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T-cell activation state differentially contributes to neuropsychiatric complications in women with HIV

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ABSTRACT

Neuropsychiatric complications are common among women with HIV (WWH). The pathophysiological mechanisms underlying these complications are not fully known but likely driven in part by immune modulation. We examined associations between T-cell activation states which are required to mount an effective immune response (activation, co-stimulation/normal function, exhaustion, senescence) and neuropsychiatric complications in WWH. 369 WWH (78% HIV RNA undetectable/<20cp/mL) enrolled in the Women's Interagency HIV Study completed neuropsychological testing and measures of depression (Center for Epidemiological Studies Depression Scale-CES-D), self-reported stress levels (Perceived Stress Scale-10), and post-traumatic stress (PTSD Checklist-Civilian Scale). Multiparametric flow cytometry evaluated T-cell activation state. Partial least squares regressions were used to examine T-cell phenotypes and neuropsychiatric outcome associations after confounder adjustment. In the total sample and among virally suppressed (VS)-WWH, $CD4^+$ T-cell exhaustion was associated with poorer learning and attention/working memory (P's < 0.05). In the total sample, $CD4^+$ T-cell activation was associated with better attention/working memory and $CD8^+$ T-cell co-stimulation and senescence was associated with poorer executive function (P's < 0.05). For mental health outcomes, in the total sample, $CD4^+$ T-cell

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activation was associated with more perceived stress and $CD4^+$ T-cell exhaustion was associated with less depressive symptoms (*P*'s < 0.05). Among VS-WWH, $CD4^+$ senescence was associated with less perceive stress and $CD8^+$ T-cell co-stimulation and senescence was associated with higher depression (*P's* < 0.05). Together, results suggest the contribution of peripheral $CD4^+$ and $CD8^+$ T-cell activation status to neuropsychiatric complications in WWH.

1. Introduction

Neuropsychiatric complications, including cognitive impairment and mental health disorders (depression, anxiety disorders, post-traumatic stress disorder [PTSD]), are highly prevalent among people with HIV (PWH). Mild cognitive impairment without any changes in everyday function persists in 24% of PWH and mild cognitive impairment with some decline in everyday function persists in approximately 13% (Wang et al., 2020). The overall pooled prevalence of depression and depressive symptoms in two recent meta-analyses was 27% and 31% (95%CI 28–34) (Rezaei et al., 2019; Wang et al., 2017a) and for PTSD and PTSD symptoms was 33% (Ayano et al., 2020). These relatively high prevalence estimates alone demonstrate an urgent need to understand the pathophysiological mechanisms of neuropsychiatric complications in PWH, particularly among women with HIV (WWH) who appear to be more vulnerable to these conditions then men with HIV (Rubin et al., 2019a, 2019b, 2020a).

One likely contributor to neuropsychiatric complications in PWH is through immune system modulation, including the production of proinflammatory cytokines, trafficking of peripheral immune cells into the central nervous system (CNS), and chronic inflammation. Myeloid cells have been attributed as the predominate source of HIV-related neuroinflammation and the primary target of HIV infection in the brain (Joseph et al., 2015; Leon-Rivera et al., 2021; Rubin et al., 2020b; Veenhuis et al., 2021; Williams et al., 2014; Zhang and Gensel, 2014); however, T-cells are also involved in the neuropathogenesis of HIV. $CD4^+$ T-cells are the predominate population of cells infected by HIV in the periphery and are responsible for stimulation of $CD8^+$ T-cells, which mediate killing of virally infected cells. Like monocytes, T-cells can also migrate across the BBB into the brain (Nishihara et al., 2020), and can be associated with the severity of neuropsychiatric complications (Lynall et al., 2020; Wang et al., 2017b). While known to occur during homeostatic states, T-cell migration across the BBB occurs to a greater degree in inflammatory (Castro Dias et al., 2021; Qiu et al., 2021) and neurodegenerative conditions, including Parkinson's disease (Brochard et al., 2009), Alzheimer's disease, and Multiple Sclerosis (Oliveira-Giacomelli et al., 2021). Aberrant T-cells have also been mechanistically linked to neuropsychiatric complications (Kipnis et al., 2004; Woolley et al., 2011). T-cells are implicated in mental health disorders, including major depression (Beurel and Lowell, 2018; Woelfer et al., 2019). There is also a precedence for T-cells in promoting neuropsychiatric complications during HIV. In PWH, the presence of interferon gamma expressing T-cells in cerebrospinal fluid indicated a higher risk for cognitive impairment (Schrier et al., 2015). Furthermore, *in vitro* studies showed that leukotriene C4, an eicosanoid found in the CNS of PWH, promoted the migration of HIV-infected T-cells across a BBB model, implicating their role in the neuropathogenesis of HIV (Bertin et al., 2014). Additionally, T-cells from PWH migrated across an endothelial barrier to a greater extent than cells from controls (Birdsall et al., 1997). Together, these findings suggest that T-cells can enter the CNS during inflammatory, infectious, and neuropsychiatric disorders and contribute to the development of neurologic disease.

While the contribution of T cells to CNS disease is clear, the functional contribution of these cells to neuropsychiatric complications, including that which occurs in the context of HIV, is not completely understood. This is particularly true for the series of steps required to mount an effective and well-regulated immune response. T-cells are integral in inducing the adaptive immune response. To do this, they must first undergo a two-step process. Step one, termed activation, occurs when T cells receive extracellular signals mediated by T-cell receptor complexes (Hwang et al., 2020). Next, T-cells undergo co-stimulation (normal function) through interactions with antigen presenting cells. Both steps must occur to have an activated T-cell and these cells will not elicit an immune response if the steps occur in the wrong order, or if they receive only one signal (Hwang et al., 2020). Equally important are mechanisms to stop the immune response at the appropriate time (Bohineust et al., 2018). When these mechanisms fail, T-cells become exhausted and lose their functional responses, including efficient killing of infected cells, proliferative capacity, and cytokine responses (Fenwick et al., 2019). Chronic inflammatory states, like HIV, are hallmarked by T-cell exhaustion due to continual, repeated antigen stimulation. This continual stimulation results in T-cell dysfunction that results in reduced effector functions, changes to cytokine production, inhibitory receptors, proliferative capacity, transcriptional landscape, and epigenetic regulatory mechanisms (Blank et al., 2019; Im and Ha, 2020; Pawelec, 2019). Importantly, this occurs even in the context of viral suppression with antiretroviral therapy (Hunt et al., 2003).

The relationship between T-cell activation, co-stimulation, senescence, and exhaustion with neuropsychiatric complications is not well understood during HIV. However, T-cell functional states contribute to the development of neuropsychiatric complications through multiple mechanisms. An imbalance in the proportion of T-cell subsets occurs in people with obsessive-compulsive disorder (Rodriguez et al., 2019), and is implicated in promoting activation of inflammatory pathways that induce neuroinflammation, neuronal damage, and alterations in synaptic pruning. Further, alterations in T-cell subsets are implicated in abnormalities in white matter microstructure, reduced neurotransmitter levels, and reductions in immune tolerance (Poletti et al., 2017) that can occur as these cells acquire a senescence and exhaustion phenotype. Alterations in T-cell effector functions are implicated in mood disorders, including depression and anxiety (Vieira et al., 2010). Rodent models demonstrate that the loss of appropriate T-cell regulatory mechanisms contributes to depression-related behaviors (Cohen et al., 2006; Laumet et al., 2020; Shi et al., 2022; Westfall et al., 2021). Similar relationships occur for cognition, where impaired T-cell functional states contribute to decreases in spatial learning and memory (Ron-Harel et al., 2008; Ziv et al., 2006). The repeated antigen stimulation that occurs during autoimmune disorders is also associated with dysfunctional T-cell activation states that promote neuropsychiatric complications. This occurs in the context of systemic lupus erythematosus (SLE), where a loss of T-cell tolerance towards self-antigens occurs that is associated with alterations in neurotrophic factors, including brain-derived neurotrophic factor (Tian et al., 2019) and infiltration of activated $CD4^+$ T cells into the choroid plexus that have functional effector phenotypes (Jain et al., 2018). Further, dysfunctional T-cell activation states also contribute to neuropsychiatric complications in additional autoimmune disorders, including multiple sclerosis (Brasanac et al., 2021; Kant et al., 2018). These findings highlight the importance of appropriate T-cell functional state in the development of neuropsychiatric disease and provide important pathways that contribute to cognitive and mental health disorders.

Due to the importance of T-cell activation states, as well as the relevance of T-cells in HIV CNS disease, our goal was to assess the association of T-cell dysregulation with neuropsychiatric complications in PWH. We were interested specifically in WWH due to the increased rates of neuropsychiatric complications in this population (Rubin et al.,

2019a, 2019b, 2020a) as well as sex differences in the relationships between immune function and neuropsychiatric complications (Rubin et al., 2019a; Vecchio et al., 2020). Importantly, our analyses included an evaluation of a subset of WWH who were virally suppressed (VS) to provide mechanistic insight into how dysfunctional T-cell phenotypes (activation, co-stimulation/normal function, senescence, exhaustion status) contribute to neuropsychiatric complications in the absence of viral replication. We hypothesized that greater T-cell senescence and exhaustion would relate to poorer cognitive function and greater mental health symptoms.

2. Methods

2.1. Participants

Participants were enrolled in the Women's Interagency HIV study (WIHS), an ongoing, multisite prospective cohort study of the natural and treated history of WWH, that enrolled WWH and HIV-uninfected women in 1994–1995 at six sites (Bronx/Manhattan NY, Brooklyn NY, Chicago IL, Washington DC, Los Angeles CA, San Francisco CA). Additional enrollment occurred in 2001–2002, 2011–2012 and in 2014–2015, the WIHS added four southern sites (Atlanta GA, Chapel Hill NC, Miami FL, Birmingham AL) and closed its Los Angeles site. WIHS methods and study characteristics have been previously described (Adimora et al., 2018; Bacon et al., 2005; Barkan et al., 1998). In brief, biological specimens, physical exams, and extensive sociodemographic, behavioral, and clinical data (including the Center for Epidemiological Studies Depression scale [CES-D]) are collected semiannually. Participants complete neuropsychiatric assessments including neuropsychological (NP) testing, the Perceived Stress Scale (PSS-10), and the Post-Traumatic Stress Disorder (PTSD) Checklist-Civilian Scale (PCL-C) every two years starting in 2009.

For this study, we identified 430 WWH who were on ART, did not have a diagnosis of autoimmune diseases, cancer, or hepatitis B or C virus infection, had biospecimens in storage that were collected between 2013 and 2016, and had functional T-cell phenotypic characterization data measured in a previous study (Peters et al., 2021). Six participants did not have the covariate data needed for this analysis and were excluded. Of the remaining 424 individuals, 373 had complete data on the primary neuropsychiatric outcome measures concurrent or after the date biospecimens were available and constituted the study population for this study. For these individuals, NP, PCL-C, and PSS-10 data was available on average 1.22 years following the T-cell data (median = 1.01 years, interquartile [IQR] range = 0.19 years).

2.2. T-cell phenotypic characterization

T-cell phenotypic characterization was performed by multiparameter flow cytometry on frozen/thawed viable peripheral blood mononuclear cells (PBMCs) using BD Vacutainer ® CPT™ (BD Biosciences). A water bath was set to 37 °C and PBMCs were removed from LN_2 storage before being thawed rapidly in the water bath. Once thawed, they were washed and stained with fluorochrome-conjugated monoclonal antibodies to CD3, CD4, CD8, CD57, CD28, PD-1, HLA-DR, and CD38 (BD Biosciences). To assess the viability of the cells, Aqua Live/Dead cell stain kit (Invitrogen) was utilized on the PBMCs prior to cell surface staining. After staining, the cells were washed, fixed in 2% formaldehyde, and analyzed within 24 h on a LSRII flow cytometer (BD) using FACS Diva software v6.11. FlowJo 9.9.3 (Tree Star Inc) was utilized to analyze the data. Analyses of immune activation (CD38+HLA-DR+), co-stimulation/normal function ($CD57^{-}CD28^{+}$) exhaustion (PD-1+), and senescence ($CD57^{+}CD28^{-}$) were performed after stringent gating on singlet live (Aqua-) $CD3^{+}CD4^{+}$ or $CD3^{+}CD8^{+}$ T-cells (Fig. 1). FMO controls were stained and analyzed to define the gaiting strategies used to identify the phenotypic profiles of the T-cell subsets.

2.3. Cognitive outcomes

The following cognitive domains and related neuropsychological (NP) tests were used: *learning and memory*, Hopkins Verbal Learning Test-Revised (HVLT-R; learning outcomes: total learning; memory = delay free recall); *attention/working memory*, Letter-Number sequencing (outcomes = control and experimental conditions total correct); *executive function*, Trail Making Test Part B (mental flexibility) and Stroop Test color-word trial (behavioral inhibition) (outcomes = time to completion); *psychomotor speed*, Symbol Digit Modalities Test (outcome = total correct) and Stroop Test color-naming trial (outcome = time to completion); *fluency*, letter (outcome = total correct) and semantic (outcome = total correct); and *motor function*, Grooved Pegboard (outcome time to completion, dominant and nondominant hand). Timed outcomes were log transformed to normalize distributions and reverse scored so that better performance equaled higher values. Demographically adjusted (age, years of education, Wide Range Achievement Test-vocabulary subtest, race/ethnicity) T-scores were calculated for each outcome and T-scores were used to create domain scores consistent with previous large-scale WIHS-wide studies (Rubin et al., 2017, 2018). For each domain, a composite T-score was derived by averaging the T-scores for domains with $\geq$2 outcomes. If only one test in a domain was completed, the T-score for that test was used.

2.4. Self-report neuropsychiatric outcomes

Participants completed: the: 1) Center for Epidemiological Studies Depression scale (CES-D) which assesses depressive symptoms (Radloff, 1977); 2) Perceived Stress Scale (PSS)-10 which measures perceptions of stress; the degree of uncontrollability, unpredictability, and overload in the respondent's daily life (Cohen et al., 1983; Cohen and Williamson, 1988); and 3) PTSD Checklist-Civilian Scale (PCL-C) which assesses post-traumatic symptom burden anchored to stressful experiences rather than a specific event (Weathers et al., 1991). Primary outcome measures on each of the scales were the total scores (continuous). Additionally, subscale scores were computed on the CES-D (somatic, negative affect, positive affect, and interpersonal symptoms) and the PCL-C (avoidance, arousal, re-experiencing) to assess symptom subtypes. For those with multiple CES-D measurements, we selected the measurement that was concurrent with the other neuropsychiatric assessments.

2.5. Statistical Analyses

Prior to analyses, we examined the normality of our data. A series of partial least squares regressions (PLSR) were used to examine associations between T-cell phenotypes and neuropsychiatric outcomes in the total sample and stratified by viral suppression status (Geladi and Kowalski, 1986). PLSR is a method to model the relationship between multiple outcomes and predictors that accounts for the covariation amongst multiple outcome variables. This method also avoids the need for multiple comparison corrections for *P*-values which would be the case if we ran multiple parallel models. Here the predictor matrix for all analyses included the eight variables assessing T-cell phenotypes (surface markers of activation [%CD38+HLADR+], senescence [$\%CD57^{+}CD28^{-}$], exhaustion [%PD-1+], and co-stimulation/normal function [$\%CD57^{-}CD28^{+}$] on $CD4^{+}$ and $CD8^{+}$ T cells). For NP function, the outcome matrix included the seven cognitive domain T-scores. For mental health, the outcome matrix included the total CES-D, PCL-C, and PSS-10 scores. When significant associations were seen between T-cell phenotypes and the total CES-D and/or PCL-C score, sub-analyses were conducted to examine T-cell phenotypes and subscale scores on the CES-D (e.g., somatic, negative affect) and PCL-C (e.g., arousal, avoidance). For each model, regression coefficients and *P*-values were obtained to determine the specific relationships between each T-cell phenotype-outcome association. The significance of each coefficient was determined by an approximate T-test based on jack-knife variance

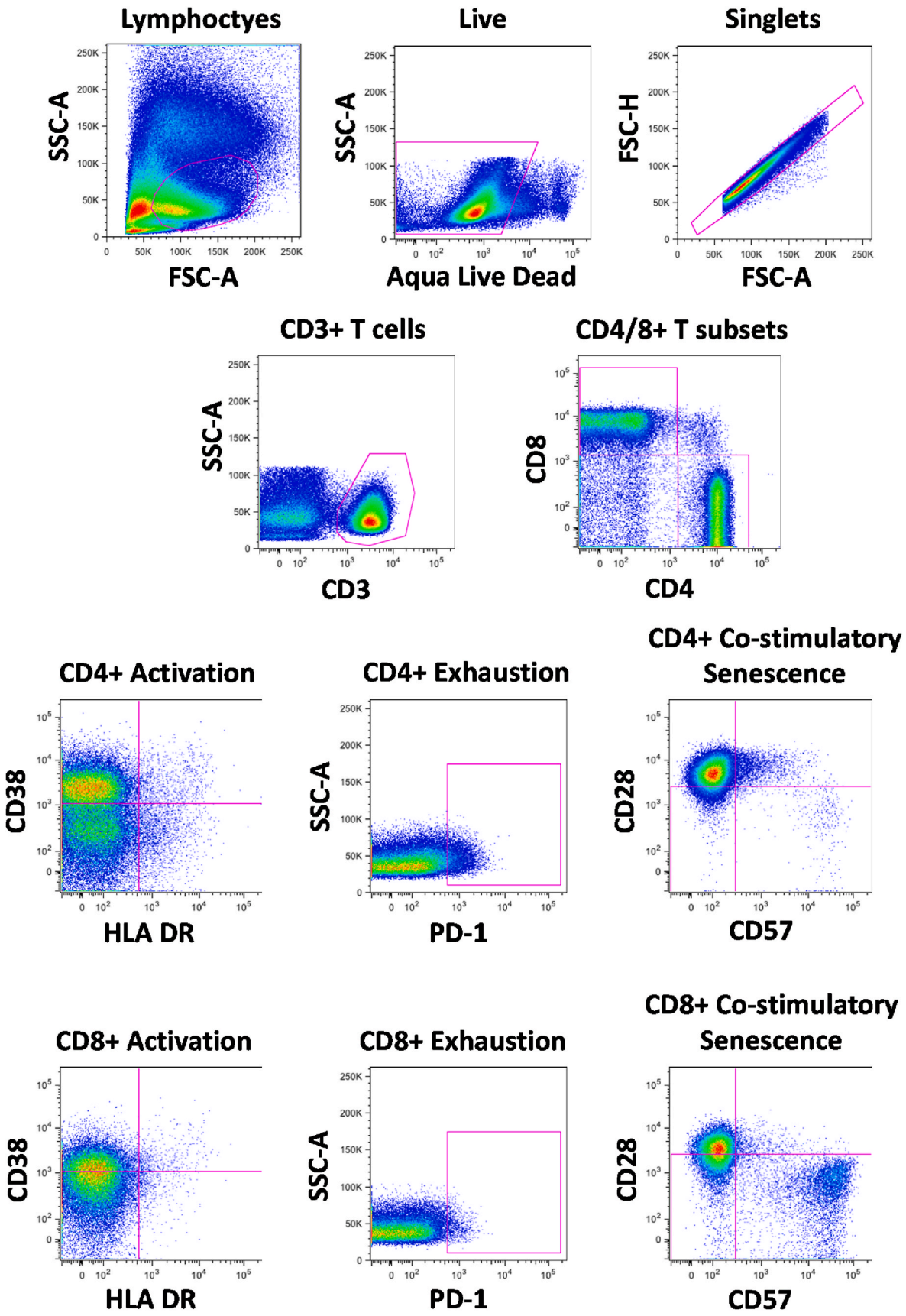

Fig. 1. Representative flow cytometric analyses of frozen/thawed PBMC. Analyses of immune activation (CD38+HLA-DR+), co-stimulation ($CD57^{-}CD28^{+}$), exhaustion (PD-1+), and senescence (CD57 + $CD28^{-}$) after stringent gating on lymphocytes > live (Aqua-) > singlet > $CD3^{+}CD4^{+}$ or $CD3^{+}CD8^{+}$ T-cells. Results are reported as the % of the parental $CD3^{+}CD4^{+}$ or $CD3^{+}CD8^{+}$ T-cell populations.

estimates, which computes the standard error of each coefficient by aggregating the coefficient estimates from resampling data (Martens and Martens, 2000).

As the resulting P-values from the jack-knife approach are not exact, we did not adjust for multiple testing. We examined all variables in Table 1 as potential confounders of the associations between T-cell phenotypes and neuropsychiatric outcomes. The only variables identified as confounders which were included in all models were: current smoking and heavy alcohol use (reflects >7 drinks/week or ≥4 drinks in one sitting) as well as body mass index. Analyses were conducted in R 3.6.2 with package 'pls' (Bjorn-Helge et al., 2019).

Table 1
Sociodemographic, clinical, and behavioral characteristics of the overall sample of women with HIV (WWH) and by viral suppression (VS) status.

	Total Sample (N = 373) Mean (SD)	VS only (n = 291) Mean (SD)	Viremic only (n = 82) Mean (SD)
Age	44.5 (8.3)	45.0 (8.3)	42.8 (8.3)
Years of education	12.8 (3.1)	13.0 (3.1)	12.4 (2.8)
WRAT-3 reading subtest	91.0 (18.3)	91.4 (18.1)	89.5 (19.1)
Race/ethnicity, n (%)			
Black, non-Hispanic	300 (80)	235 (81)	65 (80)
White, non-Hispanic	35 (9)	29 (10)	6 (7)
Hispanic	26 (7)	18 (6)	8 (10)
Other	12 (3)	9 (3)	3 (4)
Annual household income <$12,000/year, n (%)	165 (44)	130 (45)	35 (43)
Depressive symptoms (CES-D)†	11.2 (11.2)	10.9 (11.1)	12.4 (11.9)
Perceived stress symptoms (PSS-10)†	13.3 (7.8)	13.1 (7.8)	13.8 (7.9)
Reported use of the following non-ART medication types, n (%)			
Antidepressants	45 (12)	36 (12)	9 (11)
Antipsychotics	13 (3)	11 (4)	2 (2)
Anticonvulsants	14 (4)	10 (3)	4 (5)
Antihistamines	18 (5)	14 (5)	4 (5)
Opioids	11 (3)	8 (3)	3 (4)
PTSD symptom burden (PCL-C)†	30.8 (13.7)	30.7 (13.8)	31.2 (13.6)
Current smoking status, n (%)	115 (31)	83 (29)	32 (39)
Recent heavy alcohol use, n (%)	42 (11)	33 (11)	9 (11)
Recent marijuana use, n (%)	64 (17)	53 (18)	11 (13)
Recent Crack, cocaine, and/or heroin use, n (%)	12 (3)	10 (3)	2 (2)
Body mass index	33.3 (9.6)	33.0 (9.4)	34.5 (10.2)
Efavirenz use at visit, n (%)	81 (22)	74 (25)	7 (9)
Integrase inhibitor use at visit, n (%)	115 (31)	83 (29)	32 (39)
Nadir CD4 count in WIHS, median (IQR)	293 (284)	298 (313)	267 (259)
Current CD4 count, median (IQR)	623 (410)	645 (418)	501 (408)
Undetectable HIV RNA, <20cp/mL, n (%)	291 (78)	291 (100)	0 (0)
Adherence (≥95%) to cART, n (%)	320 (86)	258 (89)	62 (76)
ART duration (years), M (SD)	9.1 (6.2)	8.9 (6.1)	9.8 (6.4)
cART duration (years), M (SD)	8.5 (5.5)	8.4 (5.5)	9.1 (5.5)
Prior AIDS diagnosis, n (%)	73 (20)	52 (18)	21 (26)

Note. ART = antiretroviral therapy; cART = combination ART; CES-D = Center for Epidemiological Studies Depression scale (range of scores: 0–60); current refers to within the past week; heavy alcohol use reflects >7 drinks/week or ≥4 drinks in one sitting; IQR = interquartile range; recent, refers to within 6 months of the most recent WIHS visit; PTSD = post traumatic stress disorder; PCL-C=PTSD Civilian Checklist (range of scores: 17–85); PSS-10 = Perceived Stress Scale (range of scores: 10–50); SD = standard deviation; WIHS=Women's Interagency HIV Study; WRAT-3 = Wide Range Achievement Test standard score; UD = undetectable. † higher scores = more symptoms.

3. Results

3.1. Participants

The socio-demographic, behavioral, and clinical factors for the total sample and by VS status are depicted in Table 1. WWH had a mean age of 44.5 years (standard deviation [SD] = 8.3) and 80% identified as Black, non-Hispanic. The average years of education was 12.6 (SD = 2.8) and 44% had annual income ≤$12,000. Thirty percent reported current smoking, 11% current heavy alcohol use, and 17% recent (past six months) marijuana use. HIV RNA was <20 copies/mL for 78%, median CD4 count was 623 cells/mm^3 (IQR = 410), and 19% of women had a prior diagnosis of AIDS. Thirty-one percent were on an integrase strand inhibitor-based regimen and 21% were on efavirenz.

The mean percentage of cell surface markers of CD4$^+$ and CD8$^+$ T-cell activation, co-stimulation/normal function, senescence, and exhaustion as well as cognitive performance are in the total sample and by VS status are depicted in Table 2. Viremic women had higher CD4$^+$ T-cell activation ($P = 0.003$) and exhaustion ($P = 0.003$) levels as well as higher CD8$^+$ T-cell activation ($P < 0.001$), co-stimulation/normal function ($P = 0.01$), senescence ($P = 0.009$), and exhaustion ($P < 0.001$) levels. Cognitive performance on each of the domains in the total sample as well as in VS-WWH and viremic women were in the normal range (T's ≥ 40).

3.2. T-cell phenotypes and cognition

Among WWH, higher CD4$^+$ T-cell activation was associated with better attention/working memory ($P = 0.02$), whereas higher CD4$^+$ T-cell exhaustion was associated with poorer attention/working memory ($P < 0.001$) and verbal learning ($P = 0.04$ Fig. 2A). Higher CD8$^+$ T-cell co-stimulation ($P = 0.03$) and senescence ($P = 0.02$) were associated with poorer executive function. Among the subset of VS-WWH, two associations remained significant (Fig. 2B). Specifically, higher CD4$^+$ T-cell exhaustion was associated with poorer attention/working memory ($P < 0.001$) and verbal learning ($P = 0.04$). Among the subset of viremic women, there were no significant associations between T-cell phenotypes and cognition (Fig. 2C).

Table 2
T-cell activation states and domain-specific cognitive function in the overall sample of women with HIV (WWH) and by viral suppression (VS) status.

	Total Sample (N = 373) Mean (SD)	VS only (n = 291) Mean (SD)	Viremic only (n = 82) Mean (SD)
T-cell activation states			
%CD4+			
Activation	3.8 (3.6)	3.3 (2.6)	5.8 (5.5)
Co-stimulation/normal function	75.1 (16.0)	75.5 (16.5)	73.6 (14.4)
Senescence	4.9 (6.2)	4.9 (6.3)	5.0 (6.0)
Exhaustion	14.5 (9.0)	13.2 (7.3)	19.0 (12.5)
%CD8+			
Activation	7.8 (6.8)	6.3 (4.9)	13.2 (9.3)
Co-stimulation/normal function	28.7 (17.9)	30.0 (18.5)	23.9 (14.6)
Senescence	35.2 (15.5)	33.9 (15.8)	39.7 (13.6)
Exhaustion	12.2 (7.7)	10.9 (6.8)	17.0 (8.9)
Cognitive function			
Learning	49.6 (9.9)	49.7 (9.5)	49.0 (11.2)
Memory	49.6 (9.0)	49.3 (8.7)	50.8 (10.0)
Executive function	48.1 (10.0)	48.1 (9.7)	48.3 (11.3)
Fluency	49.6 (9.7)	49.6 (9.6)	49.8 (10.2)
Attention/working memory	47.8 (10.2)	48.1 (10.1)	47.0 (10.7)
Processing speed	49.9 (9.1)	50.2 (8.8)	48.7 (10.1)
Motor function	49.7 (9.6)	49.8 (9.8)	49.4 (8.8)

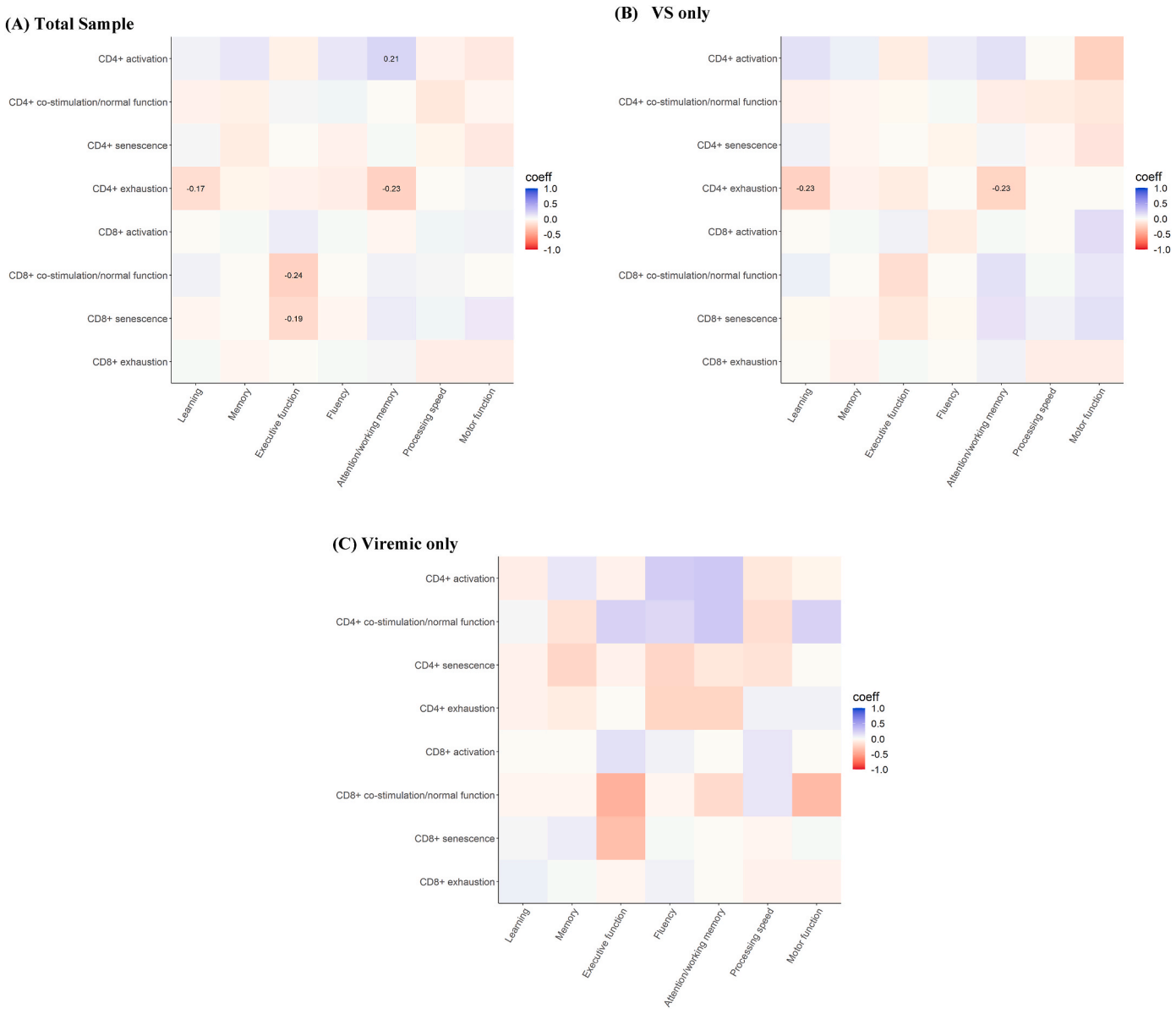

Fig. 2. Associations between T-cell activation states and domain-specific cognitive function in the total sample (A), in virally suppressed (VS) (B), and in viremic (C) women with HIV. Markers used for determining activation status of the T-cells are as follows: $CD4^+$ activation ($CD3^+CD4^+CD38+HLA\text{-}DR+$), $CD4^+$ co-stimulation/normal function ($CD3^+CD4^+CD57^-CD28^+$), $CD4^+$ senescence ($CD3^+CD4^+CD57 + CD28^-$), $CD4^+$ exhaustion ($CD3^+CD4+PD\text{-}1+$), $CD8^+$ activation ($CD3^+CD8^+CD38+HLA\text{-}DR+$), $CD8^+$ co-stimulation/normal function ($CD3^+CD8^+CD57^-CD28^+$), $CD8^+$ senescence ($CD3^+CD8^+CD57 + CD28^-$), $CD8^+$ exhaustion ($CD3^+CD4+PD\text{-}1+$). The cognitive domains are described in further detail in **Methods**. The numbers in the figure reflect the magnitude of adjusted regression coefficients (see **Statistical Analyses**). Coeff = coefficient, (A) Total Sample, (B) VS only,(C) Viremic only.

3.3. T-cell phenotypes and mental health outcomes

Among WWH, higher $CD4^+$ T-cell activation was associated with higher anxiety whereas higher $CD4^+$ T-cell exhaustion ($P = 0.04$) was associated with lower depressive symptoms ($P = 0.03$) (Fig. 3A) particularly negative affect ($\beta = -0.19$, $P = 0.02$). $CD8^+$ T-cell phenotypes were not significantly associated with any mental health outcomes. However, in the subset of VS-WWH, higher $CD4^+$ T-cell senescence was associated with less perceived stress ($P = 0.03$) whereas higher $CD8^+$ T-cell co-stimulation ($P = 0.02$) and $CD8^+$ T-cell senescence ($P = 0.03$) was associated with higher depressive symptoms (Fig. 3B), particularly somatic symptoms ($\beta = 0.41$, $P < 0.001$ and $\beta = 0.29$, $P < 0.001$, respectively). Among viremic women, higher $CD4^+$ T-cell activation was associated with greater perceived stress ($P < 0.001$), whereas higher $CD4^+$ T-cell exhaustion was associated with less perceived stress ($P = 0.01$). Higher $CD4^+$ T-cell co-stimulation was associated with greater depressive symptoms ($P = 0.03$), particularly negative affect ($\beta = 0.46$, $P = 0.01$), as well as higher $CD4^+$ T-cell senescence was associated with greater PTSD symptom ($P = 0.04$) particularly avoidance symptoms ($\beta = 0.27$, $P = 0.05$).

See **Supplemental Material** for all regression coefficients and *P*-values for all analyses conducted in the total sample, VS, and viremic women with HIV.

4. Discussion

To the best of our knowledge, we are among the first to examine an understudied contributor to neuropsychiatric complications in WWH: dysfunctional T-cell activation states. We not only examined associations in the total sample of WWH, but also identified associations among

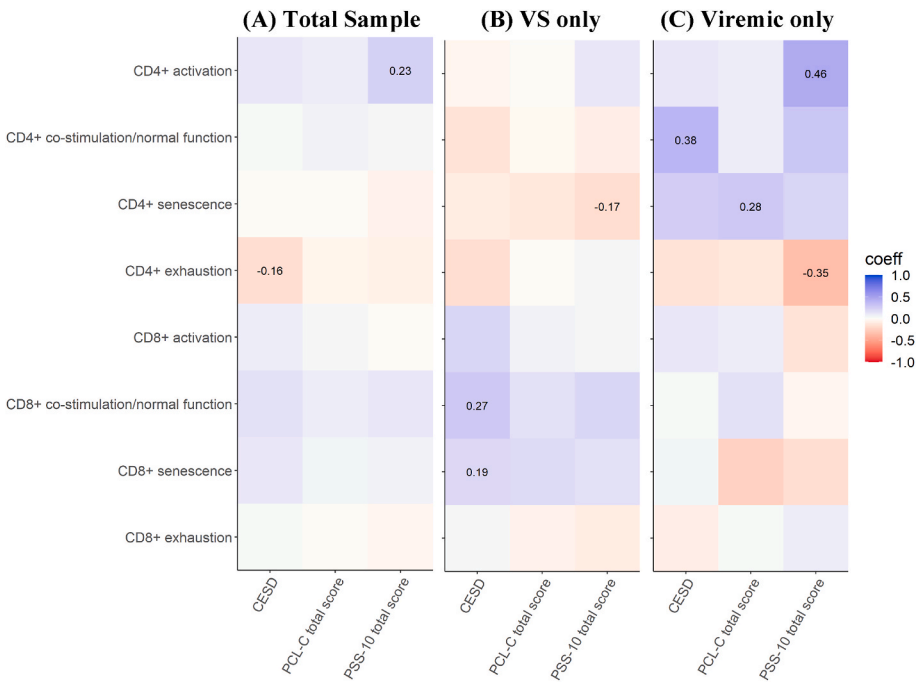

Fig. 3. Associations between T-cell activation states and mental health symptoms in the total sample and by viral suppression (VS) status. Markers used for determining activation status of the T-cells are as follows: $CD4^+$ activation ($CD3^+CD4^+CD38+HLA\text{-}DR+$), $CD4^+$ co-stimulation/normal function ($CD3^+CD4^+CD57^-CD28^+$), $CD4^+$ senescence ($CD3^+CD4^+CD57 + CD28^-$), $CD4^+$ exhaustion ($CD3^+CD4+PD\text{-}1+$), $CD8^+$ activation ($CD3^+CD8^+CD38+HLA\text{-}DR+$), $CD8^+$ co-stimulation/normal function ($CD3^+CD8^+CD57^-CD28^+$), $CD8^+$ senescence ($CD3^+CD8^+CD57 + CD28^-$), $CD8^+$ exhaustion ($CD3^+CD4+PD\text{-}1+$). Center for Epidemiological Studies Depression scale (CES-D); Post-Traumatic Stress Disorder (PTSD) Checklist-Civilian Scale (PCL-C); and Perceived Stress Scale (PSS)-10 are described in further detail in **Methods**. The numbers in the figure reflect the magnitude of adjusted regression coefficients (see **Statistical Analyses**). Coeff = coefficient, (A) Total Sample (B) VS only (C) Viremic only.

VS-WWH to mechanistically examine associations in the absence of viral replication which differed from the associations or lack of associations among viremic women. We found similar associations with dysfunctional T-cell activation states and cognition in WWH and among the subset of VS-WWH only. Strikingly, in contrast to the pattern of associations with cognition, associations with mental health outcomes differenced in VS-WWH and viremic women.

Our findings provide key insights into the mechanisms by which T-cell activation states may contribute to neuropsychiatric complications in PWH. We found that $CD4^+$ T-cell activation was beneficial and were associated with better attention/working memory. This suggests that an initial antiviral response is protective, likely due to the T helper functions that occur following activation. $CD4^+$ T-cell differentiation into T helper 1 effectors is essential for helping mount cytotoxic $CD8^+$ T-cell responses that kill virally infected cells (Swain et al., 2012). $CD4^+$ T-cells can also differentiate into T follicular helper cells that induce B cells to produce mature antibodies (Benova et al., 2020), including those with specificity to HIV proteins. $CD4^+$ T-cells that have undergone activation can also serve as additional primers to boost innate immune responses to HIV, including macrophage (Martinez and Gordon, 2014) and NK cell functions (Jost et al., 2014) through cytokine production and the additional recruitment of effector cells to sites of viral replication through local chemokine production in infected tissues (Swain et al., 2012). Further, $CD4^+$ T-cells may also have direct antiviral benefits by acquiring cytotoxic functions that promote the direct killing of infected cells through MHC II-dependent mechanisms (Juno et al., 2017). Together, these effector functions help mount an anti-HIV response that may have non-detrimental or protective neuropsychiatric implications. In addition to their immunologic benefits, $CD4^+$ T-cell activation is required for the maintenance of neurogenesis during adulthood (Kipnis et al., 2012; Ron-Harel et al., 2008; Wolf et al., 2009), providing a direct mechanism by which they can be protective against neuropsychiatric complications during HIV. Unlike that which occurred for activation, $CD4^+$ exhaustion was detrimental and was associated with poorer attention/working memory and verbal learning. T-cell exhaustion is an adaptive response to persistent antigen stimulation that helps limit tissue damage by decreasing antiviral functions through the upregulation of inhibitory receptors (Barnova et al., 2021; Budimir et al., 2021; Castelli et al., 2021). This suggests that, while aiming to have a beneficial impact, quelling the T-cell antiviral response or alterations in the integrity of the adaptive immune system (Kipnis et al., 2004) may be detrimental to neurologic function and can mechanistically contribute to the development of neuropsychiatric complications.

In contrast to $CD4^+$ T-cells, $CD8^+$ T-cell activation states were detrimental and were associated with poorer executive function and more depressive symptoms. While it may be surprising that the cytotoxic functions mediated by $CD8^+$ T-cells are deleterious and contribute to neuropsychiatric complications in WWH, it is important to note that $CD8^+$ T-cells remain only marginally functional during HIV, even in the context of fully viral suppressive ART. Due to the persistent exposure to viral antigens and chronic inflammation that occurs, $CD8^+$ T-cells have increased expression of inhibitory receptors that suppress appropriate functional activation signaling. Further, aberrant $CD8^+$ T-cells counts (Helleberg et al., 2015; Tanko et al., 2018), expression of activation and exhaustion markers (Perdomo-Celis et al., 2018; Trautmann et al., 2006), and their functional capacities remain impaired and are not fully restored by ART (Buggert et al., 2014; Migueles et al., 2009). Additionally, due to the decline in HIV antigens that occurs following exposure to ART, there is a decrease in the frequency of HIV-specific $CD8^+$ T-cells (Casazza et al., 2001; Ogg et al., 1999; Rinaldo et al., 2000). It is evident that the loss of HIV-specific $CD8^+$ T-cells is directly related to ART, as these cells significantly increased upon treatment interruption or failure (Altfeld et al., 2002; Casazza et al., 2001; Mollet et al., 2000). These aberrant $CD8^+$ T-cell immune responses are not restricted to the periphery, and their presence in the CNS may also directly contribute to neurologic decline. $CD8^+$ T-cells may enter the brain parenchyma and cerebrospinal fluid of PWH (Ganesh et al., 2016; Ho et al., 2013; Kessing et al., 2017). This may not be beneficial, as interferon-gamma expressing $CD8^+$ T-cells in the cerebrospinal fluid was strongly correlated with cognitive status (Schrier et al., 2015). Despite their presence in the CNS, it remains unclear whether these cells maintain any functional capacity to kill infected cells (Ratto-Kim et al., 2018; Trautmann et al., 2012). This is particularly salient as $CD8^+$ T-cells do not efficiently kill myeloid cells (Clayton et al., 2018; Rainho et al., 2015), the primary cell infected within the brain, suggesting that the presence of $CD8^+$ T-cells may not necessarily eradicate the CNS viral burden. In fact, repeated challenge of $CD8^+$ T-cells with HIV antigens promotes microglial activation and neurotoxicity (Prasad et al., 2021),

as well as the development of $CD8^+$ T-cell encephalitis (Cheema et al., 2019; Ishiguro et al., 2020; Lescure et al., 2013; Santana et al., 2020). In this context, it is not surprising that $CD8^+$ T-cell activation states can contribute to neuropsychiatric complications during HIV.

There are a number of study limitations including lack of HIV-uninfected controls with T-cell activation data available, a small sample of viremic women, and the cross-sectional nature of the analysis. Not only are longitudinal assessments important for better addressing causality but would also be important to elucidate any potential mediating pathways (e.g., mental health – T-cell activation – NP impairment). In addition, we utilized self-report screeners of mental health symptoms (depressive, PTSD, non-specific anxiety) rather than a structured diagnostic interview. Current and lifetime psychiatric diagnostic data were not available in the cohort during the time frame that the T-cell markers were assessed. The World Health Organization's Composite International Diagnostic Interview Diagnoses (CIDI), which is a computer-assisted diagnostic interview for DSM-V criteria is now being administered and will be available for future studies. Another limitation is that T-cell markers are likely to change over time and they were not always measured concurrent with neuropsychiatric outcomes. Additionally, the T-cell markers used may not encompass all T-cell states. However, the markers selected were chosen to allow for a general assessment of cellular function and were used in previously published work in the WIHS (Peters et al., 2021). It is important to note that we evaluated T lymphocyte activation states in PBMCs obtained from peripheral blood. While our findings have implications for T-cell trafficking into the brain, we did not evaluate their migration across the BBB. Finally, the sample of WIHS women focused only on WWH on ART and those without cancer, hepatitis B/C, or autoimmune disorders. Thus, our findings are only generalizable to this subgroup of WWH and importantly cannot be generalized to men with HIV given known sex/gender differences in the immune system and neuro-immune interactions (Klein and Flanagan, 2016; Markle and Fish, 2014).

Importantly, our current study provides insight into the contribution of T-cell activation states to neuropsychiatric complications in WWH. Our findings indicate that $CD4^+$ activation is beneficial for neuropsychiatric function, while exhaustion is detrimental. This is not surprising and suggests that an initial $CD4^+$ T-cell response is protective, but due to the sustained stimulation that occurs in the context of a chronic viral infection, damage occurs once a senescent and exhaustive phenotype occurs. Conversely, all $CD8^+$ activation states are associated with worsened neuropsychiatric function, indicating that targeting HIV-infected or cells expressing HIV antigens in the CNS is deleterious and disrupts the delicate balance of the CNS required for proper neuronal function.

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Declaration of competing interest

LHR is a consultant for Digital Artefacts, Inc. All coauthors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100498.

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