Sleep-Based Brain Age Is Increased In Adults with Treated HIV

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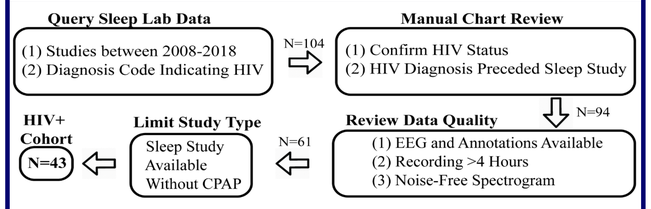
Background: Brain Age

Diagnostic biomarkers for brain aging are lacking. Our lab previously developed a machine learning model that predicts an estimate of chronological age (CA) from sleep EEG. This estimate is called brain age (BA). The difference between BA and CA is the brain age index (BAI). **BAI may serve as a brain health biomarker. Previously we found that BAI independently predicts mortality, and is increased by cardiovascular comorbidities and dementia.**

Background: HIV and Brain Age

People with HIV are living longer, fuller lives thanks to modern antiretroviral therapy (ART). However, adults with HIV have increased risk of age-related diseases such as neurocognitive impairment. Co-morbidities, side effects of ART, and inflammation may promote risk of excess brain aging in this population.
Sleep EEG-Based BAI may serve as a biomarker of brain aging among adults with HIV. **In this study, we assessed brain age index (BAI) in HIV+ adults compared to matched HIV- controls.**

Methods



Sleep EEGs from 43 subjects with HIV on ART (HIV+) and 3,155 controls (HIV-) were gathered, along with covariates.

We used doubly robust estimation, a method in the causal inference literature, to estimate the effect of HIV infection on BAI, and on individual EEG features.

We then performed mediation analysis to determine the effect contributed by the following comorbidities:

Framingham Risk Score (FRS), hyperlipidemia, obesity, insomnia, obstructive sleep apnea, heart valve disorders, hypertension, gastroesophageal reflux disease, pneumonia, mood disorder, anxiety, and fatigue

We computed the following decomposition of the Total Effect of HIV on BAI:

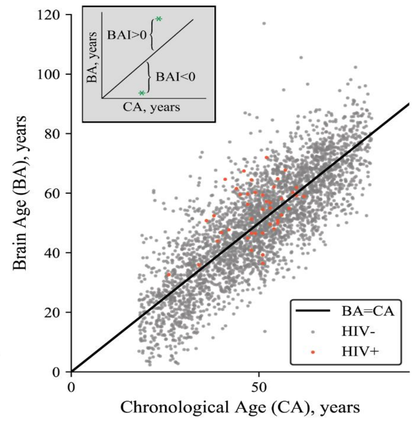
$$TE = CDE + CIE + IntMed$$

TE: Total Effect
CDE: Controlled Direct Effect
CIE: Controlled Indirect Effect
IntMed: Mediated Interaction

Results: Cohort and Brain Age Index (BAI)

	HIV+	HIV-	p-value
Number of Subjects	43	3155	
Male (n, %)	34 (79%)	1594 (51%)	< 0.01
Age (median, IQR)	49 [46, 54]	50 [38, 62]	0.765
White (n, %)	30 (70%)	2481 (79%)	0.16
Matched conditions (n, %)			
Tobacco use disorder	20 (46%)	686 (21%)	< 0.01
Alcoholism	16 (37%)	267 (8%)	< 0.01
AIDS History	19 (44%)		

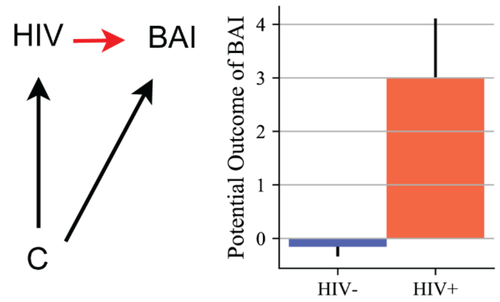
HIV+ subjects differed by gender, age, race, tobacco use, and alcohol use compared to HIV- controls, and had elevated BAI (4.4 years versus -0.18 years, $p < 0.05$).

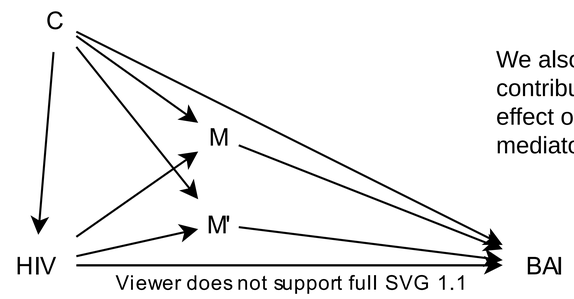


Results: Effect of HIV and Mediators on BAI

We used doubly robust estimation to adjust for potential confounders (age, sex, race, tobacco use disorder, alcoholism), in order to estimate the effect of HIV on BAI.

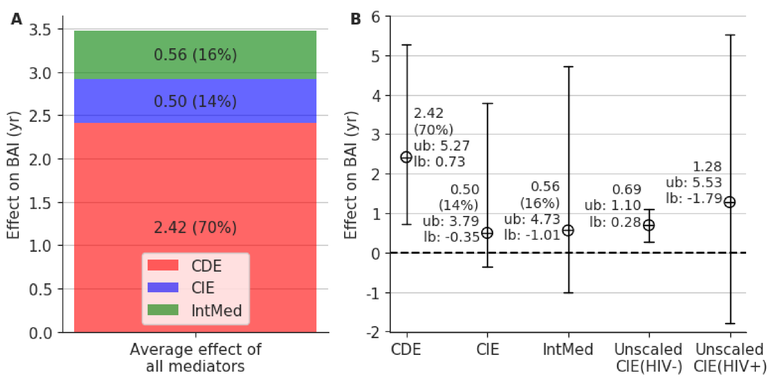
For each subject, the model predicts their BAI had they been diagnosed with HIV or not. We compared the group averages of these potential outcomes. **This difference in average BAI was 3.17 years ($p = 0.02$, CI = [0.40, 5.51]) .**





We also performed mediation analysis to estimate the contributions of mediation and interaction to the total effect of HIV on BAI. Our causal diagram with two mediators are shown as an example.

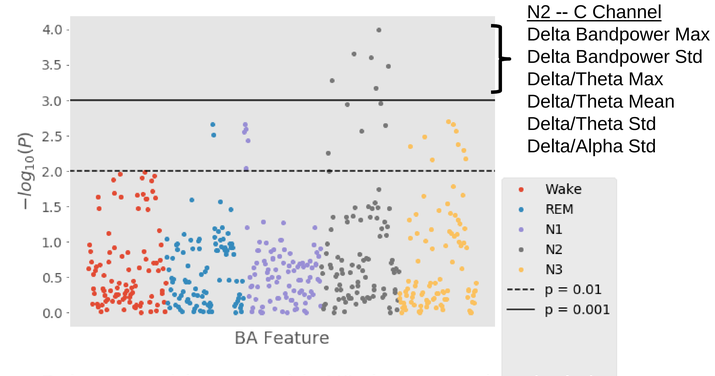
Due to limited sample size, we averaged effects across the twelve mediators to improve precision.



We found that mediation and interaction (CIE + IntMed) accounted for 30% of the total effect on average. The average controlled direct effect was 2.42 and significant.

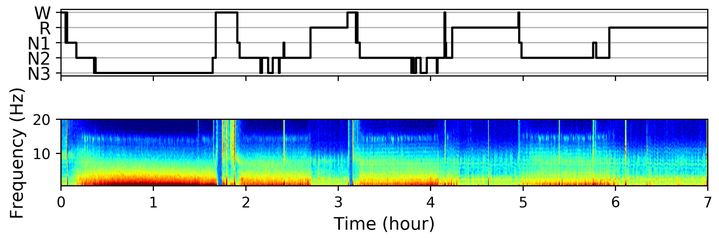
Results: BA Features

Comparison of BA features between cohorts

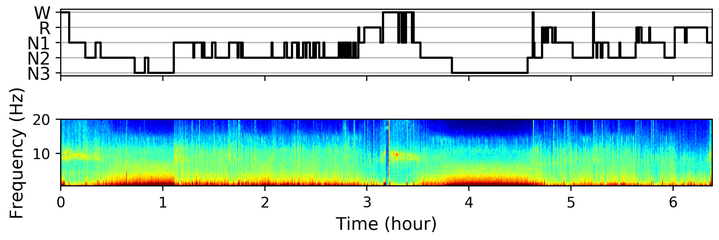


Delta power (slow waves) in N2 sleep are reduced relative to alpha and theta in HIV+ subjects

Example Spectrogram for HIV+ subject



Example Spectrogram for HIV- control subject



Conclusion

Our retrospective analysis provides new evidence that people with HIV experience accentuated aging, and that this process is reflected in the EEG of sleep. In particular, the reduction in slow waves during non-REM sleep that we observed in HIV is implicated in cognitive decline and dementia risk. We also found that multiple mediators account for increased brain age in HIV. An interventional study may be warranted to test whether treating these mediators would mitigate brain aging in HIV.

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