Published in final edited form as:

J Neurovirol. 2019 December ; 25(6): 741–753. doi:10.1007/s13365-019-00761-y.

Associations of regional amyloid- β plaque and phospho-tau pathology with biological factors and neuropsychological functioning among HIV-infected adults

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Abstract

With increasing age, the general population is increasingly vulnerable to the development of cerebral amyloid- β (A β) plaque and neuronal phospho-tau (p-tau) pathology. In HIV disease, prior studies of these neuropathologic changes were relatively limited. Here, we characterized A β plaques and p-tau lesions by immunohistochemistry in relevant brain regions (prefrontal neocortex, putamen, basal-temporal neocortex, and hippocampus) of HIV-infected adults. We used multivariable logistic regression to predict regional A β plaque or p-tau pathology based on demographic factors, apolipoprotein E (*APOE*) genotypes, HIV disease-related factors, and regional gliosis. We used multiple linear regression to predict T-scores in neuropsychological domains based on regional A β plaque or p-tau pathology. We found that *APOE* ϵ 4 alleles, older age, and higher plasma HIV-1 RNA predicted prefrontal A β plaques (odds ratio (OR) 5.306, 1.045, and 0.699, respectively, $n = 168$). Older age predicted putamen A β plaques (OR 1.064, $n = 171$). *APOE* ϵ 4 alleles, hepatitis C virus seropositivity, and higher plasma HIV-1 RNA predicted hippocampus A β plaques (OR 6.779, 6.138, and 0.589, respectively, $n = 56$). The p-tau lesions were sparse in the vast majority of affected cases. Lifetime substance use disorder and higher plasma HIV-1 RNA predicted putamen p-tau lesions (OR 0.278 and 0.638, respectively, $n = 67$). Older age and gliosis predicted hippocampus p-tau lesions (OR 1.128 and 0.592, respectively, $n = 59$). Prefrontal A β plaques predicted lower speed of information processing ($n = 159$) and putamen A β plaques predicted lower levels of attention and working memory ($n = 88$). Regional p-tau lesions were not significantly predictive of any neuropsychological domains. In conclusion, A β plaque or p-tau pathology in different brain regions was predicted by different sets of biological factors. A β plaques in prefrontal neocortex and putamen predicted poorer functioning in

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Conflict of interest The authors declare that they have no conflict of interest.

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cognitive domains relevant to these brain regions. The absence of significant impact of regional p-tau lesions on neuropsychological functioning might be explained by the subthreshold burden of p-tau lesions.

Keywords

Amyloidosis; Astrogliosis; Gliosis; Microgliosis; Neurodegeneration; Tauopathy

Introduction

Due to widespread implementation of highly active antiretroviral therapy (HAART), the life expectancy of HIV-infected persons has drastically increased (Teeraananchai et al. 2017). The prevalence of older HIV-infected persons is increasing. For instance, in the USA, persons aged 50 years or older accounted for 48.2% of all HIV-infected people in 2016 and constituted 17% of new HIV diagnoses in 2017 (Centers for Disease Control and Prevention 2017). With increasing age, the general population is increasingly susceptible to the development of cerebral extracellular amyloid- β (A β) plaques and neuronal phospho-tau (p-tau) lesions (Braak et al. 2011), putatively involved in the pathogenesis of Alzheimer's disease (Hyman et al. 2012). Importantly, these neuropathologic changes may contribute to aging-related neuropsychological decline in certain functioning domains (Jicha et al. 2012; Price et al. 2009).

Based on large-scale non-selected general autopsy studies (Braak et al. 2011; Thal et al. 2015), A β plaque pathology first appears in the cerebral neocortex of adults in their fourth decade of life and progresses with age to involve the allocortex, striatum, and other brain regions in a characteristic sequence. It is estimated that A β plaque pathology affects 75% of people by their tenth decade (Braak et al. 2011). On the other hand, the cerebral involvement of neuronal p-tau pathology starts in the allocortex and expands into the basal-temporal and prefrontal neocortex (Braak et al. 2011). Nonetheless, p-tau pathology can develop in some contexts other than natural brain aging and exhibit different patterns of regional progression, such as that p-tau pathology described in chronic traumatic encephalopathy (McKee et al. 2013).

Compared with non-HIV control participants, HIV-infected adults showed evidence of accelerated brain aging in structural (Pfefferbaum et al. 2014) and functional (Ances et al. 2010) magnetic resonance imaging studies and in DNA methylation epigenetic analyses (Horvath and Levine 2015; Levine et al. 2016a). Accordingly, HIV-infected persons may be vulnerable to the premature development of cerebral A β plaque or p-tau pathology. A number of autopsy studies of HIV-infected individuals described cerebral A β plaque or p-tau pathology (Anthony et al. 2006; Esiri et al. 1998; Gelman and Schuenke 2004; Green et al. 2005; Izzycka-Swieszevska et al. 2000; Rempel and Pulliam 2005; Smith et al. 2014; Soontornniyomkij et al. 2012a). Nonetheless, these previous studies were relatively limited in terms of biological factors predicting these neuropathologic changes and the neuropsychological implications.

In the present study, we characterized A β plaques and p-tau lesions in four brain regions (i.e., prefrontal neocortex, putamen, basal-temporal neocortex, and hippocampus), considered pertinent to both HIV disease (Wiley et al. 1998) and the regional progression of these neuropathologic changes (Braak et al. 2011; Thal et al. 2015). We investigated what clinically relevant biological factors (i.e., demographic factors, apolipoprotein E (*APOE*) genotypes (Bennett et al. 2009; Polvikoski et al. 1995), HIV disease-related factors, and regional gliosis) could predict regional A β plaque or p-tau pathology. Moreover, we assessed whether regional A β plaque or p-tau pathology could predict functioning in individual neuropsychological domains.

Methods

Study cohort

We studied 285 autopsy HIV-infected adult cases that had paraffin-embedded tissue samples from at least one of middle frontal gyrus, putamen, and basal-temporal region/ hippocampus blocks available in the National NeuroAIDS Tissue Consortium (NNTC) in the USA (Request # R432 and # R458). In the basal-temporal region/hippocampus block, neuropathologic changes were assessed in two separate brain regions: basal-temporal neocortex and hippocampus. The University of California San Diego Human Research Protections Program approved the project. All study participants provided written informed consent to participate, and the written consent to autopsy was obtained. Our study included only participants whose races/ethnicities were Caucasian, African American, or Hispanic, because of the relatively small number of participants of other races/ethnicities. The biological factors, confounders, neuropathological outcomes, and neuropsychological domain T-scores are summarized in Table 1. Of 285 cases studied, not every case had all brain tissue samples and biological data.

Using univariable logistic regression, we evaluated individually 10 biological factors considered clinically relevant to neuropathological outcomes studied (i.e., A β plaque and p-tau pathology) in the context of HIV disease: age at death, sex, race/ethnicity, presence of one or two *APOE* ϵ 2 or ϵ 4 alleles (Bennett et al. 2009; Polvikoski et al. 1995), hepatitis C virus (HCV) seropositivity, lifetime substance use disorder (current or past substance abuse or dependence of any of alcohol, cannabis, cocaine, methamphetamine, and opiates, diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders), use of HAART regimens at the last clinical assessment (vs. use of non-HAART regimens, discontinuation of antiretroviral therapy (ART), or being ART-naïve), plasma HIV-1 RNA load (log₁₀ copies/ml) at the last clinical assessment, presence of HIV encephalitis, and regional gliosis.

There might be NNTC site differences in biological factors (e.g., those related to geographical areas or social environs) for which could not be specifically accounted in our study. In addition, we could not exclude a possibility of certain interlaboratory preanalytical differences that were relevant to immunohistochemistry, including materials and equipment from different manufacturers. We, therefore, included the NNTC site difference, as well as the postmortem delay (> 12 h), as confounders in logistic regression models (Bao and Swaab 2018; Price et al. 2009).

Neuropsychological assessment

HIV-infected participants were evaluated with a multidomain neuropsychological test battery within 1 year prior to death. Seven domains of neuropsychological functioning were assessed: executive functions, speed of information processing, attention and working memory, learning, delayed recall, verbal fluency, and motor (Woods et al. 2004). Individual neuropsychological test T-scores were assigned using normative data correcting for age, sex, race/ethnicity, and education when indicated and possible (Woods et al. 2004). The neuropsychological domain T-scores (with possible ranges of 19 to 80) were derived from averaging individual test T-scores in the same domains. Higher domain T-scores indicated higher levels of neuropsychological functioning.

Histopathology and APOE genotyping

Histopathologic diagnoses were made by site neuropathologists in the NNTC. HIV encephalitis was defined as multiple foci of microgliosis, multinucleated giant cells, and astrogliosis in the brain (Budka et al. 1991). *APOE* genotypes ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles) were determined at the University of California Los Angeles Biological Samples Processing Core. The Autopure LS nucleic acid purification instrument was used to extract DNA from frozen occipital cortex tissue samples. Single nucleotide polymorphism genotyping (*rs429358* and *rs7412*) was performed on the Sequenom MassARRAY iPLEX platform (Agena Bioscience, San Diego, CA, USA), as previously described (Levine et al. 2016b). The presence of one or two *APOE* $\epsilon 4$ alleles was not statistically significantly different across the race/ethnicity groups ($\chi^2 = 2.383$, $df = 2$, $n = 254$, $p = 0.304$, Pearson chi-square test). On the other hand, there was a difference in the frequency of participants with one or two *APOE* $\epsilon 2$ alleles across the race/ethnicity groups ($\chi^2 = 6.990$, $df = 2$, $n = 254$, $p = 0.030$, Pearson chi-square test). In particular, the *APOE* $\epsilon 2$ allele was rare among Hispanic participants (Table 1).

To assess the predictive effects of *APOE* $\epsilon 4$ and $\epsilon 2$ alleles on A β plaque or p-tau pathology, we first simultaneously tested for dominant main effects and an interaction effect between $\epsilon 4$ and $\epsilon 2$ alleles in order to allow the inclusion of participants carrying the *APOE* $\epsilon 4/\epsilon 2$ genotype. Symbolically, this model was represented as:

$$\begin{aligned} \text{Logit}(Y) = & \alpha + \beta_{\epsilon 4} I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}} \\ & + \beta_{\epsilon 2} I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}} \\ & + \gamma_{\epsilon 4\epsilon 2} I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}} I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}} \end{aligned}$$

where $I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}} = 1$ if the *APOE* genotype was $\epsilon 4/\epsilon 4$, $\epsilon 4/\epsilon 3$, or $\epsilon 4/\epsilon 2$ and = 0 otherwise, and $I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}} = 1$ if the *APOE* genotype was $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 4/\epsilon 2$ and = 0 otherwise. This three-parameter model represented our most general model for the effects of *APOE* and allowed for difference in effects from the referent genotype $\epsilon 3/\epsilon 3$ to be determined. When a more parsimonious model with fewer parameters was statistically supported, e.g., a model with only the dominant effect of *APOE* $\epsilon 4$ over both $\epsilon 2$ and $\epsilon 3$ could not be rejected ($\text{Logit}(Y) = \alpha + \beta_{\epsilon 4} I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}}$), we used the model with fewer parameters. The specific model used is specified in the footnotes of Tables 2 and 3.

Immunohistochemistry

We conducted immunohistochemistry on 5- μ m-thick tissue sections prepared from three paraffin-embedded formalin-fixed brain blocks: middle frontal gyrus, putamen, and basal-temporal region/hippocampus. Primary antibodies used were directed against A β _{17–24} (clone 4G8, SIG-39220, Covance, Princeton, NJ, USA; dilution 1:20,000), p-tau (clone AT8, MN1020, Pierce Biotechnology, Rockford, IL, USA; 1:1000), ionized calcium-binding adapter molecule-1 (Iba1, microglia/macrophage marker; 019–19741, Wako, Richmond, VA, USA; 1:1000), and glial fibrillary acidic protein (GFAP, astroglia marker; Z0334, Dako, Carpinteria, CA, USA; 1:1000). The immunohistochemical staining procedures were carried out with diaminobenzidine (DAB) as a chromogen, as previously described (Soontornniyomkij et al. 2012b, 2016). The A β and p-tau immuno-labeled tissue sections were counterstained with Mayer hematoxylin. Neocortex sections from an Alzheimer's disease brain (a gift from Dr. Eliezer Masliah, Departments of Pathology and Neurosciences, University of California San Diego) were used as the positive tissue controls for A β and p-tau immunohistochemistry in all staining batches.

Assessments of regional A β plaque and p-tau pathology

A β plaque pathology was designated as *present* when extracellular A β -immunoreactive plaques were observed, regardless of their type (Duyckaerts et al. 2009) or density. The density of A β plaques was graded as *absent*, *focal*, or *widespread*, as described previously (Soontornniyomkij et al. 2012a). Neuronal p-tau pathology was designated as *present* when there were p-tau-immunoreactive neuropil threads, pretangle neuronal soma, neurofibrillary tangles, or their combinations (Duyckaerts et al. 2009; Soontornniyomkij et al. 2018). The density of neuropil threads was graded as 0 (absent), 1 (barely present at $\times 100$ magnification), 2 (easily noted at $\times 100$ magnification), or 3 (notable with naked eye inspection), a scoring system adapted from a BrainNet Europe Consortium study (Alafuzoff et al. 2008), as previously described (Soontornniyomkij et al. 2018).

Assessments of regional gliosis

We regarded regional microgliosis (Ransohoff and Cardona 2010) and astrogliosis (Sofroniew and Vinters 2010) as summed neuropathologic indicators of inflammatory and reparative responses to neural injury accumulating in the course of HIV disease and its comorbidities. Immunohistochemistry for Iba1 showed resident microglia and perivascular macrophages, and that for GFAP showed diffusely distributed astroglia of variable density, as previously described (Soontornniyomkij et al. 2016).

Quantifications of Iba1 and GFAP immunoreactivity on the DAB tissue slides were performed by using a microscope slide scanner (Aperio ScanScope GL, Leica Biosystems, Buffalo Grove, IL, USA), Aperio ImageScope software, and Image-Pro Analyzer software (Version 6.3, Media Cybernetics, Bethesda, MD, USA), as described previously (Soontornniyomkij et al. 2018). The DAB intensity was quantified within each area of interest (i.e., the prefrontal neocortex (layers II–VI), basal-temporal neocortex (layers II–VI), putamen, and hippocampal CA1). The DAB intensity per unit area (i.e., DAB density) was calculated, as described previously (Soontornniyomkij et al. 2012b). To adjust for the between-batch variation, one brain section from the same positive tissue control block was

included in each immunostaining batch. The control DAB density value (in a specified area) was used to normalize all the DAB density values of studied cases in the same batch, generating the *immunoreactivity density* values (continuous variables).

In the prefrontal neocortex, putamen, basal-temporal neocortex, and hippocampal CA1, the immunoreactivity density values of Iba1 and GFAP showed direct correlations (Spearman's ρ 0.293, 0.422, 0.482, and 0.559; $n = 268, 171, 71$, and 71 , respectively; $p < 0.001$ all). Therefore, in each of the brain regions, we transformed each of the Iba1 and GFAP immunoreactivity density values into a score of 1, 2, or 3 by tertile cutoffs, and generated a *gliosis score* (composite score of microgliosis and astrogliosis: 2, 3, 4, 5, or 6) by summing Iba1 and GFAP scores.

Statistical analysis

We performed univariable logistic regression analyses regressing each regional A β plaque or p-tau pathology against each of the biological factors and confounders (Table 2). To reduce bias in small sample sizes and deal with the issue of quasi-complete separation, we used the Firth penalized maximum likelihood method (with profile penalized log likelihood confidence intervals [CI]), instead of standard maximum likelihood estimation (Allison 2012). Because of the small sample sizes, we needed to limit the number of predictors to be included in the subsequent multivariable logistic regression even when using Firth penalized logistic regression. Thus, we chose the four most significant biological factors or confounders having $p < 0.10$ to be subsequently included in the multivariable Firth penalized logistic regression model of prediction. We then used a backward stepwise model selection approach to determine the final model (Table 3): each regional A β plaque or p-tau pathology was regressed on those biological factors and confounders. We presented the effect sizes as odds ratios (OR) and included their 95% CI.

We conducted multiple linear regression analyses to predict each neuropsychological domain T-score based on regional A β plaque or p-tau pathology, controlling for age, sex, and race/ethnicity (Table 4). In the process of assigning individual neuropsychological test T-scores, the statistical correction for potential covariates might not be uniformly applied to all neuropsychological tests and participants. We therefore uniformly included age, sex, and race/ethnicity in multiple linear regression models for predicting each neuropsychological domain T-score. General linear model (univariate): Each neuropsychological domain T-score was regressed on each regional A β plaque or p-tau pathology, along with age, sex, and race/ethnicity. The unstandardized coefficient (B) measured the effect size.

Of 285 cases studied, not every case had all brain tissue samples and biological data (Table 1). The statistical analyses were performed on available cases, with pairwise exclusion. Two-sided p values were considered statistically significant if $p < 0.05$. The p values reported in the present study were not adjusted for the family-wise type I error in multiple comparisons. The statistical analyses were performed using R (The R Project for Statistical Computing) Version 3.5.2 and IBM SPSS Statistics Version 25.

Results

A β plaque pathology

The vast majority of A β plaques found in four brain regions examined were of diffuse type (Fig. 1a–d), as previously described (Soontornniyomkij et al. 2012a). A β plaque pathology (Table 1) was present in 79 (focal in 59 and widespread in 20) of 268 cases (29.5%) in the prefrontal neocortex, 24 (focal in 22 and widespread in 2) of 171 cases (14.0%) in the putamen, 16 (focal in 6 and widespread in 10) of 71 cases (22.5%) in the basal-temporal neocortex, and 22 (focal in 18 and wide-spread in 4) of 71 cases (31.0%) in the hippocampus. The youngest case having focal A β plaque pathology in the prefrontal neocortex was 30 years old at death, in the putamen 33 years, in the basal-temporal neocortex 34 years, and in the hippocampus 33 years. The youngest case having widespread A β plaque pathology in the prefrontal neocortex was 44 years old at death, in the putamen 57 years, in the basal-temporal neocortex 46 years, and in the hippocampus 49 years.

The confounders, postmortem delay and NNTC site difference, were significantly associated only with putamen A β plaque pathology in the univariable logistic regression analyses (Table 2) and therefore included only in that multivariable analysis. In multivariable logistic regression analyses (Table 3), the presence of one or two *APOE* ϵ 4 alleles and increasing age predicted higher likelihood of prefrontal A β plaque pathology (OR 5.306 [95% CI 2.355, 11.952], $p < 0.001$, and OR 1.045 [95% CI 1.001, 1.092], $p = 0.031$, respectively), whereas higher plasma HIV-1 RNA load predicted lower likelihood (OR 0.699 [95% CI 0.540, 0.905], $p = 0.005$, $n = 168$). Increasing age predicted higher likelihood of putamen A β plaque pathology (OR 1.064 [95% CI 1.009, 1.121], $p = 0.019$), controlling for postmortem delay and NNTC site difference ($n = 171$). The presence of one or two *APOE* ϵ 4 alleles and HCV seropositivity predicted higher likelihood of hippocampus A β plaque pathology (OR 6.779 [95% CI 1.323, 34.738], $p = 0.016$, and OR 6.138 [95% CI 1.443, 26.113], $p = 0.008$, respectively), whereas plasma HIV-1 RNA load predicted lower likelihood (OR 0.589 [95% CI 0.355, 0.980], $p = 0.028$, $n = 56$). For basal-temporal A β plaque pathology, no biological factors or confounders met the p value threshold in the univariable analyses (Table 2), and so the multivariable analysis was not conducted.

Neuronal p-tau pathology

Representative features of neuronal p-tau pathology in four brain regions examined are shown in Fig. 1e–h. In the prefrontal neocortex, p-tau pathology (Table 1) was present in 119 of 268 cases (44.4%). Of these 119 cases, 112 cases had neuropil threads of grade 1 density, four cases with grade 2, and one case with grade 3; the remaining two cases having pretangle or tangle-bearing neuronal soma without neuropil threads. In the putamen, p-tau pathology was present in 37 of 122 cases (30.3%). Of these 37 cases, 34 cases had neuropil threads of grade 1 density and one case with grade 2; the remaining two cases having pretangle or tangle-bearing neuronal soma without neuropil threads. In the basal-temporal neocortex, p-tau pathology was present in 45 of 71 cases (63.4%). Of these 45 cases, 36 cases had neuropil threads of grade 1 density, eight cases with grade 2, and the remaining case with grade 3. In the hippocampus, p-tau pathology was present in 40 of 71 cases (56.3%). Of these 40 cases, 35 cases had neuropil threads of grade 1 density and three cases

with grade 2; the remaining two cases having pretangle or tangle-bearing neuronal soma without neuropil threads.

The confounder NNTC site difference was significantly associated in the univariable logistic regression analyses of prefrontal, basal-temporal, and hippocampus p-tau pathology (Table 2) and so included in these multivariable analyses. In multivariable logistic regression analyses (Table 3), lifetime substance use disorder and higher plasma HIV-1 RNA load predicted lower likelihood of putamen p-tau pathology (OR 0.278 [95% CI 0.079, 0.979], $p = 0.032$, and OR 0.638 [95% CI 0.436, 0.934], $p = 0.013$, respectively, $n = 67$). Increasing age predicted higher likelihood of hippocampus p-tau pathology (OR 1.128 [95% CI 1.040, 1.224], $p < 0.001$), whereas gliosis score predicted lower likelihood (OR 0.592 [95% CI 0.365, 0.961], $p = 0.024$, $n = 59$). Gliosis score, the only biological factor significantly associated with lower likelihood of prefrontal p-tau pathology in the univariable analysis, showed no significant association when controlling for NNTC site difference ($n = 268$).

Although using the Firth penalized maximum likelihood method improved the stability of logistic regression models over standard maximum likelihood estimation (data not shown), the effect size of HAART use (OR 7.740 [95% CI 0.902, 66.405], $p = 0.028$, $n = 59$) on hippocampus p-tau pathology (Table 3) might be imprecisely estimated. The instability was most likely due to the small sample size. Similarly, the effect sizes of African American race/ethnicity (OR 11.527 [95% CI 1.145, 116.01], $p = 0.018$) and HCV seropositivity (OR 12.363 [95% CI 1.749, 87.381], $p = 0.002$) on basal-temporal p-tau pathology, controlling for NNTC site difference, might be considered biased and imprecise due to the small sample size ($n = 61$).

Neuropsychological functioning

For neuropsychological functioning (Table 4), prefrontal A β plaque pathology predicted lower speed of information processing ($B = -3.928$, $p = 0.032$, $n = 159$) and putamen A β plaque pathology predicted lower levels of attention and working memory ($B = -6.269$, $p = 0.020$, $n = 88$), when controlling for age, sex, and race/ethnicity. Regional p-tau pathology was not significantly predictive of any neuropsychological functioning domains.

Discussion

In the present study of HIV-infected adults, the vast majority of A β plaques found in four brain regions examined were of diffuse type, consistent with the early stages of A β plaque development (Duyckaerts et al. 2009). The occurrence of A β plaque pathology in the four brain regions was predicted by different sets of biological factors. For instance, the presence of *APOE* $\epsilon 4$ alleles was associated with A β plaque pathology in the prefrontal neocortex and hippocampus, but not in the putamen or basal-temporal neocortex. The APOE isoforms differentially regulate A β clearance and aggregation probably by multiple pathways such as binding to lipoprotein receptors involved in A β clearance (Verghese et al. 2013; Zhao et al. 2018). There may be brain region-dependent factors that can modulate A β metabolism, such as the microvascular architecture and function regulating A β clearance via vascular basement membrane pathways (Morris et al. 2016).

With regard to neuropsychological functioning, we found that A β plaque pathology in the prefrontal neocortex and putamen was associated with poorer functioning in speed of information processing and attention/working memory, respectively, cognitive domains relevant to these brain regions (Arsalidou et al. 2013; Dux et al. 2009). Our findings in HIV-infected adults agree with the observation that with age the general population is increasingly susceptible to diffuse A β plaque pathology, which may contribute to aging-related neuropsychological decline in certain functioning domains (Jicha et al. 2012; Price et al. 2009).

Among the four brain regions examined, we found that older age was associated with neuronal p-tau pathology only in the hippocampus. This finding is in agreement with the natural age-dependent sequence of cerebral regional progression of p-tau pathology, starting in the allocortex (Braak et al. 2011). It was difficult to interpret the effect of HAART use on hippocampus p-tau pathology because the OR 95% CI value was wide (Table 3), indicating the instability of the logistic regression model, which was most likely due to the small sample size (de Irala et al. 1997). The same scenario could also apply to the interpretation of the effects of race/ethnicity and HCV seropositivity on basal-temporal p-tau pathology (with wide OR 95% CI values); however, our findings are suggestive of the predictive effects and further studies using larger sample sizes are warranted.

In our study, although neuronal p-tau pathology was found in approximately one third to two thirds of cases, depending on brain regions, these p-tau lesions were sparse (i.e., neuropil threads of grade 1 density) in the vast majority of affected cases. We found that regional p-tau pathology was not significantly predictive of any neuropsychological functioning domains. Considering the extent and density of p-tau lesions characteristically found in symptomatic cases of sporadic late-onset Alzheimer's disease (Duyckaerts et al. 2009; Hyman et al. 2012), the absence of significant impact of regional p-tau pathology on neuropsychological functioning in our study might be explained by the subthreshold burden of p-tau lesions, as well as the small sample sizes especially regarding the basal-temporal neocortex and hippocampus regions (Jicha et al. 2012).

Our present study had limitations inherent to research work using autopsy human specimens. HIV-infected individuals were recruited into the NNTC because they were at known risk of death. Not every study case had all brain tissue samples and biological data of interest (Table 1), which led to limited statistical power in multivariable logistic regression analyses. For example, the basal-temporal region/hippocampus block was available in only approximately one fourth of cases that had the middle frontal gyrus block available. The present study did not assess other neuropathologic changes that might also play a role in neuropsychological decline, including cerebrovascular disease, neocortical alpha-synucleinopathy, and TAR DNA binding protein (TDP-43) proteinopathy (Hyman et al. 2012; Jicha et al. 2012). Further studies on these neuro-degenerative changes are warranted.

In conclusion, our study showed that occurrence of A β plaque or p-tau pathology in different brain regions of HIV-infected adults was associated with different sets of biological factors. A β plaque pathology in the prefrontal neocortex and putamen was associated with poorer functioning in cognitive domains relevant to these brain regions. The absence of significant

impact of regional p-tau pathology on neuropsychological functioning might be explained by the subthreshold burden of p-tau lesions or insufficient statistical power. Systematic multi-region assessments of a broad range of neurodegenerative changes in large HIV cohorts may expand our understanding of the development of aging-related neuropsychological decline or neurodegenerative disorders in their early stages.

Acknowledgments

We are grateful to Dr. Eliezer Masliah (Departments of Pathology and Neurosciences, University of California San Diego) for providing Alzheimer's disease neocortex sections.

Funding information This research work was supported by the US National Institutes of Health (NIH) grants R56 AG059437 (V. Soontornniyomkij, D. J. Moore, B. Gouaux), R01 MH096648 (A. J. Levine, D. J. Moore, V. Soontornniyomkij, B. Gouaux), U24 MH100928 (D. J. Moore, V. Soontornniyomkij, B. Gouaux), and P50 DA026306 (V. Soontornniyomkij). This publication was made possible from NIH funding through the NIMH and NINDS Institutes by the following grants: Manhattan HIV Brain Bank (MHBB): U24 MH100931, Texas NeuroAIDS Research Center (TNRC): U24 MH100930, National Neurological AIDS Bank (NNAB): U24 MH100929, California NeuroAIDS Tissue Network (CNTN): U24 MH100928, Data Coordinating Center (DCC): U24 MH100925. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the National NeuroAIDS Tissue Consortium (NNTC) or NIH.

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Fig. 1.

Representative features of amyloid- β plaque (**a–d**) and neuronal phospho-tau (**e–h**) pathology in HIV-infected adults. Immunohistochemistry for amyloid- β shows diffuse plaques (arrows and insets) in the prefrontal neocortex (**a**), putamen (**b**), basal-temporal neocortex (**c**), and hippocampus (**d**) of a 66-year-old Caucasian man. Immunohistochemistry for phospho-tau shows neuropil threads (arrowheads and insets) and neurofibrillary tangle-bearing neurons (arrows and insets) in the prefrontal neocortex (**e**) of a 44-year-old African American man, the putamen (**f**) of a 44-year-old Caucasian man, and the basal-temporal neocortex (**g**) and hippocampus (**h**) of a 66-year-old Caucasian man (the same case as in **a–d**). Scale bars, 300 μ m for amyloid- β plaque and 100 μ m for phospho-tau pathology

Table 1

Summary of biological factors, confounders, neuropathological outcomes, and neuropsychological domain T-scores

Biological factors	
Age at death (years): range, mean [95% CI], <i>n</i>	26–70, 46.95 [45.88, 48.03], 285
Sex (men vs. women), <i>n</i>	235 (82.5%) vs. 50 (17.5%)
Race/ethnicity, <i>n</i>	
Caucasian	156 (54.7%)
African American	64 (22.5%)
Hispanic	65 (22.8%)
<i>APOE</i> ε4 (absent vs. present) ^a , <i>n</i>	184 (72.4%) vs. 70 (27.6%)
<i>p</i> = 0.304 (Pearson chi-square test)	Absent vs. present
Caucasian	98 (71.5%) vs. 39 (28.5%)
African American	39 (67.2%) vs. 19 (32.8%)
Hispanic	47 (79.7%) vs. 12 (20.3%)
<i>APOE</i> ε2 (absent vs. present) ^a , <i>n</i>	219 (86.2%) vs. 35 (13.8%)
<i>p</i> = 0.030 (Pearson chi-square test)	Absent vs. present
Caucasian	114 (83.2%) vs. 23 (16.8%)
African American	48 (82.8%) vs. 10 (17.2%)
Hispanic	57 (96.6%) vs. 2 (3.4%)
HCV seropositivity, <i>n</i>	77 (40.1%)
Lifetime substance use disorder ^b , <i>n</i>	74 (49.3%)
HAART use ^c , <i>n</i>	153 (82.7%)
Plasma HIV-1 RNA ^d : range, mean [95% CI], <i>n</i>	1.30–6.00, 3.72 [3.48, 3.96], 177
HIV encephalitis, <i>n</i>	19 (9.6%)
Glutosis score ^e : mean [95% CI], <i>n</i>	
Prefrontal neocortex	3.99 [3.84, 4.15], 268
Putamen	4.00 [3.80, 4.20], 171
Basal-temporal neocortex	3.97 [3.64, 4.30], 71
Hippocampus	3.97 [3.63, 4.31], 71
Confounders	

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Postmortem delay (> 12 h), <i>n</i>	120 (42.4%)
NNTC site difference, <i>n</i>	
CNTN	120 (42.1%)
NNAB	78 (27.4%)
TNRC	48 (16.8%)
MHBB	39 (13.7%)
Neuropathological outcomes	
Amyloid-β plaque pathology, <i>n</i>	Absent vs. present
Prefrontal neocortex	189 (70.5%) vs. 79 (29.5%)
Putamen	147 (86.0%) vs. 24 (14.0%)
Basal-temporal neocortex	55 (77.5%) vs. 16 (22.5%)
Hippocampus	49 (69.0%) vs. 22 (31.0%)
Neuronal phospho-tau pathology, <i>n</i>	Absent vs. present
Prefrontal neocortex	149 (55.6%) vs. 119 (44.4%)
Putamen	85 (69.7%) vs. 37 (30.3%)
Basal-temporal neocortex	26 (36.6%) vs. 45 (63.4%)
Hippocampus	31 (43.7%) vs. 40 (56.3%)
Neuropsychological domain T-scores: mean [95% CI], <i>n</i>	
Executive functions	45.94 [44.04, 47.85], 160
Speed of information processing	42.53 [40.94, 44.13], 165
Attention and working memory	44.70 [43.16, 46.23], 163
Learning	40.95 [39.34, 42.55], 166
Delayed recall	40.54 [38.95, 42.13], 166
Verbal fluency	45.95 [44.13, 47.76], 164
Motor	37.55 [35.69, 39.41], 155

CI confidence interval, *APOE* apolipoprotein E, *HCV* hepatitis C virus, *NNTC* National NeuroAIDS Tissue Consortium, *CNTN* California NeuroAIDS Tissue Network, *NNAB* National Neurological AIDS Bank, *TNRC* Texas NeuroAIDS Research Center, *MHBB* Manhattan HIV Brain Bank

In italics, *p* < 0.05 (statistically significant)

^aWith one or two alleles

^bCurrent or past substance abuse or dependence of any of alcohol, cannabis, cocaine, methamphetamine, and opiates, diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders

^cUse of highly active antiretroviral therapy (HAART) regimens at the last clinical assessment (vs. use of non-HAART regimens, discontinuation of antiretroviral therapy (ART), or being ART-naïve)

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Plasma HIV-1 RNA load (log10 copies/ml) at the last clinical assessment
 p

Composite score of microgliosis and astrogliosis (range 2–6)
 p

Table 2
Univariable logistic regression analysis models for predicting neuropathological outcomes

<i>p</i> value, <i>n</i>	Amyloid- β plaque pathology ^a Prefrontal neocortex	Putamen	Basal-temporal neocortex	Hippocampus
Biological factors				
Age (each-year increase)	< 0.001 (+), 268	0.015 (+), 171	0.153, 71	0.208, 71
Sex (vs. men)	0.024 (-), 268	0.899, 171	0.186, 71	0.713, 71
Race/ethnicity (vs. Caucasian)				
African American	0.456, 268	0.715, 171	0.782, 71	0.067 (+), 71
Hispanic	0.263, 268	0.884, 171	0.425, 71	0.950, 71
<i>APOE</i>				
$\epsilon 4$	0.002 ^g (+), 241	0.543 ^h , 146	0.143 ^h , 68	0.0012 ^h (+), 68
$\epsilon 2$	0.1255 ^g , 241	n/a	n/a	n/a
Omnibus	0.0033 ^g , 241	n/a	n/a	n/a
HCV seropositivity	0.427, 177	0.210, 141	0.127, 61	0.015 (+), 61
Lifetime substance use disorder ^b	0.366, 148	0.477, 71	0.843, 51	0.847, 51
HAART use ^c	0.857, 180	0.288, 107	0.279, 59	0.198, 59
Plasma HIV-1 RNA ^d	0.002 (-), 171	0.708, 90	0.279, 65	0.007 (-), 65
HIV encephalitis	0.491, 192	0.499, 99	0.993, 70	0.822, 70
Gliososis score ^e	0.234, 268	0.055 (-), 171	0.357, 71	0.257, 71
Confounders				
Postmortem delay (> 12 h)	0.907, 266	0.019 (-), 171	0.215, 71	0.919, 71
NNTC site difference (vs. CNTN) ^f				
NNAB	0.110, 268	< 0.001 (+), 171	0.979, 71	0.651, 71
TNRC	0.925, 268	n/a	n/a	n/a
MHBB	0.545, 268	n/a	n/a	n/a
<i>p</i> value, <i>n</i>	Neuronal phospho-tau pathology ^g Prefrontal neocortex	Putamen	Basal-temporal neocortex	Hippocampus
Biological factors				
Age (each-year increase)	0.189, 268	0.698, 122	< 0.001 (+), 71	< 0.001 (+), 71

<i>p</i> value, <i>n</i>	Amyloid- β plaque pathology ^a Prefrontal neocortex	Putamen	Basal-temporal neocortex	Hippocampus
Sex (vs. men)	0.245, 268	0.179, 122	0.629, 71	0.676, 71
Race/ethnicity (vs. Caucasian)				
African American	0.299, 268	0.916, 122	< 0.001 (+), 71	0.031 (+), 71
Hispanic	0.402, 268	0.984, 122	0.171, 71	0.501, 71
<i>APOE</i>				
$\epsilon 4$	n/a	n/a	n/a	n/a
$\epsilon 2$	0.192 ^j , 241	0.127 ^j , 114	0.543 ^j , 68	0.403 ^j , 68
HCV seropositivity	0.305, 177	0.163, 100	0.004 (+), 61	0.291, 61
Lifetime substance use disorder ^b	0.621, 148	0.028 (-), 68	0.269, 51	0.688, 51
HAART use ^c	0.145, 180	0.238, 91	0.309, 59	0.026 (+), 59
Plasma HIV-1 RNA ^d	0.104, 171	0.061 (-), 88	0.006 (-), 65	0.117, 65
HIV encephalitis	0.760, 192	0.159, 93	0.588, 70	0.813, 70
Gilosis score ^e	0.003 (-), 268	0.902, 122	0.062 (-), 71	0.010 (-), 71
Confounders				
Postmortem delay (> 12 h)	0.319, 266	0.902, 122	0.277, 71	0.754, 71
NNTC site difference (vs. CNTN) ^f				
NNAB	< 0.001 (+), 268	0.541, 122	< 0.001 (+), 71	0.002 (+), 71
TNRC	< 0.001 (+), 268	n/a	n/a	n/a
MHBB	< 0.001 (+), 268	n/a	n/a	n/a

APOE apolipoprotein E, *HCV* hepatitis C virus, *NNTC* National NeuroAIDS Tissue Consortium, *CNTN* California NeuroAIDS Tissue Network, *NNAB* National Neurological AIDS Bank, *TNRC* Texas NeuroAIDS Research Center, *MHBB* Manhattan HIV Brain Bank, *n/a* not applicable

^aUnivariable logistic regression analysis model. Each regional amyloid- β plaque or neuronal phospho-tau pathology was regressed on each biological factor or confounder. Denoted in italics are the four most significant biological factors or confounders by the univariable analyses that have *p* values of less than 0.10 (with direct (+) or inverse (-) association) for each regional neuropathological outcome. These factors and confounders were subsequently included in the multivariable logistic regression analysis model and the final model was selected using a backward stepwise approach (Table 3)

^bCurrent or past substance abuse or dependence of any of alcohol, cannabis, cocaine, methamphetamine, and opiates, diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders

^cUse of highly active antiretroviral therapy (HAART) regimens at the last clinical assessment (vs. use of non-HAART regimens, discontinuation of antiretroviral therapy (ART), or being ART-naïve)

^dPlasma HIV-1 RNA load (log10 copies/ml) at the last clinical assessment

^eComposite score of microgliosis and astrogliosis (range 2–6)

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^fThe paraffin-embedded tissue samples from putamen and basal-temporal region/hippocampus blocks were not available from TNRC or MHBB

^gTested dominant acting models for $\epsilon 4$ and $\epsilon 2$. The best fitting model by the Akaike information criteria (AIC) was $\text{Logit}(Y) = \alpha + \beta_{\epsilon 4} I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}} + \beta_{\epsilon 2} I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}}$ where $I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}} = 1$ if the *APOE* genotype was $\epsilon 4/\epsilon 4$, $\epsilon 4/\epsilon 3$, or $\epsilon 4/\epsilon 2$ and = 0 otherwise, and $I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}} = 1$ if the *APOE* genotype was $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 4/\epsilon 2$ and = 0 otherwise. That is, the best fitting model had dominant effects of $\epsilon 4$ and $\epsilon 2$ (codominant effects of $\epsilon 4$ and $\epsilon 2$) when the referent genotype was $\epsilon 3/\epsilon 3$

^hTested dominant acting models for $\epsilon 4$ and $\epsilon 2$. The best fitting model by AIC was $\text{Logit}(Y) = \alpha + \beta_{\epsilon 4} I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}}$ where $I_{\{\epsilon 4/\epsilon 4, \epsilon 4/\epsilon 3, \epsilon 4/\epsilon 2\}} = 1$ if the *APOE* genotype was $\epsilon 4/\epsilon 4$, $\epsilon 4/\epsilon 3$, or $\epsilon 4/\epsilon 2$ and = 0 otherwise. We found that the best fitting model had a dominant effect of $\epsilon 4$ over both $\epsilon 2$ and $\epsilon 3$ such that individuals with *APOE* genotypes $\epsilon 4/\epsilon 4$, $\epsilon 4/\epsilon 3$, or $\epsilon 4/\epsilon 2$ were predicted to be at increased risk relative to individuals with *APOE* genotypes $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 3/\epsilon 3$

ⁱTested dominant acting models for $\epsilon 4$ and $\epsilon 2$. The best fitting model by AIC was $\text{Logit}(Y) = \alpha + \beta_{\epsilon 2} I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}}$ where $I_{\{\epsilon 2/\epsilon 2, \epsilon 2/\epsilon 3, \epsilon 4/\epsilon 2\}} = 1$ if the *APOE* genotype was $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 4/\epsilon 2$ and = 0 otherwise. We found that the best fitting model had a dominant effect of $\epsilon 2$ over both $\epsilon 3$ and $\epsilon 4$ such that individuals with *APOE* genotypes $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 4/\epsilon 2$ were predicted to be at decreased risk relative to individuals with *APOE* genotypes $\epsilon 4/\epsilon 4$, $\epsilon 4/\epsilon 3$, or $\epsilon 3/\epsilon 3$ albeit these risks were not statistically significant

Table 3
Multivariable logistic regression analysis models for predicting neuropathological outcomes

OR [95% CI], <i>p</i> value	Amyloid- β plaque pathology ^a Prefrontal neocortex (<i>n</i> = 168)	Putamen (<i>n</i> = 171)	Basal-temporal neocortex (<i>n</i> = 71)	Hippocampus (<i>n</i> = 56)
Biological factors				
Age (each-year increase)	1.045 [1.001, 1.092], 0.031	1.064 [1.009, 1.121], 0.019	n/a	n/a
Sex (vs. men)	NS	n/a	n/a	n/a
Race/ethnicity (vs. Caucasian)				
African American	n/a	n/a	n/a	NS
Hispanic	n/a	n/a	n/a	NS
<i>APOE</i> ^b				
$\epsilon 4$	5.306 [2.355, 11.952], <0.001	n/a	n/a	6.779 [1.323, 34.738], 0.016
$\epsilon 2$	NS	n/a	n/a	NS
HCV seropositivity	n/a	n/a	n/a	6.138 [1.443, 26.113], 0.008
Lifetime substance use disorder ^c	n/a	n/a	n/a	n/a
HAART use ^d	n/a	n/a	n/a	n/a
Plasma HIV-1 RNA ^e	0.699 [0.540, 0.905], 0.005	n/a	n/a	0.589 [0.355, 0.980], 0.028
HIV encephalitis	n/a	n/a	n/a	n/a
Gliososis score ^f	n/a	NS	n/a	n/a
Confounders				
Postmortem delay (> 12 h)	n/a	0.302 [0.098, 0.932], 0.028	n/a	n/a
NNTC site difference (vs. CNTN) ^g				
NNAB	n/a	3.510 [1.343, 9.171], 0.009	n/a	n/a
TNRC	n/a	n/a	n/a	n/a
MHBB	n/a	n/a	n/a	n/a
OR [95% CI], <i>p</i> value	Neuronal phospho-tau pathology ^g Prefrontal neocortex (<i>n</i> = 268)	Putamen (<i>n</i> = 67)	Basal-temporal neocortex (<i>n</i> = 61)	Hippocampus (<i>n</i> = 59)
Biological factors				
Age (each-year increase)	n/a	n/a	NS	1.128 [1.040, 1.224], <0.001
Sex (vs. men)	n/a	n/a	n/a	n/a

OR [95% CI], <i>p</i> value	Amyloid- β plaque pathology ^a Prefrontal neocortex (<i>n</i> = 168)	Putamen (<i>n</i> = 171)	Basal-temporal neocortex (<i>n</i> = 71)	Hippocampus (<i>n</i> = 56)
Race/ethnicity (vs. Caucasian)				
African American	n/a	n/a	11.527 [1.145, 116.01], 0.018	n/a
Hispanic	n/a	n/a	NS	n/a
<i>APOE</i> ^b				
$\epsilon 4$	n/a	n/a	n/a	n/a
$\epsilon 2$	n/a	n/a	n/a	n/a
HCV seropositivity	n/a	n/a	12.363 [1.749, 87.381], 0.002	n/a
Lifetime substance use disorder ^c	n/a	0.278 [0.079, 0.979], 0.032	n/a	n/a
HAART use ^d	n/a	n/a	n/a	7.740 [0.902, 66.405], 0.028
Plasma HIV-1 RNA ^e	n/a	0.638 [0.436, 0.934], 0.013	n/a	n/a
HIV encephalitis	n/a	n/a	n/a	n/a
Gliositis score ^f	NS	n/a	n/a	0.592 [0.365, 0.961], 0.024
Confounders				
Postmortem delay (> 12 h)	n/a	n/a	n/a	n/a
NNTC site difference (vs. CNTN) ^g				
NNAB	4.807 [2.516, 9.185], < 0.001	n/a	25.361 [3.446, 186.63], 0.002	NS
TNRC	5.788 [2.516, 12.172], < 0.001	n/a	n/a	n/a
MHBB	4.614 [2.752, 9.871], < 0.001	n/a	n/a	n/a

OR odds ratio, CI confidence interval, *APOE* apolipoprotein E, HCV hepatitis C virus, NNTC National NeuroAIDS Tissue Consortium, CNTN California NeuroAIDS Tissue Network, NNAB National Neurological AIDS Bank, TNRC Texas NeuroAIDS Research Center, MHBB Manhattan HIV Brain Bank, *n/a* not applicable

^aMultivariable logistic regression analysis: OR [95% CI] and *p* values calculated using Firth penalized maximum likelihood. Each regional amyloid- β plaque or neuronal phospho-tau pathology was regressed on the four most significant biological factors and confounders having *p* values of less than 0.10 in the univariable analyses (Table 2). The final model (in italics) was selected using backward stepwise regression. NS not statistically significant and not included in the final model

^bModels assumed that the *APOE* $\epsilon 4$ and $\epsilon 2$ alleles acted independently with dominant effects of $\epsilon 4$ or $\epsilon 2$ alleles in the presence of an $\epsilon 3$ allele and a codominant effect for the $\epsilon 4/\epsilon 2$ genotype

^cCurrent or past substance abuse or dependence of any of alcohol, cannabis, cocaine, methamphetamine, and opiates, diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders

^dUse of highly active antiretroviral therapy (HAART) regimens at the last clinical assessment (vs. use of non-HAART regimens, discontinuation of antiretroviral therapy (ART), or being ART-naïve)

^ePlasma HIV-1 RNA load (log10 copies/ml) at the last clinical assessment

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The paraffin-embedded tissue samples from putamen and basal-temporal region/hippocampus blocks were not available from TNRC or MHBB
Composite score of microgliosis and astrogliosis (range 2–6)
_f
_g

Table 4
Multiple linear regression analysis models for predicting neuropsychological domain T-scores

Unstandardized coefficient (<i>B</i>), <i>n</i> , <i>p</i> value ^a	Executive functions	Speed of information processing	Attention and working memory
<i>Amyloid-β</i> plaque pathology			
Prefrontal neocortex	-0.776, 154, 0.721	-3.928, 159, 0.032	-3.083, 157, 0.078
Putamen	-4.208, 85, 0.163	-4.248, 88, 0.096	-6.269, 88, 0.020
Basal-temporal neocortex	-1.489, 59, 0.655	1.078, 61, 0.726	-2.468, 61, 0.421
Hippocampus	3.208, 59, 0.317	2.912, 61, 0.311	2.138, 61, 0.469
Neuronal phospho-tau pathology			
Prefrontal neocortex	1.279, 154, 0.512	1.666, 159, 0.309	0.089, 157, 0.955
Putamen	-1.936, 82, 0.495	1.517, 85, 0.528	-0.777, 85, 0.762
Basal-temporal neocortex	4.994, 59, 0.161	-0.885, 61, 0.784	-2.752, 61, 0.410
Hippocampus	3.800, 59, 0.262	0.968, 61, 0.747	-0.587, 61, 0.854
Unstandardized coefficient (<i>B</i>), <i>n</i> , <i>p</i> value ^a	Learning	Delayed recall	Motor
<i>Amyloid-β</i> plaque pathology			
Prefrontal neocortex	-2.072, 160, 0.268	-0.751, 160, 0.679	1.698, 158, 0.410
Putamen	-1.625, 89, 0.541	-1.254, 89, 0.633	-3.759, 88, 0.205
Basal-temporal neocortex	2.562, 63, 0.407	-0.720, 62, 0.799	-2.451, 62, 0.523
Hippocampus	2.705, 63, 0.351	2.265, 62, 0.404	6.240, 62, 0.087
Neuronal phospho-tau pathology			
Prefrontal neocortex	0.205, 160, 0.903	1.276, 160, 0.434	0.007, 158, 0.997
Putamen	-1.727, 86, 0.485	-1.513, 86, 0.534	3.494, 85, 0.217
Basal-temporal neocortex	-4.078, 63, 0.216	-2.313, 62, 0.449	-1.932, 62, 0.642
Hippocampus	-1.219, 63, 0.693	-0.794, 62, 0.782	5.385, 62, 0.163
			1.833, 57, 0.648

^aGeneral linear model (univariate, IBM SPSS Statistics Version 25). Each neuropsychological domain T-score was regressed on each regional amyloid-β plaque or neuronal phospho-tau pathology, along with age, sex, and race/ethnicity

In italics, *p* < 0.05 (statistically significant)