

Supplementary Online Content

Sanford R, Fellows LK, Ances BM, Collins DL. Association of brain structure changes and cognitive function with combination antiretroviral therapy in HIV-positive individuals. *JAMA Neurol*. Published online November 13, 2017.
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eAppendix. Methods

eFigure 1. White Matter Tissue Reductions in HIV-Positive Patients Compared With Controls Revealed With Voxel-Based Morphometry

eFigure 2. Minimum Detectable Difference Between Groups in Brain Volume Changes Over Time

eFigure 3. Minimum Detectable Difference Between Groups in Cortical Thickness Changes Over Time

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

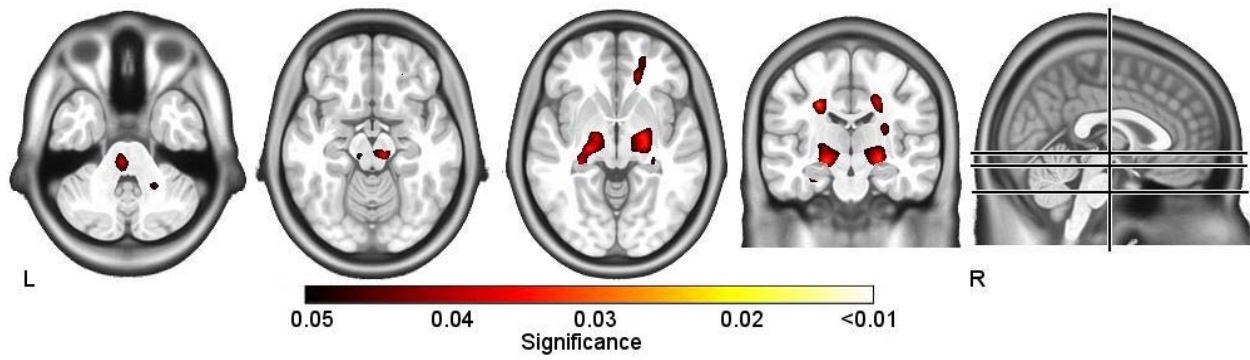
Statistical analysis

We used multivariable mixed-effects modeling to compare raw neuropsychological test scores and brain volume estimates between the HIV+ and HIV- groups, and to determine if HIV serostatus significantly influences changes in these measures over the study period. Mixed-effects models have become a powerful statistical technique for longitudinal data analysis because they can account for intra-subject correlations, missing data, and biases due to attrition¹. Any mixed effects model requires a combination of fixed and random effects. The fixed effects structure can provide estimates for overall group responses (i.e. group comparisons) and response changes over time. The interaction between these fixed effects can be used to compare the response changes over time by group. The random effects structure models subject-specific responses to account for within-subject correlations and minimizes biases in estimation due to attrition.

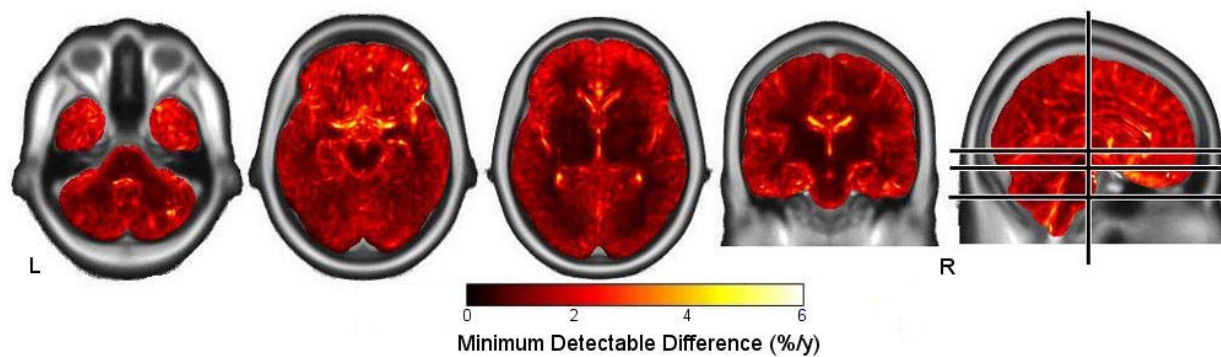
The mixed-effects models included all available data from both visits. To assess neuropsychological performance and regional brain volumes in the mixed-effects model, these measures were considered as the dependent variable in the models. The fixed effects structure included HIV serostatus, time (years from baseline visit), average age (mean age of at baseline and follow-up), sex, and the interaction between HIV serostatus and time. Within the HIV+ and HIV- groups, separate mixed-effects models assessed the change in neuropsychological performance or brain volumes between visits by including time, age and sex as a fixed effects to determine if greater-than-age related changes occurred in these measures over time. With only HIV+ participants, neuropsychological performance and brain volumes were regressed against current CD4, CD4 nadir and duration of infection. The random effects structure for all models included a subject-level random intercept.

In all the models raw neuropsychological test scores, voxel-wise brain volumes, vertex-wise cortical thickness estimates, age, education, time, measures of immune status (current and nadir CD4 cell counts), CPE score, and duration of HIV infection were treated as continuous variables, while gender and ethnicity were treated as binary variables (i.e. 0 and 1).

Optimal model structures were selected by minimizing the Akaike Information Criterion (AIC)², while the fit of different mixed-effects models were compared via the likelihood ratio test. If two mixed-effects models had similar AIC values, and the model with more fixed effects did not significantly improve model fit, the simplest model was chosen. All mixed-effects models were estimated with the maximum-likelihood method. To verify that this study had sufficient statistical power to detect clinically-meaningful structural brain volume changes over two years in the HIV+ group compared to HIV- controls, the minimum detectable difference between the groups in the change in brain volumes over time was calculated.

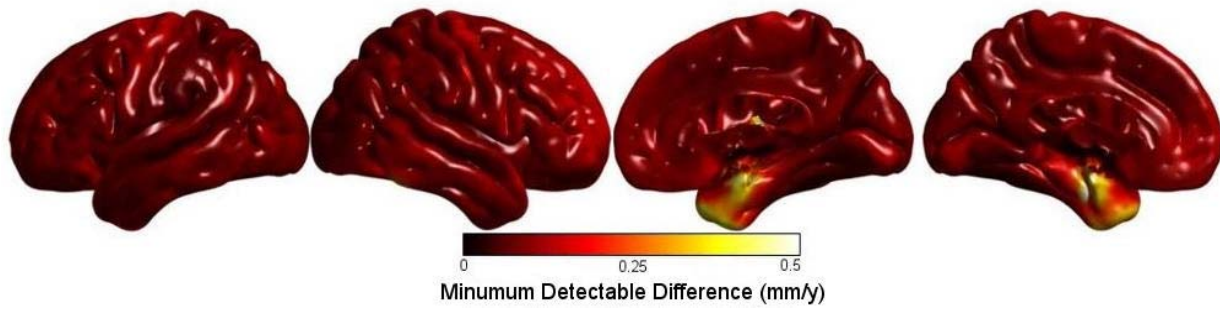


eFigure 1. White Matter Tissue Reductions in HIV-Positive Patients Compared With Controls Revealed With Voxel-Based Morphometry



eFigure 2. Minimum Detectable Difference Between Groups in Brain Volume Changes Over Time

Visualization of the smallest difference between the groups in brain volume change over time that could be detected with tensor-based morphometry.



eFigure 3. Minimum Detectable Difference Between Groups in Cortical Thickness Changes Over Time

Visualization of the smallest difference between the groups in cortical thickness changes over time that could be detected from cortical thickness estimates.

eReferences

1. Locascio JJ, Atri A. An Overview of Longitudinal Data Analysis Methods for Neurological Research. *Dement Geriatr Cogn Dis* 2011;1:330-357.
2. Akaike H. A New Look at the Statistical Model Identification. *IEEE Trans Autom Control*. 1974;AC-19(6):716-723.