Aerobic Exercise Attenuates Cognitive Decline and Brain Volume Loss Associated with HIV

Brian Basco [1], Mario Ortega [1], Laurie Baker [2], Beau Ances[1, 3, 4, 5,6]

[1]Department of Neurology, Washington University in St. Louis, [2]Department of Psychology, University of Missouri, St. Louis, [3]Department of Biomedical Engineering, Washington University in St. Louis, [4]Department of Microbiology, Washington University in St. Louis, [5]Hope Center for Neurological Disorders, Washington University in St. Louis, [6]Department of Radiology, Washington University in St. Louis

Introduction

- Currently, an estimated 1.5 million individuals are infected with the human immunodeficiency virus (HIV) in the United States. [1]
- Breakthroughs in highly antiretroviral therapy (HAART) have decreased morbidity and mortality and extended the lifespan of HIV-infected individuals.[7]
- HIV can cause neurological impairments and atrophy leading to dementia and neurocognitive disorders. While HAART has reduced HIV associated neurocognitive disorders (HAND), many individuals still have milder forms of cognitive impairment.
- Currently, there is no therapy or medication to eradicate HAND, so alternative modifying treatments are necessary to alleviate HAND symptoms in the HAART era.
- One effective non-pharmacological intervention that increases both cognitive performance and brain volume in normal adults is physical activity. (PA). PA interventional studies in HIV- populations have shown increases in total gray and white matter in physically active individuals.
- HAND is currently assessed by neuropsychological performance (NP) testing, which reveals subcortical and cortical cognitive abnormalities that are reflected in magnetic resonance imaging (MRI) pathology in those brain regions.[2]
- Past HIV studies on PA have focused on benefits to body morphology and metabolism, with only a handful investigating brain health.
- A pair of studies found a correlation between exercise history and cognition. However, the exercise marker (any self-reported history of elevated heart rate in the prior 72 hours) lacks sensitivity and specificity. [4,5]
- While studies have shown that an active lifestyle is beneficial, the quantitative effects of exercise on brain health through neuroimaging remains unknown.

Objective

We used a validated exercise questionnaire[3] to examine the correlation between the levels of fitness and cognitive function of our HIV+ individuals. Through the use of metabolic equivalents (METs), we are able to accurately assess the exercise levels of our subjects over one year.

We hypothesized that a previous history of exercise would have a benefit on neuropsychological performance and neuroimaging.

Methods

- **Participants** (see Table 1)
  - Subjects underwent neuroimaging and neuropsychological evaluations
  - 48 sedentary and 22 physically active HIV+ individuals
  - Neuropsychological battery tests: Trail Making Tests A and B, Hopkins Verbal Learning Test Revised (HVLT-R), Digit-Symbol Coding, F-A-S, Verb Fluency and Grooved Pegboard Non-Dominant
- **Neuropsychological Testing**[6,8]
  - Executive composite score (NPZe): HVLT-R, Trail Making Test B, F-A-S, Verb Fluency
  - Motor composite score (NPZm): Trail Making Test A, Digit-Symbol Coding, Grooved Pegboard Non-Dominant
- **Exercise Quantification**
  - Participants were considered physically active if weekly exertion of physical activity was greater than normal metabolic rate (MET > 1.0); individuals who reported no exercise (METs ≤ 1.0) were defined as sedentary. A validated historical exercise questionnaire was used to calculate PA for the prior year[3]
- **MRI Acquisition and Volumetric Analysis**
  - Structural T1 Images from 3T Siemens Scanner, voxel size= 1.0 mm^3
  - FreeSurfer was used to calculate normalized brain volumes by analyzing acquired MP-RAGE images.
  - Volumetrics from caudate, putamen, hippocampus, total gray matter and total white matter were tabulated and averaged across groups.

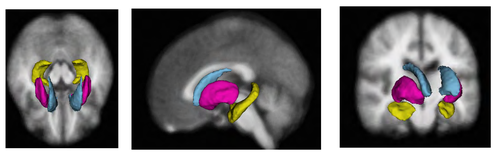


Figure 1: Axial, sagittal and coronal views of regions of interest (ROIs)

- **Statistical analysis**
  - Demographic and NP data was collected and then compiled using REDCap electronic data capture tools hosted at Washington University in St. Louis
  - Statistical analyses were done using Rstudio (Version 0.98, Boston, MA). Unadjusted (independent samples t-tests) and adjusted (backward multivariate from univariable analysis at p = 0.2 level; adjusted for age, gender, viral load) analyses were used to assess neuropsychological performance. Linear regression analyses were used in an analysis of covariance (ANCOVA) to examine the exercise effect on NPZ domain scores and volumes in each respective group after adjusting for gender and duration of infection.

Results I - Neuropsychology

Table 1. Demographics

	HIV+ physically active (n = 22)	HIV+ sedentary (n=48)	*p*-value
Age, yrs, mean (SD)	44.1 (17.2)	40.5 (15.6)	.41
Education, yrs, mean (SD)	14.0 (2.7)	12.6 (2.6)	.06
Male Gender, N (% male)	5 (23)	20 (42)	.11
Race, N (% African American)	17 (77)	34 (71)	.85
Nadir CD4 count, mean cells/mL (IQR)	207 (36, 320)	275 (127, 358)	.19
Current CD4 count, mean cells/mL (IQR)	575 (268, 888)	614 (463, 808)	.64
Plasma log_{10} HIV viral load, mean copies/mL (SD)	1.5 (.52)	1.59 (.83)	.59
Duration of Infection, mo, mean (SD)	100.5 (70.4)	144.5 (113.34)	.11
Intracranial Volume, (cm^3) (SD)	1,303 (211)	1,389 (294)	.23

Table 1: definitions: SD = Standard Deviation, IQR= Interquartile Range
Demographic and clinical characteristics for physically active and sedentary HIV+ individuals, all individuals were under stable HAART treatment

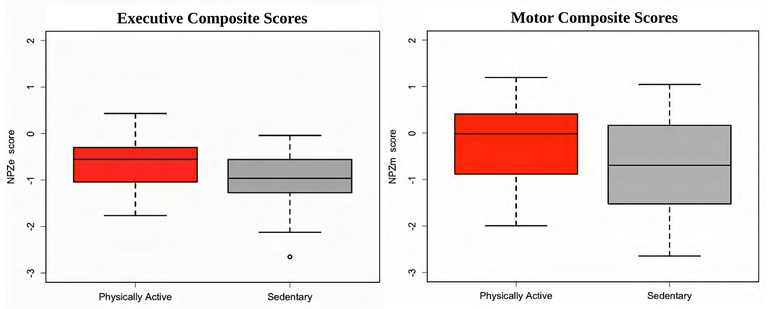


Figure 2: The mean adjusted neuropsychological z-scores (NPZ) for the executive (NPZe) (left panel) and motor (NPZm) (right panel) composite scores. The mean z-scores for executive function performance were significantly higher in physically active people (***p = 0.04***, univariable z-score adjusted model; ***p = 0.06***). However, within the motor tests, the sedentary and physically active groups had similar performance (p = 0.13, univariable z-score adjusted model; p = 0.13 adjusted)

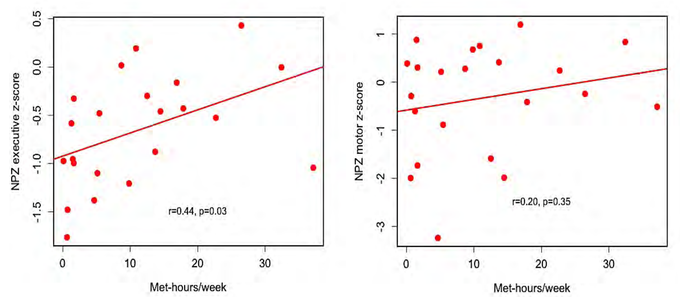


Figure 3: Significant positive correlation were found for the executive composite score and amount of exercise. Adjusted R values are shown.

Results II - Imaging

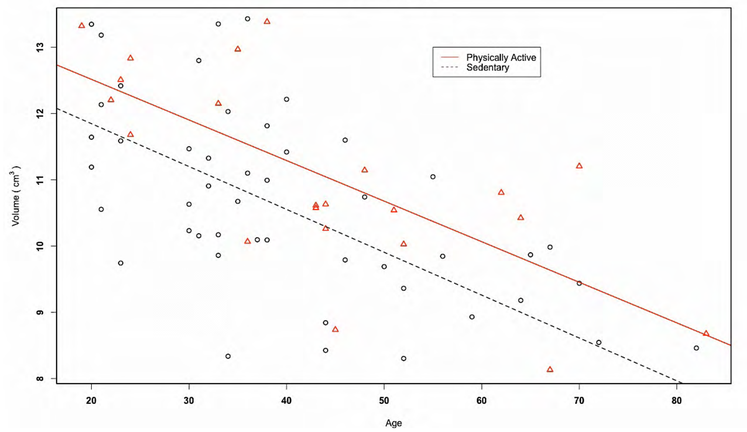


Figure 4: Putamen volumes are reduced with aging for HIV+ individuals. Physically active individuals (triangles, solid line) had significantly higher putamen volumes across the age-span than sedentary individuals (circles, dashed line) (***p = 0.04*** for group additive effect, adjusted for duration of infection and gender)

Conclusion

- Exercise was associated with improved executive functioning but not motor function on neuropsychological performance.
- PA HIV+ individuals had larger regional brain volumes through the lifespan, with putamen volumes significantly larger for physically active compared to sedentary individuals (p = 0.02).
- This means that a 40-year old sedentary HIV+ individual has a putamen volume comparable to that of an active HIV+ individual in his early 50s.
- Greater duration of exercise is associated with a greater executive function (NPZe) benefit
- Intervention studies in HIV+ individuals would show more of the causative effects of exercise in addition to correlations shown

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