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Research Article

The prefrontal cortex, but not the medial temporal lobe, is associated with episodic memory in middle-aged persons with HIV

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Abstract

Objective: Identifying persons with HIV (PWH) at increased risk for Alzheimer's disease (AD) is complicated because memory deficits are common in HIV-associated neurocognitive disorders (HAND) and a defining feature of amnestic mild cognitive impairment (aMCI; a precursor to AD). Recognition memory deficits may be useful in differentiating these etiologies. Therefore, neuroimaging correlates of different memory deficits (i.e., recall, recognition) and their longitudinal trajectories in PWH were examined. **Design:** We examined 92 PWH from the CHARTER Program, ages 45–68, without severe comorbid conditions, who received baseline structural MRI and baseline and longitudinal neuropsychological testing. Linear and logistic regression examined neuroanatomical correlates (i.e., cortical thickness and volumes of regions associated with HAND and/or AD) of memory performance at baseline and multilevel modeling examined neuroanatomical correlates of memory decline (average follow-up = 6.5 years). **Results:** At baseline, thinner pars opercularis cortex was associated with impaired recognition ($p = 0.012$; $p = 0.060$ after correcting for multiple comparisons). Worse delayed recall was associated with thinner pars opercularis ($p = 0.001$) and thinner rostral middle frontal cortex ($p = 0.006$) cross sectionally even after correcting for multiple comparisons. Delayed recall and recognition were not associated with medial temporal lobe (MTL), basal ganglia, or other prefrontal structures. Recognition impairment was variable over time, and there was little decline in delayed recall. Baseline MTL and prefrontal structures were not associated with delayed recall. **Conclusions:** Episodic memory was associated with prefrontal structures, and MTL and prefrontal structures did not predict memory decline. There was relative stability in memory over time. Findings suggest that episodic memory is more related to frontal structures, rather than encroaching AD pathology, in middle-aged PWH. Additional research should clarify if recognition is useful clinically to differentiate aMCI and HAND.

Keywords: Aging; cognition; Alzheimer's disease; infectious disease; HIV-associated neurocognitive disorders; neuroimaging

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Introduction

HIV-associated neurocognitive disorders (HAND) remain prevalent in the era of combination antiretroviral therapy (ART; 20–50%; Heaton et al., 2010; Saloner & Cysique, 2017). HAND is usually non-progressive (Clifford & Ances, 2013) and the majority of neurocognitive deficits remain in the mild-to-moderate range (Heaton et al., 2010). HIV is known to particularly impact fronto-striatal systems (i.e., basal ganglia and prefrontal structures; Ances & Hammoud, 2014). Similarly, HAND has been associated with fronto-striatal circuits as well as cortical structures (Alakkas et al., 2019; Ances & Hammoud, 2014; Nichols et al., 2019). This fronto-striatal involvement associated with HAND is thought to account for its "subcortical" cognitive presentation, with characteristic deficits in executive functioning, learning, and memory (specifically recall, as opposed to recognition; Salmon & Bondi, 2009). Indeed, such deficits are most common in HAND (Heaton et al., 2011), and this "subcortical" presentation has been observed even as PWH age (Scott et al., 2011).

Although HAND is not typically progressive, some evidence suggests episoidic memory may be particularly affected in older PWH (Pasipanodya et al., 2019; Seider et al., 2014). For example, Seider et al. (2014) found that verbal memory declines more rapidly with age in PWH as compared to HIV-negative comparison participants. Additionally, episodic memory decline has been associated with hippocampal atrophy in PWH

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(Pfefferbaum et al., 2014; Wang et al., 2015). However, most of these studies examining memory in PWH have primarily focused on delayed recall and did not consider other potential etiologies beyond HAND.

In contrast to HAND, Alzheimer's disease (AD) is a neurodegenerative disease associated with progressive cognitive decline and functional impairment (Alzheimer's Association, 2017). AD is characterized by the accumulation of amyloid plaques ($A\beta_{42}$) and tau neurofibrillary tangles (NFT) in the brain. NFTs are thought to initially accumulate predominantly in the medial temporal lobe (MTL) and result in atrophy of the MTL and later more widespread atrophy in adjacent cortices (Jack et al., 2018). Given the central role of the MTL in episodic memory processes, AD typically presents with changes in memory, including learning, delayed recall, *and* recognition (Smith & Butts, 2016), with changes in language and executive functioning sometimes also observed in the early stages of the disease (Edmonds et al., 2015; Kirova et al., 2015). Brain changes associated with future cognitive decline and incident AD dementia can be observed as early as midlife (Ritchie et al., 2015; Sutphen et al., 2015). Additionally, longitudinal studies have shown that more subtle differences in episodic memory in midlife (e.g., worse memory performance than "non-decliners" but not necessarily in the "impaired" range) is associated with a decline in memory years later (Clark et al., 2016; Kremen et al., 2014; Okonkwo et al., 2014). Moreover, Jak et al. (2015) found that worse midlife memory performance in people without HIV is associated with hippocampal atrophy.

As PWH age, they may face increased risk of AD and its precursor, amnestic mild cognitive impairment (aMCI), due to the compounding effects of HIV and aging on the brain, as well as higher prevalence of vascular and metabolic risk factors among PWH (Milanini & Valcour, 2017; Rubin et al., 2019). Due to the overlap in memory impairments, older PWH may be misclassified as having HAND instead of being on an AD trajectory. Recent case reports have highlighted the risk of delayed diagnosis of AD in PWH, the complexities in determining the etiology of cognitive impairment, and the need for non-invasive tools to differentiate HAND and aMCI (Calcagno et al., 2021; Hellmuth et al., 2018; Morgello et al., 2018).

Comparative studies between PWH with HAND and HIV-negative participants with MCI or AD have shown differences in brain structures. Smaller hippocampal volumes were observed in MCI/AD compared to HAND, while HAND often presented with greater frontal gray matter atrophy (Milanini et al., 2019; Zhang et al., 2016). However, most studies have focused solely on HAND and have not explored other etiologies of cognitive impairment in PWH (Holt et al., 2012; Kuhn et al., 2018). Recent work by Sundermann et al. (2021) has begun to examine neuropsychological methods for identifying aMCI in PWH using adapted Jak/Bondi MCI criteria (Jak et al., 2009) that requires recognition memory impairment. This study found that middle-aged and older PWH classified as aMCI were 3.5 times more likely to have the presence of $A\beta_{42}$ plaques associated with AD, indicating that recognition memory impairment could serve as a clinical marker of AD risk in PWH. Further research is needed to validiate the link between recognition memory and other known AD markers, such as MTL integrity, among PWH.

To address gaps in the literature and specifically examine memory in PWH with the idea that multiple etiologies could be contributory (i.e., HAND and AD), we investigated the relationship between brain integrity and aspects of epidosic memory performance (i.e., delayed recall *and* recognition) in middle-aged PWH aged 45–68 years. The lower age range was selected given that Alzheimer's pathology is known to start accumulating in mid-life, the majority of PWH are in this mid-life age range (Centers for Disease Control and Prevention, 2018), and mid-life is when the research has demonstrated early preclinical changes in memory can start to show differences in those at greater risk of AD as described above. The first aim of the study was to examine the neuroimaging correlates of delayed recall and recognition in aging PWH using structural MRI data, focusing on the MTL, basal ganglia, and prefrontal cortex. We hypothesized that 1) recognition memory would be most strongly related to MTL structures given its association in AD and 2) delayed recall would be associated with MTL structures as well as fronto-striatal circuit structures, given the reliance on retrieval strategies and the associations found in both AD and HAND. To further validate the specificity of recognition-MTL relationships, processing speed and psychomotor skills were analyzed, with the hypothesis that they would be more strongly associated with basal ganglia and prefrontal cortex structures *and* are relatively preserved in aMCI (Paul et al., 2008; Weintraub et al., 2012; Wright et al., 2016; note, executive functioning was not selected given the overlap in both HAND and aMCI). The second aim was to examine if baseline structural neuroimaging was associated longitudinally with amnestic decline, with the hypothesis that smaller baseline MTL structures would be associated with a greater and/or faster decline in recognition and delayed recall. For all analyses, we examined covariates that may also be contributing to cognition including HIV-disease characteristics, risk factors associated with AD (e.g., *APOE* status), and comorbid conditions.

Methods

Participants

Our study analyzed data from individuals enrolled in the longitudinal MRI arm of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) program, which is a study aimed broadly at understanding the nervous system complications in HIV, particularly in relation to ART (Heaton et al., 2010; Jernigan et al., 2011). After excluding participants who did not meet inclusion/exclusion criteria as detailed below, 92 PWH between the ages of 45 to 68 years old were included in this study. All participants underwent a structural MRI scan between 2008 and 2010 using a standardized acquisition, as well as comprehensive neuropsychological, neuromedical, and neuropsychiatric evaluations; the baseline in this case was not the first visit in the CHARTER study overall but the first visit with this specific MRI protocol, which changed across the life of the study. MRI and neuropsychological, neuromedical, and neuropsychiatric evaluations were completed within 3 months (average difference from MRI to other evaluations was 6 days). Most participants ($n = 91$) completed at least one follow-up neuropsychological, neuromedical, and neuropsychiatric study visit occurring in approximately 6-month intervals. Participants were drawn from five of the six participating CHARTER sites (i.e., those with comparable imaging capabilities): Johns Hopkins University, the Icahn School of Medicine at Mount Sinai, University of California San Diego, University of Texas Medical Branch, and University of Washington. All CHARTER study procedures were approved by each sites university Institutional Review Boards, all participants provided written informed consent, and the research was completed in accordance with the Helsinki Declaration.

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Participant characterization and inclusion/exclusion criteria

CHARTER initial inclusion criteria were minimal. To determine the extent to which non-HIV-related comorbidities have contributed to neurocognitive impairment, participants with severe "confounding" comorbidities, as defined by Frascati criteria (i.e., current HAND nosology; Antinori et al., 2007; Heaton et al., 2010), were excluded from this project. To study the effect of aging, the age range was restricted to participants who were aged 45 or older at the time of the MRI scan. Additionally, one participant was excluded from the study given that their T1 structural MRI scan was inadequate and did not yield usable data.

Neuropsychological evaluation

At each study visit, participants completed a standardized battery of neurocognitive tests. Before neuropsychological testing, participants passed the Hiscock Digit Memory Test, a free-standing performance validity test. The test battery assessed seven cognitive domains commonly affected by HIV (Heaton et al., 2010); given the aims of this study the tests of memory, processing speed, and psychomotor skills were the focus of this analysis.

Tests of memory in the CHARTER study included the Hopkins Verbal Learning Test – Revised (HVLT-R) and the Brief Visuospatial Memory Test-Revised (BVMT-R). Tests of processing speed included WAIS-III Digit Symbol and Symbol Search, Trail Making Test Part A, and the Stroop Color Trial. Psychomotor skills were examined via the bilateral Grooved Pegboard Test. Raw delayed recognition discrimination scores on the HVLT-R and BVMT-R were converted to *Z*-scores (M = 0, SD = 1) that account for demographic variables (i.e., age, sex, education, and race/ethnicity) using normative data from the HIV Neurobehaviroal Research Program (Norman et al., 2011). The two recognition discrimination *Z*-scores were then averaged to create a recognition composite. The recognition analyses did not meet assumptions for linear regression (i.e., evidence of heteroscedasticity, residuals were non-normally distributed). Therefore, delayed recognition was dichotomized into an impaired recognition group (i.e. < -1.0 SD below the demographically corrected mean) and an unimpaired recognition group. Given that practice effect correction was not available for delayed recognition and participants had a varying number of previous administrations, number of prior neuropsychological evaluations was included as a covariate in analyses examining delayed recognition. Raw delayed recall, processing speed, and psychomotor scores were converted to T-scores (M = 50, SD = 10) that account for demographic variables (i.e., age, sex, education, and race/ethnicity) and practice effects using normative data from the HIV Neurobehavioral Research Program (Cysique et al., 2011; Heaton et al., 2003; Norman et al., 2011). Practice-effect corrected T-scores from all tests in each cognitive domain were then averaged to obtain a domain T-score. The Wide Range Achievement Test-III was utilized to estimate premorbid verbal IQ.

Neuromedical evaluation

Participants completed a neuromedical evaluation at each study timepoint. HIV disease characteristics were collected from most participants at each visit including (1) current CD4+ T lymphocyte count measured via flow cytometry; (2) nadir CD4 recorded via a combination of self-report and medical records; (3) HIV RNA in plasma measured by ultra-sensitive PCR (Amplicor, Roche Diagnostic System, Indianapolis IN; lower limit of detection <50 copies/ml); (4) estimated duration of HIV disease collected via self-report; and (5) current ART regimen. Comorbid medical conditions in Table 1 were determined by self-report and/or by their taking medication for the condition. Comorbid psychiatric and substance use conditions were determined with the Composite International Diagnostic Interview (World Health Organization, 1997). Additionally, CHARTER participants have *APOE* genotype data (see Morgan et al. (2013) for additional information). *APOE* genotype was dichotomized into those at highest genetic risk of AD (i.e., the *APOE* ε4+ group which included genotypes ε34 and ε44) and those at approximately average or lower genetic risk of AD (i.e., the *APOE* ε4- group including genotypes ε22, ε23, ε33, ε24; Rasmussen et al., 2018).

Table 1. Participant demographic and clinical characteristics (N = 92)

	M (SD), median [IQR], *n* (%)
Demographic variables	
Age (years), M (SD)	51.4 (5.9) Range = 45–68 years
Male, *n* (%)	78 (85.7%)
Race/Ethnicity [a], *n* (%)	
African American/Black	46 (50.5%)
Non-Hispanic white	35 (38.4%)
Hispanic/Latino	8 (8.8%)
"Other"	2 (2.2%)
Education (years), M (SD)	13.0 (2.4)
Baseline neurocognitive functioning	
Global T-Score, M (SD)	49.2 (7.1)
Delayed Recall T-Score, M (SD)	50.4 (9.3)
Delayed recall impairment, *n* (%)	18 (19.6%)
HVLT-R Delayed recall raw score, median [IQR]	9 [7–11]
BVMT-R Delayed recall raw score, median [IQR]	9 [7–10.75]
Recognition Z-Score, M (SD)	−0.1 (1.07)
Recognition Impairment, *n* (%)	12 (13.2%)
HVLT-R Recognition, median [IQR], (range)	11 [10–12], (6–12)
BVMT-R Recognition, median [IQR], (range)	6 [6–6], (4–6)
Processing Speed T-Score, M (SD)	50.5 (9.8)
Psychomotor Skills T-Score [b], M (SD)	44.3 (10.8)
Premorbid Verbal IQ, M (SD)	93 (14.9)
Comorbid conditions	
Hyperlipidemia [c], *n* (%)	20 (22.7%)
Hypertension [c], *n* (%)	36 (40.9%)
Diabetes mellitus [c], *n* (%)	18 (20.5%)
Hepatitis C [c], *n* (%)	47 (53.4%)
LT MDD, *n* (%)	53 (57.6%)
Current MDD, *n* (%)	10 (10.9%)
LT substance use disorder, *n* (%)	68 (73.9%)
Current substance use disorder [c], *n* (%)	4 (4.5%)
***APOE* genotype**	
APOE ε4+ [a], *n* (%)	22 (26.2%)
HIV characteristics	
AIDS, *n* (%)	68 (73.9%)
Current CD4 [d], median [IQR]	496 [342–689]
Nadir CD4, median [IQR]	114 [22–214]
Duration of HIV disease (years) [c], median [IQR]	15.6 [9.9–19.6]
On ART [c], *n* (%)	78 (88.6%)
Undetectable viral load [c], *n* (%)	64 (72.7%)

Note: [a] *n* = 91; [b] *n* = 90; [c] *n* = 88; [d] *n* = 87; HVLT-R=Hopkins Verbal Learning Test-Revised; BVMT-R=Brief Visuospatial Memory Test-Revised; LT = lifetime; MDD = major depressive disorder; ART = antiretroviral therapy.

Neuroimaging

MRI data were acquired on six General Electric 1.5-Tesla scanners at five site locations that participated in this MRI protocol. A three-dimensional sagittal T1-weighted spoiled gradient recalled (SPGR) acquisition was acquired: section thickness = 1.3 mm, FOV 24 cm,

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matrix size 256 × 256 × 124; TR = 20 ms, TE = 6 ms, flip angle = 30. In addition, coronal 2D T2 and proton density (PD) weighted fast spin echo sequences with a slice thickness of 2.0 mm were acquired and, for the present study, provided direct a measure of intracranial vault volume (ICV) as detailed in previous tissue segmentation work (Fennema-Notestine et al., 2013; Fennema-Notestine et al., 2016; Jernigan et al., 2011).

FreeSurfer (Dale et al., 1999; Desikan et al., 2006; Fischl, 2012) version 7.1.1 was used to obtain cortical thickness and subcortical volume measures (similar to previous work Fennema-Notestine et al., 2011; Lansing et al., 2016). All T1 scans were visually inspected to check for proper segmentation; in addition to the one participant excluded from all analyses as described above, one participant's hippocampal data were excluded from analysis given inaccurate probabilistic segmentation (overestimation). Neocortical thickness regions of interest included MTL structures (i.e., entorhinal and parahippocampal), and prefrontal (i.e., rostral and caudal midfrontal areas; inferior frontal regions of pars opercularis, pars triangularis, and pars orbitalis) cortical areas. Volumetric subcortical regions of interest included the hippocampus (MTL structure) as well as the basal ganglia (caudate nucleus and putamen). Each structure was analyzed separately as bilateral estimates; left and right volumes or cortical thicknesses for these regions of interest were averaged.

The differences in scanner from site to site were corrected by regressing scanner from the data prior to analyses, given that differences in estimated values across scanners have been well-documented (Fennema-Notestine et al., 2007; Jernigan et al., 2011). For volumetric data, differences in head size were accounted for by including estimated total ICV as a covariate. Mean overall cortical thickness was included as a covariate in regional cortical thickness analyses. Additionally, age was included as a covariate to adjust for the normal age differences in the brain.

Data analytic approach

Findings were considered significant at $p < 0.05$. The false discovery rate method was utilized to correct for multiple-comparisons for the main analyses (Benjamini & Hochberg, 1995). JMP Pro 16 statistical software was used for aim 1, and R version 4.2.1 software was used to examine aim 2.

Aim 1

Logistic regression was used for dichotomous recognition analyses. A series of multivariable linear regressions were used to model individual continuous outcomes (i.e., delayed recall, processing speed, psychomotor skills T-scores). Imaging variables (i.e., thickness of MTL and prefrontal structures and volume of MTL and basal ganglia structures) were tested separately.

Age and imaging covariates (i.e., ICV or mean cortical thickness) were included in every model; scanner effects were accounted for prior to these analyses as noted above. The number of prior neuropsychological evaluations was included as a covariate in recognition models. Additional covariates (i.e., demographic variables (excluding site), comorbid conditions, HIV disease characteristics, and *APOE* status are listed in Table 1) were selected by evaluating the bivariate relationships between potential covariates and outcomes. If a potential covariate was associated with an outcome at $p < 0.10$ it was then entered as a covariate. Covariates were retained in the model if the covariate remained associated with the outcome (via backwards selection) at $p < 0.10$. Using this methodology, AIDS status and *APOE* group were included as covariates in delayed recall analyses, and estimated duration of HIV disease, viral detectability, and race/ethnicity were included as covariates in psychomotor analyses. For recognition memory and processing speed no additional covariates were included.

Aim 2

This aim utilized multi-level modeling to examine dichotomous recognition and continuous delayed recall across follow-up visits. Outcomes (i.e., recognition and delayed recall) were examined separately. The "lme4 version 1.1–30" R package was used to conduct mixed-effects regressions (Bates et al., 2014). Mixed-effects logistic regression models were used to examine dichotomous recognition as the outcome. Linear mixed-effects models were used to examine continuous delayed recall as the outcome. Analyses included a random intercept and a random effect for years since baseline (modeled continuously). A cross-level interaction was used to test if baseline MTL structures (i.e., hippocampus, entorhinal cortex, parahippocampal gyrus) is associated with longitudinal recognition impairment or decline in delayed recall. Between-persons covariates included age at baseline, imaging covariate, and covariates identified in aim 1.

Results

Participant characteristics

Baseline demographic and clinical characteristics are displayed in Table 1. Delayed recognition and recall were correlated at = 0.358 ($p < 0.001$). Of the 18 participants who were impaired on delayed recall, 7 were impaired and 11 were not impaired on recognition.

Aim 1: Examining the neuroanatomical correlates of memory using structural neuroimaging data

Delayed Recognition

MTL and basal ganglia structures were not significantly associated with odds of being classified as having a recognition impairment—with odds ratios close to one indicating little association. Within the prefrontal cortex, thinner pars opercularis thickness was associated with greater odds of being impaired on recognition (OR = 0.336 for every one standard deviation increase in pars opercularis thickness, $p = 0.012$); however, this finding was just short of significance after correcting for multiple comparisons ($p = 0.060$). No other prefrontal cortex structures were associated with being classified as having a recognition impairment. See Table 2 for model statistics.

Delayed Recall

Worse delayed recall was significantly associated with thinner rostral middle frontal cortex ($\beta = 0.40$, $p = 0.006$) and thinner pars opercularis cortex ($\beta = 0.46$, $p = 0.001$). These associations remained significant after correcting for multiple comparisons ($p = 0.005$ and $p = 0.015$, respectively). See Figure 1 for significant relationships between delayed recall and prefrontal structures and Table 3 for model statistics. In these models examining the rostral middle frontal cortex and the pars operculars, AIDS diagnosis ($\beta = 0.32$, $p = 0.003$; $\beta = 0.36$, $p < 0.001$, respectively) and being in the *APOE* ε4+ group ($\beta = 0.19$, $p = 0.061$; $\beta = 0.28$, $p = 0.007$) were associated with worse delayed recall. Delayed recall was not significantly associated with MTL or basal ganglia structures.

Given possible effects of ART and viral detectability on cognition and the brain as well as the known effects of

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Table 2. Logistic and multivariable regression examining the relationship between the medial temporal lobe, prefrontal cortex, and basal ganglia and likelihood of recognition impairment

	Logit	95% Confidence interval	Odds ratio	*p*
Medial temporal lobe				
Hippocampus	0.135	[−0.633, 0.891]	1.145	0.725
Entorhinal cortex	0.156	[−0.512, 0.829]	1.168	0.645
Parahippocampal gyrus	0.265	[-0.379, 0.943]	1.304	0.425
Prefrontal cortex				
Caudal middle frontal	−0.139	[−1.121, 0.815]	0.870	0.775
Rostral middle frontal	−0.480	[−1.377, 0.384]	0.619	0.277
Pars opercularis	−1.091	[−2.036, −0.235]	0.336	0.012*
Pars triangularis	−0.751	[−1.748, 0.126]	0.472	0.112
Pars orbitalis	0.329	[−0.398, 1.069]	1.382	0.372
Basal ganglia				
Caudate nucleus	0.127	[−0.619, 0.848]	1.136	0.730
Putamen	0.114	[−0.636, 0.833]	1.120	0.759

Note: Logits and odds ratios were calculated for a 1 standard deviation increase in the medial temporal lobe, prefrontal cortex, or basal ganglia volumes. Reference group for recognition is Unimpaired Recognition. All models include age, imaging covariate (ICV or mean cortical thickness), and number of previous neuropsychological assessments. Recognition represents the average demographically-corrected Z-score of the two recognition discrimination measures; impairment was defined as a Z-score < −1.0.
*$p<0.05$ before correcting for multiple comparisons.
** $p<0.05$ after correcting for multiple comparisons.

methamphetamine on the brain and cognition, post hoc sensitivity analyses excluded participants who were not on ART, had a detectable viral load, or those with a current methamphetamine use disorder (note, methamphetamine was the only current substance use disorder at baseline other than alcohol or cannabis). In total, 62 participants were in post hoc analyses, and the findings were similar, as thinner rostral middle frontal ($\beta = 0.58$, $p = 0.004$) and thinner pars opercularis ($\beta = 0.47$, $p = 0.016$) remained significantly associated with worse delayed recall. Other prefrontal structures were not associated with delayed recall ($ps > 0.156$). Note, recognition models were not re-examined given that, with these exclusions, only 7 participants were impaired on the recognition composite. We also examined if results would differ if we examined those that were impaired on memory (either recognition or recall; $n = 22$). Again, we did not see any involvement of the MTL ($ps > 0.450$), with minmal effects. Other brain regions were also non-significant, but the effect of rostral middle frontal was similar to the overall sample ($\beta = 0.45$, $p = 0.440$), but the effect of the pars opercularis was reduced ($\beta = 0.13$, $p = 0.764$).

Processing speed and psychomotor functioning

Processing speed ($ps > 0.164$) and psychomotor functioning ($ps > 0.142$) were not associated with the MTL, prefrontal cortex, or basal ganglia.

Aim 2: To examine if baseline structural neuroimaging predicts amnestic decline

Ninety-one participants had at least one follow-up visit and were included in these analyses. Participants were followed for an average of 6.5 years (range: 0.6–11.9 years) with an average of 6.6 (range: 1–11) follow-up neuropsychological assessments. Thirty-six (39.6%) with at least one follow-up visit had a consistently undetectable viral load (<50 copies/ml; not including 67 counts of missing data). Sixty-nine participants (75.8%) were on ART for all visits (excluding 16 counts of missing data across all timepoints). No participants converted to AIDS during follow-up. Regarding substance use, 16 participants (17.6%) met criteria for a drug or alcohol use disorder during the study (excluding 9 counts of missing data across all timepoints).

Delayed Recognition

Of the 12 participants who were impaired on recognition at baseline, only two were impaired across all follow-up visits. Two of the 12 participants were not impaired at any subsequent visit, and the other eight were impaired between 25% and 86% of follow-up visits. Of the 79 participants unimpaired in recognition at baseline, 44 (56%) were unimpaired for all visits. Of those that were impaired on recognition at any follow-up visit, only four participants showed consistent recognition impairment; however, these participants had a limited follow-up after the initial recognition impairment (i.e., 1–2 visits). We further examined recognition impairment by specific measure (i.e., HVLT-R and BVMT-R) and both demonstrated considerably variability across time. Recognition composite values across time are depicted in Figure 2. The simplest random-slope and random-intercept model did not converge, and some dimensions of the variance-covariance matrix were estimated at exactly zero. This result indicates poor model fit, and this method could not examine a cross-level interaction.

Delayed Recall

In the random slopes and random intercept model with no additional covariates, the average slope was –0.041, indicating that, on average, the delayed recall T-score decreased by 0.041 every year. The standard deviation of the slope was 0.678. In the model including all covariates (i.e., imaging outcome covariate (e.g. ICV), age, *APOE* group, and AIDS status), none of the years since baseline by MTL cross-level interactions were significant ($ps > 0.412$) indicating that MTL volumes did not moderate delayed recall performance over time. See Table 4 for full model statistics. Delayed recall scores across time and slope are depicted in Figure 2.

Given that the rostral middle frontal and pars opercularis were associated with delayed recall at baseline, we conducted post hoc analyses to examine if prefrontal structures were associated with delayed recall longitudinally; none of the cross-level interactions were significant ($ps > 0.157$). In post hoc analyses, we also examined if those who performed in the impaired range on either recognition or recall at baseline ($n = 22$) were more vulnerable to decline. In the model with no covariates, the average slope was 0.566, indicating that, on average, the delayed recall *T*-score significantly increased by 0.566 every year ($p = 0.009$). MTL and significant prefonfrontal regions by time interactions were examined, and none were significant but there was a trend towards a greater entorhinal thickness being associated with greater improvement across time (beta = 0.262; $p = 0.083$).

Discussion

We examined the relationship between episodic memory, particularly delayed recognition and recall, and brain integrity both cross-sectionally and longitudinally in middle-aged PWH without significant confounding comorbid conditions. This is one of the first studies to use neuroimaging to specifically address the concern that accelerated cognitive aging in mid-life PWH may be due to multiple etiologies such as AD as well as use neuroimaging to inform neuropsychological findings. This study did not support

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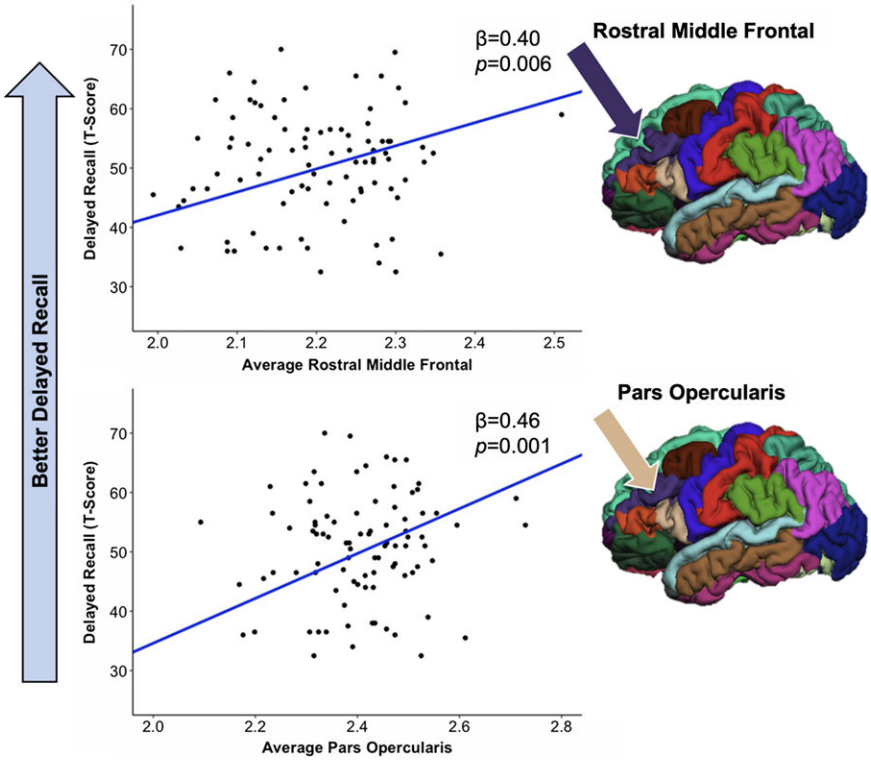

Figure 1. Significant relationships between delayed recall and prefrontal cortex in the entire sample. *Note.* Regression lines adjust for age (centered), AIDS status (reference: non-AIDS), *APOE* group (reference: *APOE* 4- group) and mean cortical thickness (centered).

our hypothesis that recognition is associated with more AD-related markers, such as the integrity of the MTL. It did demonstrate a potential association between delayed recall and recognition in middle-aged PWH in frontal systems, which is known to occur in HIV. Regarding longitudinal follow-up, the recognition discrimination composite was quite variable over time, indicating that in this middle-age range, it may not be useful in discriminating PWH with HAND compared to an early AD trajectory. Moreover, there was minimal longitudinal decline in delayed recall over multiple years among this group of middle-aged PWH, and thus we did not find evidence of an accelerated memory decline even when restricting to those at possibly greater risk of decline (i.e., those that were impaired at baseline). Taken together, episodic memory in middle-aged PWH appears to be more associated with frontally mediated involvement possibly due to HIV and, on average, we did not see concerning signs that accelerated memory decline reported in the literature is driven primarily by AD.

In our cohort of PWH, there was no significant association found between MTL structures and impairment on delayed recognition or recall. Effect sizes were minimal, indicating clinically insignificant associations. However, a thinner pars opercularis was significantly associated with greater odds of impairment in delayed recognition, although the finding fell to trend-level after correcting for multiple comparisons. Also, thicker rostral middle frontal gyrus and pars opercularis were associated with better delayed recall. This association remained when limiting the sample to virally suppressed PWH. Given that delayed recall was examined as a continuous variable, this does not imply that these prefrontal regions are associated with delayed recall impairment *per se,* rather with performance generally. Moreover, including overall mean cortical thickness in the models as a covariate allowed for observing associations with specific cortical regions while controlling for average overall cortical thickness. Clinical research on persons with HIV has consistently shown structural changes throughout the brain, including frontal regions, compared to persons without HIV (Ances & Hammoud, 2014; Holt et al., 2012), along with accelerated "brain aging" in middle-aged and older PWH (Clifford et al., 2017; Milanini et al., 2019). Thus, it is possible that changes in the prefrontal cortex are contributing to the observed associations with memory in this population.

Comparing the results of this study to the literature on middle aged samples in persons without HIV is difficult. Many such studies examine a memory composite and do not consider possible associations between brain integrity and delayed recognition. Additionally, many studies focus on the MTL. From the limited midlife research that examines both memory and region-specific neuroimaging, there is some indication that memory is associated with several neuroimaging correlates, including integrity of the MTL. For example, the Wisconsin Registry for Alzheimer's Prevention (WRAP) study, focusing on adults aged 40–65, has found some association between poorer memory and worse MTL indices (Doherty et al., 2015; Schultz et al., 2015), but did not examine prefrontal structures. Of note, the WRAP study differs from the CHARTER demographics in terms of both race/ethnicity and sex/gender.

It is difficult to differentiate the effect of HIV itself versus lifestyle factors associated with risk of contracting HIV and the downstream effects of HIV (e.g., increased risk of cerebro/cardiovascular disease). Cysique & Brew (2019) propose that vascular abnormalities are implicated in the pathogenesis of neurocognitive impairment in PWH, and a recent meta-analysis by McIntosh et al., (2021) found that cardiovascular disease is associated with an increased risk of cognitive impairment in PWH. CVD has also been associated with brain changes in PWH (Calon et al., 2020; Samboju et al., 2021). Several vascular risk factors were

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Table 3. Multivariable linear regressions examining the relationship between the medial temporal lobe, prefrontal cortex, and basal ganglia and delayed recall

	Beta	95% Confidenceinterval	Std. beta	*p*
Medial temporal lobe				
Hippocampus	0.143e-2	[−0.552e-2, 0.838e-2]	0.053	0.683
Entorhinal cortex	−5.428	[−14.211, 3.355]	−0.136	0.222
Parahippocampal gyrus	0.557	[−9.647, 10.762]	0.012	0.914
Prefrontal cortex				
Caudal middle frontal	4.759	[−19.686, 29.203]	0.063	0.700
Rostral middle frontal	38.986	[11.538, 66.433]	0.397	0.006**
Pars opercularis	37.813	[14.999, 60.627]	0.457	0.001**
Pars triangularis	24.321	[−4.347, 52.989]	0.249	0.095
Pars orbitalis	−1.064	[−19.728, 17.600]	−0.013	0.910
Basal ganglia				
Caudate nucleus	−0.714e-2	[−1.739e-2, 0.312e-2]	−0.161	0.170
Putamen	−0.331e-2	[−0.808e-2, 0.147e-2]	−0.160	0.172

Note: All models include age, imaging covariate (ICV or mean cortical thickness), AIDS Status, and *APOE* status.
*$p<0.05$ before correcting for multiple comparisons.
**$p<0.05$ after correcting for multiple comparisons.

examined as covariates in the current study and were not significantly associated with cognitive outcomes, although participants with more significant vascular comorbidities (e.g., stroke or myocardial infarction) were excluded from analyses. Therefore, further exploration of vascular risk factors and their association with cognition and brain aging in PWH more broadly is warranted.

Given our finding that episodic memory in middle-aged PWH may be more likely related to frontally mediated etiologies, this pattern of association may indicate that at this age range, preclinical AD is not likely a contributor to memory functioning. However, the existing literature does not provide a good estimate of when to expect differences in memory and medial temporal structures in those that are on an AD trajectory; therefore, it is possible that the current CHARTER group is too young to appreciably detect preclinical AD effects. This is further complicated by the demographically disparate composition of our CHARTER sample from most other studies in this area (e.g., in terms of race/ethnicity representation).

Regarding longitudinal follow-up in the current study, delayed recognition impairment status was variable over time. This observation could reflect the heterogeneous and fluctuating course of HAND over time (Heaton et al., 2015). Additionally, this variability over time may be in part due to the psychometric properties of the HVLT-R and the BVMT-R. Recognition for both the BVMT-R and the HVLT-R are skewed with known ceiling effects, meaning that there is more limited variability in this measure (Benedict et al., 1998; Benedict, 1997). Additionally, the HVLT-R and BVMT-R test-retest reliability of delayed recognition scores show adequate test-retest stability coefficients, but test-retest reliability of recognition is less reliable than other test measures such as delayed recall (Benedict et al., 1998; Benedict et al., 1996; Strauss et al., 2006; Woods et al., 2005). Lastly, it is important to again note that our dichotomous recognition "impairment" classification was not corrected for practice effects, so small fluctuations across the "impairment" cutoff could be due to practice effects rather than lack of reliability. Ultimately, combining two measures with some psychometric concerns may have led to greater variability across time; however, both measures individually were quite variable across time. This, in addition to the lack of MTL findings, leads us to conclude that recognition impairment at one timepoint in this group may not be indicative of future decline associated with neurodegenerative disease. Future studies may want to employ of additional memory tests (e.g., story memory) or those that are either somewhat harder (and thus could have greater variability) or have better psychometric properties for the recognition trial.

Notably, there was little decline in delayed recall over time in our sample of PWH. While some individuals in this group may be experiencing objective decline, on average, we did not observe a decline in age-corrected delayed recall T-scores over time. Other studies of primarily middle-aged PWH have observed a greater-than-expected effect of aging on episodic memory (e.g., in the Multicenter AIDS Cohort Study (Goodkin et al., 2017)), and a recent systematic review found accelerated neurocognitive aging in 75% of longitudinal studies in PWH (Aung et al., 2020). Some researchers have questioned if accelerated aging could be due to a neurodegenerative cause such as AD. Emerging studies have demonstrated some possible ways to disentangle HAND and aMCI (e.g., olfaction, memory performance; Sundermann et al., 2021a; Sundermann et al., 2021b); yet, it remains unclear if PWH are at increased risk of AD and if AD could account for some of the observed accelerated aging. For example, Milanini et al. (2020) showed a low frequency of amyloid positivity among virally

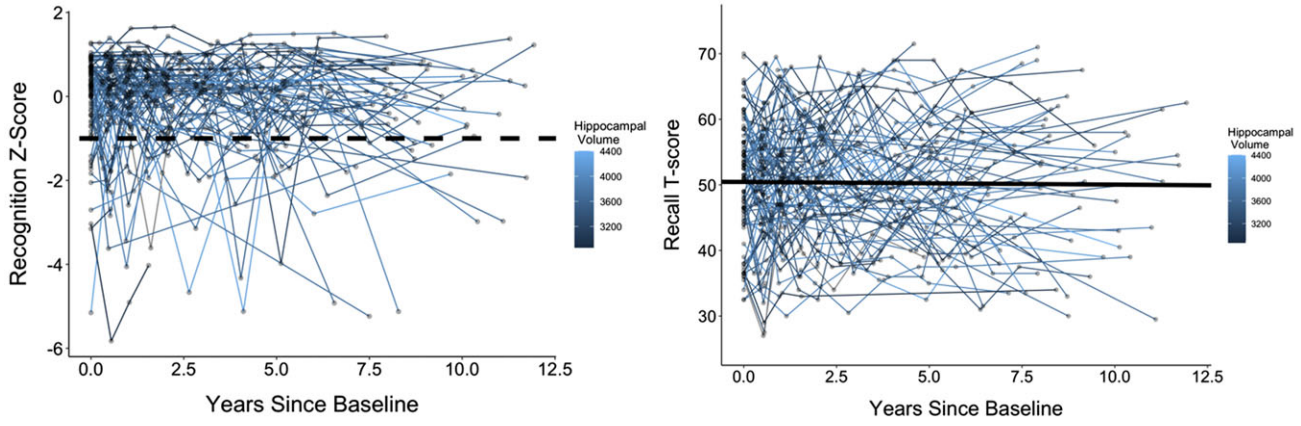

Figure 2. Recognition composite Z-scores and recall T-scores graphed across years since baseline. *Note.* Dashed line on the left panel depicts the -1 standard deviation cut-off. Participant visits below this line were impared on recogniton. Solid black line on the right panel depicts the average change in delayed recall over time (i.e., slope).

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Table 4. Linear mixed-effects results examining whether baseline medial temporal lobe structures are associated with change in delayed recall

	Estimate	95% Confidence interval	*p*
Hippocampus			
Within-person level			
Years since baseline	1.162	[−1.677, 4.040]	0.430
Between-person level			
Baseline Age (mean centered)	−0.048	[−0.354, 0.258]	0.766
Hippocampal volume (standardized)	12.861	[−11.838, 37.824]	0.324
ICV (standardized)	−1.413	[−3.727, 0.891]	0.243
APOE (ref: 4-)	−2.406	[−7.196, 2.382]	0.341
AIDS status (ref: AIDS)	5.883	[1.549, 0.102]	0.012
Cross-level interaction			
Hippocampal volume*years since baseline	−1.178	[−4.051, 1.664]	0.424
Entorhinal cortex			
Within-person level			
Years since baseline	0.259	[−3.054, 3.622]	0.880
Between-person level			
Baseline Age (mean centered)	−0.075	[−0.369, 0.220]	0.627
Entorhinal cortex (standardized)	−1.370	[−3.252, 0.514]	0.169
Mean cortical thickness (standardized)	−1.061	[−2.940, 0.822]	0.285
APOE (ref: 4-)	−4.500	[−9.0580, 0.056]	0.063
AIDS status (ref: non-AIDS)	6.217	[2.049, 10.398]	0.006
Cross-level interaction			
Entorhinal cortex*years since baseline	−0.019	[−0.264, 0.224]	0.880
Parahippocampal cortex			
Within-person level			
Years since baseline	−1.313	[−4.419, 1.829]	0.414
Between-person level			
Baseline age (mean centered)	−0.072	[−0.372, 0.228]	0.647
Parahippocampal cortex (standardized)	−0.562	[−2.551, 1.424]	0.592
Mean cortical thickness (standardized)	−1.365	[-3.350, 0 0.622]	0.195
APOE (ref: 4-)	−3.744	[−8.277, 0.788]	0.119
AIDS status (ref: non-AIDS)	6.174	[1.935, 10.425]	0.007
Cross-level interaction			
Parahippocampal cortex*years since baseline	0.107	[−0.148, 0.359]	0.412

Note: ICV = intracranial volume.

suppressed PWH over the age of 60. However, studies using insurance enrollee data found a higher prevalence of AD and related disorders among PWH (Yang et al., 2019; Yu et al., 2022). Overall, we did not detect clear signs of preclinical AD in our study. Again, it is not clear if these associations should be expected in a middle-aged cohort of PWH; therefore, it would be beneficial to re-examine this analysis in an older cohort of PWH.

Additional limitations should be considered. First, in terms of generalizability, the sample was predominantly male (i.e., 85.7%), which somewhat reflects of the current demographics of PWH in the United States (Centers for Disease Control and Prevention, 2017). Nevertheless, there are known sex differences on cognition in HIV and AD (Dreyer et al., 2022; Laws et al., 2018) that this project was underpowered to test. Relatedly, all participants in this analysis did not have significant "confounding" comorbid conditions and most, although not all, were on suppressive ART; therefore, these findings may not generalize to individuals that are discordant from our group. Second, this study is also limited in that our CHARTER sample does not include an HIV-negative comparison group, and many prior studies are demographically and psychosocially disparate from our group. Future studies would benefit from a demographically and psychosocially diverse HIV-negative comparison group to better understand the specificity of associations between memory and neuroimaging correlates in PWH. Third, delayed recall and recognition were examined separately rather than dichotomously splitting participants into aMCI versus non-aMCI as in Sundermann et al. (2021a). Examining delayed recognition and recall individually was an important first step to inform future diagnostic improvements. Additionally, examining delayed recall continuously was advantageous because it increased variability; more subtle differences observed in mid-life may not be captured by inflexible diagnostic cut-points. With that said, associations between biological markers associated with AD (e.g., olfactory dysfunction, elevated rates of $A\beta_{42}$ plaques) have been found in older (age 50+) PWH using aMCI criteria (Sundermann et al., 2021a; Sundermann et al., 2021b). Therefore, future studies could consider using a more comprehensive approach to examining episodic memory.

This study has several clinical implications. It showed that memory in these middle-aged participants was associated with prefrontal structures but not MTL structures, suggesting that episodic memory in middle-aged PWH is more associated with frontally mediated involvement in HIV rather than etiologies associated with the MTL. It will be important to replicate this study in older (e.g., aged 65 and up) PWH to examine if this trend continues into older age, particularly as greater numbers of PWH reach this age range. The findings also suggest that in middle-aged PWH with high rates of ART use and relatively limited comorbid conditions, there may not be a greater than expected decline in delayed recall. Lastly, recognition "impairment" appeared to be quite variable over time. Due to this variability over time, recognition may not serve as a good clinical marker to help distinguish aMCI from HAND in this middle-aged group; however, research examining recognition trajectories among older PHW at higher risk for AD is needed.

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