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Clinical, laboratory, and neuroimaging characteristics of fatigue in HIV-infected individuals

Giovanni Schifitto · Lijuan Deng · Tzu-min Yeh · Scott R. Evans · Thomas Ernst · Jianhui Zhong · David Clifford

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Abstract Fatigue is among the most common symptoms reported by HIV-infected individuals. Previous reports suggest that the prevalence of fatigue varies by disease status with rates close to 80% in patients with AIDS. However, most studies have not been conducted in the setting of a controlled trial and have not assessed the association of fatigue with cellular markers of brain activity. Data for this study were derived from baseline and longitudinal evaluations in ACTG A5090, a randomized, double-blind, placebo-controlled trial of the Selegiline Transdermal System for the treatment of HIV-associated cognitive impairment. Fatigue was assessed using the Fatigue Severity Scale with scores of >4 considered "fatigued". Participants in a substudy underwent brain magnetic resonance spectroscopy (MRS) imaging, an in vivo method for assessing brain metabolites associated with neuronal and glia activity. Differences between fatigued and non-fatigued participants were evaluated with respect to demographics and clinical characteristics, plasma and CSF HIV-1 RNA concentration, CD4 counts, and brain metabolites. One hundred and twenty-eight participants were enrolled (88% male, median age=45 years) and 82 participants (64%, 95% confidence interval 55%, 72%) were fatigued at baseline. MRS was conducted in 62 of the 128 participants. Fatigued participants were significantly younger (p=0.011), had lower Karnofsky scores (p=0.032), and had higher levels of depressive symptoms on the Center for Epidemiologic Studies Depression (CES-D) scale (p<0.001) than non-fatigued participants. Statistically significant differences between fatigued and non-fatigued groups were not detected for plasma and CSF HIV-1RNA concentration, CD4 counts, or on neuropsychological tests. MRS revealed significantly lower levels of the cellular energy marker total creatine (p=0.002) in the basal ganglia of fatigued participants. Statistically significant differences in other brain metabolites were not detected. Longitudinal data showed that fatigue persisted and worse fatigue at baseline was predictor of future fatigue. Among the cognitive tests, baseline Stroop score was associated with future fatigue. Fatigue was present in 64% of A5090 study participants and persisted during the 24 weeks of follow-up. Fatigue was associated with worse functional performance and depressive mood. Lower cellular energy levels in the basal ganglia, as measured by MRS total creatine concentration, suggest energy dysmetabolism in this brain region. This observation, taken together with the association between fatigue and neuropsychological tests of frontal lobe performance is consistent with the hypothesis of a striatal–cortical circuitry involvement in the symptoms of fatigue.

Keywords HIV · Fatigue · MRS

G. Schifitto · J. Zhong
University of Rochester,
Rochester, NY, USA

L. Deng · T.-m. Yeh · S. R. Evans
Harvard School of Public Health,
Boston, MA, USA

T. Ernst
John A Burns School of Medicine, University of Hawaii,
Honolulu, HI, USA

D. Clifford
Washington University School of Medicine,
St. Louis, MO, USA

G. Schifitto (✉)
1351 Mount Hope Avenue Suite 223,
Rochester, NY 14620, USA
e-mail: giovanni_schifitto@urmc.rochester.edu

Introduction

The prevalence of fatigue associated with HIV infection has been reported to vary according to the disease status, from no fatigue in HIV-infected individuals with preserved immune function, to almost 80% in those with AIDS (Darko et al. 1992; Ferrando et al. 1998; Phillips et al. 2004; Breitbart et al. 1998; Justice et al. 1999; Perkins et al. 1995; Voss 2005; Sullivan and Dworkin 2003). Despite a significant disparity in the prevalence rates among studies, likely due to differences in the population selection criteria and the definition and instrument chosen to measure fatigue, the overall pattern that has emerged from previous investigations is that fatigue is among the most common symptoms reported by HIV-infected individuals, significantly affecting their well-being (Ferrando et al. 1998; Cleary et al. 1993; Wilson and Cleary 1996) and having a deleterious impact on antiretroviral medication adherence (Molassiotis et al. 2002; Duran et al. 2001).

Because of fatigue's largely subjective and multidimensional nature, investigating and treating fatigue can be quite challenging. For example, fatigue is one of the cardinal symptoms of depression; therefore, it is not surprising that there is considerable overlap between fatigue and depressive symptoms in HIV-infected individuals. However, several large studies have shown that although depressive and fatigue symptoms are intertwined, fatigue is present independently of depression (Breitbart et al. 1998; Sullivan and Dworkin 2003; Lyketsos et al. 1996). Similarly, fatigue and cognitive impairment often coexist (Perkins et al. 1995) but are not necessarily highly correlated (Millikin et al. 2003).

Chaudhuri and Behan (2000) have emphasized that metabolic, toxic, inflammatory, viral, and neurodegenerative disorders that affect the basal ganglia or the dopaminergic system are often associated with fatigue. For example, fatigue is among the most disabling symptoms reported by patients with Parkinson disease (Herlofson and Larsen 2003; Shulman et al. 2001; Witjas et al. 2002) and is present in over 30% of early diagnosed, levodopa-naïve patients (Schifitto et al. 2008). The hypothesis of fatigue modulated by a central circuitry involving the basal ganglia is particularly relevant to HIV infection given that basal ganglia neuropathology is one of the hallmark of HIV-associated CNS injury (Navia et al. 1986).

In this analysis, we have investigated the relationship between clinical, immunological, virological, and neuroimaging biomarkers and fatigue in the context of a randomized clinical trial for the treatment of HIV-associated cognitive impairment (Schifitto et al. 2007).

Methods

Fatigue was a secondary outcome of AIDS Clinical Trial Group study A5090, a 24-week, double-blinded, placebo-controlled, of Selegiline Transdermal System in HIV-infected participants with impaired cognitive functioning (Schifitto et al. 2007). One hundred twenty-eight participants were enrolled in A5090. Sixty-two of these 128 participants underwent proton magnetic resonance spectroscopy (1H-MRS; Schifitto et al. 2009).

Fatigue was assessed at baseline, and weeks 12 and 24, using the Fatigue Severity Scale (FSS; Krupp et al. 1989). The FSS, although not specifically validated in the HIV-infected population, has been validated in conditions that affect the immune system with or without CNS involvement (Krupp et al. 1989) and in chronic viral infections such as hepatitis C (Kleinman et al. 2000).

The FSS is a self-report questionnaire consisting of nine statements describing the severity of fatigue symptoms. Participants completing the FSS are asked to rate how accurately each item describes personal fatigue levels on a scale from 1 (strongly disagree) to 7 (strongly agree). The FSS score is obtained by dividing the sum of all item scores by 9. Participants scoring >4 were classified as "fatigued" and participants scoring ≤4 were considered to be "non-fatigued".

Neuropsychological evaluations were performed at screening, and weeks 12 and 24 using a standard battery of neuropsychological tests which included: the Rey Auditory Verbal Learning Test (alternate forms at each visit); Symbol Digit Test; Grooved Pegboard (dominant and non-dominant hands); Trail-making A and B, Timed Gait; Stroop Color Interference Task (Kaplan adaptation of the Comalli Stroop), and the California Computerized Assessment Package (CalCAP) reaction time test and were performed at the initial screening and at 12 and 24 weeks. Overall cognitive performance was summarized using the composite z-score, the NPZ-8 (Schifitto et al. 2007).

Single-voxel proton spectra were acquired using a GE Signa 1.5T scanner at baseline, and weeks 12 and 24 as previously described (Schifitto et al. 2009). Briefly, 20×20×15 mm^3 voxels were prescribed on the midline of the frontal lobes (gray matter), right or left centrum semi-ovale (white matter), and right or left basal ganglia. The LCModel MRS analysis software (http://S-provencher.com) was used to calculate the metabolite ratios of N-acetyl aspartate (NAA) to total creatine (Cr), choline (Cho) to Cr, myo-inositol (MI) to Cr, and the combined peak of glutamate plus glutamine (Glx) to Cr. Absolute quantitation of these metabolites was performed using the technique described by Kreis, Ernst, and Ross

(Kreis et al. 1993), and yielded metabolite concentrations corrected for the percentage of CSF in each voxel.

Statistical methods

The differences between fatigued (FSS>4) and non-fatigued (FSS≤4) participants at baseline are summarized using descriptive statistics by fatigue status. Kruskal–Wallis tests were used to compare continuous characteristics, exact tests were used for comparing nominal categorical characteristics, and the Score test was used for comparing ordinal categorical characteristics between the two groups. Differences between the two groups are estimated by shift parameters and with exact 95% confidence intervals. This non-parametric approach assumes that if observations from the fatigued group are shifted by a certain constant (shift parameter), then that shift will bring them into the same distribution as that displayed by the non-fatigued group.

Each participant's fatigue status (FSS scores) was observed at up to 3 time points (screening, week 12, week 24). Associations between fatigue and several clinical, laboratory, and imaging characteristics were examined by modeling FSS (or the dichotomized fatigued vs. non-fatigued status) as a function of potential risk factors using Generalized Estimating Equations (GEE) using the identity link (or logit link for the dichotomized "fatigue status" version (FSS≤4 vs. >4)) and data from all available timepoints. Baseline predictors of future fatigue (i.e., week 12 and 24) were evaluated using similar GEE models. Approximately 55 univariate associations were investigated for each model analysis while significance was assessed at the 0.05 level (and thus two to three spurious associations would be expected for each model analysis). Results should be interpreted cautiously within this multiplicity context.

Results

Sixty-four percent (95%CI, [55%, 72%]) of the 128 participants were fatigued according to their Fatigue Severity Score (FSS) at baseline (FSS>4), with 63% of 116 (95% CI, 53%, 72%) fatigued at 12 weeks, and 55% of 110 (95% CI, 46%, 65%) fatigued at week 24. Comparisons between fatigued and non-fatigued participants at baseline are summarized in Table 1. Age, CES-Depression Score, and Karnofsky Score were significantly different ($p<0.05$) between fatigued and non-fatigued groups at baseline. Specifically, fatigue participants were younger, had more depressive symptoms, and lower functioning than non-fatigued participants.

Table 2 displays MRS baseline characteristics by fatigue status. The fatigued group had lower basal ganglia Cr and Glx concentrations than the non-fatigued group. Furthermore, the basal ganglia MI/Cr of the fatigued group is higher than that of the non-fatigued group; however, the higher MI/Cr ratio is primarily due to the lower Cr concentration in the fatigued group (i.e., denominator metabolite), given that there is no significant difference in the MI concentration.

Concurrent characteristics associated with fatigue

Table 3 summarizes the results of the association estimates of clinical, immunological, and virological variables with concurrent: (1) fatigue status and (2) FSS score. The two approaches show similar associations between fatigue status and CES-D score, Karnofsky score, and years of education. In addition, there are significant associations between the FSS score with age, race, and Memorial Sloan Kettering (MSK) stages.

Table 4 shows the relationships between cognitive performance with fatigue status and FSS score. Although the association between fatigue and overall cognitive performance was not statistically significant, the association with Stroop color naming was.

Table 5 summarizes the relationship between brain metabolites with fatigue status and FSS. For brevity we report only those brain regions and metabolites (absolute values and ratios) that approached significance. The association between concurrent fatigue and basal ganglia Cr approached significance but the relationship was weaker than that observed in the baseline comparison (Table 2). A significant positive association was found between FSS score and NAA/Cr in the centrum semi-ovale. This is counter intuitive as we would expect an opposite relationship. However, it should be noted that being a ratio, it is influenced by Cr concentration and in this case the Cr estimate is negative. Furthermore, the association between FSS score and NAA was not significant. The relationship between dichotomized fatigue and NAA/Cr was also not significant.

Concurrent fatigue and higher mid-frontal Cho/Cr ratio was the strongest association found. However, as above for NAA, the association between Cho absolute concentration and concurrent fatigue was not statistically significant.

Association between baseline characteristics and future fatigue status

In Table 6, we summarize the associations that approached significance. The analyses using fatigue status and FSS score yielded similar associations between future fatigue

Table 1 Demographic and clinical characteristics at baseline by fatigue status

		Total	Fatigue status		*p* Value
			Non-fatigued	Fatigued	
Age (years)	*N*	128	46	82	0.011[a]
	Median (IQR)	45 (41.5, 52)	48 (43, 54)	44 (41, 50)	
Education (years)	*N*	128	46	82	0.053[a]
	Median (IQR)	13 (12,16)	12 (11, 15)	14 (12, 16)	
Gender, *N* (%*N*)	Male	112 (88%)	41 (89%)	71 (87%)	0.785[b]
	Female	16 (13%)	5 (11%)	11 (13%)	
Race/ethnicity, *N* (%*N*)	White Non-Hispanic	65 (51%)	19 (41%)	46 (56%)	0.264[c]
	Black Non-Hispanic	46 (36%)	19 (41%)	27 (33%)	
	Other	17 (13%)	8 (17%)	9(11%)	
MSK stage, *N* (%*N*)	Equivocal/ subclinical	44 (34%)	19 (41%)	25 (30%)	0.103[d]
	Mild	71 (55%)	25 (54%)	46 (56%)	
	Moderate	13 (10%)	2 (4%)	11 (13%)	
FSS score	*N*	128	46	82	<0.001[a]
	Median (IQR)	4.67 (3.44, 5.78)	2.78 (2.33, 3.56)	5.44 (4.75, 6.22)	
CD4+ count (mm^3)	*N*	120	44	76	0.963[a]
	Median (IQR)	425.5 (261.5, 691.5)	443.5 (268,649)	419 (225, 729)	
Plasma HIV RNA (copies/ml), *N* (%*N*)	>50	54 (43%)	19 (41%)	35 (43%)	0.854[b]
	≤50	73 (57%)	27 (59%)	46 (57%)	
CSF HIV RNA (copies/ml), *N* (%*N*)	>50	22 (26%)	12 (34%)	10 (20%)	0.208[b]
	≤50	63 (74%)	23 (66%)	40 (80%)	
ART usage	*N* (%)	122 (95)	42 (91)	80 (98)	0.187[b]
NRTI usage	*N* (%)	118 (92)	41(89)	77 (94)	0.494[d]
CES-D scale score	*N*	127	46	81	<0.001[a]
	Median (IQR)	19 (12, 29)	14.5 (7, 22)	24 (17, 34)	
Karnofsky scale score	*N*	127	45	82	0.032[a]
	Median (IQR)	80 (80,90)	90 (80, 90)	80 (80,90)	
NPZ-8	*N*	128	46	82	0.704[a]
	Median (IQR)	−0.95 (−1.55, −0.51)	−0.92 (−1.46, −0.48)	−0.96 (−1.57, −0.52)	

[a] Kruskal–Wallis test

[b] Fisher's Exact test

[c] Exact Test for R×C Tables

[d] Score Test for Ordinal Categorical Data

and baseline FSS and CES-D scores, years of education, Stroop color naming, and baseline fatigue status. Slight differences were present between the two approaches with Stroop interference (significant association with fatigue status but not with FSS score) and Karnofsky score and race (significant associations only with FSS score). None of the baseline brain metabolites concentrations were significantly associated with future fatigue status.

Discussion

The prevalence of fatigue in this cohort, selected on the basis of cognitive impairment, was within the range of fatigue previously reported in unselected cohorts (Darko et al. 1992; Ferrando et al. 1998; Phillips et al. 2004; Breitbart et al. 1998; Justice et al. 1999; Perkins et al. 1995; Voss 2005; Sullivan and Dworkin 2003). This longitudinal study suggests not only that fatigue persists during the 24-week follow-up but also that participants with more severe fatigued at baseline, tend to be even more severely fatigued at follow-up visits.

Several factors were associated with fatigue. Consistent with previous studies, depressive mood showed a strong relationship with fatigue, and depressive mood was also a predictor of future fatigue status. Fatigue and depression share common symptomatology and potentially common CNS pathways which inevitably lead to an overlap of these two conditions.

We also observed that younger and more educated patients tend to report more fatigue symptoms than older and less-educated patients. One possible explanation is that

Table 2 Baseline neuroimaging characteristics by fatigue status

		Fatigue Status		Estimate and 95% CI for shift parameters (non-fatigued–fatigued)	*p* Value[a]
		Non-fatigued	Fatigued		
Basal ganglia	*N*	20	24		
	Cr	8.84 (8.28, 9.17)	7.86 (7.09, 8.46)	0.93 (0.38, 1.48)	0.002
	N	25	35		
	NAA	12.17 (10.76, 13.46)	11.48 (10.12, 14.39)	0.45 (−0.92, 1.68)	0.403
	NAA/Cr	1.39 (1.22, 1.63)	1.41 (1.31, 1.71)	−0.08 (−0.23, 0.08)	0.284
	N	25	35		
	Cho	2.17 (1.98, 2.39)	2.17 (1.98, 2.31)	0.03 (−0.15, 0.23)	0.715
	Cho/Cr	0.23 (0.22, 0.27)	0.26 (0.24, 0.30)	−0.02 (−0.04, 0.00)	0.102
	N	25	35		
	MI	4.90 (4.14, 6.17)	5.52 (4.64, 6.36)	−0.51 (−1.38, 0.24)	0.206
	MI/Cr	0.58 (0.45, 0.70)	0.70 (0.60, 0.82)	−0.12 (−0.22, −0.01)	0.032
	N	25	35		
	Glx	18.00 (16.67, 20.16)	16.33 (13.53, 19.09)	1.87 (0.05, 4.19)	0.047
	Glx/Cr	1.95 (1.88, 2.27)	2.07 (1.75,2.25)	0.00 (−0.19, 0.20)	0.976
Centrum semi-ovale	*N*	20	26		
	Cr	8.15 (7.06, 9.22)	8.09 (7.24, 8.78)	0.13 (−0.63, 0.93)	0.731
	N	25	35		
	NAA	13.97 (12.39, 14.78)	13.95 (12.64, 14.88)	0.09 (−1.01, 0.99)	0.938
	NAA/Cr	1.68 (1.54, 1.98)	1.76 (1.65, 1.95)	−0.07 (−0.21, 0.08)	0.382
	N	25	35		
	Cho	2.75 (2.44, 3.05)	2.65 (2.33, 3.18)	0.00 (−0.28, 0.24)	1.000
	Cho/Cr	0.34 (0.31, 0.38)	0.35 (0.33, 0.37)	−0.01 (−0.04, 0.01)	0.386
	N	25	35		
	MI	7.47 (6.32, 8.69)	7.07 (6.19, 8.03)	0.24 (−1.15, 1.36)	0.621
	MI/Cr	0.92 (0.78, 1.06)	0.88 (0.77, 1.12)	−0.03 (−0.17, 0.11)	0.668
	N	25	35		
	Glx	15.75 (12.99, 17.28)	13.95 (12.70, 15.38)	0.96 (−0.80, 3.07)	0.296
	Glx/Cr	1.83 (1.59, 2.03)	1.88 (1.62, 2.03)	−0.02 (−0.17, 0.14)	0.776
Mid-frontal gray matter	*N*	18	21		
	Cr	9.37 (8.08, 10.90)	9.52 (8.61, 10.93)	−0.32 (−1.51, 0.97)	0.622
	N	25	35		
	NAA	12.59 (11.54, 14.22)	12.46 (12.24, 13.45)	0.07 (−1.15, 1.50)	0.877
	NAA/Cr	1.38 (1.27, 1.50)	1.42 (1.27, 1.48)	0.02 (−0.08, 0.12)	0.726
	N	25	35		
	Cho	2.09 (1.80, 2.30)	2.13 (1.96, 2.41)	−0.08 (−0.36, 0.19)	0.632
	Cho/Cr	0.22 (0.21, 0.25)	0.22 (0.21, 0.25)	−0.01 (−0.02, 0.01)	0.536
	N	25	35		
	MI	6.27 (5.48, 8.31)	7.41 (6.46, 8.13)	−0.78 (−2.05, 0.54)	0.181
	MI/Cr	0.76 (0.62, 0.83)	0.76 (0.71, 0.83)	−0.05 (−0.14, 0.02)	0.205
	N	25	35		
	Glx	20.53 (19.49, 21.68)	18.67 (15.53, 21.82)	1.67 (−1.10, 4.32)	0.175
	Glx/Cr	2.23 (1.88, 2.36)	2.07 (1.76, 2.34)	0.08 (−0.09, 0.28)	0.370

Values are median (interquartile range) unless otherwise stated.

[a] Kruskal–Wallis test

Table 3 Concurrent clinical, immunological, and virologic associations with fatigue status and FSS score

Variable	Fatigue vs. no fatigue			FSS score		
	OR estimate	95% CI	*p* Value	Estimate	95% CI	*p* Value
Age/10 (years)	0.750	0.517; 1.089	0.131	−0.32	−0.61; −0.03	0.044
Gender, female (vs. male)	0.537	0.135; 2.133	0.377	−0.147	−0.852; 0.559	0.684
Race, Black Non-Hispanic (vs. White Non-Hispanic)	0.822	0.371; 1.823	0.630	−0.534	−1.001; −0.067	0.025
Race, other (vs. White Non-Hispanic)	1.076	0.336; 3.445	0.901	−0.426	−1.131; 0.28	0.237
Years of education/4 (Years)	1.689	1.114; 2.562	0.014	0.416	0.152; 0.676	0.006
Weight/20 (lbs)	1.151	0.962; 1.377	0.124	0.1	−0.02; 0.22	0.097
Karnofsky score/10	0.708	0.531; 0.943	0.018	−0.29	−0.52; −0.06	0.016
CES-D score/10	2.347	1.853; 2.973	<0.001	0.67	0.54; 0.79	<0.001
MSK stage, ≥1 vs. 0.5	1.992	0.811; 4.895	0.133	0.508	0.154; 0.861	0.005
ART, no (vs. yes)	1.000	0.510; 1.959	1.000	0.006	−0.234; 0.246	0.961
NRTI, no (vs. yes)	1.000	0.488; 2.049	1.000	−0.023	−0.27; 0.224	0.855
CD4+ count/50 (mm^3)	0.986	0.939; 1.035	0.578	0	−0.05; 0	0.441
Plasma HIV RNA (copies/ml) ≤50 vs. >50	0.502	0.217; 1.165	0.109	−0.251	−0.580; 0.079	0.136
CSF HIV RNA (copies/ml) ≤50 (vs. >50)	1.572	0.781; 3.165	0.205	−0.122	−0.663; 0.420	0.660

younger and more educated subjects have higher functional expectations than older and less-educated subjects and therefore may be more affected by fatigue symptoms.

While fatigued and non-fatigued subjects did not differ at baseline in terms of cognitive performance, baseline performance on the Stroop test, which is designed to assess frontal lobe functions, was a predictor of fatigue. Furthermore, patients with higher MSK staging reported more concurrent fatigue during the study period. However, it should be noted that MSK staging and overall cognitive performance as assessed by NPZ summary scores differ as MSK incorporates both cognitive and functional evaluations. In this regard, the association between fatigue and MSK staging is consistent with the association between decline in functional activity, as measured by the Karnofsky score, and fatigue. Karnofsky score also predicted future fatigue status.

Another potential cause for fatigue might be use of antiretroviral drugs. In a large cohort of HIV-negative and HIV-positive women, Silverberg et al. (2004) showed that more HIV-infected women reported fatigue compared to HIV negative women, but there was no substantial difference in fatigue between HIV-infected HAART-naïve and HAART-stable patients. However, there may be a

Table 4 Concurrent neuropsychological associations with fatigue status and FSS score

Variable	Fatigue vs. no fatigue			FSS score		
	OR estimate	95% CI	*p* Value	Estimate	95% CI	*p* Value
Symbol digit	0.987	0.791;1.231	0.905	−0.073	−0.242; 0.095	0.409
Trail-making B	0.937	0.722; 1.215	0.622	−0.11	−0.314; 0.094	0.338
Rey Auditory Verbal Learning Test	0.905	0.729; 1.125	0.368	−0.098	−0.255; 0.06	0.237
Trail-making A	0.996	0.774; 1.281	0.972	−0.036	−0.210; 0.138	0.687
Sequential Reaction Time	0.960	0.774; 1.189	0.706	−0.039	−0.92; 0.114	0.624
Choice Reaction Time	0.919	0.768; 1.100	0.358	−0.06	−0.192; 0.072	0.361
Grooved Pegboard Dominant Hand	0.937	0.781; 1.124	0.482	−0.079	−0.217; 0.059	0.272
Grooved Pegboard Non-dominant	0.946	0.786; 1.138	0.554	−0.065	−0.206; 0.076	0.371
Timed Gait	0.876	0.715; 1.073	0.200	−0.111	−0.261; 0.038	0.105
STROOP Color Naming	0.703	0.544; 0.907	0.007	−0.227	−0.427; −0.028	0.037
STROOP Interference Trial	0.817	0.616; 1.082	0.158	−0.126	−0.344; 0.092	0.243
STROOP Word Reading	0.877	0.691; 1.113	0.281	−0.057	−0.246; 0.131	0.552
NPZ-8	0.881	0.648; 1.199	0.421	−0.162	−0.41; 0.087	0.197

Table 5 Concurrent brain metabolite associations with fatigue status and FSS score

Variable	Fatigue vs. no fatigue			FSS score		
	OR estimate	95% CI	*p* Value	Estimate	95% CI	*p* Value
Basal ganglia, Cr	0.789	0.617;1.009	0.059	−0.166	−0.387; 0.055	0.164
Centrum semi-ovale, Cr	0.950	0.699; 1.292	0.744	−0.033	−0.277; 0.212	0.793
Centrum semi-ovale, NAA	1.022	0.824; 1.267	0.846	0.107	−0.075; 0.289	0.262
Centrum semi-ovale, NAA/Cr	2.494	0.574; 10.830	0.223	1.166	0.129; 2.202	0.042
Mid-frontal–Voxel, Cr	0.952	0.750; 1.207	0.684	0.033	−0.161; 0.228	0.738
Mid-frontal–voxel, Cho	1.319	0.628; 2.770	0.464	0.463	−0.041; 0.967	0.156
Mid-frontal–voxel, Cho/Cr[a]	2.065	1.162; 3.669	0.013	6.249	1.853; 10.646	0.023

[a] Scaled such that interpretation is per 0.1 unit increment for the Odds Ratio (OR) of fatigue vs. no-fatigue

mechanistic link with at least one class of antiretroviral drugs, nucleoside reverse transcriptase inhibitors (NRTIs). NRTIs have been associated with mitochondrial toxicities as indicated by the occurrence of lactic acidosis, hepatic steatosis, pancreatitis, myopathy, and neuropathy (Carr and Cooper 2000; Dalakas et al. 2001; Brinkman et al. 1999; Kakuda et al. 1999). Protease inhibitors can also be associated with mitochondrial abnormalities (Kim et al. 2007). Increased fatigue is a typical presentation of mitochondrial disorders and may be present even when there is minimal clinical evidence in the affected organ (Cote et al. 2002; Delgado et al. 2001; Carr et al. 2000). NRTIs are known to inhibit mitochondrial DNA polymerase-γ (pol-γ) leading to depletion of mitochondrial DNA (mtDNA). Interestingly, decreased mtDNA is also present in antiretroviral-naïve subjects (Cote et al. 2002) suggesting that mitochondrial toxicity is associated with HIV infection itself.

In this study, the proportion of subjects using NRTIs was very high, and did not differ between fatigued and non-fatigued groups.

Fatigue has also been associated with cytokine dysregulation. For example, some investigations in cancer and multiple sclerosis (MS) have implicated pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α in the pathogenesis of fatigue (Collado-Hidalgo et al. 2006; Kos et al. 2008; Heesen et al. 2006). Cytokine dysregulation is a common feature of HIV infection and its associated neurological complications (McArthur et al. 2005; Schifitto et al. 2005; Jones and Power 2006). However, patients on a stable antiretroviral regimen usually have only mild evidence of increased products of immune activation (McArthur et al. 2005; Clifford et al. 2002). We did not assess cytokines but patients were on a stable antiretroviral regimen and plasma and CSF HIV viral load, and CD4 count did not differ among fatigued and non-fatigued patients.

There is mounting evidence in other neurological disorders, such as MS, that disruption of the striatal–cortical or striatal–thalamic–cortical circuitry will predispose patients to fatigue (Chaudhuri and Behan 2000). A recent positron-emission tomography (PET) imaging study (Roelcke et al. 1997), using ^{18}F-fluorodeoxyglucose, revealed significant metabolic alteration in the lateral and medial prefrontal cortex, in the premotor cortex, putamen, and in the right supplementary motor area of fatigued MS

Table 6 Significant baseline associations with future fatigue status and FSS score

Variable	Fatigue vs. no fatigue			FSS score		
	Estimate	CI	*p* Value	Estimate	CI	*p* Value
FSS at baseline	1.949	1.513; 2.511	<0.001	0.54	0.41; 0.68	<.001
CES-D Score/10	1.732	1.265; 2.371	0.001	0.48	0.28; 0.68	<.001
Karnofsky Score/10	0.747	0.507; 1.099	0.138	−0.31	−0.61; −0.01	0.04
Years of Education/4 (Years)	1.848	1.118; 3.054	0.017	0.42	0.13; 0.71	0.01
Stroop color naming	0.622	0.435; 0.888	0.009	−0.24	−0.49; 0.01	0.09
Stroop interference trial	0.612	0.394; 0.951	0.029	−0.21	−0.55; 0.12	0.22
Stroop word reading	0.817	0.577; 1.155	0.252	−0.05	−0.29; 0.19	0.70
Non-fatigued (vs. fatigued) at baseline	4.667	0.995; 21.895	0.051	−1.30	−1.77; −0.82	<.001
Race Black Non-Hispanic (vs. White Non-Hispanic)	1.111	0.190; 6.492	0.907	−0.60	−1.14; −0.07	0.03

patients. There were also metabolic changes in the white matter extending from the rostral putamen toward the lateral head of the caudate nucleus. These findings are supported by a recent fMRI study (Deluca et al. 2008).

Additional support for basal ganglia dysregulation in fatigue states comes from fatigue associated with interferon-alpha treatment (Capuron et al. 2007).

Our findings that markers of energy metabolism (Cr concentration) and glutaminergic transmission (lower concentration of Glx) in the basal ganglia are associated with fatigue are in line with the above observations in other diseases. The Cr peak observed on ^{1}H MRS reflects the sum of creatine plus phosphocreatine, and the Glx peak represents the sum of glutamate plus glutamine. Since the high-energy phosphate metabolism, as well as the synthesis of glutamate via the TCA cycle, involves the mitochondria, reductions in the Cr and Glx concentrations suggest lower cellular energy levels in the basal ganglia of subjects with fatigue. One prior study found lower concentrations of basal ganglia Cr in a group of subjects with, but not in those without HIV-associated dementia (Chang et al. 2002), but the effect of fatigue was not evaluated specifically.

In summary, this study emphasizes that fatigue is common and persistent in HIV-positive subjects, and is associated with decreased functioning. A neuronal circuitry that involves striatal–cortical pathways may play an important role in HIV-associated fatigue, and may be amenable to therapeutic intervention. In this regard, therapeutic advances directed at fatigue may also benefit cognition and mood. A recent trial of modafinil that ameliorated fatigue and also improved mood and cognitive performance in HIV-infected individuals is consistent with this concept. (Rabkin et al. 2004; McElhiney et al. 2009; Rabkin et al. 2010).

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University of Washington, Seattle: C. Marra; S. Dunaway, M. Perrin;

University of Pennsylvania, Philadelphia: D. Kolson;

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