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HIV and Low Omega-3 Levels May Heighten Hippocampal Volume Differences Between Men and Women With Substance Use

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ABSTRACT

Background: Sex differences in hippocampal volumes are well-documented, but their interaction with HIV status and omega-3 fatty acids—particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—remains unclear, especially in underserved populations. This study examines how HIV and omega-3 fatty acids influence sex differences in hippocampal volume and explores whether cognitive performance related to episodic memory modifies the association of omega-3 levels with hippocampal volume, considering both HIV status and sex.

Methods: We enrolled 166 participants aged over 45 years from a Baltimore, Maryland cohort. Brain MRIs were performed using a 3.0-T Siemens scanner, and volumetric segmentation was conducted with FreeSurfer (version 6.0), adjusting for intracranial volume (ICV).

Results: Our study found that: (1) Among HIV-negative participants, females had significantly lower hippocampal volumes than males in 1 of 26 regions, whereas HIV-positive females had lower volumes in 13 of 26 regions ($p < 0.006$ for HIV-negative vs. HIV-positive females), (2) In HIV-positive individuals with EPA levels ≤0.40 %, females exhibited lower volumes in 11 of 26 regions, compared to no differences in those with EPA levels >0.40 % ($p = 0.0003$ for ≤0.40 % vs. >0.40 %), (3) Across all participants, lower EPA and DHA levels were associated with greater sex differences in hippocampal volumes, which diminished or disappeared at higher EPA and DHA levels ($p < 0.00001$ for EPA ≤0.40 % vs. >0.40 %; $p = 0.004$ for DHA ≤2.0 % vs. >2.0 %), and (4) Among Adults with lower episodic memory, higher log-scaled EPA levels were independently associated with greater hippocampal volume.

Conclusions: HIV may amplify sex differences in hippocampal volumes, disproportionately affecting females. Higher EPA and DHA levels may mitigate these effects, suggesting a protective role against hippocampal atrophy. Further studies are warranted to confirm these findings and explore whether the benefits extend to males with HIV or individuals without HIV.

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1. Introduction

The hippocampus is a complex structure composed of histologically distinct subfields, each playing roles in functions such as memory consolidation, spatial navigation, and pattern separation. These critical functions are often compromised in individuals with brain disorders like Alzheimer's disease (AD), which is characterized by diminished hippocampal volume (van der Meer et al., 2020; Hofman and Swaab, 1991). Sexual dimorphism in the human brain, including the hippocampus, has been recognized since the early 1990s (Gould et al., 1990; Yagi and Galea, 2019). The variability in factors influencing sex differences in hippocampal volume often leads to inconsistencies across individual studies and meta-analyses (Yagi and Galea, 2019; Ruigrok et al., 2014; Tan et al., 2016). While studies generally show that hippocampal volumes are larger in men than women, these differences often become non-significant when adjusted for total brain volume or intracranial volume (Yagi and Galea, 2019; Voevodskaya et al., 2014).

The hippocampus is highly sensitive to sex hormones, such as estrogen and testosterone, which can influence its structure and function. For instance, estrogen was shown to enhance neurogenesis and synaptic plasticity in the hippocampus, potentially contributing to observed differences in volume and function between males and females (Kight and McCarthy, 2020). Additionally, research suggests that conditions like Alzheimer's disease impact hippocampal volume differently in men and women, with women typically experiencing a more rapid decline in hippocampal volume and cognitive function (Williamson et al., 2022). During development, sex differences in hippocampal volume are evident, particularly during critical periods such as puberty, when hormonal changes play a significant role (Zheng et al., 2017). These findings highlight the importance of considering sex differences in studies of hippocampal structure and function.

While the association between HIV and changes in brain morphology is established (Sui et al., 2021), the interaction between HIV and sex differences in brain structure remains relatively unexplored. HIV is known to trigger neuroinflammatory responses (Sanford et al., 2018; Deeks et al., 2013; Mudra Rakshasa-Loots et al., 2022). High viral loads are reported in the hippocampus and its subfields and reduced hippocampal volumes are observed in adults with HIV, even in the era of antiretroviral therapy (ART) (Fleischman et al., 2018; Nir et al., 2021; Kallianpur et al., 2013). Although the sex differences in hippocampal volume and its subfields are recognized, there remains a gap in our understanding of their potential interaction with HIV-related influences, as these aspects have not yet been jointly investigated. There is abundant literature highlighting the potential anti-inflammatory and neuroprotective properties of omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on neural tissue (Barberger-Gateau et al., 2007; Michael-Titus and Priestley, 2014; Bazinet and Layé, 2014; Orr and Bazinet, 2008). However, the association between EPA and DHA levels and neuroinflammation among adults with HIV remains poorly characterized.

The hippocampus, a critical brain region for memory and cognitive function, is especially susceptible to structural and functional changes due to factors like inflammation, neurodegeneration, and hormonal influences. While the neuroprotective effects of omega-3 fatty acids, specifically EPA and DHA, are documented, emerging evidence suggests that these effects may vary between sexes due to hormonal differences. For example, estrogen is known to enhance the neuroprotective effects of DHA, leading to sex-specific variations in hippocampal structure and function (Cao et al., 2009; Barberger-Gateau et al., 2007). This suggests that females may derive greater neuroprotective benefits than do men from DHA, potentially resulting in more significant influences on hippocampal volume. Moreover, EPA and DHA are recognized for their ability to enhance synaptic plasticity and promote neurogenesis—processes essential for maintaining hippocampal volume (Cutuli, 2017; Bazinet and Layé, 2014). These omega-3 fatty acids also regulate the expression of brain-derived neurotrophic factor (BDNF), a crucial molecule involved in neurogenesis and neuronal survival. Evidence indicates that BDNF expression may respond differently in males and females (Boga and Basak, 2023; Pontifex, 2020; Majou and Dermenghem, 2024). Given these sex-specific differences, it is essential to investigate whether there are sex differences regarding the influences of EPA and DHA on hippocampal volume, particularly in HIV, a condition that exacerbates neuroinflammation and cognitive decline.

Since 2000, we recruited and followed approximately 1500 adult men and women, 93 % of whom are African Americans (AAs) from the inner city of Baltimore, Maryland, thereby establishing the Heart Study cohort. The is an over 20-year investigation supported by the National Institute on Drug Abuse that explores the effects of HIV, ART exposure, and substance use (including cocaine and other substances) on subclinical coronary artery disease in inner-city Baltimore, Maryland. Among the participants, 950 were living with HIV. Participants with HIV were recruited from the Johns Hopkins Bartlett Specialty Clinic, while participants without HIV were recruited from the local community, where most participants with HIV also resided. In 2018, the study was expanded to include data collection on HIV-associated neurological comorbidities. Since 2018, 922 study participants have undergone neurocognitive assessments using the NIH Toolbox Cognition Battery (NIHTB-CB) (NIH Toolbox® Scoring and Interpretation Guide for the iPad, 2016). To further enrich our research, brain MRI was incorporated into the study starting in 2022. As of March 2023, brain MRI data had been collected on 166 participants >45 years of age of the 922 enrolled participants.

This study had three primary objectives: (1) To assess sex differences in the volume of the hippocampus and its subfields in adults with and without HIV, (2) To compare sex differences in the volume of the hippocampus and its subfields between adults with lower and higher levels of EPA, as well as between adults with lower and higher levels of DHA, (3) To evaluate how EPA and DHA levels affect sex differences in the volume of the hippocampus and its subfields in adults with and without HIV, and (4) To explore whether cognitive performance related to episodic memory modifies the association of omega-3 levels with hippocampal volume, considering both HIV status and sex.

2. Materials and methods

2.1. Participants

From February 2022 through March 2023, 166 of the 922 adults, who had undergone neurocognitive assessments and were older than 45 years also underwent brain MRI studies. The inclusion and exclusion criteria for this study population were:

Inclusion criteria: (1) HIV status, determined by ELISA and confirmed by Western blot; (2) self-reported estimates of duration and frequency of use of psychoactive substances, including cocaine, heroin, tobacco, marijuana, and alcohol; and (3) all races, as self-designated. **Exclusion criteria** were: (1) significant neurological diseases; (2) baseline MRI brain scan showing evidence of infection, infarction, other focal lesions, multiple lacunes, or lacunes in critical memory structures; (3) contraindications to MRI; (4) history of schizophrenia or bipolar disorder within the prior year, or presence of psychotic features, agitation, or behavioral problems within the prior three months; (5) pregnancy, lactation, or childbearing potential; and (6) limitations in activities of daily living.

The study protocol was approved by the Institutional Review Boards at the Johns Hopkins School of Medicine and the University of Maryland, Baltimore. All participants provided written informed consent. The study design and procedures adhered to institutional guidelines, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 in the United States, local and federal regulations, and the Declaration of Helsinki. \Although the overall investigation is a longitudinal cohort study, the data available for these analyses are only cross-sectional.

2.2. Interview, medical chart review, physical, and laboratory examination

Study participants underwent comprehensive interviews to collect information on sociodemographic characteristics, medical history, alcohol consumption, psychoactive substance use, cigarette smoking, and prescribed psychotropic medication use. The Zung Self-Rating Depression Scale was administered to all participants (Biggs et al., 1978). For participants with HIV, additional data were gathered on HIV risk factors, duration of known HIV, and medication history including ART use. Medical chart reviews were conducted to verify participants' medical history and prescribed medication information.

Physical examinations were performed and vital signs recorded. Routine clinical laboratory tests included blood chemistry analysis of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), fasting glucose, EPA, DHA, and homocysteine levels. Plasma phospholipid omega-3 fatty acids (EPA plus DHA as a percentage of total plasma phospholipid fatty acids) were measured using liquid chromatography–tandem mass spectrometry by Quest Diagnostics (Albert et al., 2021). The 2013 ACC/AHA guideline on the assessment of cardiovascular risk was used to calculate the atherosclerotic cardiovascular disease (ASCVD) risk score, with a score of <7.5 % defined as low ASCVD risk (Goff et al., 2014).

2.3. Brain MRI

2.3.1. Acquisition

Brain MRI was performed using a 3.0-T Siemens Prisma MRI Scanner (Siemens Healthineers) at the Department of Radiology, University of Maryland School of Medicine. All image data were uploaded to the cloud-based QMENTA Platform, where image processing and analysis were performed using their volumetric analysis tools (QMENTA Inc., 2023).

2.3.2. Anatomical imaging

3D T1-weighted (T1w) MPRAGE, 3D T2-weighted (T2w), and 3D T2-weighted FLAIR sequences were collected in the sagittal plane. The imaging parameters were as follows: T1w: TE/TR/TI = 2.22 ms/2500 ms/1110 ms, flip angle = 8°, bandwidth (BW) = 220 Hz/Px, resolution = 0.8x0.8 × 0.8 mm^3, field of view (FOV) = 208x300x320 mm^3. T2w: TE/TR = 349/3200 ms, turbo factor = 280, BW = 781 Hz/Px, resolution = 1x1x1 mm^3, FOV = 176x256x256 mm^3. FLAIR: TE/TR/TI = 390/5000/1800 ms, turbo factor = 280, BW = 781 Hz/Px, resolution = 1x1x1 mm^3, FOV = 192x256x256 mm^3.

Additionally, to improve segmentation in the automatic volumetric analysis, 104 participants underwent a 2D coronal T2-weighted high-resolution hippocampal sequence with a resolution of 0.39x2x0.39 mm^3, FOV = 448x29 × 448 mm^3, and TE/TR = 52/8020 ms.

2.3.3. Image analysis on the QMENTA Platform

The 3D T1w and T2w images were processed using FreeSurfer software package (version 6.0) (Fischl 2012; Iglesias et al., 2015). The FreeSurfer pipeline includes skull stripping, bias field correction, registration, anatomical segmentation, cortical surface reconstruction, and parcellation. Hippocampal subfields were segmented to calculate hippocampal volume, which served as one of the primary outcome measures. Additionally, the brain segmentations generated by FreeSurfer were used to extract regional imaging metrics from other imaging modalities.

2.4. Statistical analysis

Statistical analyses were conducted using SAS software (version 9.4, SAS Institute, Cary, NC). Continuous parameters are presented as means with standard deviations (SDs), while categorical parameters are denoted as proportions. To assess between-group differences in demographic and clinical characteristics, lipid profiles, and other factors, t-tests were used for continuous variables, and chi-square tests were applied for categorical variables.

Sex differences in hippocampal volumes (totaling 26) were initially evaluated using t-tests or Fisher's exact tests. After applying the Bonferroni correction, the significance threshold was set at $p < 0.00192$ (0.05/26).

Given that intracranial volume (ICV) may influence hippocampal volume and considering potential non-linearity in this relationship (Im et al., 2008), along with uncertainty regarding the best method for normalizing regional volumes by ICV, we chose to use the ratio of hippocampal volume to the natural logarithm of ICV (log(ICV)) to account for ICV variations. In our adjusted analyses, outcome variables were derived from the ratio of the hippocampal and its subfields' volumes to log (ICV). ICV-adjusted results are presented in the main tables, while unadjusted findings are provided in the supplementary material.

To minimize the impact of potential confounding factors, generalized linear models (GLMs) were employed for the primary data analyses, with both adjusted and unadjusted results presented. Female sex was treated as the independent variable of interest, while the volumes of the hippocampus and its subfields were considered the outcome variables.

Compared to conventional linear multiple regression models, which assume a continuous, normally distributed outcome variable and a linear relationship between the independent and outcome variables, GLMs offer greater flexibility. They accommodate various outcome variable distributions, including normal, binomial, and Poisson, among others from the exponential family, and do not require normally distributed residuals (Dunn and Smyth, 2018).

The unadjusted GLM analyses examined sex differences in the volumes of the hippocampus and its subfields relative to HIV status without adjustments. Subsequently, multivariate GLMs were employed to control for potential confounders, including age, education level, annual income, cocaine use, Zung self-rating depression score, and the ASCVD risk score. In analyses specific to participants with HIV, the nadir CD4 count was also adjusted for in the models.

To assess the potential influence of EPA or DHA on sex differences, the medians of EPA (0.40 %) and DHA (2.0 %) were used as stratifying variables within GLMs for both participants with and without HIV.

Generalized Linear Models (GLMs) were used to examine whether EPA and DHA were independently associated with hippocampal volume (Field and Wilcox, 2017), adjusting for age, educational attainment, sex, and HIV status. Since the Fully Adjusted T-scores for the five cognitive domains did not significantly contribute to the model in assessing their impact on the association between omega-3 levels and hippocampal volume, we refined our approach. Given prior evidence suggesting that omega-3 supplementation provides cognitive benefits, particularly among individuals with existing cognitive decline (Mazereeuw et al., 2012), we evaluated whether episodic memory performance modified the association between omega-3 levels and hippocampal volume. To achieve this, we created a binary variable for lower episodic memory, defined as a Picture Fully Adjusted T-Score <48 (the median). We then conducted stratified GLMs to examine the relationship between omega-3 levels and hippocampal volume within each subgroup. This stratified approach accounts for the well-established association between hippocampal volume and episodic memory (Loring et al., 2019).

All reported p-values are two-tailed. A p-value of <0.05 was considered statistically significant, except for comparisons between men and women regarding hippocampal volumes, where the significance threshold was set at $p < 0.00192$ to adjust for multiple comparisons.

3. Results

3.1. General characteristics

The demographic, behavioral, laboratory characteristics, and

hippocampal volumes, including its subfields, of all 166 participants aged over 45 years are presented by sex in Table 1. The mean age of the participants was 57.3 ± 6.4 years; 40.4 % were female; 62.7 % were HIV-infected; and 98.8 % were African American (AA). Women were more likely than men to have less than a high school education (44.8 % vs. 29.3 %, p = 0.04), a low ASCVD risk score (58.2 % vs. 28.3 %, p = 0.0001), and a DHA level greater than 2.0 % (53.7 % vs. 37.4 %, p = 0.04). Among the 26 hippocampal and subfield volumes assessed (with the left hippocampus and its 12 subfields shown in Fig. 1 and Supplementary Fig. 1), 12 were significantly larger in men compared to women, and none were larger in women than in men (Table 1).

3.2. HIV and its potentially greater adverse impact on hippocampal volumes in women

Table 2 shows that after adjusting for age, education, income, cocaine use, Zung depression score, and ASCVD risk score, 3 of the 26 hippocampal volume comparisons were lower in women than in men among participants without HIV. In contrast, among participants with HIV, 13 of the 26 comparisons indicated lower volumes in women than men. The difference between these groups (13/26 in HIV-infected vs. 3/26 in HIV-uninfected) was statistically significant (Fisher's exact p-value <0.006).

3.3. Higher Omega-3 levels May mitigate the detrimental effects of HIV on hippocampal volumes in women

Table 3A shows that among individuals with HIV and EPA levels ≤0.40 %, 11 of 26 hippocampal volume comparisons showed lower volumes in women than in men. However, for those with EPA levels >0.40 %, none of the 26 comparisons revealed lower volumes in women, and no significant sex differences were observed (11/26 vs. 0/26, Fisher's exact p-value = 0.0003 for EPA levels ≤0.40 % vs EPA levels >0.40 %).

Table 3B shows that among individuals with HIV and DHA levels ≤2.0 %, 4 of 26 hippocampal volume comparisons were lower in women than in men. For those with DHA levels >2.0 %, 3 of the 26 comparisons showed lower volumes in women (4/26 vs. 3/26, Fisher's exact p-value = 1.00).

3.4. Omega-3 May have a more pronounced protective effect on hippocampal volumes in women compared to men

Table 4A shows that after controlling for potential confounders, among all (HIV-infected and HIV-uninfected) participants with lower EPA levels, 14 of 26 hippocampal volume comparisons showed lower volumes in women than in men. However, in participants with higher EPA levels, no such sex differences were observed. The difference between the two EPA groups (EPA ≤0.40 % vs. EPA >0.40 %) was significant (14/26 vs. 0/26, Fisher's exact p-value <0.00001).

Table 4B shows that among participants with lower DHA levels, 12 of 26 hippocampal volume comparisons indicated lower volumes in women than in men. In participants with higher DHA levels, only 2 of the 26 comparisons showed a sex difference. The difference between these DHA groups (DHA ≤2.0 % vs. DHA >2.0 %) was significant (12/26 vs. 2/26, Fisher's exact p-value = 0.004).

3.5. Omega-3 May have a more pronounced protective effect on hippocampal volumes in adults with lower episodic memory

Table 5 shows that among adults with lower episodic memory, higher log-scaled EPA levels were independently associated with greater hippocampal volume after adjusting for age, educational attainment, HIV status, and sex. However, this association was not observed in individuals with higher episodic memory. In contrast, no significant association was found between DHA levels and hippocampal volume.

Table 1
Characteristics of 166 study participants aged >45 Years who underwent brain MRI in Baltimore, Maryland, by sex.

Characteristic	Total (N = 166)	Female (N = 67)	Male (N = 99)	P-value
Age >55 years, (%)	62.7	52.2	69.7	0.02
African Americans, (%)	98.8	98.5	99.0	0.78
< high school education, (%)	35.5	44.8	29.3	0.04
Annual family annual income <$20,000, (%)	65.1	65.7	64.7	0.89
Married, (%)	20.5	23.9	18.2	0.37
Cigarette smoking, (%)	72.2	75.8	69.7	0.41
Cocaine use, (%)	76.2	80.7	73.0	0.28
Alcohol use, (%)	78.8	74.2	82.0	0.25
Marijuana use, (%)	77.1	71.6	80.8	0.17
Heroin use, (%)	45.7	45.2	46.1	0.91
Zung depression score >40, (%)	32.5	35.8	30.3	0.46
Low ASCVD risk, (%)	40.4	58.2	28.3	0.0001
HIV infection, (%)	62.7	61.2	63.6	0.75
EPA >0.40 (%)	48.8	46.3	50.5	0.59
DHA >2.0 (%)	44.0	53.7	37.4	0.04
Volumes of hippocampus and hippocampal subfields[a]				
Left hippocampal tail	465.3 ± 78.9	450.9 ± 73.2	475.0 ± 81.4	0.054
Right hippocampal tail	486.2 ± 77.8	464.4 ± 71.0	500.9 ± 79.0	0.003
Left subiculum_	387.7 ± 52.8	375.4 ± 47.5	396.0 ± 54.8	0.01
Right subiculum	390.0 ± 53.4	375.4 ± 42.9	399.9 ± 57.5	0.002
Left CA1	569.4 ± 83.7	542.3 ± 72.2	587.7 ± 86.3	**0.0005**
Right CA1	599.4 ± 88.2	569.5 ± 76.6	619.7 ± 90.0	**0.0003**
Left hippocampal fissure	131.2 ± 30.6	121.7 ± 28.0	137.6 ± 30.8	**0.0008**
Right hippocampal fissure	137.3 ± 33.9	125.6 ± 31.0	145.3 ± 33.6	**0.0002**
Left presubiculum	255.2 ± 39.5	243.6 ± 33.4	263.0 ± 41.6	0.002
Right presubiculum	249.4 ± 40.8	238.9 ± 32.8	256.5 ± 44.1	0.004
Left parasubiculum	55.9 ± 12. 7	53.9 ± 12.9	57.2 ± 12.5	0.10
Right parasubiculum	55.1 ± 13.7	52.5 ± 10.7	56.9 ± 15.3	0.03
Left molecular layer	442.4 ± 68.3	421.2 ± 66.2	456.8 ± 66.1	**0.0009**
Right molecular layer	453.4 ± 71.4	428.3 ± 66.1	470.4 ± 70.1	**0.0001**
Left GC-ML-DG	271.4 ± 39.1	258.2 ± 33.1	280.2 ± 40.4	**0.0003**
Right GC-ML-DG	286.1 ± 39.6	270.3 ± 33.2	296.9 ± 40.1	**<0.0001**
Left CA2/3	183.1 ± 32.5	174.3 ± 27.7	189.0 ± 34.2	0.004
Right CA2/3	202.4 ± 32.5	192.7 ± 29.6	209.0 ± 32.9	**0.0010**
Left CA4	227.9 ± 31.5	216.1 ± 26.3	235.9 ± 32.3	**<0.0001**
Right CA4	241.0 ± 31. 5	226.8 ± 26.5	250.5 ± 31.2	**<0.0001**
Left fimbria	71.8 ± 20.8	71. 9 ± 18.7	71.7 ± 22.2	0.96
Right fimbria	68.8 ± 24.0	66.0 ± 22.2	70.8 ± 25.1	0.21
Left HATA	54.6 ± 9.7	52.5 ± 9.8	56.0 ± 9.3	0.02
Right HATA	56.8 ± 9.8	54.7 ± 9.5	58.3 ± 9.7	0.02
Left whole hippocampus	2984.6 ± 370.2	2860.4 ± 327.5	3068.6 ± 75.2	**0.0003**
Right whole hippocampus	3088.7 ± 382.5	2939.5 ± 328.0	3189.7 ± 85.3	**<0.0001**

Abbreviations: Age = age at interview (years). Zung score = Zung depression score. Low ASCVD risk, cardiovascular risk defined by the 2013 ACC/AHA

Guideline on the Assessment of Cardiovascular Risk< 7.5 %. EPA = Eicosapentaenoic acid. DHA = Docosahexaenoic acid.

[a] For volume comparisons of the hippocampus and subfields, a p-value <0.00192 (Bold) indicated statistical significance.

4. Discussion

4.1. Major findings

This study results reveal three key findings: (1) In adults without HIV, females exhibited a lower volume in one hippocampal region compared to males whereas in adults with HIV, females exhibited lower volumes than men in 13 of the 26 hippocampal regions, (2) In adults with HIV, the sex differences in hippocampal volumes were no longer present when EPA levels were greater than 0.4 %, (3) Regardless of HIV status females had lower volumes in 14 of the 26 hippocampal regions compared to males when EPA levels were below the median level (<0.4 %), but there was no sex difference with EPA levels above 0.4 %. Similarly, regardless of HIV status, females exhibited lower volumes than did men in 11 of the 26 hippocampal regions in those with DHA levels at or below the median (≤2.0 %) but in only one region when DHA levels were above 2.0 %, and (4) Among adults with lower episodic memory, higher log-scaled EPA levels were independently associated with greater hippocampal volume after adjusting for age, educational attainment, HIV status, and sex.

4.2. HIV May exacerbate sex differences in hippocampal volumes in the ART era

The results of this study suggest that HIV alters the pattern of morphological sex differences in hippocampal volumes, dramatically exacerbating an existing sex differences in the volumes of the whole hippocampus and its subfields, including the hippocampal tail, subiculum, CA1, CA2/CA3, CA5, and presubiculum. These subfields are critical regions of the hippocampus, contributing significantly to learning and memory functions. This preferential impact of HIV has not been previously reported and represents a significant finding in our research.

In the ART era, the primary health concerns for people living with HIV shifted. Instead of complications from HIV itself, there is an increased focus on HIV-associated comorbidities, including cardiovascular diseases, cancers, and neurocognitive dysfunctions, many of which are linked to the HIV-associated inflammatory effects (Scully, 2018; Raghavan et al., 2017).

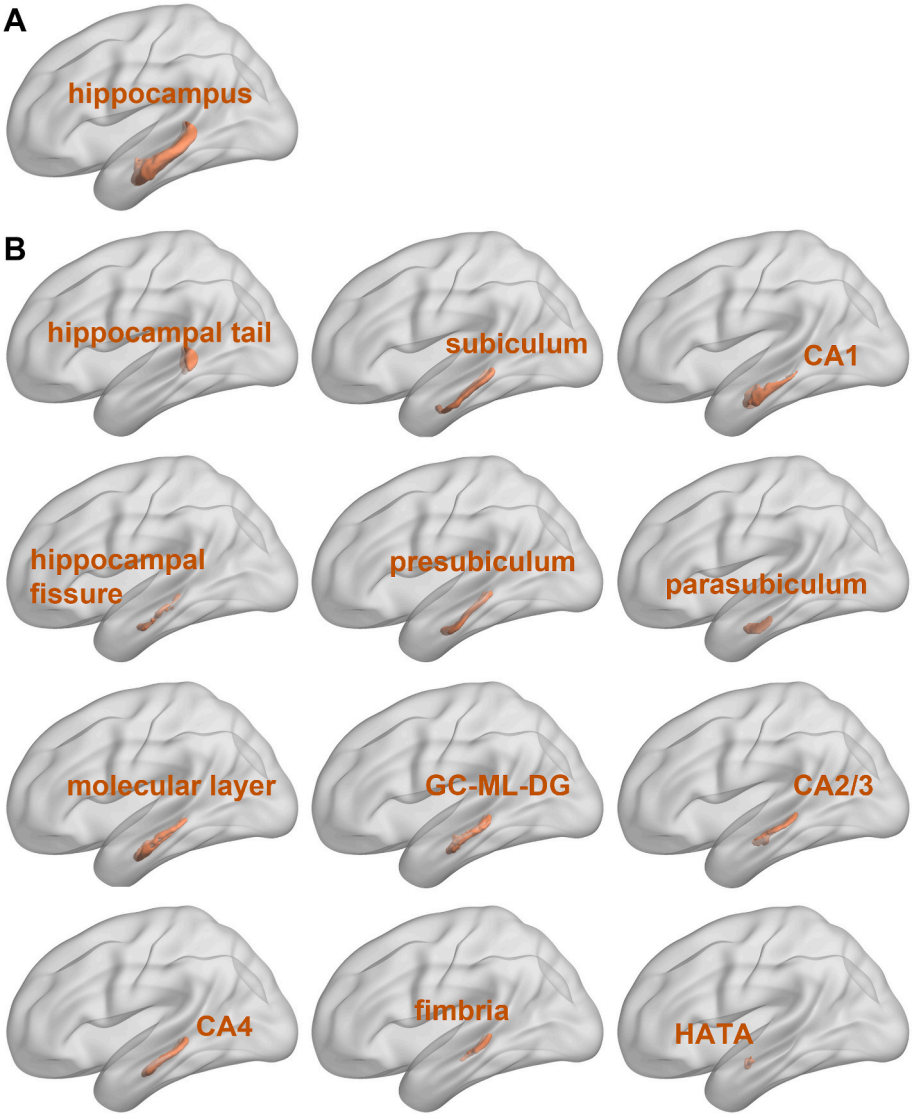

Fig. 1. 3-D rendering of (A) the left hippocampus from one subject, and (B) its 12 segmented subfields generated by FreeSurfer hippocampal subfield analysis. CA1–4: Cornu Ammonis 1-4; HATA: hippocampus-amygdala-transition-area; GC-ML-DG: Granule Cell and Molecular Layer of the Dentate Gyrus.

Table 2
Sex Differences in ICV-Adjusted Volumes of Hippocampus and its Subfields by HIV Among All Participants.

Outcome variable[a]	Unadjusted				Adjusted			
	HIV-uninfected		HIV-infected		HIV-uninfected[c]		HIV-infected[d]	
	Regression estimate (95 %CI)	p-value[b]	Regression estimate (95 %CI)	p-value[b]	Regression estimate (95 %CI)	p-value[b]	Regression estimate (95 %CI)	p-value[b]
Left hippocampal tail	−0.6 (−3.4, 2.2)	0.68	−1.9 (−3.9, 0.0)	0.06	−2.0 (−5.4, 1.4)	0.25	−3.4 (−5.5, −1.3)	**0.0017**
Right hippocampal tail	−1.7 (−4.2, 0.9)	0.20	−2.7 (−4.7, −0.7)	0.009	−2.1 (−5.2, 1.0)	0.19	−3.7 (−6.0, −1.5)	**0.0010**
Left subiculum	−1.2 (−2.8, 0.5)	0.16	−1.3 (−2.6, 0.1)	0.07	−2.1 (−4.3, 0.2)	0.07	−2.3 (−4.1, −0.4)	0.02
Right subiculum	−1.7 (−3.5, 0.1)	0.07	−1.4 (−2.6, −0.1)	0.03	−2.4 (−4.9, 0.1)	0.057	−2.7 (−4.2, −1.3)	**0.0002**
Left CA1	−2.3 (−5.1, 0.4)	0.09	−3.2 (−5.3, −1.1)	0.003	−4.2 (−7.7, −0.7)	0.02	−5.1 (−7.7, −2.5)	**<0.0001**
Right CA1	−3.1 (−5.7, −0.5)	0.02	−3.2 (−5.5, −0.9)	0.006	−4.6 (−7.8, −1.4)	0.005	−5.1 (−7.7, −2.6)	**<0.0001**
Left hippocampal fissure	−1.0 (−1.9, 0.0)	0.05	−1.1 (−1.9, −0.3)	0.01	−0.5 (−1.4, 0.5)	0.32	−1.4 (−2.5, −0.3)	0.01
Right hippocampal fissure	−1.3 (−2.5, −0.2)	0.02	−1.3 (−2.2, −0.4)	0.003	−0.7 (−1.9, 0.6)	0.28	−1.7 (−2.8, −0.6)	0.002
Left presubiculum	−1.7 (−3.1, −0.3)	0.02	−1.0 (−1.9, 0.0)	0.05	−2.1 (−3.7, −0.5)	0.01	−1.5 (−2.8, −0.3)	0.01
Right presubiculum	−1.5 (−2.9, −0.1)	0.04	−0.9 (−1.8, 0.1)	0.08	−2.2 (−3.9, −0.4)	0.03	−1.4 (−2.5, −0.4)	0.006
Left parasubiculum	−0.5 (−0.9, −0.1)	0.02	0.0 (−0.4, 0.3)	0.87	−0.4 (−0.9, 0.1)	0.13	0.0 (−0.5, 0.5)	0.89
Right parasubiculum	−0.7 (−1.2, −0.3)	0.002	0.0 (−0.4, 0.3)	0.91	−0.8 (−1.4, −0.2)	0.008	0.0 (−0.4, 0.4)	0.99
Left molecular layer	−3.4 (−5.6, −1.2)	0.003	−1.6 (−3.4, 0.3)	0.09	−3.8 (−6.2, −1.5)	**0.0010**	−2.6 (−4.9, −0.3)	0.03
Right molecular layer	−4.2 (−6.4, −1.9)	**0.0003**	−1.8 (−3.6, 0.0)	0.05	−4.3 (−6.8, −1.8)	**0.0007**	−2.9 (−5.1, −0.6)	0.01
Left GC-ML-DG	−1.1 (−2.4, 0.1)	0.08	−1.6 (−2.5, −0.6)	**0.0015**	−2.2 (−3.8, −0.6)	0.006	−2.1 (−3.3, −0.9)	**0.0006**
Right GC-ML-DG	−1.4 (−2.6, −0.3)	0.02	−1.9 (−2.9, −0.9)	**0.0002**	−2.4 (−3.8, −0.9)	**0.0010**	−2.5 (−3.7, −1.4)	**<0.0001**
Left CA2/3	−0.7 (−1.7, 0.3)	0.18	−1.1 (−1.9, −0.2)	0.01	−1.3 (−2.6, 0.0)	0.05	−1.6 (−2.6, −0.6)	**0.0018**
Right CA2/3	−0.5 (−1.4, 0.4)	0.30	−1.4 (−2.3, −0.5)	0.003	−1.0 (−2.0, 0.0)	0.06	−1.9 (−3, −0.9)	**0.0003**
Left CA4	−1.1 (−2.1, −0.1)	0.03	−1.4 (−2.2, −0.6)	**0.0005**	−1.8 (−3.1, −0.5)	0.006	−1.9 (−2.8, −0.9)	**<0.0001**
Right CA4	−1.3 (−2.2, −0.4)	0.005	−1.7 (−2.5, −0.9)	**<0.0001**	−1.8 (−2.9, −0.6)	0.002	−2.2 (−3.1, −1.3)	**<0.0001**
Left fimbria	0.1 (−0.6, 0.7)	0.82	0.0 (−0.6, 0.6)	0.94	−0.6 (−1.3, 0.0)	0.06	0.3 (−0.4, 1.0)	0.43
Right fimbria	−0.1 (−0.9, 0.7)	0.82	−0.4 (−1.1, 0.2)	0.20	−0.7 (−1.7, 0.2)	0.12	−0.2 (−1.1, 0.6)	0.59
Left HATA	−0.2 (−0.5, 0.2)	0.36	−0.3 (−0.5, 0.0)	0.05	−0.3 (−0.7, 0.1)	0.14	−0.3 (−0.6, 0.0)	0.06
Right HATA	−0.3 (−0.7, 0.0)	0.07	−0.2 (−0.4, 0.1)	0.21	−0.5 (−0.9, −0.1)	0.009	−0.2 (−0.5, 0.1)	0.31
Left whole hippocampus	−12.7 (−24.6, −0.7)	0.04	−13.2 (−22.3, −4.0)	0.005	−20.9 (−36.1, −5.6)	0.007	−20.5 (−31.5, −9.4)	**0.0003**
Right whole hippocampus	−16.4 (−28.2, −4.5)	0.007	−15.5 (−24.9, −6.1)	**0.0012**	−22.7 (−37.3, −8.1)	0.002	−23.1 (−33.5, −12.6)	**<0.0001**

[a] All the outcome variables were defined as the volumes of the hippocampus and its subfields divided by log(ICV).
[b] For the volumes of whole hippocampus and hippocampal subfields, a p-value <0.00192 (Bold) indicated statistical significance.
[c] Adjusted for age >55 years, <high school education, family annual income <$20,000, cocaine use >10 years, Zung self-rating depression score>40, and the atherosclerotic cardiovascular disease (ASCVD) risk score.
[d] Adjusted for age >55 years, <high school education, family annual income <$20,000, cocaine use >10 years, Zung self-rating depression score>40, and the atherosclerotic cardiovascular disease (ASCVD) risk score.

Biological sex is one of the multifactorial determinants of these comorbidities (Raghavan et al., 2017).

A recent study (Gianella et al., 2022) reported that HIV reservoirs in women were more dynamic and declined at a significantly slower rate compared to those of men and that this difference became more pronounced with age. Although the precise mechanisms by which HIV influences these sex differences in hippocampal volume remain unclear, our study results highlight the need to further explore the role of HIV in exacerbating sex differences in hippocampal volumes (Tir et al., 2021; Putatunda et al., 2019).

4.3. Diminished sex-related volume differences in adults with HIV and higher EPA or DHA levels

A standout observation in our study was the diminished sex-related volume differences among adults with HIV who had EPA or DHA levels above the median value. An exploratory study of 2183 participants from the Framingham Study—comprising individuals without dementia or stroke, with a mean age of 46 years, 53 % women, and 22 % APOE-e4 carriers—highlighted an association between elevated omega-3 polyunsaturated fatty acid levels and larger hippocampal volumes (Satizabal et al., 2022). This was further linked to improved abstract reasoning, suggesting a potential role in strengthening cognitive resilience However, it is important to note that a substantial proportion of these study participants were White and had at least a high school education. Additionally, the EPA and DHA levels reported in that study, with median levels of 0.6 % and 4.1 %, respectively, surpass those in our study population, where the median values were 0.4 % for EPA and 2.0 % for DHA. Despite these differences, our findings suggest that increasing EPA levels to 0.4 % or higher might be associated with notable improvements in hippocampal volumes and their subfields.

Low levels of EPA and DHA have been associated with increased neuroinflammation (von Schacky, 2021). EPA and DHA both play a crucial role in modulating the inflammatory response of microglia, the primary immune cells in the brain. They achieve this by influencing the expression of various receptors on the surface of microglial cells, thereby fine-tuning the cells' inflammatory activity (Hosseini et al., 2018).

A diet deficient in omega-3 reduces brain DHA in all brain structures, with the hippocampus, which contains the highest concentration of DHA, being the most affected and the hypothalamus the least (Joffre et al., 2019). Research indicates that hippocampal subfield volumes may be affected by pro-inflammatory factors (Raz et al., 2015) and neuroinflammation can be ameliorated by pharmacological and physical interventions (Gomes da Silva et al., 2013).

This research underscores the significant roles EPA and DHA play in the sex differences in hippocampal volumes, particularly among adults with HIV and those with low omega-3 levels. Further investigations are necessary to confirm and expand upon these findings.

Table 3
Sex Differences in ICV-Adjusted Volumes of Hippocampus and its Subfields by Omega-3 Levels Among Participants with HIV.

Table 3A. Sex Differences in ICV-Adjusted Volumes of Hippocampus and its Subfields by EPA Median Level

Outcome variable[a]	Unadjusted				Adjusted[c]			
	EPA ≤0.40 %		EPA >0.40 %		EPA ≤0.40 %		EPA >0.40 %	
	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]
Left hippocampal tail	−3.6 (−6.3, −0.8)	0.01	−0.3 (−3.1, 2.4)	0.82	−3.7 (−6.6, −0.7)	0.02	−1.4 (−4.0, 1.3)	0.32
Right hippocampal tail	−4.0 (−6.8, −1.2)	0.005	−1.3 (−4.1, 1.5)	0.35	−4.2 (−7.4, −1.1)	0.009	−1.8 (−4.5, 0.9)	0.19
Left subiculum	−3.1 (−5.0, −1.2)	**0.0017**	0.6 (−1.2, 2.4)	0.53	−2.7 (−5.8, 0.3)	0.08	−0.4 (−2.3, 1.4)	0.65
Right subiculum	−3.3 (−5.0, −1.7)	**<0.0001**	0.6 (−1.2, 2.3)	0.52	−4.2 (−6.1, −2.2)	**<0.0001**	−0.2 (−2.1, 1.6)	0.79
Left CA1	−5.3 (−7.8, −2.8)	**<0.0001**	−1.1 (−4.3, 2.1)	0.51	−6.4 (−9.4, −3.5)	**<0.0001**	−2.2 (−5.8, 1.4)	0.23
Right CA1	−5.0 (−7.7, −2.3)	**0.0003**	−1.4 (−5.1, 2.2)	0.44	−6.6 (−9.8, −3.5)	**<0.0001**	−1.8 (−5.7, 2.0)	0.35
Left hippocampal fissure	−0.9 (−2.2, 0.4)	0.16	−1.2 (−2.2, −0.2)	0.02	−1.8 (−3.6, 0.0)	0.05	−1.0 (−1.9, −0.1)	0.03
Right hippocampal fissure	−1.0 (−2.4, 0.3)	0.14	−1.6 (−2.6, −0.5)	0.003	−2.3 (−4.0, −0.6)	0.009	−1.2 (−2.3, 0.0)	0.06
Left presubiculum	−2.3 (−3.6, −0.9)	**0.0015**	0.4 (−0.8, 1.5)	0.54	−2.0 (−4.0, 0.0)	0.05	−0.1 (−1.3, 1.1)	0.90
Right presubiculum	−2.1 (−3.5, −0.7)	0.003	0.3 (−0.9, 1.6)	0.59	−1.8 (−3.2, −0.3)	0.02	−0.1 (−1.5, 1.2)	0.85
Left parasubiculum	0.0 (−0.6, 0.5)	0.89	0.0 (−0.5, 0.4)	0.88	0.2 (−0.5, 1.0)	0.56	−0.3 (−0.7, 0.2)	0.22
Right parasubiculum	0.1 (−0.4, 0.5)	0.82	−0.1 (−0.6, 0.4)	0.65	0.3 (−0.1, 0.7)	0.21	−0.2 (−0.7, 0.3)	0.48
Left molecular layer	−2.5 (−4.9, −0.2)	0.04	−0.5 (−3.2, 2.2)	0.69	−4.6 (−7.8, −1.4)	0.004	−0.9 (−4.0, 2.2)	0.56
Right molecular layer	−2.8 (−5.3, −0.3)	0.03	−0.8 (−3.5, 1.8)	0.54	−5.1 (−8.4, −1.8)	0.002	−0.7 (−3.6, 2.3)	0.65
Left GC-ML-DG	−2.3 (−3.4, −1.1)	**0.0001**	−0.8 (−2.3, 0.7)	0.29	−2.8 (−4.2, −1.4)	**<0.0001**	−1.1 (−2.9, 0.7)	0.24
Right GC-ML-DG	−2.5 (−3.8, −1.1)	**0.0003**	−1.3 (−2.8, 0.2)	0.09	−3.2 (−4.5, −1.9)	**<0.0001**	−1.6 (−3.4, 0.2)	0.08
Left CA2/3	−1.9 (−3.0, −0.8)	**0.0007**	−0.2 (−1.5, 1.0)	0.72	−2.6 (−3.9, −1.4)	**<0.0001**	−0.3 (−1.8, 1.2)	0.70
Right CA2/3	−2.0 (−3.4, −0.7)	0.003	−0.7 (−1.9, 0.5)	0.24	−2.8 (−4.3, −1.3)	**0.0002**	−0.8 (−2.2, 0.5)	0.23
Left CA4	−1.9 (−2.8, −1.0)	**<0.0001**	−0.9 (−2.1, 0.4)	0.17	−2.3 (−3.3, −1.2)	**<0.0001**	−1.1 (−2.6, 0.4)	0.14
Right CA4	−2.1 (−3.2, −1.1)	**<0.0001**	−1.3 (−2.4, −0.1)	0.03	−2.6 (−3.7, −1.5)	**<0.0001**	−1.5 (−2.9, −0.1)	0.03
Left fimbria	−0.2 (−1.0, 0.7)	0.71	0.2 (−0.5, 0.9)	0.52	0.1 (−1.0, 1.2)	0.82	0.3 (−0.5, 1.1)	0.49
Right fimbria	−0.4 (−1.4, 0.6)	0.44	−0.5 (−1.3, 0.4)	0.28	−0.5 (−1.8, 0.8)	0.45	−0.3 (−1.3, 0.7)	0.53
Left HATA	−0.4 (−0.8, −0.1)	0.01	−0.1 (−0.4, 0.3)	0.68	−0.5 (−0.9, −0.2)	0.005	0.0 (−0.4, 0.4)	0.87
Right HATA	−0.4 (−0.8, −0.1)	0.02	0.1 (−0.3, 0.4)	0.64	−0.3 (−0.7, 0.1)	0.09	0.1 (−0.3, 0.4)	0.74
Left whole hippocampus	−23.4 (−34.5, −12.4)	**<0.0001**	−2.8 (−16.8, 11.3)	0.70	−27.3 (−40.6, −14.0)	**<0.0001**	−7.4 (−22.2, 7.4)	0.33
Right whole hippocampus	−24.6 (−36.4, −12.8)	**<0.0001**	−6.4 (−20.5, 7.7)	0.37	−31.1 (−44.0, −18.1)	**<0.0001**	−9.2 (−24.3, 6.0)	0.24

Table 3B. Sex Differences in ICV-Adjusted Volumes of Hippocampus and its Subfields by DHA Median Level

Outcome variable[a]	Unadjusted				Adjusted[c]			
	DHA ≤2.0 %		DHA >2.0 %		DHA ≤2.0 %		DHA >2.0 %	
	Regression estimate (95 %CI)	p-value[b]	Regression estimate (95 %CI)	p-value[b]	Regression estimate (95 %CI)	p-value[b]	Regression estimate (95 %CI)	p-value[b]
Left hippocampal tail	−2.0 (−4.4, 0.5)	0.11	−2.0 (−5.1, 1.0)	0.19	−2.1 (−5.0, 0.9)	0.17	−4.4 (−7.3, −1.5)	0.003
Right hippocampal tail	−3.2 (−5.7, −0.8)	0.009	−2.3 (−5.4, 0.8)	0.15	−2.2 (−5.0, 0.6)	0.12	−5 (−7.9, −2.0)	**0.0009**
Left subiculum	−2.4 (−4.3, −0.6)	0.01	−0.2 (−2.2, 1.7)	0.83	−3.5 (−6.1, −0.9)	0.008	−1.3 (−3.8, 1.2)	0.30
Right subiculum	−2.1 (−3.7, −0.6)	0.005	−0.6 (−2.5, 1.2)	0.50	−2.9 (−5.1, −0.8)	0.008	−2.8 (−4.7, −0.9)	0.003
Left CA1	−4.2 (−6.8, −1.7)	**0.0010**	−2.4 (−5.5, 0.7)	0.12	−5.3 (−8.7, −1.9)	0.002	−5.1 (−8.6, −1.6)	0.005
Right CA1	−4.2 (−6.9, −1.5)	0.003	−2.6 (−6.1, 0.9)	0.15	−5.3 (−8.9, −1.6)	0.005	−5.4 (−8.9, −1.8)	0.003
Left hippocampal fissure	−0.8 (−2.1, 0.5)	0.21	−1.4 (−2.5, −0.2)	0.02	−2.4 (−3.9, −0.8)	0.003	−0.9 (−2.3, 0.5)	0.20
Right hippocampal fissure	−1.4 (−2.8, 0.0)	0.06	−1.2 (−2.3, −0.1)	0.04	−3.0 (−4.9, −1.2)	**0.0012**	−0.6 (−1.8, 0.6)	0.32
Left presubiculum	−1.3 (−2.6, 0.0)	0.05	−0.6 (−1.9, 0.8)	0.41	−2.2 (−3.7, −0.6)	0.007	−1.1 (−2.9, 0.7)	0.23
Right presubiculum	−0.8 (−2.2, 0.6)	0.25	−0.9 (−2.2, 0.5)	0.20	−1.5 (−2.9, −0.2)	0.02	−1.8 (−3.1, −0.4)	0.01
Left parasubiculum	−0.2 (−0.7, 0.3)	0.43	0.2 (−0.3, 0.7)	0.48	−0.2 (−0.7, 0.3)	0.51	0.1 (−0.7, 0.8)	0.84
Right parasubiculum	0.0 (−0.5, 0.6)	0.87	0.0 (−0.4, 0.4)	0.91	0.2 (−0.4, 0.7)	0.60	−0.2 (−0.5, 0.2)	0.34
Left molecular layer	−0.9 (−3.7, 1.8)	0.50	−2.1 (−4.6, 0.4)	0.09	−2.6 (−6.7, 1.5)	0.21	−2.7 (−5.3, −0.1)	0.04
Right molecular layer	−0.6 (−3.7, 2.4)	0.68	−2.8 (−5.2, −0.5)	0.018	−2.1 (−6.4, 2.1)	0.33	−3.7 (−5.8, −1.6)	**0.0007**
Left GC-ML-DG	−1.8 (−3.0, −0.6)	0.003	−1.5 (−2.9, 0.0)	0.05	−2 (−3.4, −0.6)	0.004	−2.2 (−4.1, −0.4)	0.02
Right GC-ML-DG	−2.5 (−3.6, −1.4)	**<0.0001**	−1.5 (−3.1, 0.1)	0.06	−2.7 (−4.2, −1.2)	**0.0004**	−2.6 (−4.3, −0.9)	0.003
Left CA2/3	−0.8 (−2.0, 0.4)	0.17	−1.4 (−2.7, −0.2)	0.02	−1.2 (−2.6, 0.2)	0.09	−2 (−3.4, −0.7)	0.002
Right CA2/3	−1.5 (−2.8, −0.2)	0.02	−1.3 (−2.6, −0.1)	0.04	−2.2 (−4, −0.4)	0.02	−1.9 (−3.3, −0.5)	0.009
Left CA4	−1.4 (−2.4, −0.5)	0.004	−1.4 (−2.6, −0.2)	0.02	−2.0 (−3.1, −0.8)	**0.0007**	−1.9 (−3.3, −0.5)	0.01
Right CA4	−2.1 (−3.1, −1.2)	**<0.0001**	−1.4 (−2.6, −0.1)	0.03	−2.6 (−3.8, −1.3)	**<0.0001**	−2.1 (−3.5, −0.8)	0.002
Left fimbria	0.1 (−0.8, 1.0)	0.80	−0.1 (−0.9, 0.7)	0.85	1.1 (0.3, 1.9)	0.01	−0.1 (−1, 0.9)	0.91
Right fimbria	−0.4 (−1.4, 0.7)	0.50	−0.6 (−1.4, 0.3)	0.20	0.5 (−0.5, 1.4)	0.35	−0.6 (−1.7, 0.4)	0.25
Left HATA	−0.2 (−0.5, 0.1)	0.18	−0.3 (−0.7, 0.0)	0.08	−0.1 (−0.4, 0.3)	0.74	−0.5 (−0.9, 0.0)	0.03
Right HATA	−0.2 (−0.6, 0.2)	0.32	−0.2 (−0.5, 0.2)	0.32	0.1 (−0.4, 0.6)	0.68	−0.4 (−0.8, 0.0)	0.08
Left whole hippocampus	−15.2 (−26.8, −3.6)	0.01	−11.9 (−25.9, 2.1)	0.09	−20 (−35.3, −4.6)	0.01	−21.2 (−36.7, −5.6)	0.008
Right whole hippocampus	−17.6 (−28.7, −6.6)	**0.0018**	−14.3 (−28.7, 0.2)	0.05	−20.9 (−36.6, −5.1)	0.009	−26.3 (−39.9, −12.7)	**0.0002**

[a] All the outcome variables were defined as the volumes of the hippocampus and its subfields divided by log(ICV).
[b] For the volumes of hippocampus and its hippocampal subfields, and a p-value <0.00192 (Bold) indicated statistical significance.
[c] Adjusted for age >55 years, <high school education, family annual income <$20,000, cocaine use >10 years, Zung self-rating depression score>40, and the atherosclerotic cardiovascular disease (ASCVD) risk score, and CD4 count, nadir.

4.4. Adults with lower EPA have lower hippocampal volumes when episodic memory is not ideal

Although this study was not designed to specifically address the clinical relationship between EPA/DHA levels and hippocampal volume, our findings suggest that **EPA, but not DHA,** may be independently associated with hippocampal volume when episodic memory is suboptimal. This association remained significant after adjusting for age, educational attainment, HIV status, and sex. These findings highlight a potential opportunity to explore EPA as a target for interventional studies.

4.5. Strengths

Our study has several strengths worth highlighting: (1) To our knowledge, no previous studies explored the association of HIV and omega-3 fatty acid levels with sex differences in hippocampal volumes. This research sheds light on various aspects, including the neurobiology of HIV, the role of dietary omega-3 fatty acids, and their intersection with sex differences in brain anatomy. (2) This study provides insights into the complex interplay among HIV, diet, and sex in a critical brain region. Given the hippocampus's central role in memory and emotion, understanding its volume changes is crucial for cognition and mental well-being. (3) By focusing on HIV, we deepen our understanding of its neurobiological effects, which is essential for treating HIV-associated neurocognitive disorders. The neuroprotective properties of EPA and DHA, when understood within the context of HIV and sex differences, could offer groundbreaking insights. Ultimately, this study opens avenues for developing tailored treatments and preventive strategies based on these findings.

4.6. Limitations

Despite its strengths, our study has several important limitations that should be considered in future research. First, while the Heart Study has spanned nearly 25 years and was initially focused on HIV-associated cardiovascular comorbidities, the investigation of HIV-related brain and cognitive comorbidities, including sex differences, is a new addition. The data presented are cross-sectional, limiting our ability to establish causal relationships. We plan to conduct longitudinal analyses as follow-up data become available. Furthermore, although we examined the effect of HIV on hippocampal volumes, the absence of pre-diagnosis volume data highlights the need for longitudinal studies to better understand these associations. Second, some variables in our analyses, such as cocaine use and depression scores, rely on self-reported data, which may be subject to recall bias, response bias, or under-reporting. These biases could potentially impact the validity and reliability of the findings. Third, our research primarily focused on a predominantly African American population, a group disproportionately affected by HIV, substance use, poverty, and related socioeconomic challenges. Consequently, caution is advised when generalizing these findings to other populations. Given the potential influence of omega-3 levels on sex differences in brain structure and function, future research should include other racial and ethnic groups to test these hypotheses and expand the generalizability of the findings. Lastly, we did not collect information on participants' dietary habits or vitamin supplementation, which are key sources of omega-3 intake. Future research should account for these factors, and we plan to include dietary intake and supplementation data in upcoming studies.

5. Implications and conclusions

The findings of this study have several important implications. First, this research offers new insights into how HIV influences sex differences in hippocampal volumes, particularly highlighting the exacerbation of these differences in the presence of low omega-3 fatty acid levels. This is crucial for understanding the neurobiological mechanisms underlying HIV-associated neurocognitive disorders (HAND), especially in populations disproportionately affected by HIV, such as African American women. Second, the study underscores the potential neuroprotective role of omega-3 fatty acids (EPA and DHA) in mitigating the adverse effects of HIV on hippocampal volumes, particularly in women. This suggests that dietary interventions or omega-3 supplementation could serve as a viable, non-pharmacological strategy to reduce neurocognitive decline in HIV-infected individuals. Third, the findings emphasize the need for personalized approaches in treating HIV-associated comorbidities. Given the observed sex differences in hippocampal volumes, treatment strategies should consider gender-specific interventions, particularly in relation to nutritional supplementation and the management of neurocognitive risks. Lastly, the findings from this study may provide valuable insights for informing public health strategies and clinical guidelines in the management of HIV-infected populations. By highlighting the potential role of diet and specific nutritional deficiencies, these results suggest that incorporating dietary counseling and interventions could be beneficial as part of the comprehensive care for individuals with HIV.

To build on these findings, we will take the following steps: (1) Conduct longitudinal research to explore the causal relationships between HIV, omega-3 fatty acid levels, and hippocampal volumes to assess long-term impacts and critical intervention periods, (2) Expand the study to diverse racial and ethnic groups to evaluate the generalizability of these findings and identify population-specific vulnerabilities, (3) Design randomized controlled trials (RCTs) to test the efficacy of omega-3 supplementation in reducing hippocampal volume loss and cognitive decline, with a focus on women, (4) Investigate the biological mechanisms of how HIV and omega-3 fatty acids interact to affect brain structure, including pathways like inflammation and lipid metabolism, and (5) Assess the feasibility of integrating dietary interventions and omega-3 monitoring into standard HIV care. In conclusion, longitudinal studies or clinical trials are needed to confirm these findings and to determine: (1) whether the protective effects of omega-3 also benefit men with HIV, and (2) whether these effects extend to individuals without HIV.

CRediT authorship contribution statement

Hong Lai: Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Jiachen Zhuo:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Glenn Treisman:** Writing – review & editing, Writing – original draft. **Gary Gerstenblith:** Writing – review & editing, Writing – original draft. **David D. Celentano:** Writing – review & editing, Writing – original draft. **Yihong Yang:** Writing – review & editing, Writing – original draft. **Betty Jo Salmeron:** Writing – review & editing, Writing – original draft. **Hong Gu:** Writing – review & editing, Writing – original draft. **Thorsten M. Leucker:** Writing – review & editing, Writing – original draft. **Xiao Liang:** Writing – review & editing, Writing – original draft. **Raul N. Mandler:** Writing – review & editing, Writing – original draft. **Jag Khalsa:** Writing – review & editing, Writing – original draft. **Óscar Peña-Nogales:** Writing – review & editing, Formal analysis, Data curation. **Shaoguang Chen:** Writing – review & editing, Formal

Table 4
Sex Differences in Volumes of Hippocampus and Its Subfields by Omega-3 levels among All Participants.

Table 4A. Sex Differences in Volumes of Hippocampus and Its Subfields by EPA Median Level

Outcome variable	Unadjusted				Adjusted[b]			
	EPA ≤0.40 %		EPA >0.40 %		EPA ≤0.40 %		EPA >0.40 %	
	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]
Left hippocampal tail	−36.7(-68.5,-4.9)	0.02	−11.2(-46.4,24.0)	0.53	−45.0(-85.0,-5.0)	0.03	−25.2(-61.3,13.0)	0.17
Right hippocampal tail	−46.1(-77.0,-15.3)	0.003	−26.5(-60.4,7.5)	0.13	−52.9(-91.6,-14.2)	0.007	−35.9(-68.4,-3.4)	0.03
Left subiculum	−35.4(-58.0,-13.0)	0.002	−5.0(-26.0,15.9)	0.64	−42.4(-70.3,-14.5)	0.03	−17.4(-38.8,4.0)	0.11
Right subiculum	−40.5(-62.1,-18.9)	**0.0002**	−7.6(-28.4,13.1)	0.47	−52.2(-79.1,-25.3)	**0.0001**	−14.8(-37.4,7.9)	0.20
Left CA1	−69.0(-100.5,-37.0)	**<0.0001**	−20.3(-56.5,15.8)	0.27	−88.6(-126.6,-50.5)	**<0.0001**	−36.8(-76.0,2.5)	0.07
Right CA1	−69.4(-101.4,-37.5)	**<0.0001**	−30.0(-69.3,9.4)	0.14	−81.0(-117.9,-44.2)	**<0.0001**	−42.5(-86.6,1.6)	0.06
Left hippocampal fissure	−12.9(-26.4,0.6)	0.06	−18.9(-30.4,-7.4)	0.001	−11.4(-25.3,2.5)	0.11	−11.1(-22.6,0.4)	0.06
Right hippocampal fissure	−17.2(-31.7,-2.7)	0.02	−22.2(-35.5,-8.8)	0.001	−17.1(-32.9,-1.3)	0.03	−12.6(-25.9,0.7)	0.06
Left presubiculum	−29.4(-46.4,-12.4)	**0.0007**	−9.0(-23.5,5.5)	0.22	−32.7(-53.8,-11.6)	0.002	−13.3(-27.1,0.4)	0.06
Right presubiculum	−30.6(-47.3,-13.9)	**0.0003**	−4.1(-19.8,11.5)	0.60	−34.1(-54.2,-14.1)	**0.0009**	−7.1(-24.0,9.9)	0.41
Left parasubiculum	−3.4(-9.2,2.4)	0.25	−3.5(-8.6,1.6)	0.18	−4.0(-10.8,2.9)	0.26	−3.9(-9.7,1.8)	0.18
Right parasubiculum	−3.8(-9.4,1.8)	0.18	−5.2(-10.4,0.1)	0.06	−2.4(-8.7,3.9)	0.45	−6.2(-12.2,-0.3)	0.04
Left molecular layer	−49.6(-77.3,-21.9)	**0.0004**	−19.4(-48.8,10.0)	0.20	−61.5(-91.0,-32.0)	**<0.0001**	−24.3(-53.6,4.9)	0.10
Right molecular layer	−56.6(-85.6,-27.5)	**0.0001**	−25.9(-55.2,3.5)	0.08	−61.9(-93.8,-30.0)	**0.0001**	−25.8(-56.6,5.0)	0.10
Left GC-ML-DG	−31.7(-46.0,-17.4)	**<0.0001**	−11.4(-28.6,5.9)	0.20	−41.7(-60.0,-23.4)	**<0.0001**	−22.6(-41.4,-3.7)	0.02
Right GC-ML-DG	−34.6(-49.7,-19.4)	**<0.0001**	−18.2(-34.6,-1.9)	0.03	−43.7(-61.3,-26.1)	**<0.0001**	−25.1(-43.4,-6.9)	0.007
Left CA2/3	−21.4(-34.1,-8.7)	**0.0009**	−7.7(-21.7,6.2)	0.28	−28.2(-43.7,-12.6)	**0.0004**	−9.5(-25.3,6.2)	0.24
Right CA2/3	−22.6(-36.4,-8.8)	**0.0013**	−9.7(-22.8,3.3)	0.14	−26.4(-42.1,-10.7)	0.001	−9.2(-23.6,5.1)	0.21
Left CA4	−27.0(-38.5,-15.5)	**<0.0001**	−12.0(-25.7,1.7)	0.09	−33.6(-48.4,-18.8)	**<0.0001**	−19.3(-34.4,-4.2)	0.01
Right CA4	−29.7(-41.7,-17.7)	**<0.0001**	−17.4(-30.2,-4.6)	0.008	−34.9(-48.9,-20.8)	**<0.0001**	−20.5(-34.7,-6.4)	0.004
Left fimbria	−2.1(-10.8,6.7)	0.64	3.0(-5.8,11.7)	0.51	−6.2(-15.5,3.1)	0.19	−2.8(-12.2,6.7)	0.56
Right fimbria	−4.5(-15.0,6.0)	0.40	−5.1(-15.0,4.6)	0.30	−11.8(-23.9,0.4)	0.06	−8.9(-19.9,2.1)	0.11
Left HATA	−4.6(-8.5,-0.7)	0.02	−2.3(-6.7,2.2)	0.31	−6.6(-10.6,-2.6)	**0.0010**	−3.0(-8.0,2.0)	0.24
Right HATA	−4.9(-8.9,-0.9)	0.02	−2.1(-6.5,2.2)	0.34	−5.2(-9.8,-0.7)	0.02	−3.1(-8.1,1.9)	0.22
Left whole hippocampus	−310.1(-450.9,-169.2)	**<0.0001**	−98.8(-260.0,62.3)	0.23	−390.3(-563.9,-216.7)	**<0.0001**	−178.1(-342.9,-13.3)	0.03
Right whole hippocampus	−343.3(-487.0,-199.6)	**<0.0001**	−151.9(-313.3,9.5)	0.07	−406.6(-576.2,-236.9)	**<0.0001**	−199.1(-370.9,-27.3)	0.02

Table 4B. Sex Differences in Volumes of Hippocampus and Its Subfields by DHA Median Level

Outcome variable	Unadjusted				Adjusted[b]			
	DHA ≤2.0		DHA >2.0		DHA ≤2.0		DHA >2.0	
	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]	Regression estimate (95 %CI)	p-value[a]
Left hippocampal tail	−20.2(-53.5,13.1)	0.23	−29.7(-65.1,5.8)	0.10	34.5(-70.7,1.8)	0.06	−45.2(-85.8,-4.7)	0.03
Right hippocampal tail	−38.7(-69.8,-7.6)	0.01	−33.4(-70.1,3.3)	0.07	−46.7(-81.2,-12.1)	0.008	−51.6(-90.6,-12.5)	0.01
Left subiculum	−36.6(-57.0,-16.1)	**0.0005**	−1.8(-25.2,21.7)	0.88	−48.4(-72.3,-24.5)	**<0.0001**	−17.7(-44.7,9.2)	0.20
Right subiculum	−36.3(-56.9,-15.7)	**0.0005**	−10.4(-32.9,12.2)	0.37	−46.1(-71.5,-20.7)	**0.0004**	−29.2(-52.8,-5.6)	0.02
Left CA1	−59.3(-91.4,-27.3)	**0.0003**	−32.4(-67.8,3.0)	0.07	−87.4(-125.1,-49.8)	**<0.0001**	−56.0(-97.1,-14.9)	0.008
Right CA1	−64.9(-97.9,-31.9)	**0.0001**	−35.4(-75.1,4.2)	0.08	−85.4(-123.4,-47.4)	**<0.0001**	−53.3(-97.2,-9.5)	0.02
Left hippocampal fissure	−14.2(-26.0,-2.5)	0.02	−20.1(-34.2,-5.9)	0.005	−11.4(-23.8,1.0)	0.07	−14.2(-28.7,0.2)	0.05
Right hippocampal fissure	−23.5(-36.1,-10.9)	**0.0003**	−16.5(-31.7,-1.2)	0.03	−20.7(-34.5,-6.8)	0.004	−11.3(-26.0,3.4)	0.13
Left presubiculum	−26.3(-41.9,-10.8)	**0.0009**	−8.7(-25.5,8.1)	0.31	−31.8(-49.1,-14.6)	**0.0003**	−16.0(-35.4,3.4)	0.11
Right presubiculum	−20.4(-37.1,-3.8)	0.02	−13.2(-29.4,3.1)	0.11	−27.2(-46.3,-8.1)	0.005	−20.0(-37.3,-2.3)	0.02
Left parasubiculum	−5.4(-10.5,-0.3)	0.04	0.3(-5.7,6.2)	0.93	−5.7(-11.5,0.1)	0.06	−2.5(-10.0,5.1)	0.52
Right parasubiculum	−4.9(-10.7,1.0)	0.10	−2.7(-7.9,2.5)	0.31	−5.4(-12.4,1.6)	0.13	−4.0(-9.0,1.1)	0.12
Left molecular layer	−31.4(-60.9,-1.9)	0.04	−37.1(-66.2,-8.0)	0.01	−42.0(-72.8,-11.2)	0.008	−38.2(-68.0,-8.4)	0.01
Right molecular layer	−36.5(-68.7,-4.2)	0.03	−46.5(-74.3,-18.7)	**0.0011**	−41.1(-76.5,-5.7)	0.02	−46.0(-73.6,-18.5)	**0.0011**
Left GC-ML-DG	−26.1(-40.5,-11.6)	**0.0004**	−19.7(-37.4,-2.0)	0.03	−40.8(-57.6,-23.9)	**<0.0001**	−27.6(-49.1,-6.1)	0.012
Right GC-ML-DG	−34.3(-48.2,-20.4)	**<0.0001**	−20.0(-38.0,-2.0)	0.03	−46.3(-61.9,-30.8)	**<0.0001**	−27.7(-48.1,-7.2)	0.008
Left CA2/3	−11.8(-24.1,0.5)	0.06	−21.8(-36.5,-7.1)	0.004	−20.1(-34.2,-5.9)	0.006	−25.0(-42.8,-7.3)	0.006
Right CA2/3	−18.7(-31.2,-6.2)	0.003	−15.9(-30.4,-1.5)	0.03	−25.2(-39.4,-11.1)	0.0005	−18.2(-35.6,-0.9)	0.04
Left CA4	−22.1(-33.7,-10.6)	**0.0002**	−19.3(-33.3,-5.3)	0.007	−32.8(-46.5,-19.1)	**<0.0001**	−24.7(-41.6,-7.7)	0.004
Right CA4	−30.1(-41.2,-19.0)	**<0.0001**	−18.0(-32.2,-3.8)	0.01	−37.6(-50.0,-25.1)	**<0.0001**	−23.8(-40.2,-7.5)	0.004
Left fimbria	1.8(-6.9,10.6)	0.68	−2.0(-11.2,7.3)	0.68	−5.1(-14.6,4.5)	0.30	−3.4(-13.9,7.2)	0.53
Right fimbria	−2.9(-13.4,7.7)	0.60	−7.2(-16.9,2.4)	0.14	−9.3(-20.9,-1.6)	0.12	−9.0(-20.2,2.1)	0.11
Left HATA	−1.9(-5.7,2.7)	0.49	−6.1(-10.4,-1.8)	0.006	−3.6(-8.1,0.8)	0.11	−6.5(-11.7,-1.3)	0.01
Right HATA	−3.2(-7.3,1.0)	0.14	−4.2(-8.2,-0.2)	0.04	−4.4(-9.0,0.3)	0.06	−4.9(-9.9,0.1)	0.05
Left whole hippocampus	−38.9(-387.0,-90.8)	**0.0016**	−178.2(-340.9,-15.6)	0.03	−352.0(-519.4,-184.7)	**<0.0001**	−262.7(-451.1,-74.3)	0.006
Right whole hippocampus	−290.8(-440.3,-141.4)	**0.0001**	−206.9(-372.4,-41.4)	0.01	−374.8(-544.5,-205.1)	**<0.0001**	−262.7(-451.1,-74.3)	0.006

[a] For volume comparisons of the hippocampus and subfields, a p-value <0.00192 (Bold) indicated statistical significance.
[b] Adjusted for age >55 years, <high school education, family annual income <$20,000, cocaine use >10 years, HIV infection, Zung self-rating depression score>40, and the atherosclerotic cardiovascular disease (ASCVD) risk score.

Table 5
ICV-adjusted hippocampal volumes in relation to EPA and DHA: Impact of sex adjustment and episodic memory levels.

Table 5. 1. ICV-Adjusted Hippocampal Volumes in Relation to EPA: Impact of Sex Adjustment and Episodic Memory Levels

Outcome variable: Whole hippocampus	Lower episodic memory				Higher episodic memory			
	Without adjusting for sex		With adjusting for sex		Without adjusting for sex		With adjusting for sex	
	Regression estimate (95 %CI)	p-value	Regression estimate (95 %CI)	p-value	Regression estimate (95 %CI)	p-value	Regression estimate (95 %CI)	p-value
EPA	0.0003 (0.0001,0.0005)	0.0007	0.0003 (0.0001,0.0005)	0.0009	−0.0001 (−0.0003,0.0001)	0.56	−0.0001 (−0.0003,0.0001)	0.43
Age>55 years	−0.0003 (−0.0004,-0.0001)	0.002	−0.0003 (−0.0004,-0.0001)	0.003	−0.0001 (−0.0002,0.0001)	0.51	−0.0000 (−0.0002,-0.0002)	0.80
< high school education	0.0002 (0.0001,0.0004)	0.004	0.0002 (0.0001,0.0004)	0.006	0.0001 (−0.0001,0.0002)	0.59	0.0000 (−0.0001,0.0002)	0.74
HIV	−0.0000 (−0.0002,0.0002)	0.99	0.0000 (−0.0002,0.0002)	0.99	−0.0001 (−0.0002,0.0001)	0.54	−0.0000 (−0.0002,0.0001)	0.67
Female sex			0.0001 (−0.0001,0.0002)	0.49			0.0002 (0.0000,0.0004)	0.01

Table 5. 2. ICV-Adjusted Hippocampal Volumes in Relation to DHA: Impact of Sex Adjustment and Episodic Memory Levels

Outcome variable: Whole hippocampus	Lower episodic memory				Higher episodic memory			
	Without adjusting for sex		With adjusting for sex		Without adjusting for sex		With adjusting for sex	
	Regression estimate (95 %CI)	p-value	Regression estimate (95 %CI)	p-value	Regression estimate (95 %CI)	p-value	Regression estimate (95 %CI)	p-value
DHA	0.0000 (−0.0002.0.0003)	0.78	0.0000 (−0.0003,0.0003)	0.89	0.0002 (−0.0001.0.0004)	0.21	0.0001 (−0.0002,0.0004)	0.52
Age>55 years	−0.0002 (−0.0004,-0.0000)	0.03	−0.0002 (−0.0004,-0.0000)	0.04	−0.0001 (−0.0003,0.0001)	0.38	−0.0000 (−0.0002,0.0001)	0.63
< high school education	0.0002 (0.0000.0.0004)	0.03	0.0002 (0.0000,0.0004)	0.05	0.0001 (−0.0001.0.0003)	0.34	0.0001 (−0.0001,0.0002)	0.46
HIV	0.0000 (−0.0001,0.0002)	0.63	0.0000 (−0.0001,0.0002)	0.61	−0.0001 (−0.0002,0.0001)	0.37	−0.0001 (−0.0002,0.0001)	0.51
Female sex			0.0001 (−0.0001,0.0002)	0.44		0.028	0.0002 (0.0000,0.0003)	0.04

* the volumes of the whole hippocampus is adjusted for log(ICV), and EPA was log-transformed.
** Lower episodic memory = the NIH Toolbox Picture Fully Adjusted T-Score <48 (the median), and higher episodic memory = the NIH Toolbox Picture Fully Adjusted T-Score ≥48 (the median).

analysis, Data curation. **Shenghan Lai:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Elana Rosenthal:** Writing – review & editing, Writing – original draft. **Karl Goodkin:** Writing – review & editing, Writing – original draft. **Vincent A. Magnotta:** Writing – review & editing, Writing – original draft.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.100988.

Data availability

The data that has been used is confidential.

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