Analyzing Neuroanatomical Heterogeneity in HIV-Associated Cognitive Impairment

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BACKGROUND

Despite the success of combination antiretroviral therapy (cART) in suppressing systemic HIV, **the brain remains a reservoir for ongoing viral replication** (Becker et al., 2011; Valcour et al., 2011). At least 40% of people living with HIV (PLWH) experience neurocognitive dysfunction (Chen et al., 2022), impacting daily life and increasing with age. Although Central Nervous System (CNS) complications among people living with HIV (PWH) are common, treatments remain elusive, likely due to underlying heterogeneity.

Existing work:

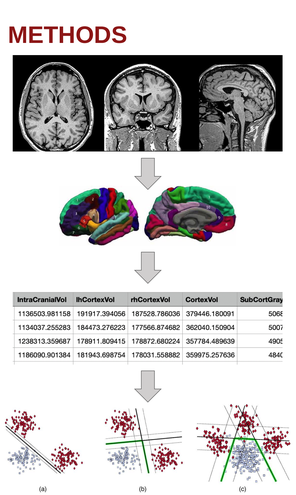
- **Frascati criteria:** most widely used symptom-based classification for HIV-associated neurocognitive disorders (HAND) but captures only 20–60% of PLWH with impairment (Nightingale et al., 2021) and yields high false-positive rates.
- **Hypothesis-driven approaches:** subtype PLWH based on viral/immune pathogenesis or viral load but rely on clinical measures that vary across studies and overlook neurobiological differences.
- **Data-driven methods:** subtype based on neuropsychological testing but fail to account for phenotypic heterogeneity.

Objective:

We aim to characterize neurobiological heterogeneity in PWH by leveraging machine learning and neuroimaging data in a large, well-characterized cohort.

Semi-supervised machine learning reveals **three distinct neuroanatomical subtypes** in HIV-related encephalopathy

METHODS

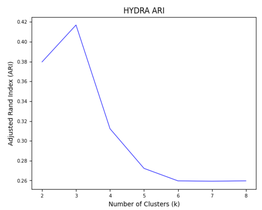


IntraCranialVol	lhCortexVol	rhCortexVol	CortexVol	SubCortGray
1136503.981158	191917.394056	187528.786036	379446.180091	5068
1134037.255283	184473.276223	177566.874682	362040.150904	5007
1238313.359687	178911.809415	178872.680224	357784.489639	4905
1186090.901384	181943.698754	178031.558882	359975.257636	4846

We analyzed structural Magnetic Resonance Imaging (sMRI) data from 610 participants: 244 persons without HIV (PWoH) and 366 PWH.

Freesurfer-derived region of interest (ROI) volumes were input to a machine learning technique termed HYDRA (Heterogeneity through Discriminative Analysis) to identify homogeneous patient subgroups.

HYDRA clusters cases based on differences from controls, accounting for confounders such as age, sex, and race.

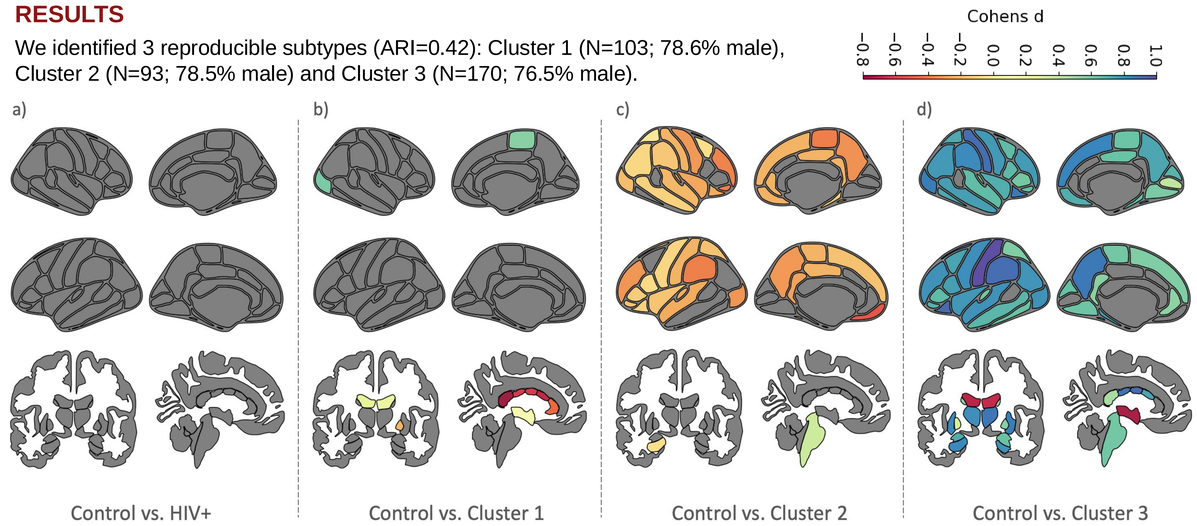


The optimal clustering solution was determined by varying the number of clusters k from 2 to 8 over 100 realizations of 10-fold cross-validation. The solution with the highest adjusted Rand index (ARI), k=3, was selected for further analysis.

We examined subtype differences in demographics, clinical measures, cognition, and imaging features (i.e., ROI volumes, resting state functional connectivity (RSFC), and cortical thickness). Demographic differences were assessed with analysis of variance and t-tests. Clinical, cognitive, and imaging differences were assessed using regression, controlling for age, sex, and race. Global Deficit Scores (GDS) were calculated by averaging cognitive domain deficit scores.

RESULTS

We identified 3 reproducible subtypes (ARI=0.42): Cluster 1 (N=103; 78.6% male), Cluster 2 (N=93; 78.5% male) and Cluster 3 (N=170; 76.5% male).



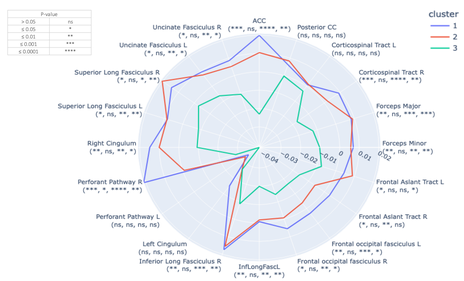
Cortical and subcortical differences in gray matter volume between three clusters. Regions with significant differences are presented with color denoting Cohen's d effect size, where cool colors indicate greater atrophy in the region and warm colors indicate increased volume or inflammation in the region.

a) Cluster 1 displayed atrophy in the lateral occipital and paracentral regions, with increased corpus callosum volume (p<0.0001) compared to PWoH.

b) Cluster 2 had widespread cortical volumetric increases,

c) Cluster 3 exhibited widespread cortical and subcortical atrophy and enlarged ventricles.

Similar atrophy patterns as seen in gray matter volume were observed in cortical thickness. Cluster 3 had significantly reduced RSFC within the dorsal attention network compared to Cluster 2. Importantly, clusters differed in clinical and cognitive aspects. PWH in Cluster 2 had a significantly lower nadir CD4 count, while Cluster 3 had the highest viral load, lowest psychomotor speed, and highest (worst) GDS.



Beta coefficients of clusters for fractional anisotropy (FA). Using diffusion tensor imaging (DTI) data independent from the clustering process, Cluster 3 consistently displayed significantly lower FA values compared to Cluster 1, Cluster 2, and controls.

CONCLUSIONS

Our findings reveal three distinct neuroanatomical subtypes in PLWH, suggesting varying degrees of disease regulation. Cluster 1 appears well-regulated, Cluster 2 presents atypical volumetric increases with cognitive decline, and Cluster 3 exhibits severe atrophy and high viral load, potentially reflecting later disease stages or a legacy effect.

	Neuroanatomical atrophy pattern	Biomarkers	Cognitive decline
Cluster 1	Mild or none in grey matter volumes, increased volume in corpus callosum	No significant differences from controls	Least steep
Cluster 2	Slight widespread increase across all cortical regions, and slight decreases in white matter volumes	Smallest viral load, lowest nadir CD4 count	Steep for psychomotor/processing speed, relatively low scores in other cognitive tests
Cluster 3	Greatest atrophies overall; mostly in frontal and parietal regions. Large increase in 3rd and 4th vent.	Significantly higher viral load than other clusters	Steepest for psychomotor/processing speed, highest GDS

Additionally, findings such as reduced resting-state connectivity in Cluster 3 (within the dorsal attention network) highlight nuanced impacts of HIV on brain function that have been masked in broader analyses assuming no heterogeneity. The identification of neurobiologically grounded biotypes of PWH may facilitate clinical trial enrichment and stratification, as well as uncover actionable features to guide development of targeted treatments.

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