Fatigue is associated with worse cognitive and everyday functioning in older persons with HIV

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Objective: The aim of this study was to determine whether there are relationships between fatigue, cognition, and everyday functioning in older persons with and without HIV and to examine if associations remain after accounting for depression, anxiety, and sleep quality.

Methods: Sixty-nine persons with HIV (PWH) and 36 persons without HIV, aged 50–74 years, were recruited from ongoing studies at UC San Diego's HIV Neurobehavioral Research Program and from the community. Participants completed neuropsychological testing, a performance-based measure of everyday functioning, and self-report questionnaires of fatigue, depression, anxiety, sleep quality, and everyday functioning. Multivariable linear regressions and logistic regressions stratified by HIV serostatus were used to examine relationships between fatigue, cognition, and everyday functioning. Psychiatric symptoms and sleep quality were examined as covariates.

Results: In this cross-sectional study, PWH had significantly greater fatigue than the HIV-negative group ($g = 0.83$; $P < 0.01$). When stratifying by HIV serostatus, greater fatigue was significantly associated with worse global cognition ($\beta = -0.56$;$P < 0.01$) in PWH even when controlling for covariates;however, fatigue was not significantly associated with global cognition in persons without HIV. In PWH and when accounting for covariates, fatigue was also associated with greater risk of self-reported everyday functioning impairment [odds ratio (OR) = 1.66 for 10-point increase in fatigue, $P = 0.04$] but not performance-based everyday functioning ($P = 0.95$).

Conclusion: Fatigue is associated with cognition, particularly measures with a speeded component, and self-reported everyday functioning in older PWH. Findings suggest that fatigue is important to assess and consider in the context of aging with HIV.

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Introduction

It is estimated that by 2030, 73% of people with HIV (PWH) will be 50 years and older [1]. With increased age comes increased risk of HIV-associated neurocognitive disorders (HAND), which is associated with functional dependence [2,3] and worse quality of life [4]. Thus, the preservation of independence and promotion of successful aging in this population has become a major focus in HIV research [5].

Fatigue is a prevalent condition that is independently experienced by both PWH and older adults. Fatigue is the feeling of physical or mental tiredness and the lack of

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energy that is not relieved with rest [6,7]. Studies to date have largely focused on fatigue in the context of chronic medical conditions, such as multiple sclerosis, Parkinson's disease, chronic fatigue syndrome, and cancers. Research has repeatedly suggested fatigue's association with a wide-range of psychosocial factors, including depression [8], anxiety [9], poor sleep quality [10], less social support [11], and overall poorer quality of life [12]. Naturally, fatigue also is associated with poorer functional outcomes, such as unemployment and disability [13].

Among PWH, fatigue is associated with various medical comorbidities, such as hypothyroidism, hepatitis C (HCV) co-infection, and anemia, as well as HIV disease severity (e.g. AIDS status) and treatment status (e.g. whether an individual is on ART) [14–16]. Although variable, the estimated prevalence of fatigue in PWH throughout the lifespan ranges from 30% to upwards of 88% [16]. In addition, among PWH, it is estimated that 30% of individuals with asymptomatic HIV disease and 50% of those diagnosed with AIDS experience symptoms of mild neurocognitive impairment [17]. The relationships between fatigue, cognitive, and functional impairment are of particular interest as all are increasingly prevalent in aging PWH [18]. Fatigue is consistently associated with subjective cognition in a number of disorders [19,20]; yet, its relationship with objective measures of cognition is less studied and the evidence is mixed [21,22]. Research on fatigue and objective cognition in PWH is even more limited, and in available studies has been examined across wide age ranges and has included a large proportion of participants off ART. In these few studies examining objective cognition among PWH, two found that fatigue was associated with subjective cognition but not with objective cognition [23,24]. Another study found a relationship between greater fatigue and worse performance on the Stroop Color-Word Interference Test [25]. To our knowledge, there have been no studies that have specifically examined fatigue and objective cognition in older PWH.

Because of the very limited research on fatigue and cognition in older PWH worldwide, this study aimed to examine the relationship between fatigue, cognition, and everyday functioning in this population. The first aim of this study was to examine if fatigue is related to objective cognition and subjective and performance-based measures of everyday functioning in persons with and without HIV aged 50 years and over. We also examined if these relationships differ by HIV serostatus. Given that fatigue is often related to psychiatric conditions and sleep disturbance, our second aim was to examine if the relationship between fatigue and neuropsychological and everyday functioning remained after accounting for depression, anxiety, and sleep disturbance.

Methods

Participants

Sixty-nine PWH and 36 HIV-negative adults aged 50 to 74 years were recruited at the UC San Diego (UCSD) HIV Neurobehavioral Research Program (HNRP) from existing studies at the research center and the broader community in San Diego. Between 2016 and 2019, participants completed study visits consisting of comprehensive neuropsychological and neuromedical evaluations. Inclusion criteria for the current study included English fluency, at least 50 years of age, and the ability to provide written, informed consent independent of participants' HIV status. Exclusion criteria included psychotic disorders (e.g. schizophrenia, schizoaffective disorder), a history of non-HIV-related neurological confounds (e.g. stroke, head injury with loss of consciousness >30 min, multiple sclerosis), and a reported learning disability or very low estimated verbal IQ via standard score less than 70 on the Wide-Range Achievement Test-4 (WRAT-4) Reading test. Additionally, participants were rescheduled if they had a positive urine toxicology or alcohol breathalyzer (with the exception of prescription medications and/or cannabis given its long duration of detection). This study was approved by UC San Diego's Institutional Review Board. All participants provided written informed consent, demonstrated decisional capacity, and were compensated for their participation. There were several components to this study and participants were compensated based on which components they completed. Participants were compensated at a rate of $15/h.

Measures and procedures

Neuropsychological evaluation

Participants completed the HNRP's comprehensive neuropsychological test battery, which assesses seven cognitive domains (i.e. verbal fluency, speed of information processing, executive function, learning, memory, attention/working memory, and complex motor skills; see Supplemental Table 1, http://links.lww.com/QAD/C433 for specific neuropsychological tests). Raw scores from these assessments were converted to demographically-adjusted *T*-scores (mean = 50, SD = 10) for each cognitive domain [26–28]. Scores also take into account practice-effects for participants with prior administrations of the battery [29].

Everyday functioning

A modified self-report Lawton-Brody Instrumental Activities of Daily Living (IADL) Questionnaire [30,31] was used to assess subjective everyday functioning. This questionnaire required participants to rate their ability to function independently on 11 daily tasks (e.g. managing finances, managing medications), including their current level and overall highest level of functioning for each. Participants were classified as 'IADL Dependent' if they reported declines (i.e. highest level of functioning

greater than current level of functioning) or need for assistance on at least 2 of the 11 IADL domains. This methodology has previously been validated in a normative sample [32].

The UCSD Performance-Based Skills Assessment-Brief (UPSA-B) [33] was administered as a performance-based measure of functional capacity. This assessment required participants to perform manual tasks in two primary domains of functioning: financial skills (e.g. counting coins and paying a bill) and communication skills (e.g. mock telephone call, setting up a medical appointment). Raw scores on each domain were converted to percentage correct, then summed for a total percentage correct score (range: 0–100%), for which higher scores represented better daily functioning. Percentage totals were converted to a final summary scores (range: 0–100). The UPSA-B has been previously shown to be able to differentiate between normal vs. impaired neuropsychological functioning among adults with HIV [34].

Fatigue

The Modified Fatigue Impact Scale (MFIS) was used to examine the impact of fatigue on cognitive, physical, and social functioning over the past 4 weeks. This is a 21-item scale that was modified from the original 40-items scale in which each fatigue item was rated on a scale from 0 (never) to 4 (almost always) [35]. The MFIS was originally developed to measure the impact of fatigue in multiple sclerosis but has since been used and validated in a number of diseases/disorders in which fatigue is common (e.g. Parkinson's disease, traumatic brain injury) [36,37]. The total scores range from 0 to 84, with higher scores indicating greater impact of fatigue. Of note, this measure queries about the *impact* of fatigue but we refer to this as 'fatigue' throughout the manuscript.

Depression, anxiety, and sleep disturbance covariates

Depression symptoms were assessed using the Beck Depression Inventory-II (BDI-II) [38], in which participants indicated the presence and severity of depressive symptoms during the past 2 weeks. Anxiety symptoms were assessed with the Beck Anxiety Inventory (BAI) [39], for which participants rated 21 items on how much they have been bothered by symptoms of anxiety over the past week. The Pittsburgh Sleep Quality Index (PSQI) [40] is a 19-item measure, which assessed participants' self-reported quality of sleep over the past month. For all three measures, higher scores indicate worse symptoms.

Neuromedical and psychiatric assessment

Medical comorbidities were determined by a combination of self-report diagnosis or use of a medication for the condition collected during a standardized neuromedical assessment. The Charlson Comorbidity Index [41], which is a weighted count of 19 different comorbid conditions, was used to assess comorbidity burden. Self-report of current medications was used to examine if participants were prescribed any sleep medications (i.e. butabarbital, doxepin, estazolam, eszopiclone, flurazepam, quazepam, ramelteon, secobarbital, suvorexant, tasimelteon, temazepam, triazolam, zaleplon, and zolpidem, trazodone, or over-the-counter insomnia drugs such as diphenhydramine, doxylamine, and melatonin) or psycho-stimulants (i.e. dextroamphetamine, methylphenidate hydrochloride, pemoline, and modafinil) that have been identified as common treatments for fatigue in PWH [42]. Psychiatric and substance use diagnoses were assessed via a computer-assisted structured interview consistent with the DSM-IV (Composite International Diagnostic Interview) [43].

HIV disease characteristics

HIV serostatus was confirmed in all participants with HIV/HCV antibody point-of-care rapid test (Miriad, MedMira, Nova Scotia, Canada) and confirmatory western blot analyses. AIDS diagnosis, estimated duration of HIV disease, antiretroviral therapy regimen, and nadir $CD4^+$ cell count were collected via self-report. Viral load detectability (>50 copies/ml) and current $CD4^+$ cell count were measured in blood plasma.

Statistical analyses

To characterize the groups, group differences by HIV serostatus were analyzed using chi-square test, Fisher's exact test, and *t*-test (or nonparametric equivalent) as appropriate. The relationship between fatigue and other psychiatric symptoms and comorbid conditions were examined using Spearman correlations or *t*-test. Multivariable linear regressions that stratified by HIV status were used to examine the relationship between fatigue and global cognition (global T-score) and then covaried for depression (BDI-II), anxiety (BAI), and sleep disturbance (PSQI) to examine if these relationships remained after accounting for these factors. Comorbidity burden, substance use, use of sleep medications, and HIV disease characteristics were not significantly related to cognition and were thus not included as covariates. Stratified analyses were utilized because of the somewhat small sample size and reduced range of fatigue in the HIVnegative group. If fatigue was significantly related to global cognition (i.e. in PWH) then follow-up analyses examined which cognitive domains and specific neurocognitive tests were driving the relationship. The relationship between fatigue and everyday functioning was examined only in PWH given that few participants in the HIV-negative group ($n = 3$) reported a decline in everyday functioning. Wilcoxon rank-sum test was initially used to examine the relationship between IADL status and fatigue and then was followed-up with a logistic regression that covaried for depression, anxiety, and sleep disturbance symptoms. Multivariable linear regression was used to examine the relationship between fatigue and UPSA-B performance and covaried for depression, anxiety, and sleep disturbance.

Table 1. Participant characteristics by HIV status.

	PWH ($n=69$)	HIV− ($n=36$)	t, Z, or χ^2	P
Demographic variables				
Age (years) [mean (SD)]	59.3 (6.2)	59.1 (6.7)	0.1	0.93
Male [n (%)]	57 (82.6%)	21 (58.3%)	7.3	<0.01
Race/ethnicity	—	—	FET	0.60
Non-Hispanic white [*n* (%)]	45 (65.22%)	23 (63.9%)	—	—
African American/black [*n* (%)]	15 (21.7%)	6 (16.7%)	—	—
Hispanic/Latino [*n* (%)]	7 (10.1%)	7 (16.7%)	—	—
Other [*n* (%)]	2 (2.9%)	1 (2.8%)	—	—
Education (years) [mean (SD)]	14.0 (2.5)	14.9 (2.5)	−1.8	0.08
Medical and psychiatric comorbidities				
Charlson comorbidity index[a] (median [IQR])	7 [2–9]	1 [1–2]	−5.6	<0.01
LT MDD [*n* (%)]	50 (72.5%)	9 (25.0%)	21.7	<0.01
Current MDD[b] [*n* (%)]	12 (17.4%)	1 (2.9%)	FET	0.06
LT substance use disorder [*n* (%)]	48 (69.6%)	17 (47.2%)	5.0	0.03
Current substance use disorder[b,c] [*n* (%)]	2 (2.9%)	1 (2.9%)	FET	1.00
Prescribed a psychostimulant	2 (2.9%)	0 (0.0%)	FET	0.55
Prescribed a sleep medication	19 (28%)	1 (3%)	FET	<0.01
BDI-II (median [IQR])	7 [2.5–14.5]	2.5 [0–4]	−3.9	<0.01
BAI (median [IQR])	5 [1–11]	1 [0–2.75]	−4.3	<0.01
PSQI (median [IQR])	8 [5–11]	7 [4.5–8.5]	−2.1	0.04
Fatigue				
MFIS total (median [IQR])	32 [12.5–46.5]	11.5 [0–27.25]	−3.8	<0.01
Cognitive and everyday functioning				
Global [mean (SD)]	48.7 (6.4)	50.1 (5.9)	−1.1	0.30
Verbal fluency[b] [mean (SD)]	50.9 (9.5)	54.2 (9.9)	−1.7	0.10
Executive function[d] [mean (SD)]	48.1 (8.0)	50.0 (7.4)	−1.1	0.26
Speed of information processing[d] [mean (SD)]	50.1 (8.7)	51.5 (8.5)	−0.8	0.42
Learning [mean (SD)]	45.2 (8.3)	45.6 (8.2)	−0.2	0.83
Delayed recall [mean (SD)]	46.3 (7.7)	46.8 (8.2)	−0.3	0.75
Working memory [mean (SD)]	50.1 (9.5)	50.5 (9.0)	−0.2	0.83
Complex motor skills[a] [mean (SD)]	48.5 (10.3)	48.8 (9.5)	−0.13	0.90
IADL (dependent)[d] [*n* (%)]	32 (47.1%)	3 (8.3%)	FET	<0.01
UPSA-B[e] [mean (SD)]	81.8 (10.4)	84.9 (8.7)	−1.5	0.14
HIV characteristics				
AIDS [*n* (%)]	46 (66.7%)	–	–	–
Current $CD4^+$ (median [IQR])	699 [545–894]	–	–	–
Nadir $CD4^+$ (median [IQR])	166 [42–300]	–	–	–
Duration of HIV disease (years) (median [IQR])	23.8 [17.5–28.9]	–	–	–
On ART [*n* (%)]	65 (94.2%)	–	–	–
Undetectable viral load[f] [*n* (%)]	62 (96.9%)	–	–	–

ART, antiretroviral therapy; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; FET, Fisher's Exact Test; IADL, instrumental activities of daily living; LT, lifetime; MDD, major depressive disorder; PWH, persons with HIV; UPSA-B, UCSD Performance-Based Skills Assessment-Brief.
[a]$n=102$.
[b]$n=103$.
[c]All current substance use disorder was cannabis use disorder.
[d]$n=104$.
[e]$n=101$.
[f]$n=64$.

Results

Participants

Participant characteristics are presented in Table 1. On average, participants were in their late fifties (HIV−− mean age = 59.3; PWH mean age = 59.1), had some college education, and the majority identified as non-Hispanic white (65%). PWH and the HIV-negative group were fairly similar with respect to demographic variables with the exception of sex (PWH: 83% male; HIV−−: 58% male). PWH had high rates of ART use (94%) and undetectable viral load (97%).

Fatigue

PWH reported significantly greater fatigue than HIVnegative participants [PWH: median 32 (12.5–46.5); HIV−−: median = 11.5 (0–27.25); $P< 0.001$, Hedges' $g=0.83$]. Although there is no well established cutoff, a cut-off of 38 has been suggested [44]. Using this cutoff, 38% ($n=26$) of PWH are at or above this cutoff as compared with only 6% ($n=2$) of those in the HIV-negative group. See Table 1 for fatigue by HIV status and Fig. 1 for the distribution of fatigue by HIV status. Fatigue was moderately to strongly associated with lifetime history of major depressive disorder (PWH:

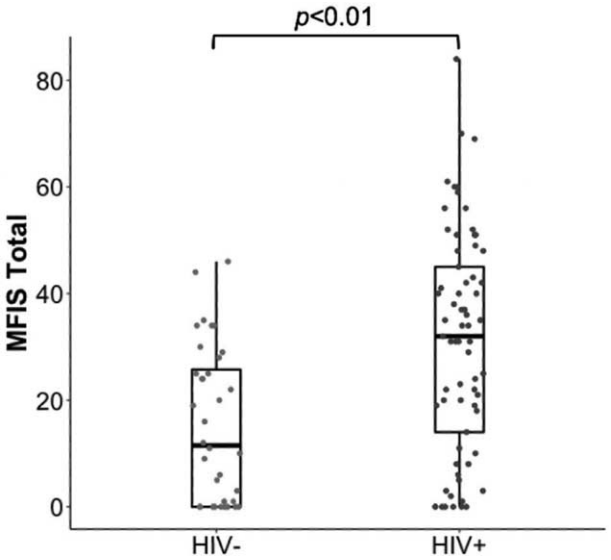

Fig. 1. Persons with HIV report greater fatigue than HIV-negative adults. Higher scores indicate greater fatigue impact; MFIS, Modified Fatigue Impact Scale.

$g = 0.81$, $P = 0.003$; HIV−: $g = 0.87$, $P = 0.029$), depressive symptoms (PWH: $\rho = 0.74$, $P < 0.001$; HIV−: $\rho = 0.57$, $P < 0.001$), anxiety symptoms (PWH: $\rho = 0.51$, $P < 0.001$; HIV−: $\rho = 0.41$, $P = 0.013$), and sleep quality (PWH: $\rho = 0.49$, $P < 0.001$; HIV−: $\rho = 0.40$, $P = 0.021$). Demographics, comorbid conditions (as measured with the Charlson Comorbidity Index), use of sleep medications, and lifetime substance use disorder were not significantly associated with fatigue in either group (*P*s > 0.050). Within PWH, HIV disease characteristics were not significantly associated with fatigue (*P*s > 0.050).

Associations between fatigue and cognition

In stratified analyses, greater fatigue was significantly associated with worse global cognition in PWH ($\beta = -0.35$, $P = 0.003$) but fatigue was not associated with global cognition in the HIV-negative group ($\beta = -0.05$, $P = 0.751$). In PWH, the relationship between fatigue and global cognition became stronger after accounting for current depression, anxiety, and sleep quality ($\beta = -0.56$, $P = 0.005$), and depression, anxiety, and sleep quality were not related to global cognition (*P*s > 0.100). In the HIV-negative group, fatigue remained unassociated with global cognition even when accounting for depression, anxiety, and sleep quality ($\beta = -0.02$, $P = 0.921$), and only sleep quality was related to worse global cognition ($\beta = -0.41$, $P = 0.034$). See Table 2 and Fig. 2 for model estimates.

The association between cognition and fatigue in PWH was driven by several domains even when accounting for depression, anxiety, and sleep quality. Fatigue was significantly associated with worse verbal fluency ($\beta = -0.61$, $P = 0.003$), executive function ($\beta = -0.55$, $P = 0.006$), speed of information processing ($\beta = -0.49$, $P = 0.016$), working memory ($\beta = -0.60$, $P = 0.003$), and complex motor functioning ($\beta = -0.44$, $P = 0.029$). Fatigue was not significantly associated with learning ($\beta = 0.02$, $P = 0.936$) or delayed recall ($\beta = 0.17$, $P = 0.384$). See Table 2 and Fig. 3 for model estimates.

In post hoc analyses, we examined which tests were driving the significant domains in order to examine if the relationship between fatigue and cognition was driven primarily by tests involving a speed component. Indeed, we found that the specific tests driving this relationship were all tests that include a timed component including: Category (Animal) Fluency, Letter Fluency (FAS), Stroop Color-Word Test – Interference Trial, WAIS-III Symbol Search, Trail Making Test Part A, the Paced Auditory Serial Addition Test Channel 1 (PASAT), and dominant hand Grooved Pegboard (*P*s < 0.050).

Associations between fatigue and everyday functioning in persons with HIV

When examining self-reported everyday functioning in PWH, those who reported dependence in IADLs had

Table 2. Linear regressions to examine the relationship between fatigue and cognitive functioning in middle-aged and older adults with and without HIV.

Domain (*T*-scores)	Estimate	SE	95% CI	Std Estimate	*t*	*P* value
HIV-negative ($n = 36$)						
Global	−0.01	0.09	−0.20 to 0.18	−0.02	−0.10	0.922
Persons with HIV ($n = 69$)						
Global	−0.17	0.06	−0.29 to −0.05	−0.56	−2.89	0.005
Verbal Fluency	−0.29	0.09	−0.47 to −0.10	−0.61	−3.13	0.003
Executive Function	−0.21	0.08	−0.36 to −0.06	−0.55	−2.83	0.006
SIP	−0.21	0.08	−0.37 to −0.04	−0.49	−2.48	0.016
Learning	0.01	0.08	−0.16 to 0.17	0.02	0.08	0.936
Delayed Recall	0.07	0.08	−0.08 to 0.21	0.17	0.88	0.384
Working Memory	−0.28	0.09	−0.47 to −0.10	−0.60	−3.10	0.003
Complex Motor	−0.21	0.10	−0.41 to −0.02	−0.44	−2.24	0.029
UPSA-B	0.04	0.11	−0.18 to 0.26	0.08	0.35	0.724

All analyses include depression, anxiety, and sleep quality as covariates. CI, confidence interval; SE, standard error; SIP, Speed of Information Processing; UPSA-B, UCSD Performance-Based Skills Assessment-Brief.

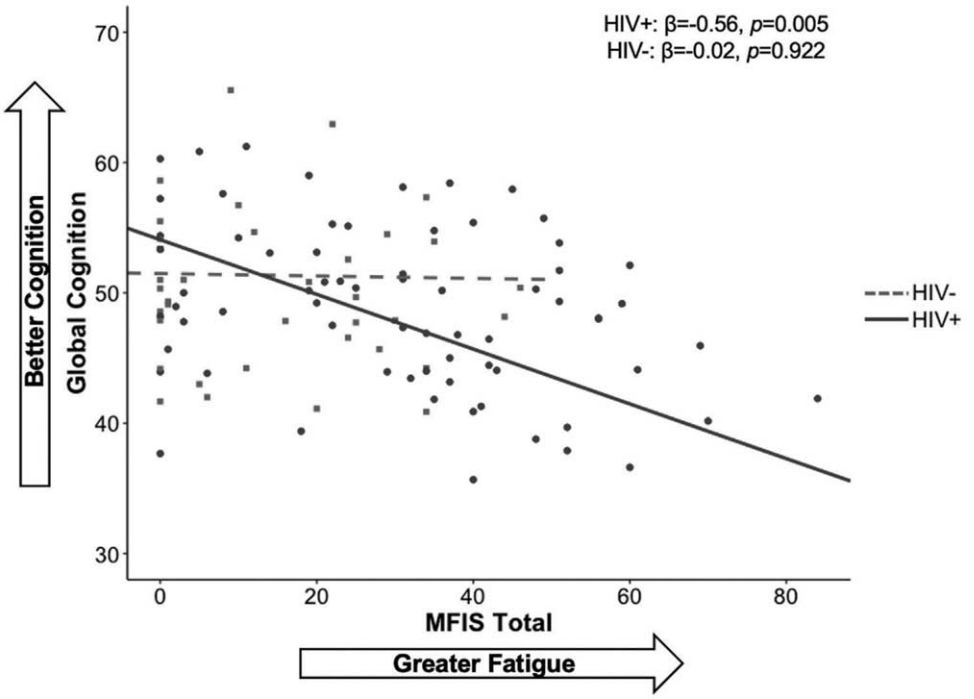

Fig. 2. Greater total fatigue is associated with worse cognitive functioning in persons with HIV. Regression lines adjust for depression, anxiety, and sleep quality symptoms (all variables were centered). MFIS, Modified Fatigue Impact Scale.

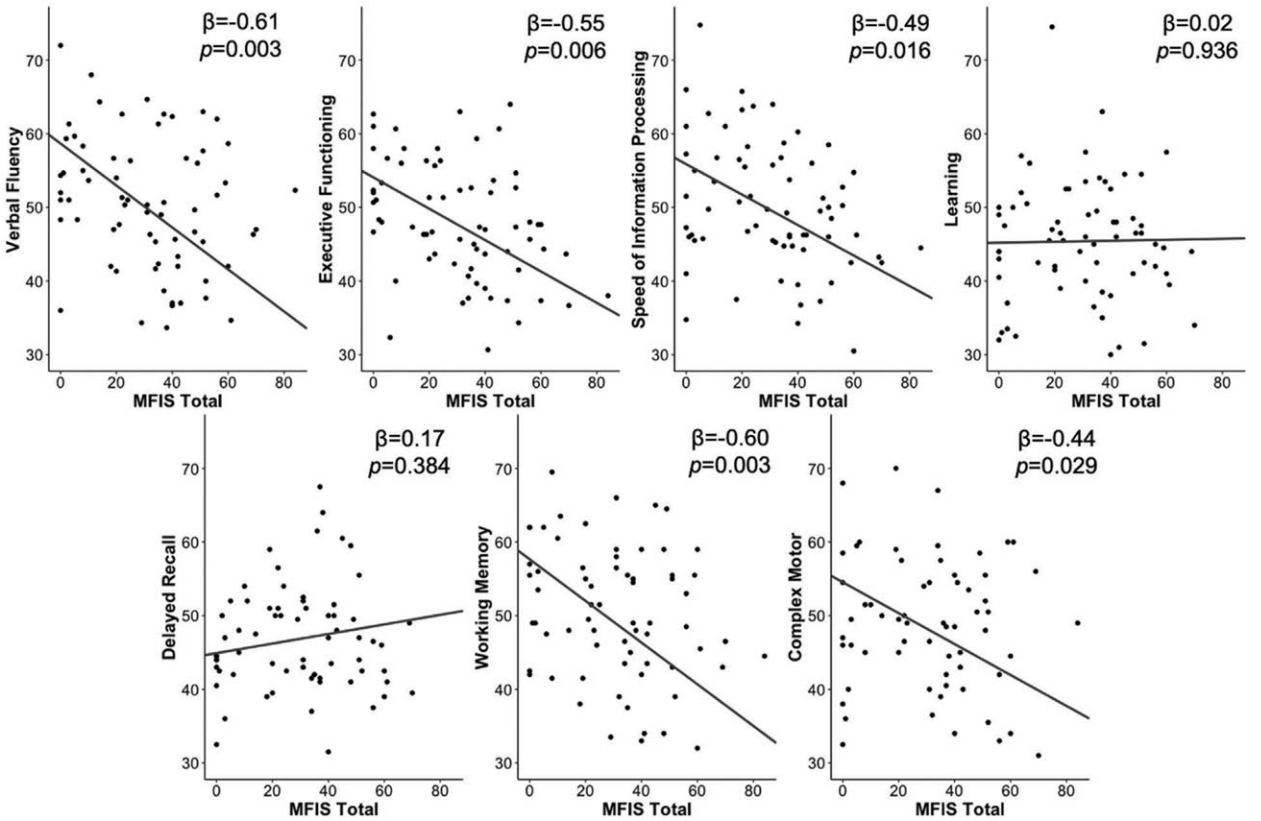

Fig. 3. Relationship between total fatigue and domain-specific cognition in persons with HIV. Regression lines adjust for depression, anxiety, and sleep disturbance symptoms (all variables were centered). MFIS, Modified Fatigue Impact Scale.

significantly greater fatigue (dependent median: 40.5 [32,51]; independent median: 19 [2,35]; $P < 0.001$). When accounting for psychiatric and sleep factors, greater fatigue was associated with higher odds of IADL dependence [odds ratio (OR): 1.66 for a 10-point increase in fatigue; $P = 0.039$] but depression, anxiety, and sleep quality were not significantly associated with greater odds of IADL dependence ($Ps > 0.15$). When examining performance-based functioning in PWH, fatigue was not univariately associated with UPSA-B performance in PWH ($\beta = 0.01$, $P = 0.952$). Accounting for psychiatric symptoms and sleep quality did not change the results ($\beta = 0.08$, $P = 0.724$; see Table 2), and anxiety, depression, and sleep quality were not significantly associated with UPSA-B performance ($Ps > 0.500$).

Discussion

Prior research has repeatedly demonstrated that there are high rates of subjective fatigue among PWH; however, there has been a relative dearth of research on the association between fatigue and objective cognition, particularly in older PWH. As expected, we found that fatigue, as measured with the Modified Fatigue Impact Scale, was significantly greater in a group of older PWH with high rates of ART use as compared with HIV-negative participants. We also found that in older PWH, greater fatigue was associated with worse global cognitive functioning, even when controlling for comorbid depression, anxiety, and sleep disturbance symptoms.

Although the relationship between fatigue and cognition among PWH was observed in a number of cognitive domains, it appeared that this association was primarily driven by neuropsychological tests that include a speed component. There are several proposed biological mechanisms, particularly involvement of thalamostriatocortical circuitry further discussed in the next paragraph, that may explain this association as processing speed may be influenced by fatigue but also may share similar underlying mechanisms. We also know that fatigue may be because of psychological conditions, such as depression [15]. Fatigue, slowed cognitive processing speed, and psychomotor retardation are common depressive symptoms, which may in part explain the underlying reasoning behind this finding; however, associations remained even after accounting for depression symptoms. In a previous study in PWH, Millikin *et al.* [23] found that fatigue was not associated with objective cognition. However, there are a number of differences between that and the current study: Millikin *et al.* used the Fatigue Severity Scale (FSS), included a wide range of ages (mean age was around 40 years old), and 30–40% of the sample was not on ART and/or had detectable viral load. In another study by Schifitto et *al.* [25], fatigue was significantly associated with the Stroop Color-Word Interference Test, which is in line with the current results as this is a timed measure of executive functioning. These associations were not observed in HIV-negative participants; however, the HIV-negative group had a more restricted range of fatigue, which was expected as some other medical conditions tied to high rates of fatigue (e.g. neurological conditions, such as stroke and multiple sclerosis) were exclusionary for this study.

There are a number of different biological mechanisms that have been explored in attempts to understand fatigue in PWH. Neuroanatomically, fatigue in PWH is thought to be modulated by the thalamostriatocortical circuitry involving the basal ganglia, which is particularly affected in HIV [45], but the relationship between fatigue and these brain regions has been more extensively studied in other diseases and disorders, such as multiple sclerosis and chronic fatigue syndrome [46,47]. This hypothesis is particularly relevant for these findings given that these brain regions are associated with processing speed. The literature on brain correlates of fatigue in PWH is limited, but one study did find that there were lower levels of a cellular energy marker (i.e. creatine) in the basal ganglia in PWH with fatigue [25]. Furthermore, among PWH, fatigue has been found to associate with increased inflammation and number of polymorphisms in genes involved in inflammatory expression [48,49]. It is well established that these brain regions and neuroinflammation are implicated in the pathogenesis of HAND [50]; therefore, fatigue and cognition may be associated with one another because of some common underlying mechanisms. Lastly, mitochondrial dysfunction in the brain is also thought to contribute to fatigue. Although this relationship has not been extensively studied in PWH, mitochondrial dysfunction is observed in PWH and has been associated with HAND [51,52]. The underlying cause of fatigue in PWH is complex and likely multifactorial; a better understanding of these underlying mechanisms may lead to improved treatment or prevention of fatigue in PWH.

In our sample of older PWH, fatigue was associated with subjective everyday function via a modified Lawton-Brody IADL Questionnaire. This is unsurprising given that fatigue has been previously associated with subjective functioning [as measured with the Patient's Assessment of Own Functioning and Medical Outcome Study (MOS) Cognitive Functioning Scale] in PWH [23,24]. However, fatigue did not relate to a performance-based measure of everyday functioning (UPSA-B), which is an untimed assessment of financial and communication skills without any physical component (e.g. standing, walking). There are many possible reasons why this relationship was not observed. For example, fatigue may not impact functioning when given enough time to complete a short nonphysical task but fatigue could impact functioning or the perception of functioning in participants' everyday life in which physical functioning and speed are often important. More

research is needed to better understand the relationships between fatigue and everyday functioning.

Our findings have a number of clinical implications. In terms of medications, a randomized, double-blind study found that PWH with fatigue that were treated with modafinil significantly improved performance on neurocognitive tests (i.e. WAIS-III Digit Symbol and Grooved Pegboard) as compared with those in the placebo group [53]. Additionally, preliminary research also suggests that medication may be a helpful adjunct to psychotherapy. For example, a pilot study found that PWH with clinically significant fatigue who received combined behavioral activation and armodafinil were more successful in attaining work-related goals than PWH than those who received armodafinil alone (63 vs. 28%) [54]. Overall, this suggests that pharmacological treatment of fatigue, potentially combined with psychotherapy, may be helpful for both cognition and everyday functioning. With regard to neuropsychological testing, the present study suggests that in PWH with significant fatigue, speed of information processing should be assessed but it is important to incorporate nonspeeded tests of other cognitive domains in order to accurately tease apart processing speed versus other cognitive abilities. Fatigue is sometimes viewed as a symptom of depression, and our study demonstrates that fatigue in older PWH may relate to objective cognitive deficits, and interventions to improve fatigue may be beneficial for both cognition and daily functioning. For example, cognitive training programs focused on improving processing speed in PWH have been shown to improve lab-based IADL functioning [55,56]. However, these studies did not specifically examine fatigue; therefore, future studies should examine if cognitive training programs can improve processing speed, and by extension everyday functioning, in PWH with fatigue.

This study adds to the limited literature examining fatigue, cognition, and everyday functioning in PWH. Our study has several strengths, as well as some limitations that should be noted in order to contextualize the findings and improve future research. First, as a cross-sectional study, it only examined associations between fatigue and cognition and cannot determine causality. As discussed above, fatigue and cognition may share some underlying mechanisms and research is needed to clarify those biological underpinnings. Second, the MFIS has not been validated in older PWH; however, it has been validated in other chronic diseases [35,36]. Moreover, the preliminary findings demonstrate some convergent validity (i.e. correlations with depression, anxiety, and sleep) but further validation of this measure in older PWH is needed. Third, PWH in this study were between the ages of50 and 74 years from the San Diego area with high rates of ART use and viral suppression, and participants were primarily male; thus, these findings may not generalize to other groups of PWH.

We should note that fatigue is a complex construct and has overlapping characteristics with a number of other constructs, such as 'brain fog' and chronic fatigue syndrome (CFS). As stated above, the MFIS was used to define fatigue as a feeling of physical tiredness and lack of energy. The scale measured how an individual rated the effect their fatigue has on their physical, cognitive, and psychosocial functioning. In many ways, questions on the MFIS aimed at capturing cognitive outcomes of fatigue (i.e. 'I have been unable to think clearly' and 'I have been less alert') overlap with 'brain fog', a term used to describe one's thinking as sluggish, fuzzy, or not sharp. The important distinction is that fatigue may be independent of cognitive changes, whereas brain fog is a subjective experience (not a medical term) that describes a state that may be caused by a variety of conditions (e.g. pregnancy, medication use jetlag). Brain fog' is a common outcome of fatigue but the two constructs can be independent of each other. In terms of CFS, the MFIS can be used to measure the severity of fatigue in this chronic condition that is defined as having extreme fatigue that lasts at least 6 months and cannot be explained by an underlying condition [57]. However, unlike CFS, fatigue has no duration constraints and can be because of conditions, such as HIV.

In conclusion, we found that greater fatigue was negatively associated with cognition in older PWH, even when covarying for depression, anxiety, sleep quality. This relationship was primarily driven by neurocognitive tests with a speeded component. Moreover, fatigue was also associated with greater risk of IADL dependence. More research is needed to better understand the biological underpinnings of fatigue in PWH as this may lead to better treatment or prevention of fatigue, which may in turn promote cognitive and everyday functioning in older PWH.

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R.C.M. provided funding acquisition, project administration, and resources, conceptualized and designed study; oversaw data collection; contributed to manuscript writing and editing.

Conflicts of interest

R.C.M. is a co-founder of Key Wise, Inc. and a consultant for NeuroUX. The terms of these arrangements have been reviewed and approved by UC San Diego in accordance with its conflict of interest policies. For the remaining authors, no conflicts of interest were declared.

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