Further Evidence of Hypertrophy in Acute Infection Identified using Machine Learning

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BACKGROUND

A recent analysis of structural brain volumes during acute HIV infection (AHI) revealed evidence of hypertrophy among individuals in Fiebig III-V compared to Fiebig I-II. Investigations of multimodal neuroimaging in AHI are lacking, particularly in combination with multidimensional biobehavioral indices. The present study expanded on this work by examining multiple neuroimaging modalities (structure and function), as well as plasma markers of inflammation and immune dysregulation, and psychosocial determinants of health. Ensemble machine learning was used to identify predictors of earlier vs. later Fiebig stages leveraging a highly dimensional data set. This method has potential to discover novel factors that better explain variability in early infection.

METHODS

- 112 Thai male people with AHI were included as part of RV254/SEARCH 010.
- People with AHI were stratified into early (Fiebig I-II; n=32) vs. late (Fiebig III-V; n=80) AHI.
- Gradient-boosted multivariate regression (GBM) with repeated cross validation identified features with the strongest value differentiating individuals in earlier vs. later Fiebig stage.
- F1 score was used as the primary metric of model performance due to the unbalanced sample sizes
- Predictors included demographic, HIV disease, cognitive, neuro exam, quality of life, substance use, plasma immune/inflammatory, and multimodal neuroimaging.
- Neuroimaging (i.e., structural volumes, resting state connectivity, diffusion, and spectroscopy) was acquired using a 3T Philips Ingenia MRI performed within 5 days of ART initiation.

Individuals enrolled in later Fiebig stages exhibited differences in multimodal neuroimaging (volumes, functional connectivity), immune markers, and substance use compared to individuals in early Fiebig stages.

RESULTS

- The GBM identified a combination of variables that classified individuals into earlier vs. later Fiebig stages with an average F1 score of 0.82, indicating good model performance with high explanatory value.
- Individuals in later Fiebig stages exhibited larger regional volumes in the olfactory cortex, putamen, raphe nucleus, and pallidum, with smaller volumes observed in the ventral tegmental area.
- Individuals in earlier Fiebig stages had higher plasma neutrophil percent and high-density lipoproteins, lower functional connectivity between the right executive control and visuospatial networks, and lower use of erectile dysfunction medication.

N=112	Fiebig I-II (n=32)	Fiebig III+ (n=80)
Age; M (SD)	27.47 (5.69) Range 20-44	27.79 (6.51) Range 20-46
Sex	100% Male	100% male
ART Regimen; N (%)		
Efavirenz	12 (44.4%)	31 (46.3%)
Dolutegravir	15 (55.6%)	36 (53.7%)
Days Infected; M (SD)	17.15 (8.18) Range 5-49	24.03 (8.71) Range 7-47
Days on ARV Prior to MRI; M (SD)	0.31 (1.47) Range -2 to 3	0.64 (1.46) Range -2 to 5
CD4 T cell count; Median (IQR)	326 (279-563)	319 (229-432)
CD8 T cell count; Median (IQR)	366 (256-493)	648 (391-995)
Plasma HIV VL copies/mL (log_{10}); M (SD)	5.31 (1.23)	6.42 (0.95)

Table. Clinical characteristics by subgroup.

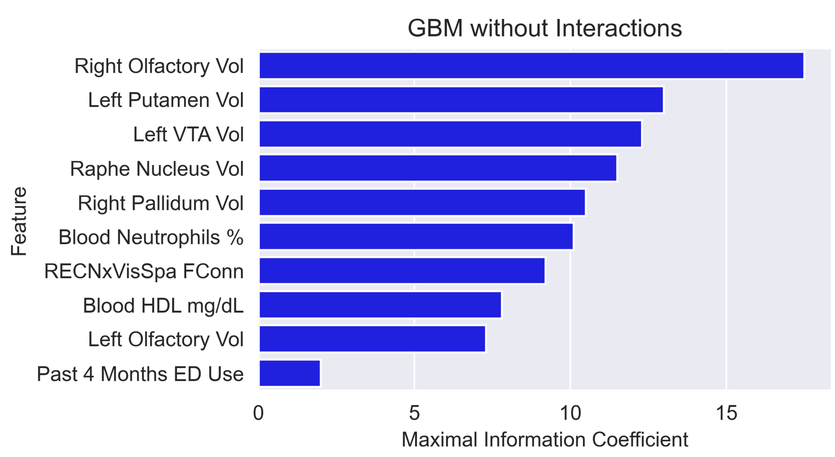


Figure. Larger regional brain volumes, lower blood neutrophils percent, greater resting state functional connectivity, HDL levels >40, and recent erectile dysfunction medication use predicted study enrollment at a later Fiebig stage.

CONCLUSIONS

- Brain alterations emerge in early infection, particularly among measures of brain volume.
- Larger regional volumes together with lower immune levels (i.e., neutrophils) suggest that viral-immune dysregulation already underway during or prior to ART initiation in later Fiebig stages manifests as hypertrophy via neuroinflammation.
- Brain-behavior relationships are implicated by the presence of both ventral tegmental area volume and recent substance use among top predictors.

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DISCLAIMER

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