T Cell Receptor Repertoire and Cognitive Performance in People With HIV

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BACKGROUND

- People with HIV (PWH) have a higher risk of neurocognitive impairment and share affected pathways with neurodegenerative disorders[1].
- T Cell Receptor (TCR) regulates immune surveillance and inflammation, influencing neurodegeneration, cognition, and psychiatric disorders[2,3].
- In animal models, TCR supports neuronal plasticity and synaptogenesis via T helper-2 responses[4].
- HIV disrupts immune homeostasis, impacting both TCR and cognition, with impairments of both persisting despite ART[5].

OBJECTIVE

To examine whether TCR clonality, richness, and diversity and the HIV reservoir in the CNS of PWH are linked to cognitive performance.

METHODS

Samples. Five central nervous system (CNS) regions (basal ganglia BG, occipital cortex OCC, frontal motor cortex FMC, hippocampus HPC, thoracic spinal cord SC) and peripheral blood mononuclear cells (PBMCs) ≤6 h post-mortem from 9 PWH enrolled in the Last Gift Rapid Autopsy Program (**Table 1**).

Data generated.

- Bulk TCR sequencing of αβ chains was performed with IMMUNOVerse.
- TCR data were analyzed using MIXCR. Clonality and Pielou's index assessed T-cell clone numbers and evenness, while richness, Shannon, and D50 (% of dominant and unique clones contributing to 50% of total CDR3s) described TCR richness and diversity.
- Cell-associated total HIV DNA was quantified by droplet digital PCR (ddPCR).

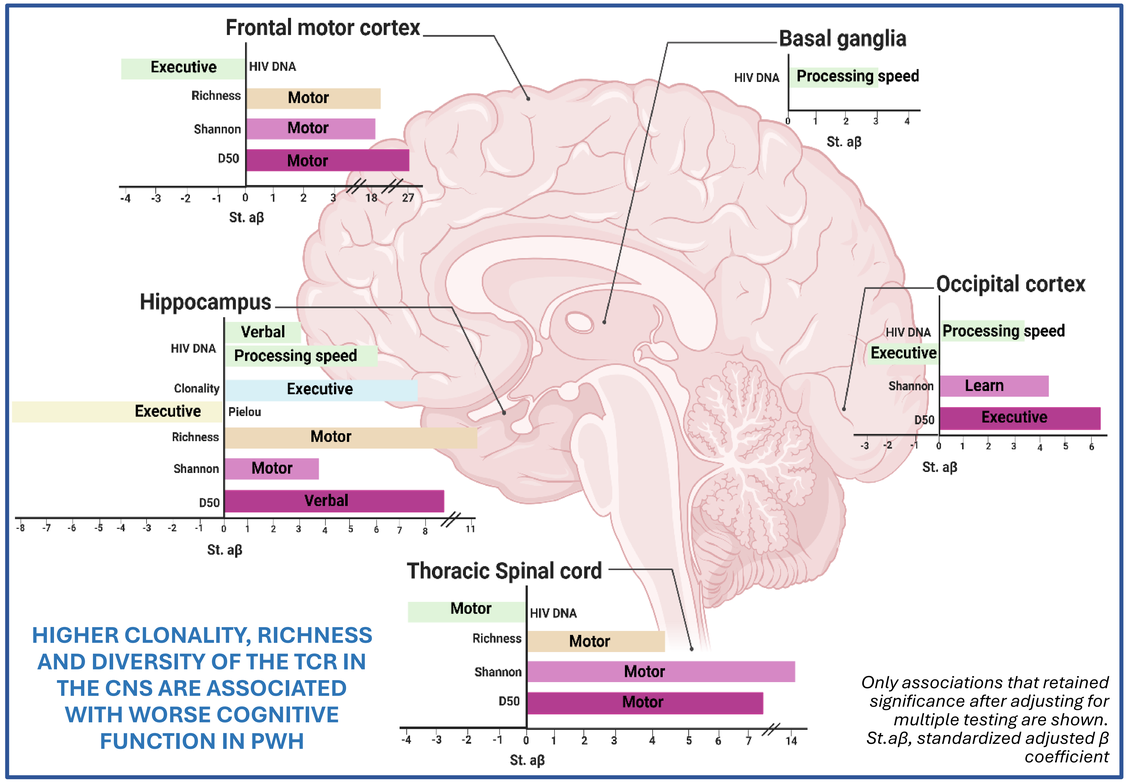
Cognition. Seven cognitive domains were assessed within a year of death and Domain Deficit Scores were calculated.

Statistical Analysis. Associations were explored through generalized linear models adjusted for age, HIV RNA, CD4 count, and nadir. Bonferroni correction was applied through familywise approach.

RESULTS

- HIV DNA and TCR richness/diversity did not differ across CNS regions (TCR richness shown in **Fig.1A**).
- TCR clonality varied between CNS regions (p=0.038): with the highest clonality in the SC and PBMCs and the lowest in FMC (**Fig.1B**).
- HIV DNA levels were not associated with TCR metrics.
- No associations were found between blood TCR metrics and cognitive performance.

FIG.2 TCR CHARACTERISTICS AND HIV DNA LEVELS IN THE CNS ARE ASSOCIATED WITH COGNITIVE FUNCTIONS IN PWH



HIGHER CLONALITY, RICHNESS AND DIVERSITY OF THE TCR IN THE CNS ARE ASSOCIATED WITH WORSE COGNITIVE FUNCTION IN PWH

Only associations that retained significance after adjusting for multiple testing are shown. St.aβ, standardized adjusted β coefficient

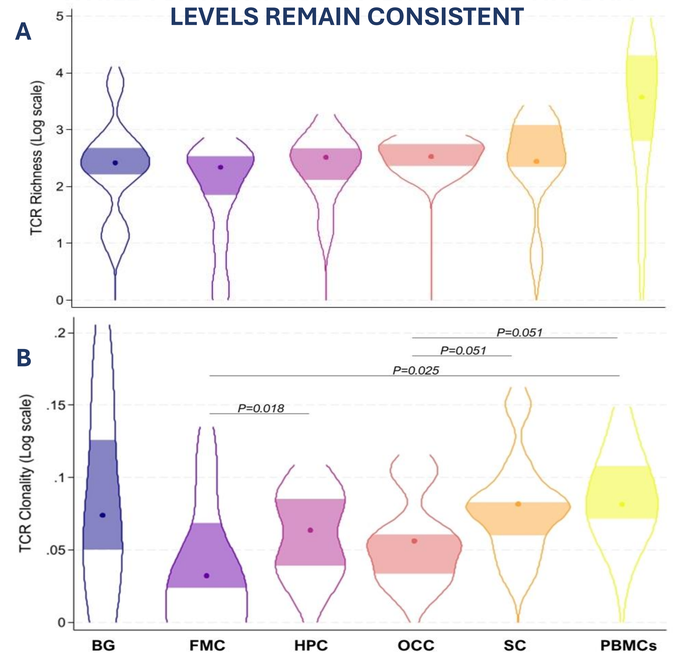
TABLE 1. STUDY POPULATION — **N=9**

Age, years	65 ± 8 years
Male sex, n	8 (88.9%)
Caucasian, n	8 (88.9%)
Education, years	15 ± 4
EDI, years	23 (22-28)
CD4⁺ T cell nadir, cells/μL	53 (40-224)
At death, CD4⁺ T Cells, cells/μL	330 (174-347)
At NCA, CD4⁺ T Cells, cells/μL	260 (202-363)
At death, Plasma HIV RNA >20 cp/mL, n	1 (11.1%)
Plasma HIV RNA, cp/mL*	48.000
At NCA, Plasma HIV RNA >20 cp/mL, n	1 (11.1%)
Plasma HIV RNA, cp/mL*	17.000
Time between death and NCA, months	5 (3-9)
Cause of death, n	
Cancer	5 (55.6%)
ALS	2 (22.2%)
End-stage organ disease	2 (22.2%)
Global Deficit Score GDS≥ 0.5, n	0.8 (0.6-0.9) 7 (77.8%)

*N, number; EDI: Estimated duration of infection, NCA, neurocognitive assessment; ALS, amyotrophic lateral sclerosis; GDS, Global deficit score. *In the participant with plasma HIV RNA > 20 cp/mL.*

- Higher TCR richness/diversity in FMC, HPC, OCC, and SC were associated with poorer performance in learning, verbal, executive, and motor domains (adj.p<0.01 for all; **Fig.2**).
- Higher TCR clonality in HPC was associated with worse executive function (adj.p<0.01; **Fig.2**).
- Higher HIV DNA levels were associated with slower processing speed (BG, HPC, and OCC) and poorer verbal function (HPC). Higher HIV DNA levels correlated with better executive and motor functions in the FMC, OCC, and SC; adj.p<0.05; **Fig.2**).
- Excluding the single participant with detectable HIV RNA did not alter the results.

FIG.1 TCR CLONALITY VARIES ACROSS CNS REGIONS, WHILE TCR RICHNESS/DIVERSITY AND HIV DNA LEVELS REMAIN CONSISTENT



Violinplots show the median (dot), interquartile range (dense area), and distribution (wider empty area) of TCR metrics across the 6 sites. Significant within-participant differences are highlighted with the corresponding p value.

CONCLUSIONS

- First evidence of an interaction between the TCR in the CNS and cognitive performance in PWH.
- Higher TCR clonality correlates with worse cognition, supporting models of chronic immune activation in neurodegenerative diseases.
- Higher TCR richness and diversity associate with poorer cognition, contrasting with general population findings, and potentially reflecting aberrant or excessive immune responses.
- Ongoing analyses with IPDA, HIV RNA, and TCR subpopulation phenotyping will further clarify these relationships.
- The absence of associations between HIV DNA and TCR suggests that factors other than HIV (e.g., co-infections) may drive the link between TCR and cognition.

ADDITIONAL KEY INFORMATION

References

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