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Authors

Milanini, Benedetta
Samboju, Vishal
Cobigo, Yann
et al.

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Longitudinal brain atrophy patterns and neuropsychological performance in older adults with HIV-Associated Neurocognitive Disorder compared to early Alzheimer's Disease

Benedetta Milanini[a], **Vishal Samboju**[a], **Yann Cobigo**[a], **Robert Paul**[b], **Shireen Javandel**[a], **Joanna Hellmuth**[a], **Isabel Allen**[c], **Bruce Miller**[a], **Victor Valcour**[a]

[a]Department of Neurology, Memory and Aging Center, University of California, San Francisco, CA, USA

[b]Missouri Institute of Mental Health, University of Missouri, St. Louis, Missouri, USA

[c]Department of Epidemiology, University of California, San Francisco, CA, USA

Abstract

Older HIV-infected patients are at risk for both HIV-Associated Neurocognitive Disorder (HAND) and Alzheimer's disease. We investigated neuroimaging and neuropsychological performance of 61 virally suppressed older adults with HAND (mean (SD) age 64.3 (3.9) years), 53 demographically-matched individuals with Mild Cognitive Impairment of the Alzheimer's type (MCI-AD; 65.0 (4.8)), and 89 healthy controls (65.0 (4.3)) cross-sectionally and over 20 months. At baseline, both disease groups exhibited lower volumes in multiple cortical and subcortical regions compared to controls. Hippocampal volume differentiated MCI-AD from HAND. Cognitively, MCI-AD performed worse on memory and language compared to HAND. Adjusted longitudinal models revealed greater diffuse brain atrophy in MCI-AD compared to controls, whereas HAND showed greater atrophy in frontal gray matter and cerebellum compared to controls. Comparing HAND to MCI-AD showed similar atrophy rates in all brain regions explored, with no significant findings. MCI-AD exhibited more pronounced language decline compared to HAND. These findings reveal the need for further work on unique cognitive phenotypes and neuroimaging signatures of HAND compared to early AD, providing preliminary clinical insight for differential diagnosis of age-related brain dysfunction in geriatric neuroHIV.

Keywords

HIV; mild cognitive impairment; Alzheimer Disease; neuroimaging; cognitive dysfunction

Corresponding Author: Benedetta Milanini; Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA; 550 16th Street, San Francisco, CA 94158; tel: +1 (415) 476 2181; Benedetta.Milanini@ucsf.edu.

INTRODUCTION

Diagnosing the etiology of cognitive changes in HIV-infected older adults is a growing clinical concern. Aging with HIV is a recent phenomenon globally in settings with access to combination antiretroviral therapy (cART). In 2015, 47% of HIV-infected patients in the US were 50 years and older and the greatest increase in HIV prevalence (57%) from 2011 to 2015 occurred among individuals age 65 and older (Centers for Disease Control and Prevention [CDC]; 2017). This trend is expected to continue, underscoring the importance of defining neuroimaging and cognitive signatures of HIV-Associated Neurocognitive Disorder (HAND) compared to Alzheimer's disease (AD). While HAND remains prevalent despite effective viral suppression, with 30-50% of all HIV-infected individuals meeting research criteria, it is not the only possible explanation for cognitive change in older patients (Antinori et al., 2007; Heaton et al., 2010; Nightingale et al., 2014; Simioni et al., 2010). Older HIV-infected adults are at a threefold risk of HAND compared to their younger counterparts (Valcour et al., 2004). However, by virtue of age, these older individuals are also at elevated risk of age-related neurodegenerative diseases, principally AD.

Some studies suggest higher risk for age-associated neurodegeneration with HIV infection, thus enhancing the risk of developing AD and lowering the threshold for clinical manifestation (Alisky, 2007; Xu and Ikezu, 2009). Others propose that increased longevity with HIV-mediated chronic inflammation combined with potential iatrogenic effects of antiretroviral therapies increases brain aging (Achim et al., 2009). While utilizing cerebrospinal fluid (CSF) AD biomarkers may improve diagnostic accuracy in this population, perturbation of these biomarkers in inflammatory conditions has led to inconsistent reports in the setting of HIV. This inconsistency is complicated in the current literature by the inclusion of study samples comprised of young participants, heterogeneous levels of viral suppression and the possible conflation of these biomarkers with more severe forms of HAND (Clifford et al., 2009; Esiri et al., 1998; Green et al., 2005; Milanini and Valcour, 2017; Turner, R. et al., 2016).

Structural magnetic resonance imaging (MRI) and neuropsychological tests are generally available in clinical settings and may help to distinguish HAND from early stage AD in older individuals. The neuropsychological phenotype typically described in HAND in older individuals appears similar to younger individuals, with prominent difficulties in processing speed, executive function and memory retrieval (rather than encoding) errors (Ciccarelli et al., 2017; Cysique et al., 2004; Scott et al., 2011). This pattern aligns with the often described subcortical profile of HIV rather than a cortical profile typical of AD. However, no studies have directly compared virally suppressed older individuals with HAND and individuals with early AD of the same age.

Structural MRI studies in HIV highlight basal ganglia atrophy patterns and volumetric reductions associated with neuropsychological performance, though some of these findings are based on participants with detectable HIV RNA and heterogeneity in cognitive functioning (Becker et al., 2011; Clifford et al., 2017; Paul et al., 2005; Pfefferbaum et al., 2014). In contrast, the atrophy patterns described in AD and Mild Cognitive Impairment (MCI), an intermediate state between age-related cognitive changes and dementia,

emphasize volume reductions of the hippocampus, parahippocampal gyrus, parietal lobes, and temporal lobes in addition to ventricular dilatation (i.e. central atrophy) (Apostolova et al., 2012; Duara et al., 2008; Echavarri et al., 2011; Petersen et al., 1999; Zhang et al., 2013). Prior work from our group investigated differential atrophy patterns in 15 individuals with HAND over age 60 years compared to 80 individuals with MCI from the Alzheimer's Disease NeuroImaging Initiative (ADNI) using machine learning (Zhang et al., 2016). Brain volumes including the left precentral, right precentral and left precuneus regions were capable of accurately classifying HAND from MCI with > 85% accuracy (Zhang et al., 2016). However, with the machine learning approach, regions contributing to the classification are impacted by others in the classification algorithm, making it less clear if individual regions can meaningfully add to diagnostic accuracy at the bedside.

In the current study, we aim to inform the clinical challenge of diagnosing older adults living with HIV and cognitive change by contrasting baseline and longitudinal neuroimaging and neuropsychological profiles in virally suppressed older individuals with HAND against participants with Mild Cognitive Impairment (MCI) clinical syndrome consistent with AD (MCI-AD).

METHODS

Cohort selection

We compared 61 HAND participants to 53 individuals with MCI-AD and 89 controls. The latter two groups were matched to the HAND group by age and gender. Participants were recruited between April 2008 and March 2018 at the UCSF Memory and Aging Center. At baseline, study participants received a standardized and multidisciplinary assessment that included a medical history, physical, neurological and neuropsychological examination and structural brain imaging with 3T MRI, with standardized approaches across research groups. Participant selection for this study was based on availability of MRI data.

Participants with HAND were recruited into the UCSF *HIV over 60 Cohort*. All were aged 60 years or older, on cART for at least 12 months, with suppressed plasma HIV RNA (<100 copies per milliliter). In accordance with the Frascati nosology, participants with confounding factors were excluded, including those with major neurological or psychiatric conditions (e.g. multiple sclerosis, severe depression), current or past brain infection, active neoplastic disease, current substance use disorder, thyroid abnormality, vitamin B12 deficiency, major stroke, or substantial traumatic brain injury. We measured CD4 cell counts and plasma HIV RNA levels if current reports (+/− 3 months) were unavailable. HAND diagnoses were determined by consensus conference with behavioral neurologists and neuropsychologists using clinical acumen informed by the Frascati criteria (Antinori et al., 2007). The HIV-infected participants were categorized as either Asymptomatic Neurocognitive Impairment (ANI, n=5) or Mild Neurocognitive Disorder (MND, n=56) (Antinori et al., 2007).

The MCI-AD participants were chosen from a larger dataset at our center determined among all cases with a clinical diagnosis of MCI and a Clinical Dementia Rating (CDR) score of 0.5, indicating mild functional decline (Morris, 1993). Individuals were diagnosed with MCI

that was clinically thought to be due to Alzheimer's disease if they had the MCI core diagnostic features, including subjective cognitive changes, objective cognitive impairment, preserved general cognitive functioning and intact activities of daily living (Petersen et al., 2009; Petersen et al., 1999; Petersen et al., 2001; Zhang et al., 2013). In some cases, structural brain imaging used in this study was included in the consensus conference to make the diagnosis. MCI-AD participants were not selected based on MCI phenotypic subtype (e.g., single versus multiple domains, amnestic versus non amnestic presentation) (Winblad et al., 2004).

The HIV-uninfected healthy controls were selected from a longitudinal cohort of healthy brain aging, as previously described (Nir et al., 2014; Wade et al., 2015; Wendelken et al., 2016). Exclusion criteria for this cohort include significant memory problems or diagnosis of a neurodegenerative disease or other major health condition. Control participants reported no memory issues or functional complaints due to cognitive decline, had MMSE ≥27, CDR of 0 and were reviewed at consensus conference to have normal cognition.

We obtained informed consent for all participants and protocols and procedures were approved by the Institutional Review Board.

Neuroimaging data acquisition

All participants underwent whole-brain imaging on either a Siemens TIM Trio 3-Tesla MRI scanner with a 12-channel head coil or Siemens Prisma fit with a 64-channel head coil. In order to limit measurement error across head coils, only participants whose baseline and follow-up scans were completed on the same scanner were included in the study. We acquired 3D-T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequences (240×256 matrix; FOV=256 mm; 160 slices; voxel size=1.0 ×1.0 ×1.0mm^3; TR=2300 ms; TE=2.98 ms; flip angle=9°). Images were visually inspected for quality; images with excessive motion or image artifact were excluded. Parameters were almost identical on the Siemens Prisma Fit scanner, but acquired with a 64-channel head coil. Cross-sectional volume extraction and longitudinal analyses used a framework previously described (Clifford et al., 2017). A single group template was created using a mix of HAND, MCI-AD and control participants for final target registration. First, images were aligned by matching gray and white matter intensities on a voxel-wise basis. A study-specific template was then created by iterative linear and non-linear warping each participant's template image and finally smoothed using an isotropic 8mm full width at half-maximum Gaussian kernel.

Regions of interest (ROIs) were chosen based on extant literature and previous work analyzing HIV-associated ROIs in older cohorts using the Desikan Atlas (Clifford et al., 2017; Desikan et al., 2006; Zhang et al., 2016). Additional ROIs included areas associated with atrophy in MCI-AD (i.e. parahippocampal gyrus, hippocampal gray, parietal gray) and regions identified to contribute to our diagnostic machine learning algorithm in our prior work (Zhang et al., 2016).

Neuropsychological assessment

Study participants underwent neuropsychological testing within 120 days of the baseline scan. The 90-minute standardized neuropsychological testing battery assessed multiple cognitive domains: learning and episodic memory [California Verbal Learning Test (CVLT II) trial 5, immediate and delayed recall, recognition (long form for HAND, short form for MCI-AD and control participants), story immediate and delayed recall, Benson figure recall and recognition]; executive functions [Modified Trails, Design Fluency, Stroop interference task, abstraction, Trails B, semantic and phonemic fluency]; processing speed [Stroop color naming task, Trails A, Wechsler Adult Intelligence Scale (WAIS-R) Digit Symbol modalities test]; language [Boston naming test, sentence repetition, word comprehension]; attention and working memory [digits forward; digits backward; CVLT II trial 1] and visuo-spatial [Benson figure copy, number location from the Visual Object and Space Perception (VOSP) battery, face matching from the Comprehensive Affect Testing System (CATS)] (Delis DC, 2000; Kramer et al., 2003; Weintraub et al., 2009). The Geriatric Depression Scale (GDS) was also administered to assess mood status (Yesavage et al., 1982). We included all cases where participants underwent cognitive testing supporting at least 4 of the 6 cognitive domains explored. In total, 6 participants (HAND=3; MCI-AD=3) had neuropsychological data available for less than 6 cognitive domains. Cross-sectional neuropsychological data were available for all HAND participants, 36/53 MCI-AD cases and 82/89 controls.

Raw neuropsychological scores were transformed into z-scores using normative data as previously published and domain-specific scores were calculated by averaging the individual z-scores (Milanini et al., 2017).

Statistical analysis

A one-way analysis of variance (ANOVA) was employed for continuous variables (i.e. education, GDS and MMSE scores) and chi-squared or Fisher's exact tests were applied for categorical variables (i.e. ethnicity, gender, remote alcohol and substance abuse) for comparisons among the three groups.

Analysis of covariance (ANCOVA) using group status to predict volume [mm^3] was applied to baseline ROI analysis models correcting for age, scanner and total intracranial volume (TIV) across all ROIs individually. Post hoc pairwise comparisons were conducted using Tukey's test. Outliers (2 HAND, and 1 control) were excluded from the final analyses. Sensitivity analyses were conducted on baseline scans using only Prisma acquisitions [n=34/89 (38%) controls; n=33/61 (54%) HAND and n=17/53 (32%) MCI-AD].

An identical statistical method was used to compare baseline neuropsychological profiles by group across the cognitive domains. Since the three groups significantly differed in educational attainment, education was entered as a covariate in the ANCOVAs.

Longitudinal models for imaging were constructed similarly with ANCOVAs using group status to predict atrophy rates [mm^3/year], adjusting for age at baseline. Tukey's test was applied for post hoc pairwise comparisons. Atrophy rates were calculated as volume at follow-up subtracted from volume at baseline divided by the inter-scan interval.

The same approach was applied to investigate differences in cognitive change over time across groups. The global and domain-specific cognitive change was calculated as the difference between follow-up performance subtracted from the baseline divided by the inter-assessment interval. Individual ANCOVAs by domain were performed to explore differences in rate of change by group, adjusting for education and age.

RESULTS

Characteristics of study participants

Clinical and demographic information by group is described in Table 1. Education was similar between the two disease groups, and approximately one year lower than the controls.

For those with HAND diagnoses, mean (SD) nadir and current CD4 cell counts were 151 (139) and 575 (251), respectively. The mean (SD) duration of HIV infection was 24 (7.3) years. All were on cART with undetectable HIV RNA for the duration of follow-up (Table 1).

A large majority of HAND participants met research criteria for MND (92%). Twenty (38%) of MCI-AD cases were diagnosed with amnestic MCI. The mean (range) MMSE was 27/30 (23-30) and 29/30 (27-30) for MCI-AD and controls ($p<0.001$). The mean (SD) Geriatric Depression Scale (GDS) score was 9.8/30 (6.9) for HAND; 6.6/30 (4.5) for MCI and 3.3/30 (3) for controls ($F=29.94$; $p<0.001$)] (Table 1).

Cross-sectional volumetrics and cognitive differences across groups

Baseline ROI volumetrics analysis by group—Cross sectional analyses, adjusting for age, TIV, and MRI scanner revealed significant disease associated smaller volumes compared to controls in multiple regions for both HAND and MCI-AD (Figure 1). Hippocampal gray [all p's<0.05; % relative difference from controls (95% Confidence Interval) MCI-AD vs. control: 7.3 (10.3:4.3)%], temporal gray [6.4 (8.7:4.0)%], and parahippocampal gyrus [5.4 (7.9:2.9)%] were selectively smaller in MCI-AD group compared to controls, while no significant differences in these regions were noticed between HAND and controls. Only smaller volume in the hippocampal gray differentiated MCI-AD from HAND [7.3 (10.3:4.3)% MCI-AD vs. 2.9 (5.3:0.4)% HAND; $p=0.040$; Table 2, Figure 2, Supplemental Figure 1].

Sensitivity analysis excluded data obtained using the Trio MRI scanner was consistent with the main findings. However, although the direction of the effects was similar in the sensitivity analysis, putamen and thalamic volumes were no longer statistically different between disease groups with controls and the nucleus accumbens between MCI-AD and controls (p's>0.05; data not shown).

Baseline neuropsychological performance by group—In models adjusted for education, both disease groups exhibited worse neuropsychological performance compared to controls on all tested cognitive domains except the visuo-spatial domain. MCI-AD participants performed worse than HAND individuals on memory (contrast=−0.6; 95% CI: −0.9:−0.2; $p=0.002$) and language (contrast=−0.6; 95% CI: −1.1 :−0.1; $p=0.017$), while the

two groups performed similarly on measures of attention (p=0.084), executive functions (p=0.265), psychomotor speed (p=0.151) and visuo-spatial abilities (p=0.690; Supplemental Table 1, Supplemental Figure 1). While we failed to find differential patterns of brain structure-function relations by disease group, we did find significant associations between higher parietal gray volumes and better psychomotor speed performance in both HAND and MCI-AD together as a group (p<0.001) and independently (HAND: p=0.041; MCI-AD: p=0.003), thus further informing the clinical implication of our findings.

Longitudinal volumetrics and cognitive changes across groups

Longitudinal atrophy rates—The mean (SD) years of inter-assessment interval was 1.8 (0.9) [1.6 (1.2) for HAND (n=19), 1.4 (0.5) for MCI-AD (n=13) and 2.1 (0.8) for controls (n=36; F=3.3; p=0.044)].

Compared to controls, the HAND group showed similar atrophy rates over the 1.8 year period in all ROIs but cerebellum [all p's<0.05; annualized % change (95% Confidence Interval) HAND: −0.6 (−1.5:0.2)% per year vs. control: 0.09 (−0.3:0.5)% per year] and frontal gray [HAND: −1.1 (−1.8:−0.4)% per year vs. control: 0.1 (−0.4:0.5)% per year]. Conversely, MCI-AD exhibited higher rates of atrophy compared to controls in almost all the regions explored excepting pallidum and left precentral gyrus (all p's<0.5). The two disease groups showed similar rates of atrophy in all the ROIs. Only a trend towards significance was found for the caudate [−1.6% (95% CI: −2.9:−0.4) for MCI-AD vs −0.2% (95% CI: −1.1:0.7) for HAND; p=0.054; Table 3, Supplemental Figure 2].

Neuropsychological change over time—Longitudinal neuropsychological data were available for 30/61 HAND, 22/53 MCI and 48/89 controls. Examining the direction of global and domain-specific change over time within each group, we found no significant decline or improvement in either disease group. The post hoc pairwise comparisons adjusted for age and education showed similar rates of cognitive change [mean (SD) years of inter-assessment interval = 1.6 (1.2)] across groups (all p's>0.05) in all the domains except language where MCI-AD participants exhibited a statistical significant decline compared to both control participants (contrast: −0.6; 95% CI:−1.1 :−0.0; p=0.038) and HAND participants (contrast:−0.6; 95% CI:−1.2:−0.1; p=0.020; Supplemental Table 2).

DISCUSSION

The concurrent risk for age-associated neurodegenerative diseases has become an important clinical concern in HIV patients given the extended life expectancy with widely-available cART. In this study, we aimed to answer the clinically-relevant question as to whether non-invasive clinical indices may be meaningful in differentiating AD from the HIV-associated cognitive changes. Compared to healthy controls, the HAND group demonstrated focal atrophy at baseline in regions previously described to be affected in HIV despite plasma HIV RNA suppression, whereas the MCI-AD group evidenced widespread atrophy. Baseline hippocampal volume differentiated MCI-AD from HAND. Longitudinally, compared to controls, MCI-AD participants exhibited greater atrophy in most brain regions examined, while HAND participants showed limited findings in the frontal and cerebellar regions. Among all the cognitive domains, the MCI-AD group showed worse baseline performance

on measures of episodic memory and language and greater decline in language functions compared to the HAND group.

Hippocampal atrophy is a hallmark feature of AD (Apostolova et al., 2012; Frisoni et al., 2010). In contrast, the hippocampal volume is not a reliable feature of HIV, particularly in aviremic HIV-infected individuals (Frisoni et al., 2010; Tesic et al., 2018). Our findings revealed smaller volume in the medial temporal lobe including the hippocampal gray, parahippocampal gyrus and temporal gray in MCI-AD compared to controls, in contrast to HAND which only showed lower parietal gray volume compared to controls. This finding is consistent with previous studies in MCI and AD and with the pattern of more profound memory deficits that we found between MCI-AD and HAND (Apostolova et al., 2012; Duara et al., 2008; Echavarri et al., 2011; Zhang et al., 2013). In contrast, HAND participants compared to controls demonstrated smaller volume in subcortical structures such as the putamen, thalamus and nucleus accumbens and cortical regions previously described to be specifically affected in HIV including the left precentral gyrus, left precuneus, right precentral gyrus, frontal gray and parietal gray (Clifford et al., 2017; Zhang et al., 2016).

Both disease groups showed significant ventricular enlargement compared to healthy controls in cross section, a finding with implications for differential diagnosis. Although the use of cerebral ventricular volume as a measure of AD progression is supported by several studies, this may not address the needed specificity to differentiate HAND from MCI-AD due to the overlapping pattern of ventricular enlargements in both diseases (Frisoni et al., 2010; Nestor et al., 2008). However, our MCI-AD group showed a ventricular expansion over time, thus providing further evidence for ventricular volume as a reliable marker for the monitoring of disease progression in AD.

Longitudinally, MCI-AD participants exhibited higher rates of atrophy in almost all the brain regions examined, whereas HAND individuals showed faster atrophy only in the cerebellum and frontal lobes compared to controls. In a separate study assessing brain volume in 24 HIV-infected participants without substance abuse compared to controls, frontal lobe deficits associated with age and HIV interaction have also been corroborated (Pfefferbaum et al., 2018). Abnormalities of cerebro-cerebellar functional connectivity have been described even among asymptomatic HIV-infected individuals and they were associated with attention and working memory impairment (Wang et al., 2018). Caudate atrophy, a trend effect in this study, has been documented in both MCI and AD (Jiji et al., 2013; Madsen et al., 2010; Rombouts et al., 2000). In a previous longitudinal analysis from our group that included some of these same participants, frontal gray and cerebellar gray were noted to be different between HAND and age-matched cognitively normal controls (Clifford et al., 2017).

Controversy still remains as to whether HIV and aging accentuate or accelerate brain changes (Ances and Letendre, 2019). Current research has been focusing on characterizing the variant patterns of atrophy within HIV, with associations of higher atrophy in older participants, low CD4, and longer duration of infection (Nir et al., 2019). Some evidence has shown the presence of progressive atrophy despite viral suppression, highlighting similar

regions investigated by our work including expansion of the ventricles and atrophy of the frontal lobes, left precuneus, and deep gray structures (Popov et al., 2019; Nir et al., 2019, Sanford et al., 2018). In contrast, other studies found volumetric reductions in HIV-infected individuals on suppressive cART compared to controls in cross-sectional analyses, but no significant differences in longitudinal rates of change in brain structure or brain function between the two groups (Cole et al., 2018; Sanford et al., 2018). In line with these results, another study examining a group of 21 virally suppressed participants, demonstrated no longitudinal differences in cortical thickness or subcortical gray atrophy; however, there was no control group for comparison and a younger (mean age 52.9 years, range 44-61) sample (Corrêa et al., 2016). The discrepant findings across studies may be attributed to differences among cohorts, particularly that related to the mean age of the sample, as well as the presence of comorbidities including cerebrovascular disease (Ances and Letendre, 2019).

In our study, the rates of cognitive change were similar by disease group with the exception of language, which declined more severely among the MCI-AD group compared to HAND. Even patients with mild AD dementia are often impaired on measures of confrontation naming, verbal fluency and semantic categorization, reflecting the progressive deterioration of the semantic language network (Weintraub et al., 2012). While cognitive performance tends to fluctuate over time in HIV, progressive cognitive decline is typically observed in AD (Antinori et al., 2007; Woods et al., 2009). The difference in cognitive trajectory over time allows for opportunities to disentangle HAND and AD. CSF biomarkers, currently available in clinical practice to increase the evidence of underlying AD pathology, may increase diagnostic accuracy in this population of patients; although, examining CSF adds an invasive step to the diagnostic evaluation and their interpretation may be less clear given the described perturbation of these markers in the setting of HIV (Ances and Letendre, 2019; Rubin et al., 2019). Future work that is powered, includes CSF AD biomarkers and has the longer follow-up required to examine the slope of change across several time points is needed to confirm this preliminary finding from our longitudinal analyses.

The combination of HIV infection and aging represents a unique challenge in geriatric neuroHIV. Early and accurate diagnosis is essential to inform prognosis and consider treatment options. Only three case studies of AD in the setting of HIV have been described (Hellmuth et al., 2018; Makitalo et al., 2015; Turner, R.S. et al., 2016). While these case reports provide suggestions for impairment patterns that may be atypical of HAND, formal longitudinal studies are needed and few centers report sufficient older adults in an age group that is associated with substantial risk for AD. Thus, the smaller sample sizes of the current study and the multiple comparisons done should be balanced with the strengths of the age group studied and the structured commonality of the examinations including case conferences and imaging.

Our study merits discussion of a number of limitations. Though we matched for age, sex, and scanner at baseline, follow-up scans were not available for many participants due to loss of follow-up or changes in the available scanner from baseline to follow-up. Sensitivity analyses targeting a single MRI scanner produced similar results as the full data, with the only difference being loss of statistical significance between groups in subcortical regions, likely due to lower statistical power. We found one HAND individual with multiple lacunar

infarcts in the thalamus. Removing this participant from the analysis did not affect the main effects. We combined ANI (n=5) and MND (n=56) to maximize power, and therefore, the results do not address potential subtypes within the HAND group. However, the distinction between ANI and MND is an ongoing debate, and therefore it is unlikely that a subtype analyses of a small number of cases would yield new information (Chiao et al., 2013). The MCI-AD group was selected to be demographically matched to the HAND group, likely affecting the relative prevalence of MCI subtypes in our sample compared to other studies.

Compared to our previous report, we found limited differences in brain atrophy between HAND and controls longitudinally, and main effects were seen in baseline analysis (Clifford et al., 2017). This could be attributed to the smaller sample size at follow-up and shorter follow-up interval (1.8 years vs 3.4 years) (Clifford et al., 2017). While longitudinal clinical data are meaningful to track cognitive change and risk of functional impairment, timely diagnosis after symptom presentation is crucial for optimal care. The participants in all three groups underwent the same neuropsychological testing battery; however, two versions of the verbal learning and memory tests were used. HAND participants completed a more challenging version (16 items) compared to the MCI-AD and control participants (9 items). Although our use of standardized scores control for absolute differences, it is worth noting that this variation could have partially impacted the findings in the memory domain. The two disease groups were classified based on clinical phenotypes that sometimes included clinical neuroimaging. Optimally, we would employ neuropathologically defined groups for comparative analyses.

In sum, our study demonstrates brain and neuropsychological abnormalities in both MCI-AD and HAND compared to healthy cognitively normal controls. However, HAND and MCI-AD groups exhibited some differential atrophy patterns and cognitive phenotypes that may provide initial insights into the clinical differentiation of HAND from AD in older individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Subcortical and cortical atrophy occurs in both HAND and MCI-AD.
- Baseline hippocampal volumes differentiate MCI-AD and HAND.
- At baseline MCI-AD perform worse on memory and language compared to HAND.
- Longitudinal results demonstrate faster atrophy in MCI-AD compared to HAND.
- MCI-AD show faster language decline compared to HAND.

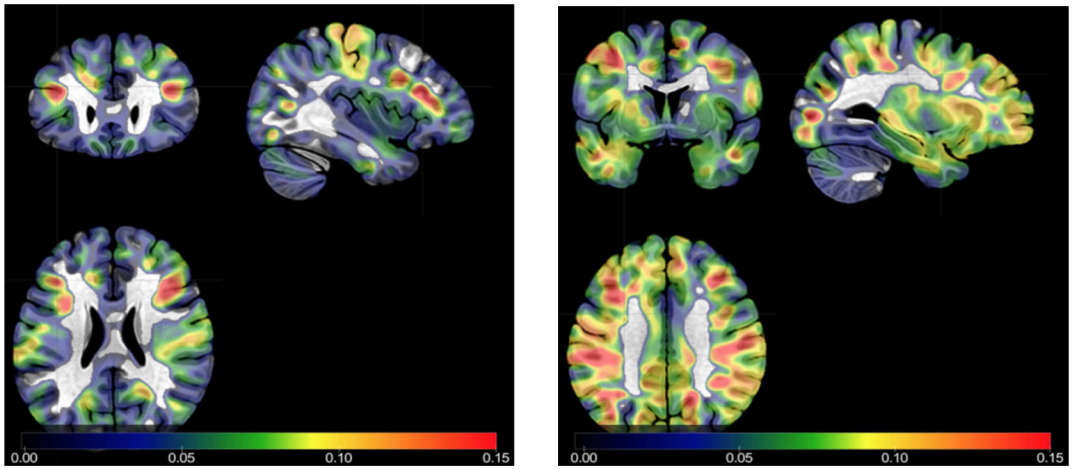

Figure 1. Percent difference from controls in HAND and MCI-AD

Heat maps reflect the percentage of relative difference in grey matter density between disease (left: HAND, right: MCI-AD) and controls. Images reflect raw calculation uncorrected for age, TIV, scanner. Warmer color signifies higher % reduction vs controls. Red represents 15% reductions and beyond.

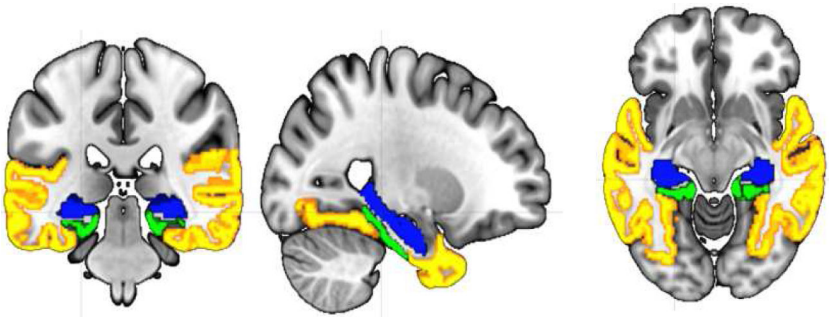

Figure 2. Regions of selective atrophy at baseline

Differential areas affected in MCI-AD identified by ANCOVA analyses show reductions in the hippocampal gray (blue, significant in MCI-AD vs controls and MCI-AD vs HAND), temporal gray (yellow), and parahippocampal gyrus (green) between MCI-AD and controls, but no significant reductions in HAND compared to controls.

Table 1.
Demographic and clinical variables stratified by group

Categorical variables reported as % and continuous variables reported as mean (SD). Values in bold indicate p-value significant at the 0.05 probability level after correction for multiple comparisons.

Variables	Controls	HAND	MCI-AD	p-values
Baseline MRI scans, n	*89*	*61*	*53*	
Age, years, mean (SD; range)	65 (4.5; 52-70)	64 (3.9; 60-80)	65 (5.5; 55-70)	0.548 $^{H/C}$; 0.905 $^{M/C}$; 0.385 $^{H/M}$
Gender, n (% male)	72 (81%)	56 (92%)	43 (81%)	0.152
Education years, mean (SD) *	17 (1.9)	16 (1.1)	16 (2.6)	**<0.001**$^{H/C}$; **0.034**$^{M/C}$; 0.145$^{H/M}$
Ethnicity, n (% Caucasian)	74 (83%)	50 (89%)	38 (72%)	0.843
Risk for HIV, MSM only (%)	-	47 (78%)	-	-
CD4 count, mean (SD)	-	575 (251)	-	-
Nadir CD4, mean (SD)	-	151 (139)	-	-
HIV duration, mean (SD)	-	24 (7.3)	-	-
on cART (%)	-	100%	-	-
Undetectable viral load (%) **	-	100%	-	-
HAND Diagnosis	-	100%	-	-
ANI	-	5 (8%)	-	-
MND	-	56 (92%)	-	-
Amnestic MCI	-	-	20 (38%)	-
Frontal/Executive	-	-	9 (17%)	-
Language	-	-	5 (9%)	-
Psychiatric	-	-	4 (8%)	-
Visuospatial	-	-	1 (2%)	-
Mixed/unspecified	-	-	14 (26%)	-
Baseline cognitive testing, n	*82*	*61*	*36*	
Age, years, mean (SD)	65 (4.3)	64 (3.9)	66 (5.2)	0.209
Gender, n (% male)	66 (80%)	56 (92%)	27 (75%)	0.067
Education, mean (SD)	17 (1.9)	16 (2.1)	17 (2.2)	**<0.000**$^{H/C}$; 0.110$^{M/C}$; 0.059$^{H/M}$
Remote alcohol abuse ***	1 (1%)	16 (26%)	1 (3%)	**<0.001**
Remote substance abuse ***	2 (2%)	10 (16%)	1 (3%)	**0.005**
Composite score, mean (SD) ****	0.16 (0.42)	−0.43 (0.47)	−0.77 (0.69)	**<0.001**$^{H/C}$; **<0.001**$^{M/C}$; **0.004**$^{H/M}$
MMSE, mean (SD)	29 (0.7)	-	27 (2.2)	**<0.001**
GDS, mean (SD)	3.3 (3)	9.8 (6.9)	6.6 (4.5)	**<0.001**$^{H/C}$; **0.004**$^{M/C}$; **0.008**$^{H/M}$

Abbreviations: HAND: HIV-associated neurocognitive disorder; MCI-AD: mild cognitive impairment clinical syndrome consistent with Alzheimer's disease; MSM: men who have sex with men; cART: combination antiretroviral therapy; ANI: asymptomatic neurocognitive impairment; MND: mild neurocognitive disorder; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale

$^{H/C}$ HAND vs. Controls; $^{M/C}$ MCI-AD vs. Controls; $^{H/M}$HAND vs. MCI-AD

* Education not available for 5 MCI-AD

** Viral load <100 copies/mL

*** From the National Alzheimer's Coordinating Center (NAAC) Uniform Data Set Health History form

**** Composite neuropsychological score calculated as the average of the individual domain-specific z-scores

Table 2.
Baseline volumetric measurements, relative reductions from control

Percent difference from control was calculated as average control volume subtracted from average disease volume divided by control volume. These values are categorized by comparing two disease groups, both HAND and MCI-AD with controls, with corresponding post hoc Tukey effects for actual baseline volume. Regions are arranged by categories documented in extant literature, light gray are HIV-related ROIs, middle gray reflect differentially affected ROIs in HAND vs MCI-AD and darkest gray are areas related to AD.

ROIs	HAND vs Controls |% relative difference| [95% CI]	MCI-AD vs Controls |% relative difference| [95% CI]	p-values
Brainstem	2.8 [5.5:0.1]	2.0 [5.0:−1.0]	0.248$^{H/C}$; 0.988$^{M/C}$; 0.415$^{H/M}$
Caudate	2.7 [5.4:−0.1]	5.1 [8.5:1.6]	0.401$^{H/C}$; 0.129$^{M/C}$; 0.796$^{H/M}$
Cerebellum gray	2.0 [4.6:−0.7]	2.4 [5.2:−0.4]	0.475$^{H/C}$; 0.801$^{M/C}$; 0.897$^{H/M}$
Frontal gray	4.2 [6.9:1.5]	7.4 [10.1:4.7]	**0.008**$^{H/C}$; **<0.001** $^{M/C}$; 0.554$^{H/M}$
Lateral ventricles *	28.1 [11.9:44.4]	29.9 [11.1:48.7]	**<0.001**$^{H/C}$; **<0.001**$^{M/C}$; 0.941$^{H/M}$
Nucleus Accumbens	4.7 [7.6:1.9]	6.7 [9.5:3.9]	**0.005**$^{H/C}$; **0.002**$^{M/C}$; 0.916$^{H/M}$
Pallidum	2.4 [5.1:−0.3]	2.8 [5.7:−0.0]	0.349$^{H/C}$; 0.787$^{M/C}$; 0.811$^{H/M}$
Putamen	3.5 [6.2:0.8]	5.3 [8.0:2.6]	**0.029**$^{H/C}$; **0.023**$^{M/C}$; 0.986$^{H/M}$
Thalamus	3.3 [5.5:1.0]	5.8 [8.2:3.4]	**0.009**$^{H/C}$; **0.001** $^{M/C}$; 0.692$^{H/M}$
Left Precentral gyrus	5.7 [8.3:3.0]	6.7 [10.0:3.4]	**0.003**$^{H/C}$; **0.005**$^{M/C}$; >0.99$^{H/M}$
Left Precuneus	4.6 [7.5:1.7]	7.4 [10.3:4.6]	**0.011**$^{H/C}$; **0.002**$^{M/C}$; 0.832$^{H/M}$
Right Precentral gyrus	5.3 [8.2:2.4]	6.1 [9.2:3.0]	**0.004**$^{H/C}$; **0.018**$^{M/C}$; 0.948$^{H/M}$
Hippocampal gray	2.9 [5.3:0.4]	7.3 [10.3:4.3]	0.205$^{H/C}$; **<0.001** $^{M/C}$; **0.040**$^{H/M}$
Parahippocampal gyrus	1.9 [4.1:−0.4]	5.4 [7.9:2.9]	0.395$^{H/C}$; **0.003**$^{M/C}$; 0.148$^{H/M}$
Parietal gray	4.8 [7.3:2.3]	7.8 [10.3:5.3]	**0.002**$^{H/C}$; **<0.001**$^{M/C}$; 0.476$^{H/M}$
Temporal gray	3.1 [5.6:0.5]	6.4 [8.7:4.0]	0.11 8$^{H/C}$; **0.001**$^{M/C}$; 0.197$^{H/M}$

$^{H/C}$ HAND vs. Controls; $^{M/C}$ MCI-AD vs. Controls; $^{H/M}$ HAND vs. MCI-AD

* Lateral ventricles were enlarged, CI reflects this

Table 3.
Longitudinal volumetric measurements

Annualized percent atrophy is reported as volume at baseline subtracted from volume at follow-up divided by baseline volume and years between scan for each group. Post hoc tests with Tukey effects are displayed in right hand column. Regions are arranged by categories documented in extant literature, light gray are HIV-related ROIs, middle gray reflect differentially affected ROIs in HAND vs MCI-AD and darkest gray are areas related to AD.

ROIs	Control n=36 [%Δ/yr (95% CI)]	HAND n=19 %/yrΔ/yr (95% CI)]	MCI-AD n=13 [%AΔ/yr (95% CI)]	p -values
Brainstem	−0.0 [−0.2:0.2]	−0.1 [−0.5:0.3]	−0.5 [−0.8:−0.3]	0.669 $^{H/C}$; **0.015** $^{M/C}$; 0.156 $^{H/M}$
Caudate	0.5 [0.0:0.9]	−0.2 [−1.1:0.7]	−1.6 [−2.9:−0.4]	0.303$^{H/C}$; **<0.001** $^{M/C}$; **0.054** $^{H/M}$
Cerebellum gray	0.09 [−0.3:0.5]	−0.6 [−1.5:0.2]	−1.1 [−1.9:−0.3]	**0.033** $^{H/C}$; **0.010** $^{M/C}$; 0.819 $^{H/M}$
Frontal gray	0.1 [−0.4:0.5]	−1.1 [−1.8:−0.4]	−1.0 [−1.9:−0.1]	**0.026** $^{H/C}$; **0.084** ^{MC}; 0.972 $^{H/M}$
Lateral ventricles	2.9 [2.3:3.5]	4.5 [2.1:6.9]	5.7 [3.4:8.0]	0.276 $^{H/C}$; **0.002** $^{M/C}$; 0.148 $^{H/M}$
Nucleus Accumbens	0.2 [−0.3:0.7]	−0.7 [−1.8:0.4]	−1.4 [−2.5:−0.3]	0.223 $^{H/C}$; **0.013** $^{M/C}$; 0.430 $^{H/M}$
Pallidum	−0.5 [−0.7:−0.2]	−0.4 [−1.0:0.2]	−0.7 [−1.3:0.0]	0.908 $^{H/C}$; 0.816 $^{M/C}$; 0.652 $^{H/M}$
Putamen	−0.1 [−0.4:0.2]	−0.5 [−1.3:0.3]	−1.3 [−2.1 :−0.6]	0.542 $^{H/C}$; **0.008** $^{M/C}$; 0.143 $^{H/M}$
Thalamus	−0.3 [−0.5:0.0]	−0.4 [−0.9:0.0]	−1.0 [−1.6:−0.5]	0.759 $^{H/C}$; **0.050** $^{M/C}$; 0.270 $^{H/M}$
Left Precentral gyrus	−0.0 [−0.7:0.6]	−1.3 [−2.6:−0.0]	−1.7 [−2.8:−0.5]	0.075 $^{H/C}$; 0.055 $^{M/C}$; 0.953 $^{H/M}$
Left Precuneus	−0.3 [−0.7:0.1]	−0.9 [−1.86:0.05]	−1.8 [−2.8:−0.8]	0.417 $^{H/C}$; **0.015** $^{M/C}$; 0.279 $^{H/M}$
Right Precentral gyrus	−0.0 [−0.5:0.6]	−0.9 [−1.9:0.1]	−2.2 [−3.5:−0.9]	0.257 $^{H/C}$; **0.003** $^{M/C}$; 0.172 $^{H/M}$
Hippocampal gray	−0.2 [−0.6:0.2]	−0.7 [−1.5:0.2]	−1.8 [−2.8:−0.8]	0.288 $^{H/C}$; **0.003** $^{M/C}$; 0.159 $^{H/M}$
Parahippocampal gyrus	0.1 [−0.3:0.61	−0.5 [−1.4:0.3]	−1.6 [−2.9:−0.3]	0.119 $^{H/C}$; **0.002** $^{M/C}$; 0.252 $^{H/M}$
Parietal gray	−0.3 [−0.7:0.1]	−0.9 [−1.7:−0.1]	−1.8 [−2.6:−0.9]	0.321 $^{H/C}$; **0.009** $^{M/C}$; 0.283 $^{H/M}$
Temporal gray	−0.2 [−0.6:0.3]	−0.9 [−1.9:0.1]	−2.0 [−3.2:−0.7]	0.200 $^{H/C}$; **0.006** $^{M/C}$; 0.312 $^{H/M}$

$^{H/C}$ HAND vs. Controls; $^{M/C}$ MCI-AD vs. Controls; $^{H/M}$ HAND vs. MCI-AD