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Understanding the association between fatigue and neurocognitive functioning in patients with glioma: A cross-sectional multinational study

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Abstract

Background. Fatigue and neurocognitive impairment are highly prevalent in patients with glioma, significantly impacting health-related quality of life. Despite the presumed association between these two factors, evidence remains sparse. Therefore, we aimed to investigate this relationship using multinational data.

Methods. We analyzed data on self-reported fatigue and neurocognitive outcomes from postoperative patients with glioma from the University of California San Francisco ($n = 100$, UCSF) and Amsterdam University Medical Center ($n = 127$, Amsterdam UMC). We used multiple linear regression models to assess associations between fatigue and seven (sub)domains of neurocognitive functioning and latent profile analysis to identify distinct patterns of fatigue and neurocognitive functioning.

Results. UCSF patients were older (median age 49 vs. 43 years, $P = .002$), had a higher proportion of grade 4 tumors (32% vs. 18%, $P = .03$), and had more neurocognitive deficits ($P = .01$). While the number of clinically fatigued patients was similar between sites (64% vs. 58%, $P = .12$), fatigue and the number of impaired neurocognitive domains were not correlated ($P = .16$–$.72$). At UCSF, neurocognitive domains were not related to fatigue, and at Amsterdam UMC attention and semantic fluency explained only 4–7% of variance in fatigue. Across institutions, we identified four distinct patterns of neurocognitive functioning, which were not consistently associated with fatigue.

Conclusions. Although individual patients might experience both fatigue and neurocognitive impairment, the relationship between the two is weak. Consequently, both fatigue and neurocognitive functioning should be independently assessed and treated with targeted therapies.

Keywords

attention | brain neoplasms | cognition | fatigue | patient-reported outcome measures

Patients with glioma often experience a myriad of symptoms, of which fatigue and neurocognitive impairment are highly prevalent and equally burdensome.[1] Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and cancer treatment that is not proportional to recent activity and interferes with usual functioning.[2] Fatigue is a self-reported symptom, and approximately half of the patients with glioma report severe fatigue throughout the disease course, which is associated with reduced health-related quality of life (HRQoL).[3] Similarly, neurocognitive impairment, as assessed by neuropsychological testing, occurs in about half of the glioma patients and also negatively affects HRQoL, family life, and the ability to return to work.[4,5] In these patients, deficits in attentional functioning, information processing speed, and working memory are specifically prevalent.[4,5]

Despite the high prevalence of both fatigue and neurocognitive impairment in patients with glioma, their etiology remains poorly understood but is thought to be multifactorial. The tumor itself, as well as the effects of surgery, radiotherapy, and chemotherapy, have been implicated in the development of these symptoms.[6,7] Whereas demographic, biomedical, and psychosocial factors such as depression and anxiety have also been linked to the development and persistence of both fatigue and neurocognitive impairment.[8,9] Given the high prevalence and the complex and overlapping nature of these associated factors, it is often hypothesized that they are related.[10] A common theory is the cognitive coping hypothesis: when faced with a cognitively demanding task or situation, patients with neurocognitive impairment must increase mental effort to complete such a task, leading to depletion of mental resources and resulting in fatigue.[10,11]

While the independent association between fatigue and patient-reported neurocognitive functioning has been established in patients with glioma, the relation between fatigue and objective neurocognitive functioning assessed with neuropsychological testing is less clear.[12] Some studies on non-central nervous system cancer and neurological disorders report fatigue and neurocognitive functioning to be related, especially pertaining about domains of information processing speed and attention. For example, fatigued breast cancer patients have demonstrated slower information processing speed and impaired attention throughout the disease trajectory,[13] and impaired attention has also been implicated to contribute to the development of fatigue in patients with neurological disorders.[14]

However, evidence connecting fatigue and neurocognitive functioning in brain tumor patients is sparse and ambiguous. Studies in patients with lower-grade glioma on active surveillance report conflicting results. While one study found no association between fatigue severity and neurocognitive impairment,[12] another demonstrated worse performance on tests of attention, memory, and executive functioning among severely fatigued patients.[4] Similarly, in primary and metastatic brain cancer, one study found an association between fatigue severity and a summary measure of neurocognitive functioning,[15] while another identified fatigue to be associated with only a single test of information processing speed.[16] These discrepancies might be the result of challenges with replication and generalizability due to the lack of large datasets, as well as variations in used neuropsychological instruments and self-reported questionnaires.[17]

Moreover, most studies investigated neurocognitive domains in isolation instead of looking at patterns of functioning across neurocognitive domains in relation to fatigue. As such, a study in multiple sclerosis investigated how different patterns of neurocognitive functioning related to symptoms and medical factors. They found that patients who had both executive and attention impairments were significantly more fatigued compared to patients with other patterns of neurocognitive functioning.[18] Perhaps identifying patterns of neurocognitive deficits that are related to fatigue might also help us to better phenotype fatigue in glioma and counsel patients on their co-occurring symptoms.

A deeper understanding of the potential intersection between fatigue and neurocognitive functioning might help better assess and address symptoms in individual patients, ultimately facilitating the development of tailored treatment models. First, we aimed to study the relationship between self-reported fatigue and seven neurocognitive domains measured with comprehensive neuropsychological testing. Based on previous literature and the cognitive coping hypothesis, we hypothesized attention and information processing speed to be related to fatigue severity in patients with glioma, irrespective of demographic and medical characteristics. Second, we aimed to identify subgroups of patients with distinct patterns of neurocognitive functioning and analyze whether these patterns of neurocognitive functioning were associated with fatigue. Again, we hypothesized finding specific subgroups of patients with attention and information processing speed deficits to be associated with fatigue. To address problems with replications and ambiguous results across previous studies, we analyzed these questions in a separate Dutch and a separate Californian cohort and in a multinational dataset of the two combined.

Methods

In this retrospective observational study, we analyzed self-reported fatigue measures and neuropsychological test results collected from patients with glioma at two institutions: the University of California San Francisco (UCSF) hospital and Amsterdam University Medical Center (Amsterdam UMC). Ethical approval for the use of clinical data for research purposes was obtained from the respective institutional review boards. At UCSF, the need to obtain informed consent was waived (21-34753), and at Amsterdam UMC, written informed consent was obtained from the patients (METc VUmc 2010.126). This study was conducted in accordance with the Declaration of Helsinki.

For the current study, we included adult patients with histologically confirmed WHO grade 2, 3, or 4 glioma who had undergone neuropsychological testing and completed a fatigue questionnaire at the time of testing. Testing was always performed after surgery but there was no limit on time since surgery. Demographics, tumor, and treatment characteristics were collected. Tumor types were classified according to the WHO 2021 classification or the WHO 2016 classification if not all histological or molecular markers were available.[19,20]

Data Collection UCSF

Since the launch of the Neurocognitive Clinic at the UCSF BrainTumor Center in 2018, neuropsychological testing has been performed upon referral for neurocognitive rehabilitation. As part of neuropsychological testing, patients routinely conducted the 14-item Fatigue Symptom Inventory (FSI).[21] This questionnaire addresses generic aspects of fatigue, as well as intensity, duration, and interference in the past week. It was validated in people with cancer with good validity and reliability.[21,22] The *FSI global score* is a

sum score of the whole questionnaire and broadly captures different dimensions of fatigue. The first three items of the questionnaire assess fatigue severity, making up the *FSI fatigue severity* subscale. An *FSI fatigue severity* of 3 or greater indicates clinically meaningful fatigue.[23]

Neuropsychological testing was conducted in English by two licensed neuropsychologists (CWJ and MB) using standardized tests with published normative data. The neuropsychological test battery included the Trail Making Test, Digit Span Test, Oral Symbol Digit Modalities Test, Hopkins Verbal Learning Test, Animal Naming Test—and when indicated other tests. Raw test scores were corrected for age, sex, and education based on published normative data and converted to *z*-scores. Educational level was assessed with years of education. Individual test scores were grouped into six neurocognitive (sub)domains: attention, information processing speed, mental flexibility, semantic fluency, verbal learning, verbal memory, and visual search (Table 1).[34,35]

Data Collection Amsterdam UMC

At Amsterdam UMC since 2010, neuropsychological testing has been routinely performed one year after elective tumor resection with awake mapping. Two previously published manuscripts also used parts of the Amsterdam UMC data, however, these manuscripts did not evaluate neurocognitive functioning.[9,36] As part of neuropsychological testing, all patients conduct the 20-item Checklist Individual Strength (CIS) at home one week before neuropsychological testing. This reliable questionnaire is widely validated in patients with cancer and evaluates different aspects of fatigue (fatigue severity, concentration problems, motivation, and activity).[24,37] The *CIS global score* is a sum score of the whole questionnaire and broadly captures different dimensions of fatigue. The *CIS fatigue severity subscale* consists of seven items and addresses fatigue severity. Clinically meaningful fatigue is defined as a score of ≥27 on the *CIS fatigue severity* subscale.[24,38]

Neuropsychological testing was conducted in Dutch by a trained test assistant supervised by a licensed neuropsychologist (MK). The neuropsychological test battery included the Stroop Color Word test, Letter Digit Substitution Test, Rey Auditory Verbal Learning Test, Animal Naming Test, Concept Shifting Test—and, when indicated, other tests. Again, raw scores were corrected for age, sex, and education based on published normative data and converted to *z*-scores. Educational level was assessed with the Verhage scoring system that comprised an 8-point scale, ranging from not having finished primary education to university level.[39] Individual test scores were grouped into six neurocognitive (sub)domains (Table 1).

Combining Two Datasets

Data from the two institutions were combined into a single dataset. The UCSF *FSI global score* and the Amsterdam UMC *CIS global score* were rescored so lower values corresponded to a higher symptom burden and rescaled and combined as one *global fatigue* variable. Following the same procedure, the *FSI fatigue severity* and *CIS fatigue severity* were combined as one *fatigue severity* variable. There are no studies directly comparing the psychometric properties of the FSI and CIS. However, studies comparing the FSI and CIS to the Medical Outcomes Study 36-Item Short Form Vitality Scale found evidence of divergent validity between both questionnaires and the Vitality Subscale.[40,41] Since there is a substantial overlap in content between the two questionnaires and their intended use, we considered the *FSI global score* and the *CIS global score* both as measures of "global fatigue," and the *FSI fatigue severity* and *CIS fatigue severity* as measures of "fatigue severity." Similarly, *z*-scores of comparable neurocognitive (sub)domains of both institutions were combined.[34,35] See Table 1.

Statistical Analyses

Analyses were conducted using RStudio (version 4.2.1). Results were considered statistically significant for *P* values <.05. Demographics, tumor and treatment characteristics, fatigue measures and neurocognitive domains, were compared between the two institutions using Mann–Whitney U tests for continuous variables and Chi-square tests for categorical variables. A *z*-score of <–1.5 standard

Table 1. Fatigue and Neurocognitive (Sub)Domains.

	University of California San Francisco	Amsterdam University Medical Center
Global fatigue	Fatigue Symptom Inventory global score[21]	Checklist Individual Strength global score[24]
Fatigue severity	Fatigue Symptom Inventory fatigue severity[21]	Checklist Individual Strength fatigue severity[24]
Attention	Digit Span Test—forward[25]	Stroop Color Word Test—color[26] Stroop Color Word Test—word[26]
Information processing speed	Oral Symbol Digit Modalities Test—60 s[27]	Letter Digit Substitution Test—oral, 60 s[28]
Mental flexibility	Trail Making Test B—digits and letters[29]	Concept Shifting Test C—digits and letters[30]
Semantic fluency	Animal Naming Test—60 s[31]	Animal Naming Test—60 s[32]
Verbal learning	Hopkins Verbal Learning Test—sum trial 1–3[33]	Auditory Verbal Learning Test—sum trial 1–5[28]
Verbal memory	Hopkins Verbal Learning Test—delayed recall[33]	Auditory Verbal Learning Test—delayed recall[28]
Visual scanning	Trail making Test A—digits[29]	Concept Shifting Test A–digits[30]

deviations below zero was used as the cut-off for neuropsychological impairment.

Relation between fatigue and neurocognitive functioning.—We investigated whether global fatigue and fatigue severity were correlated with the number of impaired neurocognitive domains with Spearman-rank tests. The main analysis consisted of multiple linear regression models to investigate whether neurocognitive functioning could explain variability in global fatigue and fatigue severity. To do so, we took three steps, for each of the two institutions. First, we used univariate linear regression models with either global fatigue or fatigue severity as the dependent variable and one of the seven neurocognitive domains, sex, tumor grade, histology, prior chemotherapy, and prior radiotherapy as the independent variable (step 1). The variables that were significantly associated with the fatigue variable were included as independent variables in a multiple linear regression model (step 2). We then performed backward selection based on the Akaike Information Criterion to find the best-fitting model (step 3).[42] This criterion quantifies how well a model fits the data and compares the goodness of fit between models. The presented *multiple* R^2 values represented the amount of variance in fatigue that the neurocognitive domains could explain. These analyses were performed for each of the two institutions separately. For each analysis, if data on an independent measure was missing, the patient was excluded from that specific analysis. For example, if for one patient data on attention was missing, this patient would be excluded from the univariate analysis on attention, but not from other univariate analyses.

Latent profile analysis.—To identify patterns of neurocognitive functioning and relate these to fatigue, we conducted a latent profile analysis for each of the two institutions.[43,44] These analyses included the seven neurocognitive domains and global fatigue. Models with 2–4 classes were examined and the optimal models were selected based on an analytic hierarchy process combining several fit indices.[43] Only patients with complete neurocognitive data were included. Demographic and clinical characteristics were compared between the identified subgroups with distinct patterns of neurocognitive functioning using Kruskal–Wallis, Dunn, and Chi-square tests.

Sensitivity analyses using the combined dataset.—To assess the robustness of the results, we performed a similar multiple linear regression model in the combined dataset. Additionally, we performed the same analysis in the combined data, after excluding patients with grade 4 tumors, to ensure tumor grade was not driving the results. We also conducted a latent profile analysis in the combined dataset, using the same statistical approach.

Results

Patient Characteristics

A total of 227 postoperative patients with glioma were included: 100 patients from UCSF and 127 patients from Amsterdam UMC. There were marked differences in demographic and medical characteristics between the two institutions. UCSF patients were significantly older (median 49 years vs. 43 years, $P = .002$); had a higher proportion of malignant tumors (grade 4 tumors 32% vs. 18%, $P = .03$); and years between diagnosis and testing was greater (2.7 vs. 1.3 years, $P < .001$) compared to Amsterdam UMC. Also, a higher proportion of UCSF patients had chemotherapy (79% vs. 41%, $P < .001$) and radiotherapy (75% vs. 59%, $P = .02$) compared to Amsterdam UMC (see Table 2). There were no statistically significant differences in patient characteristics between the patients with and without missing data (no missing data = 193, any missing data = 34, results not shown).

Prevalence of Fatigue and Neurocognitive Impairments

While patients at UCSF had more neurocognitive impairments compared to Amsterdam UMC, there was no difference in fatigue between the two institutions. The prevalence of clinically meaningful fatigue was not statistically different between the two cohorts (64% at UCSF vs. 58% at Amsterdam UMC, $P = .12$, Table 3, Supplementary Figures 1 and 2). A higher proportion of UCSF patients exhibited neurocognitive impairments in at least one neurocognitive domain (86% vs. 71%, $P = .01$, see Table 3), as well as impairments in information processing speed (59% vs. 33%, $P < .001$), semantic fluency (38% vs. 26%, $P = .04$), verbal learning (45% vs. 28%, $P = .006$), verbal memory (45% vs. 26%, $P = .002$), and visual scanning (32% vs. 17%, $P = .01$), compared to Amsterdam UMC patients.

Minimal Associations Between Fatigue and Neurocognitive Impairment

First, we investigated if fatigue was correlated with the number of impaired domains, which it was not (UCSF global fatigue: rho = –0.07, $P = .49$, UCSF fatigue severity: rho = –0.04, $P = .70$, Amsterdam UMC global fatigue: rho = 0.16, $P = .07$, Amsterdam UMC fatigue severity: rho = 0.13, $P = .16$). Second, we investigated which neurocognitive domains and demographic and tumor- and treatment-related factors were associated with global fatigue and fatigue severity. At UCSF, none of the neurocognitive domains were significantly associated with either fatigue variable (see Table 4 and Figure 1). Only grade 2 tumors, compared to grade 3 and 4, were associated with higher levels of global fatigue. At Amsterdam UMC, attention and impaired semantic fluency were significantly associated with global fatigue and fatigue severity, with limited estimated effects (see Table 4 and Figure 1). These neurocognitive domains explained only 7% of the variance in global fatigue (*multiple* $R^2 = 0.07$) and 4% of the variance in fatigue severity (*multiple* $R^2 = 0.04$). Similar analyses were conducted for the combined dataset, yielding comparable results (see Supplementary Tables 1 and 2).

Distinct Patterns of Neurocognitive Functioning are not Related to Fatigue

To identify distinct patterns of fatigue and neurocognitive functioning, we conducted a latent profile analysis

Table 2. Patient Characteristics

	UCSF (*n* = 100)	Amsterdam UMC (*n* = 127)	*P* value*	Combined (*n* = 227)
Age at assessment, median [IQR]	49.3 [40.7, 61.1]	43.0 [36.0, 54.0]	**.002**	45.9 [38.0, 57.6]
Sex, *n* (%)			.48	
Male	63 (63.0%)	77 (60.6%)		140 (61.7%)
Female	36 (36.0%)	50 (39.4%)		86 (37.9%)
Non-binary	1 (1.0%)	0 (0%)		1 (0.4%)
Level of education[&], *n* (%)	Years	Verhage scale		
	9–11 years: 7 (7.0%)	Low (1–4): 30 (23.6%)	NA	
	12 years: 13 (13.0%)	Middle (5): 38 (29.9%)		
	13 + years: 80 (80.0%)	High (6–7): 59 (46.5%)		
Handedness, *n* (%)			.97	
Left	13 (13.0%)	16 (12.6%)		29 (12.8%)
Right	85 (85.0%)	109 (85.8%)		194 (85.5%)
Ambidextrous	2 (2.0%)	2 (1.6%)		4 (1.8%)
Tumor type, *n* (%)			**<.001**	
Oligodendroglioma	32 (32.0%)	50 (39.4%)		82 (36.1%)
Astrocytoma, IDH mutated	38 (38.0%)	42 (33.1%)		80 (35.2%)
Astrocytoma, IDH status unknown	4 (4.0%)	11 (8.7%)		15 (6.6%)
Oligoastrocytoma, IDH mutated[*]	0 (0%)	2 (1.6%)		2 (0.9%)
Oligoastrocytoma, IDH-status unknown[*]	3 (3.0%)	2 (1.6%)		5 (2.2%)
Glioblastoma, IDH wildtype	21 (21.0%)	6 (4.7%)		27 (11.9%)
Glioblastoma, IDH status unknown	2 (2.0%)	14 (11.0%)		16 (7.0%)
Tumor hemisphere, *n* (%)			.24	
Left	56 (56.0%)	74 (58.3%)		130 (57.3%)
Right	37 (37.0%)	50 (39.4%)		87 (38.3%)
Both/other	7 (7.0%)	3 (2.4%)		10 (4.4%)
Tumor location, *n* (%)			.49	
Frontal	59 (59.0%)	68 (53.5%)		127 (55.9%)
Non-frontal	41 (41.0%)	59 (46.5%)		100 (44.1%)
WHO grade, *n* (%)			***.03***	
2	36 (36.0%)	65 (51.2%)		101 (44.5%)
3	32 (32.0%)	39 (30.7%)		71 (31.3%)
4	32 (32.0%)	23 (18.1%)		55 (24.2%)
Years since diagnosis, median [IQR]	2.7 [0.2, 24.3]	1.3 [0.2, 28.0]	**<.001**	1.4 [0.2, 28.0]
Prior chemotherapy, *n* (%)	79 (79.0%)	52 (40.9%)	**<.001**	131 (57.7%)
Years since most recent chemotherapy^, median [IQR]	2.4 [24.2, 0.01]	1.0 [9.2, 0.0]	**<.001**	1.2 [24.2, 0.0]
Prior radiotherapy, *n* (%)	75 (75.0%)	75 (59.1%)	**.017**	150 (66.6%)
Years since most recent radiotherapy^, median [IQR]	2.4 [23.9, 0.16]	1.14 [27.9, 0.0]	**.001**	1.2 [27.9, 0]

*Mann–Whitney U tests were used for continuous variables and Chi-square tests for categorical variables. *P* values <.05 are considered statistically significant and presented in bold.
[&]At UCSF, educational level was assessed with years of education and at Amsterdam UMC with the Verhage scoring system.[39]
*Tumor type was classified according to the WHO 2021 classification or the WHO 2016 classification when molecular information was not available.[19,20]
^In these variables, only patients who had radiotherapy or chemotherapy prior to neuropsychological assessment are represented.
Abbreviations: Amsterdam UMC, Amsterdam University Medical Center; *n*, number; NA, not applicable; SD, standard deviation; UCSF, University of California San Francisco.

Table 3. Fatigue and Neurocognitive Functioning

	UCSF (*n* = 100)	Amsterdam UMC (*n* = 127)	*P* value*	Combined (*n* = 227)
FSI global score, median [IQR]	3.81 [1.67–5.62]	-	NA	-
FSI fatigue severity, median [IQR]	4.17 [2.67, 5.33]	-	NA	-
CIS global score, median [IQR]	–	75 [48.50, 95.50]	NA	-
CIS fatigue severity, median [IQR]	–	30.0 [19.0, 39.5]	NA	-
Number of clinically fatigued patients (%)*	64 (64.0%)	74 (58.3%)	.12	138 (60.8)
Global fatigue *z*-score	–0.05 [–0.84, 0.89]	–0.18 [–0.79, 0.75]	.60	–0.13 [–0.84, 0.86]
Fatigue severity *z*-score	–0.14 [–0.72, 0.60]	–0.06 [–0.78, 0.77]	.82	–0.06 [–0.74, 0.77]
Number of patients with impairment in at least 1 neurocognitive domain	86 (86%)	90 (70.9%)	**.01**	176 (77.5%)
Impaired attention, *n* (%) < –1.5 SD	18 (18.0%)	37 (29.1%)	.09	55 (24.2%)
Impaired IPS, *n* (%) < –1.5 SD	59 (59.0%)	42 (33.1%)	**<.001**	101 (44.5%)
Impaired mental flexibility, *n* (%) < –1.5 SD	42 (42.0%)	39 (30.7%)	.16	81 (35.7%)
Impaired semantic fluency, *n* (%) < –1.5 SD	38 (38.0%)	33 (26.0%)	**.04**	71 (31.3%)
Impaired verbal learning, *n* (%) < –1.5 SD	45 (45.0%)	35 (27.6%)	**.01**	80 (35.2%)
Impaired verbal memory, *n* (%) < –1.5 SD	45 (45.0%)	33 (26.0%)	**.002**	78 (34.4%)
Impaired visual scanning, *n* (%) < –1.5 SD	32 (32.0%)	21 (16.5%)	**.01**	53 (23.3%)

*Mann–Whitney U tests were used for continuous variables and Chi-square tests for categorical variables. *P* values <.05 are considered statistically significant and presented in bold.
*Number of clinically fatigued people based on the cut-off score for the FSI fatigue severity at UCSF and the CIS fatigue severity at Amsterdam UMC.
Abbreviations: Amsterdam UMC, Amsterdam University Medical Center; IPS, information processing speed; *n*, number; NA, not applicable; SD, standard deviation; UCSF, University of California San Francisco.

including fatigue and neurocognitive data for each of the two hospitals and the combined dataset (UCSF = 82, Amsterdam UMC = 111, combined = 193). Across cohorts, we identified four subgroups of patients with a distinct pattern of neurocognitive functioning: (1) neurocognitive preservation, (2) learning and memory impairments, (3) information processing speed and mental flexibility impairments, and (4) multi-domain neurocognitive impairments (see Figure 2 and Supplementary Figure 3). At UCSF, fatigue did not play a role in discriminating between the four profiles ($P = .69$), while at Amsterdam UMC, patients with learning and memory impairments (2) had less fatigue, compared to the other domains ($P = .004$), see Supplementary Tables S3 and S5. To understand whether these profiles were robust across institutions, the same analysis was conducted for the combined dataset and, again, resulted in similar patterns of neurocognitive functioning, without a significant difference in fatigue between subgroups ($P = .64$, Supplementary Figure 3 and Supplementary Tables 4 and 6).

Furthermore, we compared patient characteristics of the 4 subgroups (see Supplementary Tables 3 and 5) and found that patients with neurocognitive preservation or learning and memory impairments were younger ($P = .001$), while patients with multi-domain impairments or information processing speed and mental flexibility impairments had a higher proportion of malignant tumors ($P = .038$). Moreover, patients with multi-domain impairments had higher proportions of left-sided tumors, and more often had chemotherapy and/or radiotherapy prior to assessment ($P \leq .01$).

Discussion

In this study, we analyzed self-reported fatigue and neurocognitive testing data collected in a multinational cohort of postoperative patients with glioma and found that while both fatigue and neurocognitive impairment were highly prevalent in both populations, there is only limited overlap between the two. Attention and semantic fluency impairments showed weak associations with fatigue and explained only a small proportion of variance in global fatigue and fatigue severity. Additionally, different patterns of neurocognitive functioning were not consistently associated with fatigue, limiting the clinical application of identifying cognitive subgroups to understand fatigue in these patients. These findings emphasize the importance of conducting comprehensive assessments of both fatigue and neurocognitive functioning. Clinically, information on neurocognitive functioning does not automatically contribute to understanding or quantifying fatigue in the individual patient, and vice versa.

While the literature on the link between self-reported fatigue and objective neurocognitive functioning is sparse in glioma, studies in other disease populations have produced mixed results. Three recent systematic reviews in epilepsy, multiple sclerosis, and different types of cancer and inflammatory disease concluded there is either insufficient or no evidence to draw solid conclusions regarding the relationship between fatigue and objective neurocognitive functioning.[45,46] Moreover, smaller studies

Table 4. Associations Between Fatigue and Neurocognitive Functioning

	UCSF						Amsterdam UMC					
	FSI global fatigue			FSI fatigue severity			CIS global fatigue			CIS fatigue severity		
	Step 1											
Variable	*N*^	Estimated effect	*P* value	*N*^	Estimated effect	*P* value	*N*^	Estimated effect	*P* value	*N*^	Estimated effect	*P* value
Attention	97	0.13	.53	97	−0.02	.92	126	−5.73	**.01**	126	−2.26	**.03**
Impaired attention		0.78	.85		0.12	.75		9.69	**.01**		3.66	**.04**
IPS	95	0.17	.49	95	0.04	.84	120	−3.08	.12	120	−1.36	.14
Impaired IPS		−0.07	.84		−0.02	.94		5.39	.16		1.46	.41
Mental flexibility	96	0.15	.44	96	0.09	.61	117	−2.09	.26	117	−1.16	.17
Impaired Mental flexibility		−0.11	.74		−0.15	.63		1.69	.67		2.01	.26
Semantic fluency	96	−0.12	.51	96	−0.23	.16	127	−2.74	.17	127	−0.99	.28
Impaired semantic fluency		0.30	.37		0.43	.15		10.4	***.01***		2.95	.11
Verbal learning	97	0.17	.42	97	−0.03	.87	127	0.19	.91	127	0.36	.66
Impaired verbal learning		−0.27	.41		−0.04	.90		0.91	.81		0.06	.98
Verbal memory	96	0.07	.72	96	−0.03	.85	127	0.29	.46	127	0.74	.36
Impaired verbal memory		−0.21	.53		−0.03	.93		−3.41	.40		−1.77	.34
Visual scanning	97	0.08	.66	97	0.09	.56	122	−0.77	.72	122	0.02	.99
Impaired visual scanning		−0.60	.09		−0.58	.06		5.50	.25		1.43	.51
Male sex	100	−0.11	.82	100	−0.04	.92	127	−8.4	.10	127	−4.34	.07
Tumor grade, 2 vs.	100			100			127			127		
3		−1.11	**.046**		−0.59	.23		1.39	.81		0.08	.98
4		−1.10	**.048**		−0.67	.17		−4.61	.50		−3.47	.27
Histology, astrocytoma vs.	100			100			127			127		
Glioblastoma		−0.77	.20		−0.50	.34		−2.52	.722		−2.98	.36
Oligoastrocytoma		0.07	.96		1.12	.36		19.53	.18		8.56	.21
Oligodendroglioma		0.16	.77		0.26	.58		3.86	.49		0.40	.88
Had chemotherapy before assessment	100	−0.66	.24	100	−0.07	.89	127	−0.18	.97	127	−0.68	.77
Had radiotherapy before assessment	100	−0.84	.11	100	−0.17	.71	127	4.19	.41	127	1.27	.59
Step 2												
Attention							126	−2.99	.42	126	−1.43	.41
Impaired attention								3.06	.63		1.75	.55
Impaired semantic fluency								6.53	.14			
								Multiple R^2 = 0.07			Multiple R^2 = 0.04	
Step 3												
Attention							126	−4.32	.07	126	−2.26	**.03**
Impaired semantic fluency								7.07	.09			
								Multiple R^2 = 0.07			Multiple R^2 = 0.04	

Univariate linear regression models were computed with the FSI global fatigue, FSI fatigue severity, CIS global fatigue, and CIS fatigue severity as the dependent factor and the neurocognitive domains, sex, tumor grade, histology, prior chemotherapy, and prior radiotherapy as independent factors (step 1). The variables that were significantly associated with fatigue in step 1 were included in a multiple linear regression model (step 2). We then performed backward selection based on the Akaike Information Criterion to find the best-fitting model (step 3). At Amsterdam UMC, attention and impaired semantic fluency explained 7% of the variance in global fatigue and attention explained 4% of the variance in fatigue severity. *P* values <.05 are considered statistically significant and presented in bold.

^*N* is the number of patients included in the analysis. Only patients with complete data were included.

Abbreviations: CIS, Checklist Individual Strength; FSI, Fatigue Symptom Inventory; IPS, information processing speed.

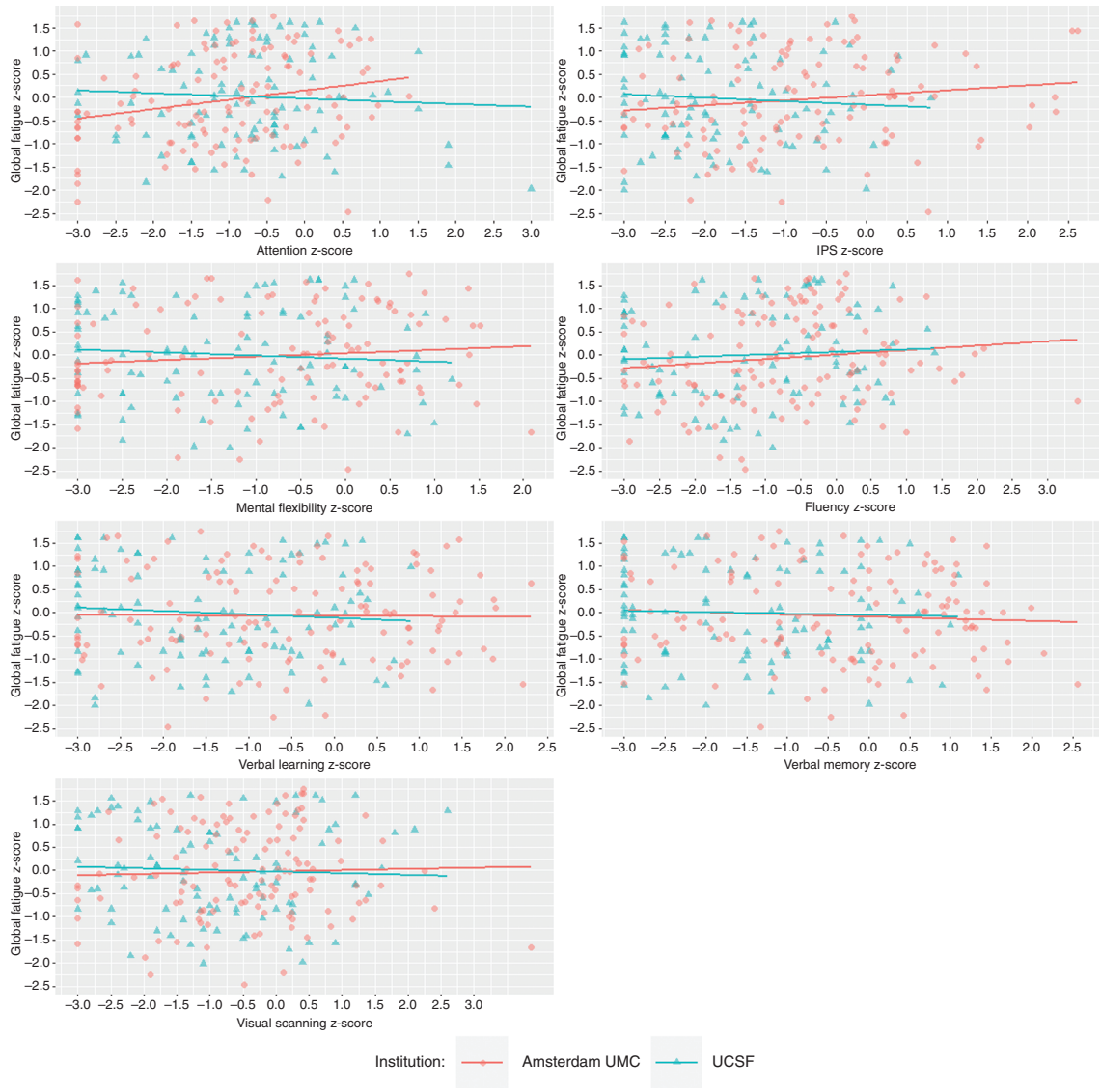

Figure 1. Scatterplots of global fatigue and the neurocognitive (sub)domains. Blue triangles represent the University of California San Francisco hospital and pink dots Amsterdam University Medical Center. The lines represent regression lines of the univariate linear regression model per institution. The global fatigue score is presented on the *y*-axis.

in stroke found no relationship between fatigue and neurocognitive functioning or only small associations between fatigue and specific domains.[47] Studies in multiple sclerosis also yielded mixed results regarding the association between fatigue and impairments in visual scanning, concentration, attention, and information processing speed.[48–51]

Based on the presented results, it is likely that self-reported fatigue and neurocognitive functioning are, at best, only very modestly related and that neurocognitive functioning is not a major contributor to fatigue. We have previously shown that factors such as HRQoL, depression, and right-sided tumors were significantly associated with fatigue and explained a much larger proportion (63%) of variance in fatigue severity.[9] Additionally, several other factors might also contribute to the observed limited association between fatigue and neurocognitive functioning. First, the assessment methods used for fatigue and neurocognitive impairments may not adequately reflect how these multimodal and complex symptoms manifest in patients' daily lives. Many fatigue inventories consider symptoms in the past few days or weeks, while neuropsychological tests only last a few minutes, limiting the impact of one on the other. And of course, even if these neurocognitive tests are psychometrically sound, they do not necessarily relate to real-life neurocognitive demands.[52] Second, it is established that self-reported cognitive functioning and formal neuropsychological testing outcomes are only modestly related in glioma[12] and other neurological diseases, demonstrating a general lack of association between self-reported measures and neurocognitive testing outcomes.[53] And third, both fatigue

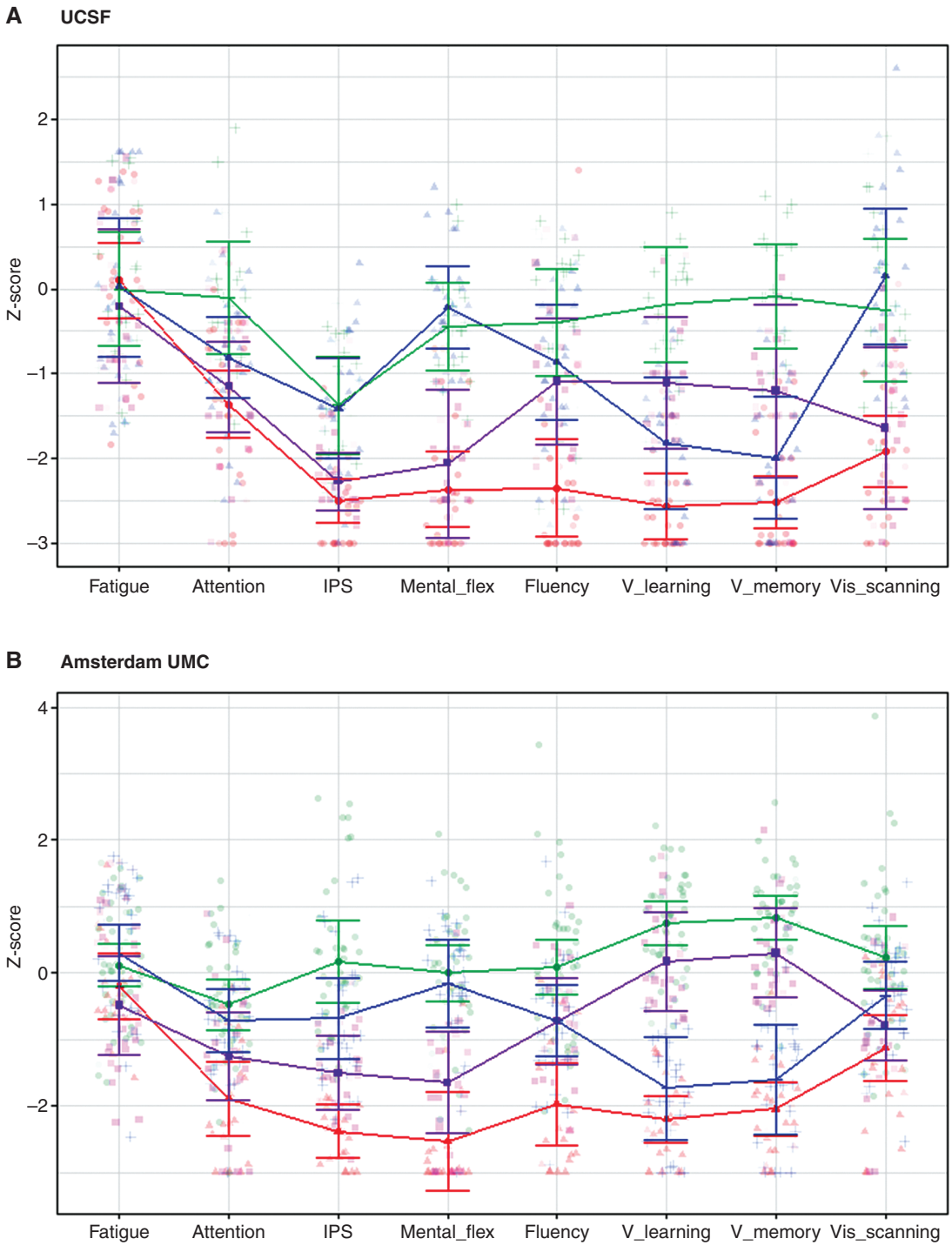

Figure 2. Subgroups based on fatigue and neurocognitive functioning. A plot of the latent profile analysis including the seven neurocognitive domains and global fatigue for each of the two institutions (UCSF $n = 82$; Amsterdam UMC $n = 111$). Each line reflects a subgroup of patients, with mean scores and 95% confidence intervals. There are four subgroups of patients: (1) neurocognitive preservation (UCSF $n = 18$; Amsterdam UMC $n = 43$), (2) learning and memory impairments (UCSF $n = 24$; Amsterdam UMC $n = 28$), (3) information processing speed and mental flexibility impairments (UCSF $n = 15$; Amsterdam UMC $n = 20$), (4) multi-domain neurocognitive impairments (UCSF $n = 25$; Amsterdam UMC $n = 20$). Figure created with BioRender.com.

Abbreviations: IPS, information processing speed; Mental_flex, mental flexibility; V_learning, verbal learning; V_memory, verbal memory; Vis_scanning, visual scanning; Amsterdam UMC, Amsterdam University Medical Center; UCSF, University of California San Francisco.

and neurocognitive impairment are heterogeneous symptoms with complex etiologies with biological, psychosocial, demographic, and tumor-related factors as known contributors.[6,7] Perhaps due to these different factors, self-reported fatigue and neurocognitive functioning are only minimally related.

Therefore, these results emphasize the need for independent assessment of fatigue and neurocognitive functioning as distinct factors. We demonstrated that when a patient has neurocognitive impairments, they are not necessarily fatigued and vice versa. Therefore, regular screening for fatigue with patient-reported measures is recommended,[54] along with frequent monitoring of neuropsychological and behavioral changes and referral to neuropsychology services if needed.[7] In general, psychosocial, self-management, coaching, and exercise interventions are recommended to alleviate fatigue,[55,56] while multidisciplinary cognitive rehabilitation remains the standard of care for treating neurocognitive impairments.[57]

A strength of this study was the use of two multinational datasets, particularly as large glioma datasets are sparse and rarely include multiple countries and data on self-reported outcome measures and neurocognitive functioning. Despite differences in neurocognitive outcomes, demographics, and medical characteristics between the two institutions, the prevalence and severity of fatigue were similar across cohorts. Moreover, investigating the link between fatigue and neurocognitive impairment for the institutions separately yielded similar results, strengthening the robustness and generalizability of the presented results. Although collecting multinational data can be challenging, it is pivotal to create such datasets and registries, particularly when aiming to understand complex problems such as fatigue and neurocognitive functioning in patients with brain tumors.[58]

However, we also note some limitations of our study. First, this study is cross-sectional and does not account for changes in neurocognitive outcomes and fatigue over the course of the disease trajectory; therefore, we cannot draw any conclusion regarding the direction of the relationship between fatigue and neurocognitive functioning. Furthermore, we included patients after surgery, primarily those with lower-grade tumors, with prior radiation and chemotherapy, who were on active monitoring. This likely limits the generalizability of our findings to newly diagnosed patients or patients close to the end of life. Furthermore, patients at UCSF were only tested when referred to cognitive rehabilitation, which may introduce selection bias. However, the effect is likely limited, given our findings of similar effects at the two institutions. Additionally, the two institutions used different fatigue questionnaires and different neuropsychological tests, requiring the transformation of the data into *z*-scores and merging of tests into domains for the sensitivity analyses. It is recommended further evaluating this relationship utilizing a standardized neuropsychological test battery, including different fatigue questionnaires and a broader patient population across countries with longitudinal measurements.[59]

In conclusion, both fatigue and neurocognitive impairment are highly prevalent among postoperative patients with glioma, irrespective of site, or cohort characteristics. Although fatigue and neurocognitive impairments can co-occur, the relationship between the two is limited with neurocognitive impairments only accounting for a small percentage of variance in fatigue between patients. Given this, fatigue and neurocognitive functioning should both be independently assessed and consequently problems should be treated with symptom management strategies specifically fatigue or neurocognitive deficits. To advance the field of symptom research and study mechanisms underlying heterogeneous symptoms such as fatigue, endeavors to share and use multinational data are encouraged.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

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Conflict of interest statement.

None declared.

Authorship statement

Conceptualization and design: J.R., J.T., L.D., C.W.J., and M.K. Data collection and curation: J.R., J.T., M.B., T.L., S.P., E.S., C.W.J., and M.K. Data analysis and interpretation: J.R., J.T., S.H.J., P.B., P.W.H., L.D., C.W.J., M.K. Visualization: J.R. Writing of the manuscript: J.R. Revising of the manuscript: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

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