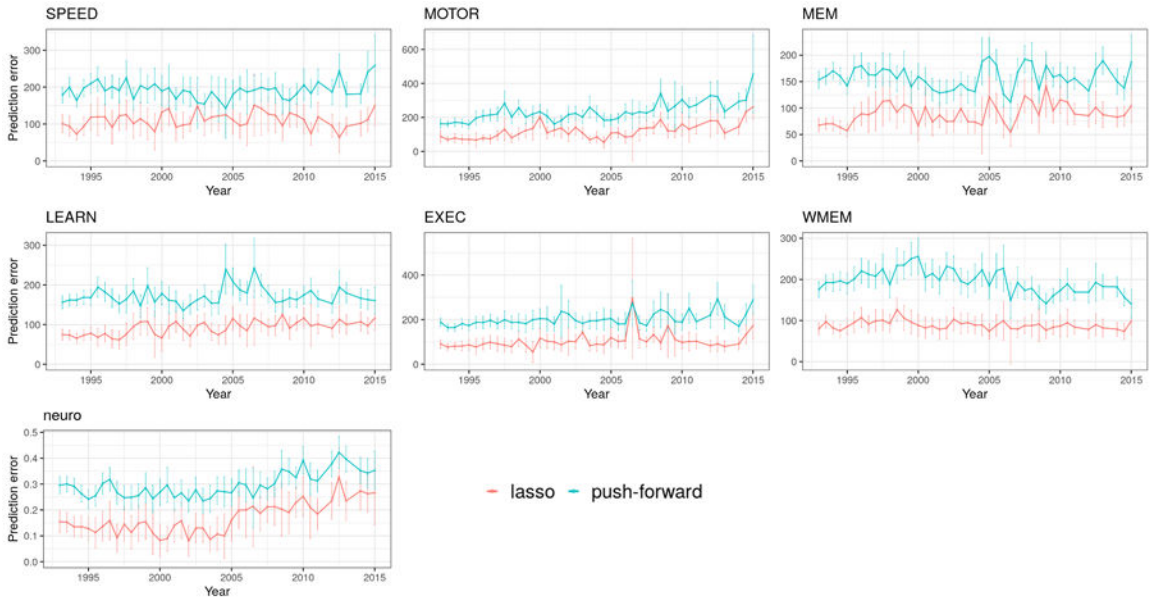

Figure 1:

Estimated prediction error (MSE or classification error) for our model (red) and push-forward model (blue) for each domain and each moving window using the doubly robust estimator. Note how the error for our model is consistently lower than the error of the push-forward model, indicating the great performance improvement we are able to obtain.

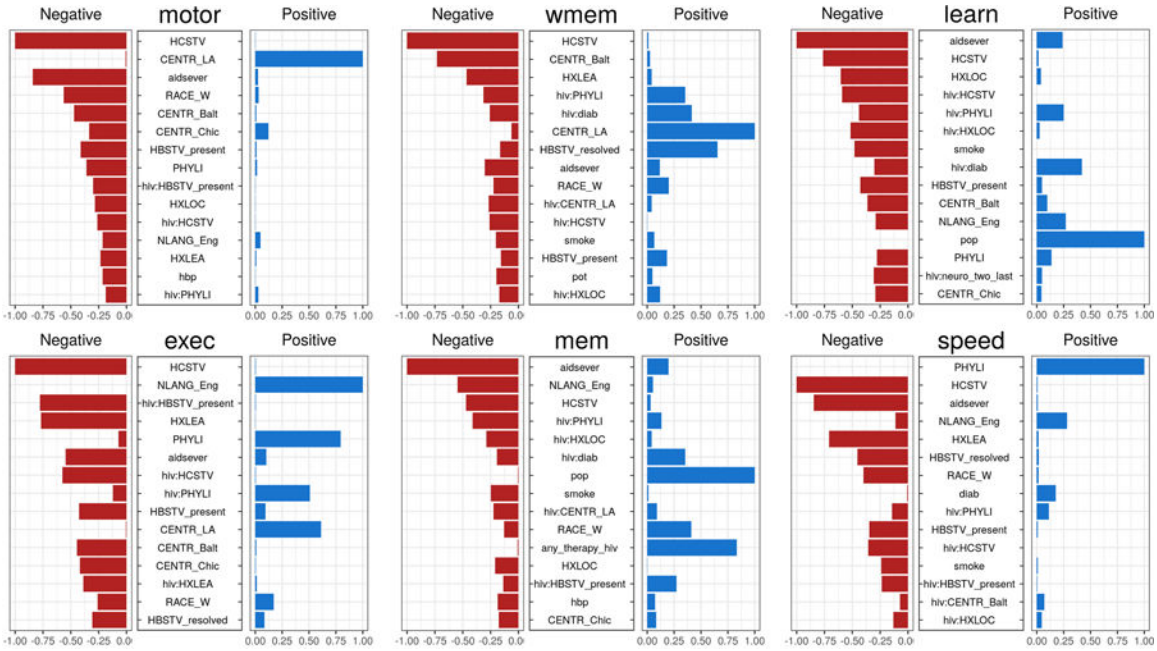

Figure 2:

For each domain, we present the highest 15 variable importance measures. Variables are ordered with respect to the Overall VI, and we present the Negative VI on the left (red, ranging from −1 to 0) and Positive VI on the right (blue, ranging from 0 to 1). The y axis shows the variable name, and the x axis is the VI measure. The larger the magnitude of the VI, the more important that predictor. Degree of importance is comparable within a domain, working as a quantitative sorting criteria.

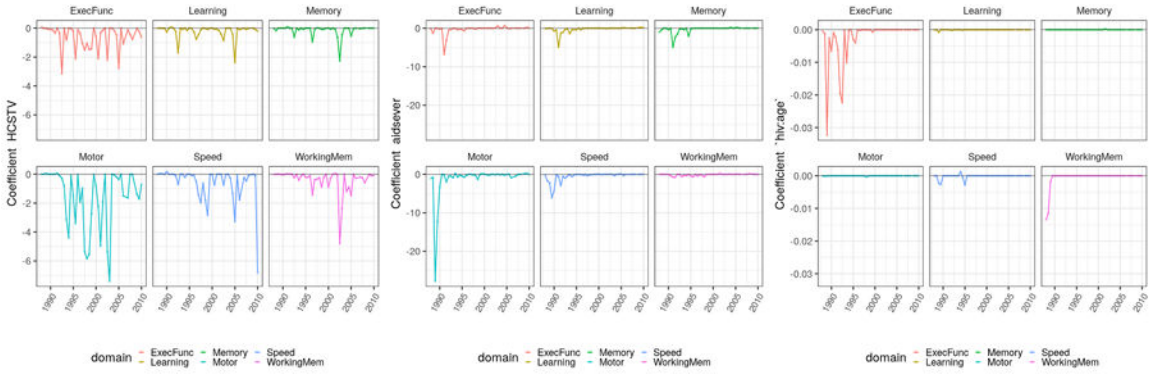

Figure 3:

Yearly averaged coefficients of LASSO models over 50 replications with 75% of the data each, divided per domain; y-axis presents the averaged coefficient and x-axis is calendar year. These work similarly as variable importance, but measured separate over each year, giving some insights on how each predictor's importance changes over time. Coefficients are presented for variables Hepatitis C, having ever beem diagnosed with AIDS, and interaction between HIV and age.

Table 1:

Characteristics of participants included in the analysis, divided by infection status.

Variable	C1C2		
	Infected	Uninfected	Percent Missing
Number	402	396	1
Age	36.8	41.59	1
Education	15.81	16.51	1
Race (% Caucasian)	86	93	1
Language (% English)	98	98	1
Loss of Consciousness (% Yes)	13	14	1
Hypertension (% Yes)	53	59	1
Diabetes (% Yes)	13	11	12
Learning T-score	51.67	50.73	1
Impaired Cognition (% Yes)	18	21	1
Hepatitis B - present (% Yes)	6	2	4
Hepatitis B - resolved (% Yes)	72	53	4
Hepatitis C (% Yes)	5	1	1
CD4+ Cell Count	476.07	657.6	3
Highest Viral Load	4.15	n/a	11
AIDS (% Yes)	2	n/a	3

All the participants considered in this table had regular visits for at least 5 years. The variables used for the table were measured in different times for different subjects; for each participant, we present values from their first visit with complete information.