Fatigue and Attention-Related Processes in Patients With Low-Grade and High-Grade Glioma

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Abstract

Fatigue is among the most common and troublesome symptoms in patients with glioma. However, studies on differences between patients with high-grade glioma (HGG) and low-grade glioma (LGG) are lacking. The coping hypothesis states that an increased effort in response to cognitive deficits will result in elevated levels of fatigue in neurological patients. The role of attention-related cognitive measures in patients with glioma is insufficiently understood. The current study examined whether the nature and severity of fatigue differ between patients with HGG versus LGG and explored the role of complex attention in fatigue. Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20) and the domain of complex attention was assessed by the computerized CNS Vital Signs test battery, both pre-neurosurgery (T0) and 12 months post-neurosurgery (T12). A total of 83 patients participated at T0 and 38 patients at T12. Patients with HGG did not have significantly higher fatigue levels compared to patients with LGG at T0 (partial η^2 = .07) and T12 (partial η^2 = .19). Although patients with HGG performed worse on complex attention in comparison to LGG, a worse performance on complex attention was not correlated with higher fatigue scores. Regression analyses confirmed the non-significant role of complex attention in fatigue in patients with LGG versus HGG. These results are not in line with the coping hypothesis. Furthermore, cognitive processes other than complex attention may play a role and should be further investigated with the goal of developing novel interventions for fatigue in patients with glioma.

Introduction

Glioma are primarily malignant brain tumors that emerge from glial or precursor cells and account for approximately 25% of all brain tumors and 75% of all malignant brain tumors (1). The World Health Organization (WHO) has developed a categorization of glioma from grade I to IV. Low-grade glioma (LGG) consist of grade I and grade II tumors (including diffuse astrocytoma, oligodendroglioma, ependymoma and oligoastrocytoma), while high-grade glioma (HGG) comprise grade III and grade IV tumors (including anaplastic astrocytoma, oligodendroglioma, oligoastrocytoma and glioblastoma) (2). In general, patients with LGG have a better prognosis than patients with HGG (3). However, both groups experience significant problems affecting daily life functioning. The main presenting symptoms are cognitive deficits, seizures, headaches and fatigue (4, 5).

Fatigue is considered one of the most common and aggravating symptoms throughout the disease trajectory for patients with cancer. There are many different definitions of fatigue that can be classified as a description of either objective or subjective fatigue. Objective fatigue is defined as ‘a failure to maintain a required output during a task’. Subjective fatigue is defined as ‘a feeling of early exhaustion with weariness, lack of energy and aversion to effort’ (6). Furthermore, fatigue is a multidimensional concept, including physical, cognitive, motivational and affective components (7). It is important to take this into account when measuring fatigue. Cancer-related fatigue (CRF) is defined as ‘a distressing, persistent, subjective sense of physical, emotional, and/or cognitive fatigue related to cancer or cancer treatment that is not proportional to recent activity, interferes with usual functioning and is not relieved by rest or sleep’ (8, 9). CRF could be the result of the cancer itself as well as a side effect of cancer treatment. There is growing evidence for the role of elevated inflammatory processes in fatigue in patients with cancer in general and in patients with brain tumors in particular (10).

The problem of disabling levels of fatigue is highly prevalent among patients with primary brain tumors (11, 12). For example, proportions of fatigue in patients with LGG vary from 39 to 77%. This wide range could be explained by differences in methodological aspects (13). Fatigue is also often mentioned as a primary complaint in patients with HGG. For example, Fox and colleagues (14) reported that 96% of the patients with HGG reported fatigue as experienced symptom. Fatigue continues to be problematic in patients with glioma throughout the course of survivorship, even more than eight years after diagnosis (15). However, only a few studies have examined the prevalence of fatigue as primary outcome in glioma and little is known about potential differences of the nature and severity of fatigue between patients with LGG and HGG.

In addition to the hypothesis of elevated inflammation in patients with cancer (i.e. CRF) as explanation for fatigue, another possible explanation for fatigue in patients with specifically glioma could be found in the 'cognitive coping hypothesis' (16). This hypothesis assumes that fatigue is mainly caused by the constant compensatory effort required for deficits in information processing to meet the demands of everyday life. During the past years, there have been several studies that support this hypothesis (17-21). However, most previous research has focused on other types of cancer (e.g. breast cancer) or neurological disorders other than brain tumors, such as traumatic brain injury (TBI) and multiple sclerosis (MS). For example, an imaging study examining differences in brain structure and function and cognitive functioning in monozygotic twins with breast cancer demonstrates that more brain activation may imply a compensation for dysfunction in neuronal networks**,** which leads to increased cognitive effort (but comparable cognitive performance) and consequently increased fatigue (22, 23).

Little is known about the relationship between cognitive functioning and fatigue in patients with a brain tumor, but inferences can be made from patients with other types of brain

pathology or dysfunction. For example, studies with patients with TBI have demonstrated a relationship between cognitive functioning and fatigue, particularly in the domains of attention (24, 25). Previous studies show that there is a relationship between fatigue and impairment on tasks requiring higher order attentional processes in patients with TBI (24). Also, associations have been found between vigilance and fatigue for a similar group of patients (21). Vigilance in the domain of cognitive functioning has been described as 'an ability to sustain attention to a task for a period of time' (26). Comparable results are expected for patients with glioma because it is also a disease of a neurological nature.

The previously mentioned coping hypothesis may explain why patients with HGG are expected to experience more fatigue compared to patients with LGG. The general pathway is that HGG is associated with more cerebral damage, which is in turn expected to result in more severe attention-related cognitive problems requiring more effort to complete a wide range of tasks in daily life. These increased efforts could be the basis of higher levels of fatigue, especially in patients with HGG. The conceptual model (Figure 1) shows the hypothesized general model for the associations examined in this project.

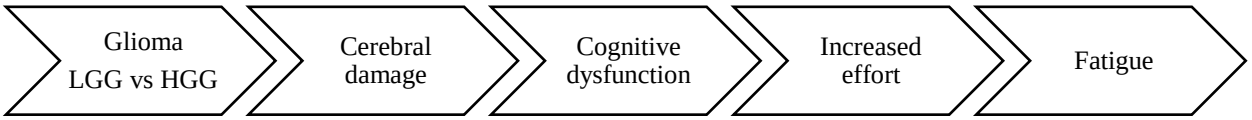

Figure 1. Hypothesized model for the 'coping hypothesis' in patients with glioma.

In addition to this explanatory model, which emphasizes the consequences of the tumor grade on fatigue, other factors also have been associated with fatigue. These multifactorial factors include demographic, medical (cancer treatment, comorbid conditions), psychosocial (depression, anxiety, chronic stress, loneliness), behavioral (sleep dysfunction, pain, physical inactivity) and biological (inflammatory cytokines) factors (27, 28).

Better knowledge of the prevalence, severity and mechanisms of fatigue (i.e. relationship with measures of higher order attention) is important to be able to identify and help patients

with primary brain tumors whose daily lives are adversely affected by high levels of fatigue. Therefore, the current project examines the nature (e.g. mental and physical components of fatigue) and severity of fatigue and the association with measures of higher-order attention in patients with glioma, both at baseline (prior to neurosurgical intervention) and at 12 months after neurosurgery. The focus is solely on the impact of cognitive functioning on fatigue, other possible mechanisms are not included. We will also consider differences between LGG (grade II) and HGG (grade III and IV). In this project, he concept of ´higher order attentional processes´ is interchangeable with the term 'complex attention'. Complex attention is described as 'the ability to track and respond to a variety of stimuli over lengthy periods of time and/or perform mental tasks requiring vigilance quickly and accurately' (28).

The specific research questions are: 1) How do patients with HGG differ from patients with LGG in terms of the nature (i.e. physical, cognitive, motivational and affective components) and severity of fatigue?; 2) How do patients with HGG differ from patients with LGG in terms of severity of complex attention?; 3) What is the relation between measures of complex attention and fatigue in patients with glioma?; 4) To what extent are potential differences in fatigue severity between HGG and LGG (research question 1) accounted for by complex attention? In order to investigate these specific research questions, the hypotheses of this study are: H1) Patients with HGG will experience higher levels of fatigue severity and nature than patients with LGG; H2) Patients with HGG have lower levels of complex attention performance compared to patients with LGG; H3) Better performance of complex attention will be related to lower fatigue levels in patients with glioma; and H4) Lower complex attentional functioning will partially account for higher fatigue levels in patients with HGG versus patients with LGG. These hypotheses are examined both at baseline (prior to surgical intervention) and at 12 months after neurosurgery. The same results are expected for both pre-neurosurgery and post-neurosurgery assessments.

Methods

Study design and procedure

Data for the present study were collected as part of a larger follow-up study in patients with brain tumors who underwent neurosurgery at the Elisabeth-TweeSteden Hospital in Tilburg, the Netherlands. There were a total of four assessment time points: one day prior to neurosurgery (T0), three months after neurosurgery (T3), twelve months after neurosurgery (T12), and twenty-four months after neurosurgery (T24). The study protocol is approved by the Medical Ethics Committee Brabant (project number NL41351.008.12). Informed consent was obtained from all patients included in the study by signing an consent form. Patients did not receive any incentives for participation in the study.

The research procedure was as follows: Patients with primary glioma who had been referred for neurosurgery at the Elisabeth-TweeSteden Hospital were asked to participate in this project. Neuropsychological assessments were administered in the hospital at all time points (T0, T3, T12 and T24). These assessments consisted of a standardized interview and a standardized computerized battery of neuropsychological tests (CNS Vital Signs; CNS VS). In addition, patients completed a set of questionnaires for research purposes at T0, T12 and T24. Pre- and postoperative questionnaires were added later on to the existing test protocol, resulting in some patients only completing the fatigue questionnaire at T12, but not at T0. The assessments at T0 and T3 were part of the standard clinical care. At T3, patients were invited by the research team to participate in the follow-up assessments T12 and T24 for research purposes only. In total, the assessment had a duration of approximately 75 minutes.

The present study focused on self-reported fatigue as measured with a well-validated fatigue questionnaire (Multidimensional Fatigue Inventory; MFI-20) and measures of complex attention as assessed with three subtasks of the CNS VS in patients with HGG and LGG at both T0 and T12. Only these time points were used in the current study as sufficient data of CNV VS and questionnaires were available for these timepoints .

Participants

Patients with histologically proven HGG or LGG (grade II, III or IV) who were scheduled for and underwent neurosurgery at the Elisabeth-TweeSteden Hospital were included. The diagnosis of LGG and HGG was based on classification of glioma from grade I to IV according to the WHO (2). In the larger follow up study, patients were excluded if they had a prior history of neurosurgery, multiple primary brain tumors, a history of severe psychiatric or neurological disease, a lack of basic proficiency in Dutch, or problems which could be a negative influence on the ability of completing the assessments (e.g. severe motor or visual problems). Specifically for the current study, patients were excluded of the dataset if there were no data available of the MFI-20 for assessment of fatigue.

Materials

Fatigue. The formal Dutch version of the Multidimensional Fatigue Inventory (MFI-20) was used for the assessment of experienced (subjective) symptoms of fatigue. It comprises 20 self-reported items and it is subdivided in the following five dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity (6). Each dimension covers four questions for which scores range from 1 to 5 points. Psychometric properties of the five dimensions are adequate, with Cronbach's α-values ranging from 0.72 to 0.87 (29). The total score was calculated by adding single item scores after recoding of reversed items, with higher scores indicating higher levels of symptoms of fatigue.

Standardized Z-scores were available and these norms were used to convert raw fatigue scores per subscale into sex- and age-corrected Z-scores for both time points, when we did not measure differences between patients with LGG versus HGG. It represented normative data from the general population of Germany (n = 2037) (30). Standardized scores for total fatigue scores were not available.

Complex Attention. The cognitive domain of complex attention was part of the computerized CNS Vital Signs test battery (31). Because the focus on this study was merely on complex attention, only this domain was thoroughly explained in this section. Complex attention as domain score was measured by a series of cognitive tests consisting of the Stroop Test (ST), Shifting Attention Test (SAT) and Continuous Performance Test (CPT). To calculate the raw domain score of complex attention, Stroop Commission Errors, SAT Errors, CPT Commission Errors, and CPT Omission Errors were added (32). The psychometric properties of these subtests are roughly similar to the properties of the conventional neuropsychological tests on which they are based (31). A lower complex attention domain score indicated a better performance.

Normative data from a Dutch sample of healthy controls were available for domain scores of complex attention (33, 34). The norms were used to convert raw complex attention domain scores in age-, sex-, and education-corrected standardized Z-scores for both T0 and T12. Furthermore, these Z-scores corrected for practice effects. A lower standardized complex attention domain score indicated a better performance.

Stroop Test (ST). The modified ST version for CNS VS consisted of three parts. In the first part, the words BLUE, GREEN, RED and YELLOW appeared at random on the screen. Participants pressed the space bar as fast as possible when they saw one of these words, which generated a simple reaction time score. In the second part, the same words (BLUE, GREEN, RED and YELLOW) appeared on the screen, now printed in color. The participants needed to press the space bar as fast as possible when the color of the ink matched its meaning. This generated a simple reaction time score as well as a complex reaction time score. In the third part, again, the same words appeared on the screen, printed in color. Now participants needed to press the space bar as fast as possible when the color of the ink did not match its meaning.

This part also generated a simple reaction time score and complex reaction time score. All three parts generated an error score as well.

Shifting Attention Test (SAT). The SAT measured the of ability of divided attention, by shifting from one instruction to another as quick and accurate as possible. Three figures were presented on the screen. Participants were asked to match the top figure to either the bottom left (press left shift key) or the bottom right figure (press right shift key), while the rules changed at random (i.e. match the figure by shape (square and circle) and match the figure by color (red and blue)). This test had a duration of 90 seconds. The scores generated by the SAT were: correct number of matches, number of errors, and response time (measured in milliseconds).

Continuous Performance Test (CPT). The CPT measured sustained attention. In this task, the participant pressed the space bar when the target stimulus 'B" appeared on the screen. In 5 minutes, the test presented 200 letters. Forty of the stimuli were targets (the letter 'B'), 160 were non-targets (other letters). The targets appeared eight times per minute, while the non-targets were presented at random. Scoring was based on the number of correct responses, commission errors (impulsive responding), and omission errors (inattention). The CPT also reported reaction times for each variable.

Covariates

Covariates in this study included sociodemographic, clinical and psychological measures that had been related to fatigue in patients with primary brain tumor in prior studies (25, 26).

Sociodemographic variables. The following sociodemographic variables were collected: age, sex, level of education, and marital status. Level of education was classified by the Dutch coding system of Verhage. This ranged from 1 (lowest education level) to 7 (highest education level). These educational levels could be combined in three levels: low (Verhage 1 to 4), middle (Verhage 5) and high (Verhage 6 and 7) (35). The variable 'marital status'

consisted of the following answering possibilities: married/cohabiting, single, widow/widower, and divorced.

Clinical variables. We reviewed clinical records for tumor hemisphere and tumor location. Tumor hemisphere was classified in three different options: left sided, right sided, and bilateral tumor. Tumor location was classified as involvement of most common locations (that means involvement of the frontal lobe, temporal lobe, parietal lobe and/or occipital lobe). Information about tumor grade, classification, location and lateralization was obtained from the electronic patient files after neurosurgery. Information about treatment (e.g. adjuvant radiation therapy and/or chemotherapy), medication (e.g. corticosteroids and/or anticonvulsants) and comorbidities (e.g.. cardiac disease, hypothyroidism and anaemia) was also obtained from the electronic patient files.

Psychological variables. The intensity of symptoms of depression and anxiety was measured by the Hospital Anxiety and Depression Scale (HADS). This screening instrument is widely used and consisted of 14 items. It refers to symptoms experienced specifically within the past week, from which an anxiety scale score (HADS-A) and a depression scale score (HADS-D) could be derived. Higher scores indicated more psychological distress. Reliability of the Dutch version of the HADS is satisfactory to good, with test-retest reliability coefficients between 0.86 and 0.90 and Cronbach's α ranging from 0.71 to 0.90 (36). This questionnaire was administered both at T0 and T12.

Statistical analysis

Data were presented as means ± standard deviation for continuous variables or frequencies (N) and percentages (%) for categorical variables. In case of not normally distributed data, descriptive statistics are presented as the median and the interquartile range. Testing of assumptions was conducted for each of the following statistical methods mentioned below

and determined which statistical analyses were eventually used. A more extensive visual representation of assumption testing is displayed in Appendix A.

We used standardized Z-scores for fatigue scores and the domain of complex attention when we did not examine differences in HGG versus LGG. Concerning the MFI-20 we used data imputation in case of a maximum of one missing item per subscale (i.e. general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue). In this case, we calculated a mean score of this particular subscale. Questionnaires were not included if more than one item per subscale was missing.

To examine whether patients with LGG experience lower levels of fatigue severity than patients with HGG (hypothesis 1), multivariate analyses of variance (MANOVA) were used examining the raw scores of fatigue subscales as multiple dependent variables in one model. We checked if assumptions of normality, linearity and homogeneity of variance-covariance matrices were met. The MANOVA operated as a gatekeeper for possible subsequent analyses on subscale level. Independent samples t-tests were used to examine the difference in raw total fatigue scores between HGG and LGG patients. Before conducting these analyses, we checked for violations of normality and homogeneity assumptions. Adjusting for demographic and clinical variables was not possible, because most of the covariates were inherent of the malignancy of the tumor grade (e.g. patients with LGG are characteristically older than patients with HGG (37)). The analyses were conducted both at T0 and T12.

Potential differences between patients with HGG versus LGG on the domain of complex attention (hypothesis 2) were evaluated using non-parametric Mann-Whitney U-tests at both time points. We were unable to use an independent samples t-test because of substantial violation of the normality and heterogeneity assumption. The independent variable was tumor grade (HGG vs. LGG), and the dependent variable was the raw domain score of complex attention.

The association between measures of the domain of attention and fatigue (both total fatigue and fatigue subscales) (hypothesis 3) in the total sample of patients with glioma, but also separately for HGG and LGG, were examined using non-parametric Spearman's rank correlation coefficients (Spearman's rho). Standardized Z-scores were used for associations in the total sample, whereas raw scores were used when examining associations in HGG and LGG separately. We used Spearman's rho because assumptions of normality, linearity and homoscedasticity were not met at both T0 and T12. Correlation coefficients between .10 and .29 reflect an association with a small effect size, coefficients between .30 and .49 a medium effect size, and coefficients of .50 and above a large effect size (38). Examinations of these analyses are conducted both at T0 and T12.

To examine to what extent potential differences in fatigue severity between patients with HGG versus LGG were accounted for by complex attention (hypothesis 4), a multiple regression analysis was conducted. A visual presentation of the relation is showed in Figure 2. To investigate the stepwise added value of independent variables on fatigue scores, hierarchical multiple regression was conducted. Measures of fatigue according to the MFI-20 (i.e. total fatigue, general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) were used as dependent (outcome) variables and the clinical domain of complex attention was the independent (predictor) variable. In step 1, tumor grade was added to the model, whereas in step 2, raw complex attention score was added to examine the additional explained variance in raw total fatigue scores. Examinations of the subscales of fatigue are presented in Appendix B. Analyses were not conducted at T12 because of the small sample size.

Statistical analyses are conducted using SPSS Statistics (version 25), with a two-sided alpha-level of 0.05 to indicate statistical significance.

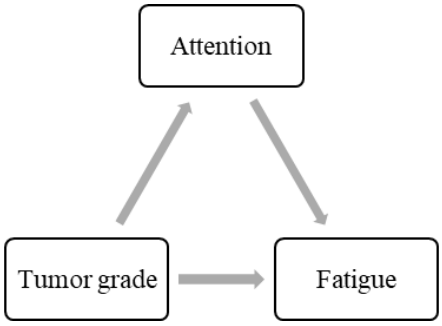

Figure 2. Hypothesized mediation model to examine to what extent differences in fatigue severity between HGG and LGG are accounted for by the complex attention domain.

Power analyses and sample size calculation

For hypothesis 1 and 2, we anticipated 55 patients with HGG and 25 with LGG at T0, and 20 each group at T12. With this sample a medium-to-large effect size (Cohen's d =0.56) can be detected at a power of 80% at a two-sided alpha of 0.05 for T0. For T12, a medium-to-large effect size (Cohen's d =0.71) can be detected at a power of 80% at a two-sided alpha of 0.05 for T12.

For the analyses of the correlation between attention and fatigue (hypothesis 3), a sample of 80 participants (HG and LGG combined) would suffice to detect a (Spearman's) correlation of 0.3 (medium effect size), with a power of 0.78 at a two-sided alpha level of 0.05. At T12, a sample of 40 participants will enable the detection of a (Spearman´s) correlation of 0.3, with a power of 0.48 at a two-sided alpha level of 0.05.

For the analyses of hypothesis 4, assuming a total sample of 80 participants, a medium effect size (f^2) of 0.25, and an alpha of 0.05, and a total of 2 predictors showed a power of 0.98 at T0. For the analyses regarding T12, with an expected total sample of 40 participants, a medium effect size (f^2) of 0.25, an alpha of 0.05, and a total of 2 predictors showed a power of 0.78 at T12.

Results

Patient characteristics

A total of 83 patients completed the MFI-20 at T0 and a total of 38 patients completed the MFI-20 at T12. Concerning the domain of complex attention, data were available for 73 patients at T0 and 33 patients at T12. One patient was excluded because of prior history of neurosurgery. Data imputation was used in three cases concerning the MFI with single missing values.

Data from pre-neurosurgical assessments (T0) of 55 patients with HGG and 28 patients with LGG were available. The mean age of patients with HGG was 55.0 ± 14.4 years and 75% were male, the mean age of patients with LGG was 49.7 ± 12.2 years and 75% were male. Data at T12 consisted of 18 patients with HGG and 20 patients with LGG. The mean age of patients with HGG was 53.4 ± 11.7 and 72.2% were male, the mean age of patients with LGG was 47.1 ± 13.1 and 80% were male. A total of 12 patients had data at both T0 and T12, 71 patients had data at T0 only and 26 patients at T12 only. Table 1 displays the sociodemographic and clinical characteristics of patients with HGG and LGG at both T0 and T12.

Table 1

Sociodemographic and clinical characteristics in patients prior to and 12 months after neurosurgery for brain tumor resection.

Characteristics	T0			T12		
	HGG means ± sd or N (%)	LGG means ± sd or N (%)	P-value	HGG means ± sd or N (%)	LGG means ± sd or N (%)	P-value
Sample size (n)	55	28	-	18	20	-
Age at T0 (years)	55.0 ± 14.4	49.7 ± 12.2	0.102	53.4 ± 11.7	47.1 ± 13.1	0.127
Sex (male)	41 (75.0)	21 (75.0)	1.000	13 (72.2)	16 (80.0)	0.585
Education [a]			0.051			**0.021**
Low	16 (29.1)	4 (14.3)		6 (33.3)	1 (5.0)	
Moderate	20 (36.4)	9 (32.1)		7 (38.9)	8 (40,0)	
High	19 (34.5)	15 (53.5)		5 (27.8)	11 (55.0)	

Marital status [a]			0.525			0.187
Married/cohabiting	51 (92.7)	24 (85.7)		14 (77.8)	18 (90.0)	
Single	3 (5.5)	4 (14.3)		2 (11.1)	2 (10.0)	
Widow/widower	1 (1.8)	0 (0.0)		1 (5.6)	0 (0.0)	
Divorced	0 (0.0)	0 (0.0)		1 (5.6)	0 (0.0)	
Symptoms of anxiety [b]	7.13; 5.00	6.29; 3.92	0.440	3.63; 2.62	4.94; 3.97	0.409
Symptoms of depression [b]	5.65; 3.92	5.86; 4.13	0.828	4.00; 3.78	4.75; 4.93	0.710
Adjuvant therapy [a]			0.818			0.054
No	44 (80)	23 (82.1)		2 (11.1)	10 (50.0)	
CT	0 (0.0)	0 (0.0)		11 (61.1)	7 (35.0)	
CT & RT	0 (0.0)	0 (0.0)		2 (11.1)	2 (10.0)	
Unknown	11 (20)	5 (17.9)		3 (16.7)	1 (5.0)	
Medication [a]			0.852			0.637
Corticosteroids only	4 (7.3)	2 (7.1)		3 (16.7)	3 (15.0)	
Anticonvulsants only	6 (10.9)	2 (7.1)		3 (16.7)	4 (20.0)	
Multiple medications	33 (60)	19 (67.9)		11 (61.1)	12 (60.0)	
Other	2 (3.6)	1 (3.6)		0 (0.0)	0 (0.0)	
None	1 (1.8)	0 (0.0)		1 (5.6)	0 (0.0)	
Unknown	9 (16.4)	4 (14.3)		0 (0.0)	1 (5.0)	
Comorbidities [a]			0.443			0.204
Yes	15 (27.3)	9 (32.1)		11 (61.1)	8 (40.0)	
No	28 (50.9)	15 (53.6)		7 (38.9)	12 (60.0)	
Unknown	12 (21.8)	4 (14.3)		0 (0.0)	0 (0.0)	

Note: significant ($p < 0.05$) differences for LGG vs. HGG were presented in bold.
[a] Percentages may not add up because of rounding.
[b] Data were available for 24 patients at T12.

Differences in Nature and Severity of Fatigue in Patients with HGG versus LGG

Table 2a and 2b display the mean values of the raw total fatigue scores and subscales of fatigue according to the MFI-20 for patients with HGG and patients with LGG for respectively T0 and T12. Figure 3a and 3b show a visual presentation of these scores.

To measure the difference in raw total fatigue score between patients with HGG ($n = 55$) and LGG ($n = 28$) preoperatively, an independent samples t-test was performed. There was no statistical significant difference between patients with HGG ($M = 56.18$, $SD = 19.48$) compared to patients with LGG ($M = 52.68$, $SD = 18.62$), $t(82) = 0.79$, $p = 0.434$, $d = 0.18$.

Similarly, at one year post surgery (T12), no differences were found in the total fatigue scores between patients with HGG (n = 18) and LGG (n = 20), respectively (M = 47.83, SD = 16.89) and (M = 58.20, SD = 20.60), $t(36) = -1.685$, $p = 0.101$, $d = 0.55$.

MFI subscales. Multivariate analyses of variance (MANOVA) were used to examine the differences in subscale scores of fatigue between patients with HGG and patients with LGG, both at T0 and T12.

At T0, the MANOVA showed statistically non-significant differences between patients with HGG (n = 55) versus LGG (n = 28) on the raw fatigue subscale scores, F (5, 77) = 1.18, $p = 0.323$, partial $\eta^2 = 0.07$. At T12, the MANOVA also showed no statistically significant difference between patients with HGG (n = 18) versus LGG (n = 20) on the fatigue subscales, F (5, 32) = 1.54, $p = 0.204$, partial $\eta^2 = 0.19$.

Table 2a

Comparisons of levels of fatigue (MFI scores) in patients with HGG and LGG at T0.

MFI Subscale	HGG T0 (n = 55)		LGG T0 (n = 28)		
	Mean	SD	Mean	SD	Partial η^2
Total Fatigue	56.18	19.48	52.68	18.62	0.18*
General Fatigue	11.51	5.09	12.50	4.40	<0.01
Physical Fatigue	11.05	5.04	10.86	4.20	<0.01
Reduced Activity	12.16	4.79	12.00	4.44	<0.01
Reduced Motivation	10.07	4.15	9.64	4.05	<0.01
Mental Fatigue	11.38	4.32	11.00	3.91	<0.01

Note: A higher score means a higher fatigue severity.
*Cohen's d for differences in total fatigue scores.

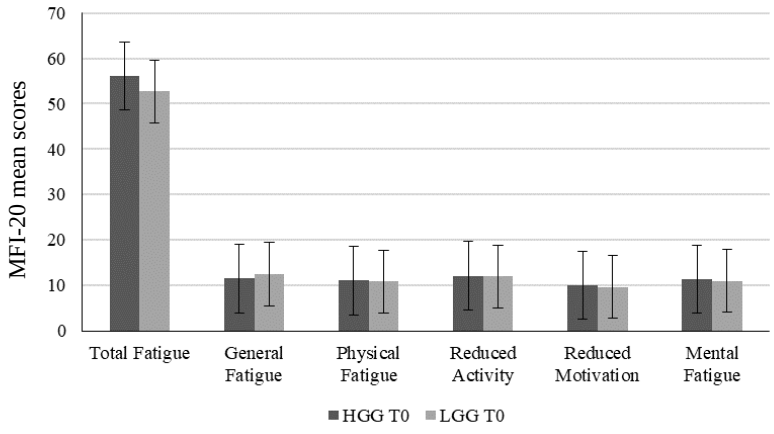

Figure 3a. Comparisons of levels of fatigue in patients with HGG and LGG at T0, with SEM.

Table 2b

Comparisons of levels of fatigue (MFI scores) in patients with HGG and LGG at T12.

MFI Subscale	HGG T12 (n = 18)		LGG T12 (n = 20)		
	Mean	SD	Mean	SD	Partial η^2
Total Fatigue	47.83	16.89	58.20	20.60	0.55*
General Fatigue	10.94	4.35	12.55	4.52	0.03
Physical Fatigue	10.39	4.51	11.15	4.85	0.01
Reduced Activity	9.22	4.31	11.85	4.89	0.08
Reduced Motivation	8.11	3.53	11.15	4.27	0.14
Mental Fatigue	9.17	3.33	11.50	4.14	0.09

Note: A higher score means a higher fatigue severity.
*Cohen's d for differences in total fatigue scores.

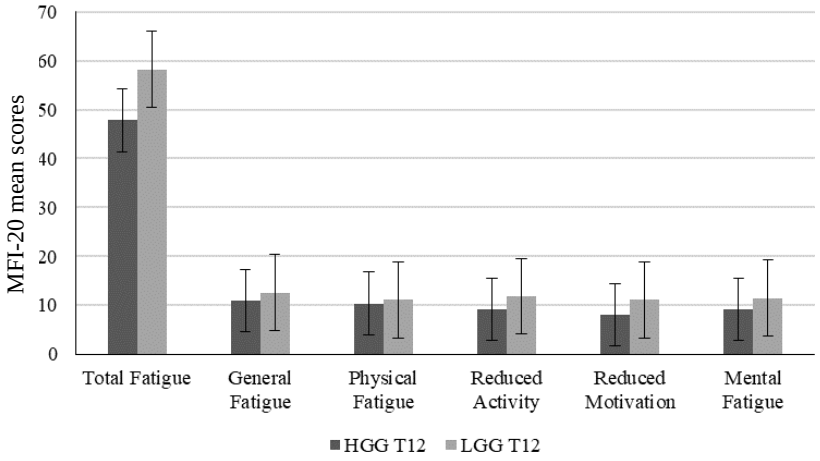

Figure 3b. Comparisons of levels of fatigue in patients with HGG and LGG at T12, with SEM.

Differences in Complex Attention in HGG versus LGG

To evaluate the difference in complex attention measures between patients with HGG (n = 50) and LGG (n = 23) preoperatively and patients with HGG (n = 16) and LGG (n = 17) 12-months postoperatively, the non-parametric Mann-Whitney U test was used. Neither the assumption of normality (Shapiro-Wilk) nor assumption of equal variances were met at both time points (Appendix A).

At T0, the Mann-Whitney *U* test showed that the raw complex attention scores of patients with HGG (*Mean Rank* = 41.51, *n* =50) were significantly higher than those of patients with LGG (*Mean Rank* = 27.20, *n* =23), *U* = 349.50, *z* = -2.68, *p* = 0.007). Table 3 shows means and standard deviations of raw complex attention scores for patients with HGG and LGG at T0. At T12, the Mann-Whitney *U* test showed that the complex attention scores of patients with HGG (*Mean Rank* = 20.13, *n* = 16) were significantly higher than those of patients with LGG (*Mean Rank* = 13.29, *n* = 17), *U* = 73.00, *z* = -2.06, *p* = 0.039. Table 3 shows means and standard deviations of raw complex attention scores for patients with HGG and LGG at T12.

Table 3

Means and SD's of raw complex attention scores for HGG versus LGG at T0 and T12.

	HGG[a]		LGG[a]		
	Mean	SD	Mean	SD	Cohen's d
Raw complex attention domain score T0	15.34	11.73	7.96	7.00	0.73
Raw complex attention domain score T12	8.13	6.57	6.88	4.40	0.22

Note: Higher raw complex attention scores indicate a worse performance.
[a]T0: n = 50 for HGG, n = 23 for LGG. T12: n = 16 for HGG, n = 17 for LGG.

Associations between fatigue severity and complex attention

Table 4 displays the Spearman correlations between the domain of complex attention and total fatigue and fatigue subscales (i.e. general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation) at both T0 and T12 in the total sample (using standardized Z-scores for both fatigue scores and the domain of complex attention) and for HGG and LGG separately (using raw scores for both fatigue scores and the domain of complex attention). Because the assumptions of normality, linearity and homoscedasticity were not met, non-parametric Spearman's rho were used.

At T0 (*n* = 73), Spearman's rho revealed no significant correlations between the domain of complex attention and total fatigue scores and fatigue subscales. At T12 (*n* = 33), Spearman's

rho showed one statistically significant negative correlation between the domain of complex attention and reduced activity for patients with LGG, r_s = -0.51, p = 0.043. The other relationships were non-significant.

Table 4

Correlations between Complex Attention and Fatigue according to the MFI at T0 and T12.

MFI Subscales	Complex attention T0			Complex attention T12		
	Total (n=73)	HGG (n=50)	LGG (n=23)	Total (n=33)	HGG (n=16)	LGG (n=17)
Total Fatigue	0.21	0.19	0.23	-0.06	0.20	-0.44
General Fatigue	-0.07	0.04	0.13	-0.15	0.10	-0.46
Physical Fatigue	0.01	0.13	0.22	-0.01	0.34	-0.11
Reduced Activity	0.12	0.23	0.22	-0.33	0.08	**-0.51**
Reduced Motivation	0.07	0.28	0.04	0.01	0.18	-0.25
Mental Fatigue	0.09	0.18	0.19	0.06	0.37	-0.28

Note: Significant correlations ($p < 0.05$) are presented in bold. A positive correlation means that higher fatigue indicates lower performance on complex attention. A negative correlation means that high fatigue indicates higher performance on complex attention.

Multiple regression of tumor grade and complex attention on fatigue

To estimate the proportion of variance in total fatigue scores that was accounted for by tumor grade and measures of the domain of complex attention at T0, hierarchical multiple regression analyses were performed (Table 5). Some of the variables displayed mild departures from normality but were mostly free from univariate outliers. Assumptions of normality, linearity and homoscedasticity of residuals were met. Multiple regression analyses for T12 were not analysed because of the relatively small sample size at this time point. Main analyses focused on the total fatigue score (subscales were not examined here to reduce potential family-wise statistical Type I error related to multiple testing). Extended analyses of the subscales of fatigue are presented in Appendix B.

In step 1 of the hierarchical MRA, tumor grade accounted for a non-significant 0.5% of the variance in raw total fatigue scores, R^2 = 0.01, F (1, 70) = 0.34, p = 0.565. In step 2, raw

complex attention scores were added to the regression equation, and accounted for an additional non-significant 1.8 % of the variances in total fatigue, $R^2_{change} = 0.02$, F_{change} (1, 69) = 1.28, $p = 0.262$. In combination, the full model explained 2.3% of the variance in total fatigue, $R^2 = 0.02$, F (2,69) = 0.81, $p = 0.450$. Unstandardized (B) and Standardized (β) regression coefficients for the predictors on both steps of the hierarchical MRA were reported in Table 5. Results of the subscales of fatigue (i.e. general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) are presented in Appendix B.

Table 5

Unstandardized and Standardized Regression Coefficients for Each Predictor Variable on Each Step of a Hierarchical Multiple Regression Predicting Total Fatigue Scores at T0.

		Unstandardized Coefficients		*Standardized Coefficients*					
Step	*Predictor*	*B*	*SE*	*β*	*p*	R^2	ΔR^2	*F*	*p*
1						0.01	0.01	0.34	0.565
	Tumor grade	-2.70	4.67	-0.07	0.565				
2						0.02	0.02	1.28	0.262
	Tumor grade	-1.00	4.90	-0.03	0.839				
	Complex attention	0.25	0.22	0.14	0.262				

Note: Statistically significant findings ($p < 0.05$) are presented in bold.

Discussion

In this study we examined the differences in the nature and severity of fatigue in patients with HGG versus patients with LGG using a multidimensional fatigue instrument (MFI-20). We also explored its association with measures of the domain of complex attention assessed by the computerized test battery CNS VS. The analyses were performed for data from both one day prior to neurosurgery (T0) and one year after neurosurgery (T12). No evidence was found for higher levels of fatigue (i.e. total fatigue, general fatigue, physical fatigue, reduced activity, reduced motivation, or mental fatigue) in patients with HGG versus LGG, both at T0 and T12. Patients with HGG performed worse on the domain of complex attention than

patients with LGG, also both at T0 and T12. Poor performances on these attentions tasks were not associated with total fatigue and subscales of fatigue at T0. At T12, in patients with LGG, more reduced activity was accompanied by a higher performance on complex attention. However, relatively poor performance on the domain of complex attention did not play a distinct role in fatigue in this sample of patients with glioma, as the difference in LGG vs HGG was not significantly different for both total fatigue and subscales of fatigue when complex attention was added to the hierarchical regression model. These results indicate that fatigue in patients with a brain tumor is not likely to reflect the severity of the brain tumor (i.e., LGG vs. HGG) or attention-related cognitive problems.

Although there were no significant differences in fatigue between HGG versus LGG, there was a trend in fatigue at T12 that may be important to investigate in future studies. Specifically, patients with LGG reported higher fatigue scores than patients with HGG. A possible explanation for this trend could be a phenomenon called ´response shift´. It refers to the phenomenon where patients with a serious illness adapt to their new situation more than patients with a relatively less serious illness. It can be considered as a recalibration of internal standards of expectations (39). In the current study, in retrospect, we expect that patients with HGG experienced this shift more than patients with LGG. Another possible explanation for the aforementioned trend concerns the survival rate of patients with HGG. Studies showed that fatigue is an independent predictor of survival, indicating that patients with lower levels of fatigue have a better prognosis (40, 41). This could result in an inaccurate reflection of actual fatigue in daily life when considering patients with HGG versus LGG. When looking into the current dataset, patients with HGG with higher levels were indeed underrepresented at T12 in comparison to patients with HGG with lower levels of fatigue.

We also showed that patients with HGG have a lower performance on complex attention compared to patients with LGG. These results were found at both T0 and T12. This is

consistent with existing literature, which states that faster cerebral damage (i.e. lesion momentum) is accompanied by less potential for neuroplastic reorganization and eventually leads to more experienced problems in cognitive functioning (42, 43).

We examined the relation between the domain of complex attention and fatigue. The only significant association that was found was a negative correlation between complex attention and reduced activity at T12 for patients with LGG. This finding indicates that more reduced activity was accompanied by a higher performance on complex attention. However, the sample of patients with LGG at T12 was very small. Although most of the correlations were not significant, there seemed to exist a different trend at T12 in HGG versus LGG, in which patients with HGG tend to perform worse on complex attention measures with higher levels of fatigue, whereas patients with LGG tend to perform better on complex attention measures with higher levels of fatigue. An explanation for the non-significant correlations could be that the cognitive effort patients with glioma have to deliver to compensate for their deficits in the long term, does not affect the complex attention domain. It could be that other cognitive functions play an important part in this relation. It is therefore likely that fatigue in patients with glioma, regardless of the tumor severity, is attributable to other factors than excessive effort related to poor complex attention abilities.

The multiple regression analysis showed that tumor grade and complex attention did not explain statistically significant variance in total fatigue. The same was true for the other subscales of fatigue. These results are in line with our other findings. There seems to be little evidence for the coping hypothesis.

The present findings should be interpreted in the context of the limitations of this study. Firstly, since this research is not experimental the direction of causality is not clear. In this project, we explained that glioma cause cerebral damage, which is in turn expected to result in more severe attention-related cognitive problems requiring more effort to complete a wide

range of tasks in daily life. These increased efforts are assumed to cause higher levels of fatigue. Extensive investigation of the direction of this association goes beyond the scope of this project. Secondly, we did not examine changes over time (from T0 tot T12) because too few patients participated in both time points (N=12). It would be of interest to investigate how fatigue severity and its association with attention-related cognitive processes change over time in HGG and LGG, but this is only possible if a larger sample size could be achieved. A larger sample size could also help to increase the statistical power of the current study. Also, large standard deviations are observed. Looking more into individual levels instead of group level could provide more information as group results may mask individual variability. Furthermore, we did not examine the possible consequences of the tumor treatment on fatigue patients with glioma have undergone at T12. Thirdly, learning effects could have been a problem at T12 because of repetition of exactly the same CNS VS test battery after 12 months. However, this problem was solved when using standardized complex attention scores corrected for learning effects. We should also note that the CPT is accompanied with ceiling effects which could influence the domain score of complex attention. Fourthly, we did not correct for demographical and clinical factors when differences between patients with LGG and HGG were examined. The reason for this was because these factors, i.e. age (37) are inherent to the malignancy of the tumor grade. Also, adjuvant treatment is more frequently implemented in HGG than LGG (44, 45), which is of particular importance for the T12 assessments. Furthermore, in the current dataset, considerably more male patients participated in this study, which is supported by prior studies (46, 47). We solved this problem partially by using standardized scores when we did not examine differences between patients with LGG versus HGG. Standardized Z-scores for the CNS VS corrected for age, sex, education level, and learning effects, while standardized Z-scores for the MFI corrected for age and sex. A strength of the current study is the low drop-out rate at T0, because this time point was part of

clinical care for patients with glioma. This resulted in a relatively large sample of patients at T0. Furthermore, we conducted a comprehensive assessment of fatigue.

To our knowledge, the differences in fatigue between LGG and HGG have not been investigated before, neither has its relation with the domain of complex attention. Thus, the current study is an important first step in investigating these relationships. More research is needed in this research area, to explore how fatigue levels develop over time and what factors exactly are involved in these relationships, because fatigue is an multifactorial concept. It is important because fatigue is considered as one of the most common and aggravating symptoms throughout the disease trajectory for patients with cancer (8, 9). Better knowledge of contributing factors in fatigue in patients with glioma could possibly help to improve rehabilitation programs to increase health-related quality of life (48, 49).

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Appendix A Extensive Assumption Testing

Concerning hypothesis 1, a further inspection of histograms further confirms that each group of scores is approximately normally distributed, both at T0 and T12. Figure 4a displays histograms of total fatigue scores for patients with HGG and LGG at T0. Figure 4b displays histograms of total fatigue scores for patients at T12.

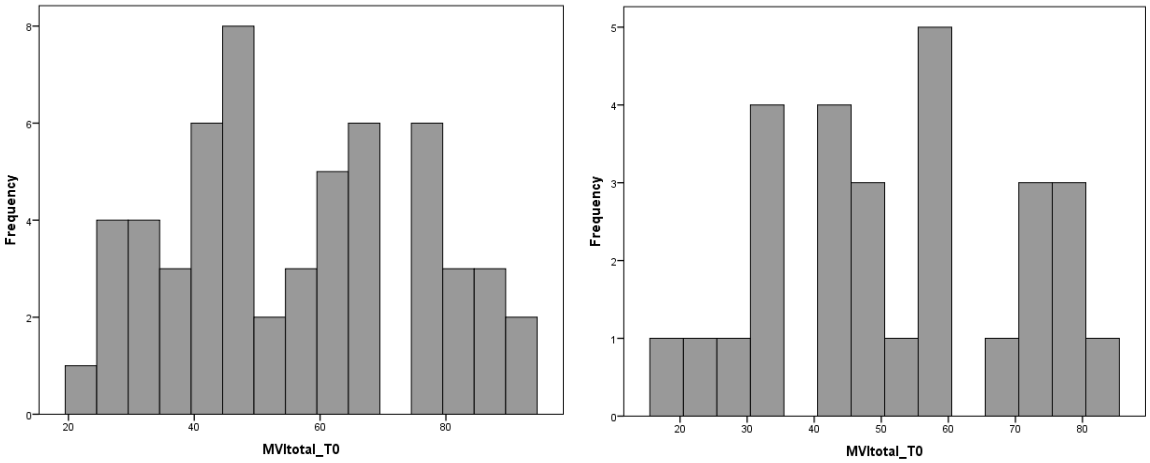

Figure 4a. Histogram of Total MFI Scores for patients with HGG (left) vs. LGG (right) at T0.

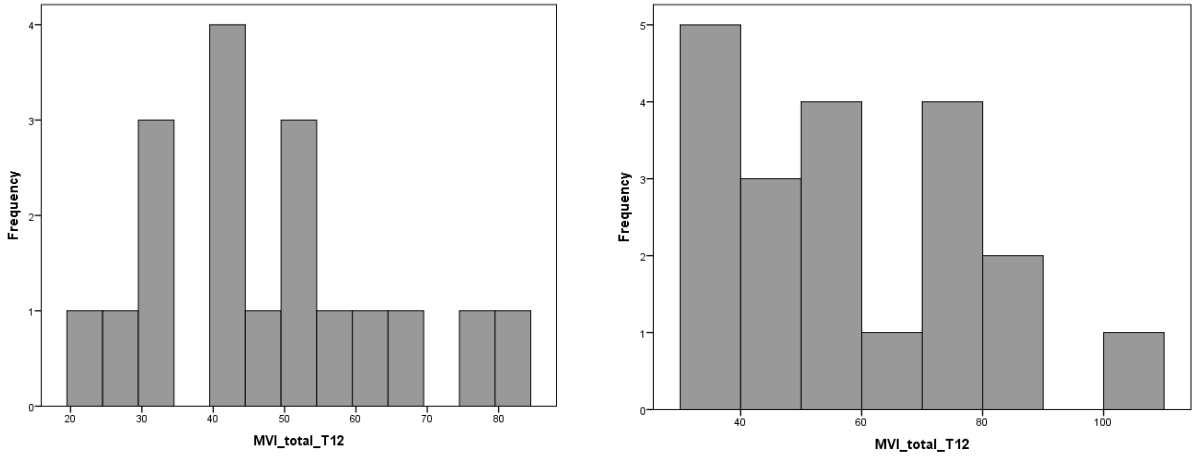

Figure 4b. Histogram of Total MFI Scores for patients with HGG (left) vs. LGG (right) at T12.

Concerning the MANOVA to measure differences between subscales of the MFI in HGG vs. LGG, both at T0 and T12, for some of the results Shapiro-Wilk test of univariate normality was statistically significant. The boxplots displayed below (Figure 5a and Figure 5b) are roughly symmetrical, which is an indication of univariate normality for both T0 and T12.

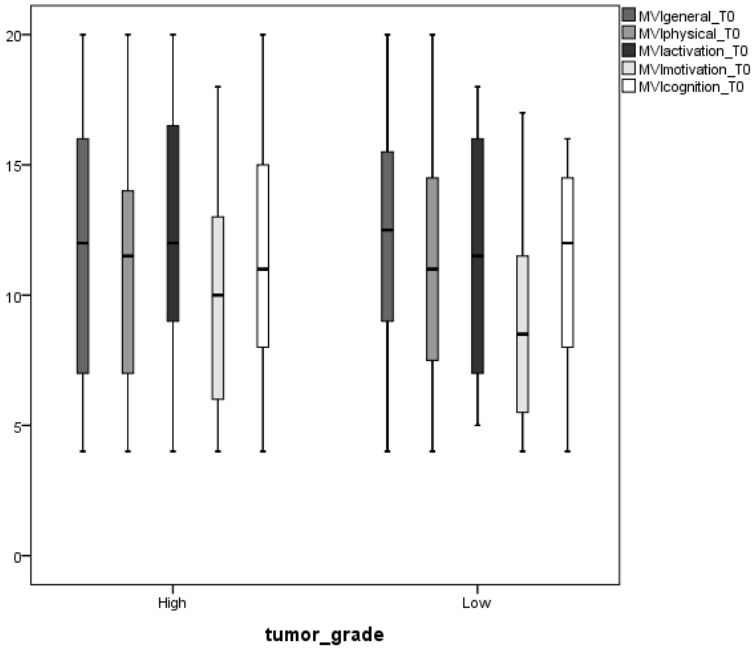

Figure 5a. Boxplot of subscales of MFI for HGG and LGG at T0.

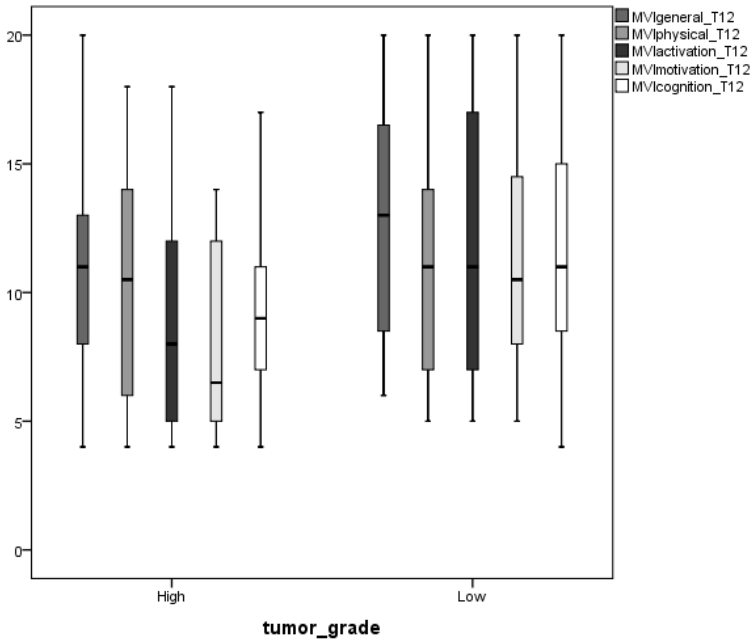

Figure 5b. Boxplot of subscales of MFI for HGG and LGG at T0.

Concerning the correlation between complex attention and fatigue scores (hypothesis 3), the assumptions of normality, linearity and homoscedasticity were not met, both at T0 and T12. A visual inspection of the scatterplots below (Figure 6) confirms that the relationship between total fatigue and complex attention is non-linear. Furthermore, there appears to be a notable difference in the amount of variability between these variables, which suggests that the relationship is heteroscedastic.

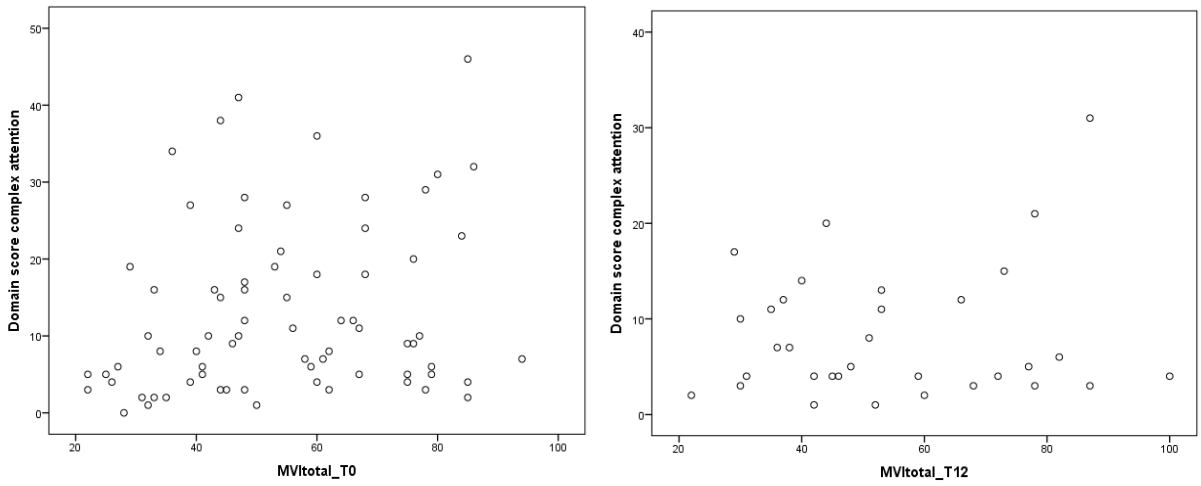

Figure 6. Scatterplots of the relationship between total MFI scores and complex attention scores at T0 (left) and T12 (right).

To visually inspect the normality assumption for hypothesis 3, histograms are used to confirm that each group of scores is not normally distributed, both at T0 and T12. Figure 7a displays histograms of complex attention scores for patients with HGG and LGG at T0. Figure 7b displays histograms of complex attention scores for patients at T12

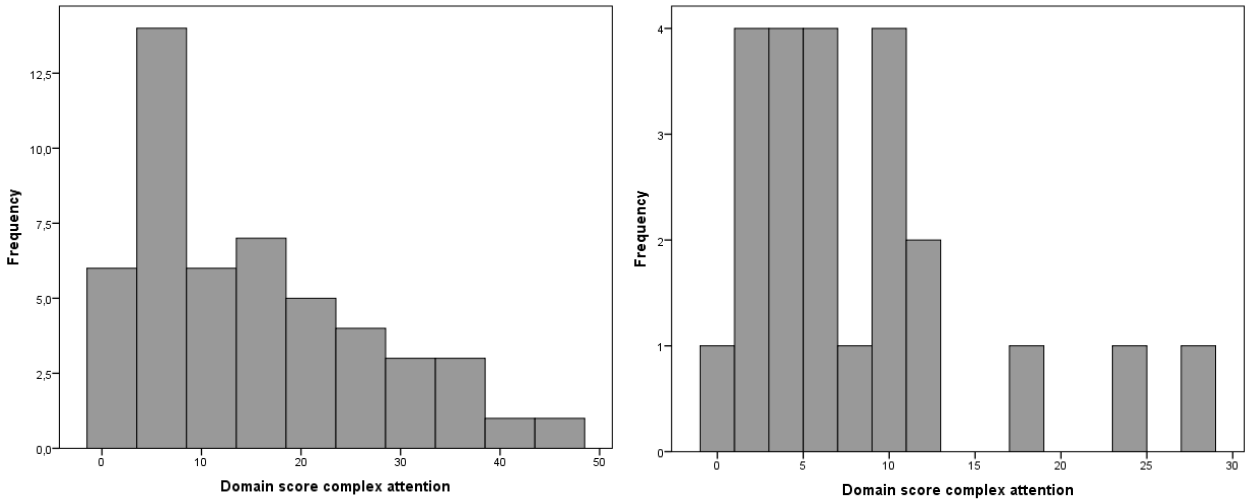

Figure 7a. Histogram of Total MFI Scores for patients with HGG (left) vs. LGG (right) at T0.

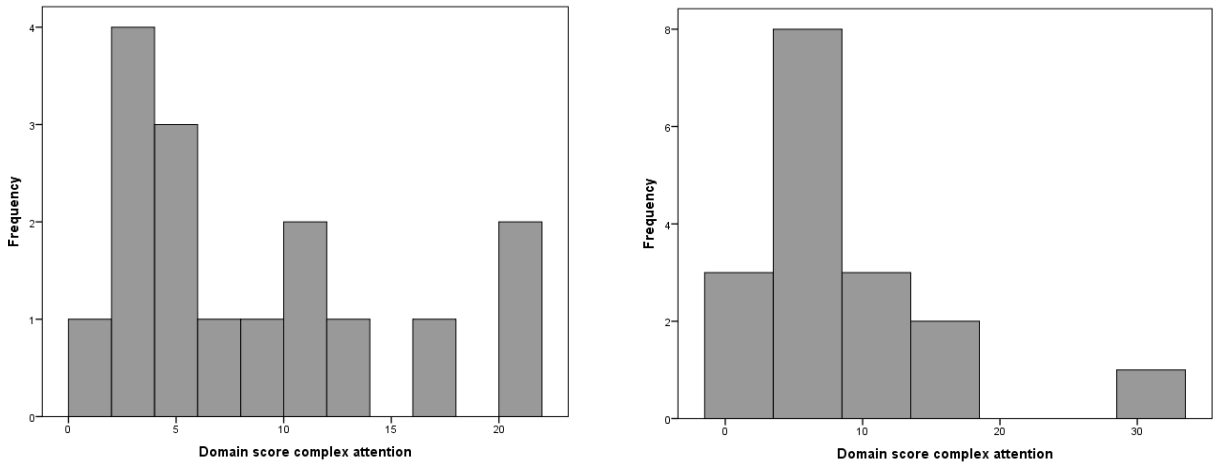

Figure 7b. Histograms of Total MFI Scores for patients with HGG (left) vs. LGG (right) at T12.

Appendix B Hierarchical Multiple Regression Subscales Fatigue

To estimate the proportion of variance in total fatigue scores that was accounted for by tumor grade at T0 and measures of the domain of complex attention, hierarchical multiple regression analyses were performed (Table 6). Analyses were performed for respectively general fatigue (Table 6a), physical fatigue (Table 6b), reduced activation (Table 6c), reduced motivation (Table 6d) and mental fatigue (Table 6e). In each of the subscales of fatigue, no significant regression coefficients were found for step 1, step 2 and the overall model.

Table 6a

Unstandardized and Standardized Regression Coefficients for Each Predictor Variable on Each Step of a Hierarchical Multiple Regression Predicting General Fatigue Scores at T0.

		Unstandardized Coefficients		*Standardized Coefficients*					
Step	*Predictor*	*B*	*SE*	*β*	*p*	R^2	ΔR^2	*F*	*p*
1						0.01	0.01	0.60	0.440
	Tumor grade	0.92	1.19	0.09	0.440				
2						0.01	0.00	0.41	0.662
	Tumor grade	1.11	1.26	0.11	0.380				
	Complex attention	0.03	0.06	0.06	0.631				

Table 6b

Unstandardized and Standardized Regression Coefficients for Each Predictor Variable on Each Step of a Hierarchical Multiple Regression Predicting Physical Fatigue Scores at T0.

		Unstandardized Coefficients		*Standardized Coefficients*					
Step	*Predictor*	*B*	*SE*	*β*	*p*	R^2	ΔR^2	*F*	*p*
1						0.00	0.00	0.22	0.644
	Tumor grade	-0.57	1.24	-0.06	0.644				
2						0.01	0.01	0.47	0.626
	Tumor grade	-0.23	1.30	-0.18	0.859				
	Complex attention	0.05	0.06	0.85	0.396				

Table 6c

Unstandardized and Standardized Regression Coefficients for Each Predictor Variable on Each Step of a Hierarchical Multiple Regression Predicting Reduced Activity Scores at T0.

		Unstandardized Coefficients		*Standardized Coefficients*					
Step	*Predictor*	*B*	*SE*	*β*	*p*	R^2	ΔR^2	*F*	*p*
1						0.01	0.01	1.01	0.319
	Tumor grade	-1.15	1.14	-0.12	0.319				
2						0.05	0.03	1.70	0.190
	Tumor grade	-0.58	1.19	-0.06	0.625				
	Complex attention	0.08	0.05	0.19	0.128				

Table 6d

Unstandardized and Standardized Regression Coefficients for Each Predictor Variable on Each Step of a Hierarchical Multiple Regression Predicting Reduced Motivation Scores at T0.

		Unstandardized Coefficients		*Standardized Coefficients*					
Step	*Predictor*	*B*	*SE*	*β*	*p*	R^2	ΔR^2	*F*	*p*
1						0.02	0.02	1.43	0.235
	Tumor grade	-1.21	1.01	-0.14	0.235				
2						0.03	0.01	1.05	0.356
	Tumor grade	-0.94	1.06	-0.11	0.379				
	Complex attention	0.04	0.05	-0.10	0.416				

Table 6e

Unstandardized and Standardized Regression Coefficients for Each Predictor Variable on Each Step of a Hierarchical Multiple Regression Predicting Mental Fatigue Scores at T0.

		Unstandardized Coefficients		*Standardized Coefficients*					
Step	*Predictor*	*B*	*SE*	*β*	*p*	R^2	ΔR^2	*F*	*p*
1						0.01	0.01	0.41	0.523
	Tumor grade	-0.70	1.09	-0.08	0.523				
2						0.02	0.01	0.69	0.505
	Tumor grade	-0.35	1.15	-0.04	0.759				
	Complex attention	0.05	0.05	0.12	0.328				