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ORIGINAL ARTICLE

The relationship between mental fatigue, cognitive functioning, and employment status in patients with low-grade glioma: a cross-sectional single-center study

Ellen M. P. van Coevorden- vanLoon[a,b,c], Majanka H. Heijenbrok- Kal[a,b], Herwin L. D. Horemans[a,b], Robin Boere[d], Rianda A. K. M. de Bat[c], Arnaud J. P. E. Vincent[e], Martin J. van den Bent[e] and Gerard M. Ribbers[a,b]

[a]Rijndam Rehabilitation, Rotterdam, The Netherlands; [b]Department of Rehabilitation Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [c]Department of Rehabilitation, Revant Rehabilitation, Goes, The Netherlands; [d]Faculty of Social and Behavioural Sciences, Leiden University, Leiden, The Netherlands; [e]The Brain Tumor Center at Erasmus MC Cancer Institute, Rotterdam, The Netherlands

ABSTRACT

Purpose: To evaluate fatigue and cognitive functioning in patients with low-grade glioma and to assess whether cognitive functioning and employment status differ between patients with severe and non-severe mental fatigue.

Methods: Cross-sectional study. Fatigue was measured with the multidimensional fatigue inventory, objective cognitive functioning with a neuropsychological test battery, and mood with the Center for Epidemiological Studies Depression Scale.

Results: Thirty-one patients, mean age 44 ± 11, mean time post-diagnosis 2.5 ± 1.4 years, participated. Severe mental fatigue was present in 55% and depression in 36% of the patients. Attention deficits were observed in 75% (Stroop's test), memory deficits in 36% (Rey Auditory Verbal Learning Test), and executive functioning deficits in 42% (Stroop's test). Severe mental fatigue patients demonstrated significantly worse scores on Stroop's test-Card-II ($p = 0.043$), Trail Making Test-B ($p = 0.014$), Trail Making Test-B/A ($p = 0.014$), and Digit-Span ($p = 0.046$), compared to non-severe mental fatigue patients. Severe mental fatigue patients worked significantly less hours per week ($p = 0.013$) and had more changes in their employment status ($p = 0.009$) after diagnosis.

Conclusions: Patients with low grade glioma show high rates of fatigue, especially in the mental domain, which might be associated with deficits in cognitive functioning and changes in employment status.

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Glioma; fatigue; cognition; employment; mental fatigue

➤ IMPLICATIONS FOR REHABILITATION

- The majority of patients with low grade glioma suffers from severe mental fatigue and has deficits in cognitive functioning, which may affect employment status.
- Patients with low grade glioma should be screened for fatigue with the multidimensional fatigue inventory, to differentiate between mental and physical fatigue.
- Patients with low grade glioma with severe mental fatigue should be screened for problems in cognitive functioning with an objective neuropsychological test battery.
- Cognitive and vocational rehabilitation programs should aim at coping with severe mental fatigue and attention deficits in patients with low grade glioma.

Introduction

Low-grade gliomas (LGGs) are the most common primary brain tumors, with a mean incidence in Europe of approximately 1:100 000 patients per year and a peak incidence in young adults aged 30–40 years [1]. The overall survival of patients with LGG has increased in recent decades, with a median survival time ranging from 10 to 15 years, due to new and improved treatment options [2,3]. Increased life expectancy may lead to new challenges with regard to daily functioning and social participation, as LGG patients often report a diverse array of symptoms/complaints, such as fatigue, cognitive disorders, and mood problems [4].

Cancer-related fatigue is considered to be one of the most prevalent and disturbing long-term effects of cancer, significantly affecting a patient's quality of life, daily functioning, and productivity [5–7]. Despite the high prevalence of cancer-related fatigue, also in LGG patients, and its major impact on patients, it is underreported, underdiagnosed, and undertreated [8], and its multifactor pathophysiology is still unknown [9,10].

A possible factor underlying fatigue complaints in LGG patients is cognitive impairment, which may impact daily life activities and quality of life [11–13]. Several cognitive domains including attention, memory, and executive functioning are frequently impaired in patients with LGG [14,15]. The cognitive coping hypothesis

CONTACT Ellen M. P. van Coevorden- vanLoon e.vancoevorden@revant.nl Revant Rehabilitation, 's-Gravenpolderseweg 114a, 4462 RA Goes, The Netherlands
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states that patients with brain injury may develop mental fatigue because of the increased cognitive efforts they have to deliver, in order to meet the demands of everyday life, including demands at work. The assumption is that these patients have to compensate for their information processing deficits [16,17].

A second explanation for a relationship between fatigue and cognitive functioning in brain injury is based on the central fatigue theory. This theory states that (mental) fatigue is a result of injury in the basal ganglia, thalamus and/or prefrontal cortex, or the connecting pathways between them, resulting in e.g., difficulties in attention, memory and a decline in overall cognitive performance over (testing)time [18–20].

Based on these theories, we hypothesized that patients with LGG who suffer from severe fatigue, especially in the mental domain, will have more cognitive and occupational problems than patients without severe mental fatigue. Therefore, the aim of this study was to evaluate the prevalence of mental fatigue in patients with LGG and to study differences in cognitive functioning and employment status between patients with and without severe mental fatigue.

Methods

Design

This study is an observational cross-sectional single-center study in patients with LGG. It is part of a larger research project (Assessment of Fatigue in Glioma Patients (AFIG)), where in addition to cognitive functioning in relation to fatigue also psychosocial and physical functioning are taken into account.

Participants

Consecutive patients were recruited between May 2016 and September 2018 from the neuro-oncology and neurosurgery department of the Erasmus University Medical Centre Rotterdam (Erasmus MC). Patients were included if they met the following inclusion criteria: (1) histologically proven grade II or III glioma, (2) time post diagnosis was $>$6 months and $\leq$5 years, (3) were in follow-up at Erasmus MC, and (4) were $\geq$18 years of age at diagnosis.

Patients were excluded in case they met the following exclusion criteria: (1) were actively treated by means of a surgical intervention, radiotherapy, and/or chemotherapy ($<$3 months), (2) were diagnosed with any additional progressive neurological disease and/or psychiatric disorder according to the DSM-IV, and (3) who insufficiently mastered the Dutch language in order to understand instructions during psychometric investigation.

Procedure

All patients completed a battery of standardized neuropsychological tests, which included tests of attention, memory, and executive functioning. The full test battery was administered in a single 65-min session at the patient's home by a trained research assistant, according to a predetermined protocol. Standardized self-report questionnaires, including fatigue and depression, were explained to the patient and were completed during the visit or could be completed at a later time and returned by postal mail.

The study was approved by the Medical Ethics Committee of the Erasmus MC (MEC-2015-577) and all patients provided written informed consent before the start of the study.

Outcome measures

Fatigue was measured with the Multi-dimensional Fatigue Index (MFI-20), which is a self-report questionnaire [21]. The MFI is a 20-item questionnaire designed to evaluate five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue [21]. Each subscale contains 4 items, with scores on a 1–5 point Likert scale. The subdomain score ranges from 4 to 20, with higher scores indicating more fatigue.

Cognitive functioning was measured with the following tests: Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test A and B (TMT-A and TMT-B), Modified Wisconsin Card Sorting Test (M-WCST), the Stroop Color and Word Test (SCWT), Digit Span (DS), and a Clock Drawing Task (Clox1). Raw scores of al tests were converted to standardized *t*-scores for outcome analyses, with higher *t*-scores representing better performance on the measured cognitive domain.

The RAVLT is an auditory verbal memory task. Patients were given a list of 15 unrelated words and were asked to repeat as many words as possible over five different trials. Scores on the different trials were added to generate a total score, with a maximum score of 75. Another performance measurement was the number of words memorized after a 20 minute interval (delayed recall). A higher score representing a better memory performance [22]. Raw scores were converted to standardized *t*-scores, with higher scores representing a better memory performance.

The TMT is a paper and pencil test that consists of two parts. TMT-A is used to assess the domain of attention. TMT-B is a test of executive functioning, since it measures higher level cognitive skills such as mental and cognitive flexibility [22,23]. In part A, patients are instructed to connect numbers in ascending order. For part B, patients were instructed to alternately connect numbers and letters in the correct order. Scoring was based on the time it took to complete the trials. There is also a performance score, in which the score on part B was corrected for part A. Higher *t*-scores are associated with a better performance on the respective domain.

The M-WCST was used to measure cognitive flexibility and problem solving skills, both important measures of executive functioning. The test required the sorting of cards with characteristics according to a sorting principle that must be derived from feedback provided by the researcher at the time of placement of the cards. The outcome measures for performance were: the number of matching categories or concepts and the number of wrong or perseverative answers [22]. Scores were converted to standardized *t*-scores. Higher *t*-scores on matching categories or concepts and a smaller amount of perseverative answers indicate better performance.

The SCWT is a test to measure divided attention (Card-I/II), as well as the ability to inhibit an automatic response, which is an aspect of executive functioning (Card-III) [24].

Card-I showed the names of four different colors, Card-II rectangles printed in these colors. The patient was instructed to name the colors as quickly as possible. Conversely, Card-III showed the names of the colors printed in a mismatched color of ink. Interference occurred when on Card-III the color had to be named instead of the word. For each card, the time to complete was considered as the outcome measure, with higher *t*-scores indicating a better performance on each domain [25].

The DS test was used to assess memory. The DS is part of the Wechsler Adult Intelligence Scale (WAIS-III-NL). This test comprises

two modalities, Digits Forward and Digits Backward. Series of digits, which increased from three to nine forward and from two to eight backward, were read aloud to the patient. The patient was asked to repeat them in the correct sequence. The performance measure was the maximum number of correctly repeated digits, which were measured distinctively for both modalities. Raw scores were converted to *t*-scores by using the WAIS-III-NL normative data, with higher scores indicating a better memory performance [25].

The Clox1 test is a commonly used neuropsychological test to measure visuo-spatial functioning and executive functioning [22]. The patient was instructed to draw a clock on an empty piece of paper containing all the numbers and to set the time to a quarter to two. Clox1 scores ranged from 0 (worse) to 15 (good), by a standard scoring system [26]. Raw scores were converted to *t*-scores, higher *t*-scores indicating better executive functioning.

Depression was measured with the Center for Epidemiological Studies Depression Scale (CES-D) and is a widely used self-report instrument for screening depressive symptoms [27]. The CES-D uses a 20-item scale, with a total score ranging from 0 to 60, and covers the most important depressive symptoms experienced by a respondent during the one-week period prior to the assessment. A higher score indicates more symptoms of depression. A score $\geq$16 indicates the presence of depression [27,28].

Disease characteristics and sociodemographic characteristics were collected by using a self-developed questionnaire. Disease characteristics included, e.g., tumor type, tumor location, undergoing treatment(s), and time-post-diagnosis. Sociodemographic characteristics included, e.g., age, social status, education, and work items (employment status, number of hours per week of paid employment and changes in type and duration of employment). The premorbid level of intelligence was estimated with the Dutch version of the National Adult Reading test (NLV) [25,29]. This test consists of a series of words with an irregular pronunciation. These words were read aloud by the patient. The performance measure was the number of correctly pronounced words. Higher scores on the test indicate a higher level of estimated premorbid intelligence.

Statistical analysis

In order to analyze the degree of cognitive impairment, raw cognitive test scores were converted to standardized *t*-scores with a mean of 50 and a standard deviation (SD) of 10, which are based on published normative values corrected for age, gender, and education [22]. Major cognitive impairment was defined as a *t*-score $\leq$30, while *t*-scores $>$30 and $\leq$40 were defined as slightly deviant, suggesting mild cognitive impairment. *t*-scores higher than 40 were considered to be normal [22].

Patients were divided into two groups, based on their *z*-score on the MFI-20 fatigue subscale. *z*-scores, which have a mean of 0 and SD of 1, were calculated using published normative values corrected for age and gender [30]. Severe mental fatigue was defined as a score more than two SDs above the mean ($>$2.0 SD) [31].

Non-parametric Mann–Whitney's tests were used to compare variables on an interval scale and Chi-square tests to compare categorical variables between severely mental fatigued patients and non-severely mental fatigued patients. For all tests, the level of statistical significance was set at a p value $<$0.05. Windows SPSS software, version 23 (SPSS Inc., Chicago, IL) was used for the analyses.

Results

Characteristics of the patients

Ninety-seven patients diagnosed with glioma fulfilled the in- and exclusion criteria, and were sent an invitation to participate in the study by their oncologist. Fifty-one patients returned the reply form, of which 20 refused participation (poor health condition ($n = 6$), duration of the assessments ($n = 7$), or unknown reason ($n = 7$)). Thirty-one patients provided written informed consent and were included in the study. The mean age of the patients was 44.2 (SD 11.0) years and the proportion of males was 68%. Thirty patients had a grade II tumor, one patient had a grade III tumor. The most common histopathological diagnoses were diffuse astrocytoma II IDH mutant (42%) and oligodendroglioma II IDH mutant/1p19q codeleted (42%). Most patients underwent a

Table 1. Baseline and clinical characteristics ($N = 31$).

	Total group ($N = 31$) Mean (SD)/*n* (%)
Socio-demographic	
Gender, male	21 (68%)
Mean age, years	44.2 (11)
Age range, years	23–62
Living with partner, yes	23 (74%)
Education, years	14.4 (3.3)
Mean estimated premorbid IQ (NLV)	110 (8.1)
Estimated premorbid IQ, range	90–127
Currently employed	24 (77%)
Employed hours/week	25.7 (13.3)
Employed hours/week, range	2–40
Change in employment status after diagnosis	10 (32%)
Histopathology	
Diffuse astrocytoma II IDH mutant	13 (42%)
Diffuse astrocytoma III IDH mutant	1 (3%)
Diffuse astrocytoma II NOS	4 (13%)
Oligodendroglioma II IDH mutant/1p19q codeletion	13 (42%)
Disease characteristics	
Time post diagnosis, months	29.3 (16.7)
Time post diagnosis, range, months	0.39–5.95
Laterality, left	20 (65%)
Location	
Frontal	18 (58%)
Parietal	2 (6%)
Temporal	3 (10%)
Diffuse	8 (26%)
Treatment characteristics	
Biopsy only	2 (6%)
Resection	29 (94%)
Chemotherapy	17 (55%)
Radiotherapy	19 (61%)
Combination treatment (SR, RT, CT)	15 (48%)
Co-morbidity	
Epilepsy	18 (58%)
AED treatment	18 (58%)
Multi AED ($\geq$2)	3 (17%)
Depressed (CES-D score $\geq$16)	11 (36%)

NLV: Dutch version of the National Adult Reading test [25,29]; IDH: isocitrate dehydrogenase; NOS: not otherwise specified; SR: surgery treatment; RT: radiotherapy treatment; CT: chemotherapy treatment; AED: anti-epileptic drugs; CES-D: Center for Epidemiological Studies Depression Scale.

Table 2. Fatigue characteristics of the patients, measured with the MFI-20, $N = 31$.

Fatigue subscales	Score, mean (SD)	Severe fatigue, *n* (%)
Mental fatigue	12.8 (4.7)	17 (55%)
Physical fatigue	11.6 (4.3)	9 (29%)
Reduced activity	11.3 (4.4)	9 (29%)
Reduced motivation	9.5 (3.6)	6 (19%)
General fatigue	13.4 (4.0)	12 (39%)

SD: standard deviation.

surgical resection (94%), and almost half of the patients underwent a combination of surgery, radiotherapy, and chemotherapy (48%). Baseline characteristics of the patients are listed in Table 1.

Fatigue: prevalence and severity

Fatigue scores and the prevalence of severe fatigue per domain are presented in Table 2. Severe mental fatigue was present in 55% of the study population. In the other fatigue domains, the prevalence of severe fatigue varied from 19% to 39%.

Between the severely mental fatigued LGG patients and non-severely mental fatigued LGG patients, no differences were found in disease characteristics, including location of the tumor ($p = 0.191$) and the percentage of depressed patients (36%), ($p = 1.0$).

Cognitive impairment: prevalence and severity

In the domain of attention, impairments were observed in 75% of the patients for Card-I of the SCWT, and 55% for Card-II, with respectively 36% and 23% of patients showing major cognitive impairment. In the memory domain, 26% mild cognitive impairment was found on the RAVLT (immediate recall and delayed recall) and 10% showed a major cognitive impairment on both immediate recall and delayed recall. Regarding executive functioning, impairments were primarily found on the Clox1 and the SCWT (Card-III) with respectively 35% and 42% of patients demonstrating mild or major cognitive impairment. Mild impairments were found in 10–16% of patients on the other tests for executive functioning. Overall results and the prevalence of mild and major cognitive impairment are detailed in Table 3.

Mental fatigue and cognitive functioning

LGG patients with severe mental fatigue demonstrated lower scores on nearly all cognitive tests. Scores on the SCWT (Card-II) in the attention domain, the DS in the memory domain and TMT (B and B/A) in the executive functioning domain were significantly lower in patients with severe mental fatigue (Table 4).

Mental fatigue and employment

LGG patients with severe mental fatigue differed from patients with no severe mental fatigue in that they worked less hours per week and/or had to make changes in their employment status after diagnosis (Table 5).

Table 3. Cognitive functioning in LGG patients; no, mild, or major impairment, $N = 31$.

Neuropsychological test	*t*-score, mean (SD)	Mild impairment, *n* (%)	Major impairment, *n* (%)	No impairment, *n* (%)
Attention				
SCWT (Card-I), time to completion	32.2 (12.2)	12 (39%)	11 (36%)	8 (25%)
SCWT (Card-II), time to completion	38.8 (13.0)	10 (32%)	7 (23%)	14 (45%)
TMT-A, time to completion	53.3 (10.5)	0 (0%)	1 (3%)	30 (97%)
Memory				
RAVLT, immediate recall	47.4 (13.5)	8 (26%)	3 (10%)	20 (64%)
RAVLT, delayed recall	45.8 (11.0)	8 (26%)	3 (10%)	20 (64%)
DS, total score	54.7 (11.4)	7 (23%)	0 (0%)	24 (77%)
Executive functioning				
M-WCST, number of matching categories	50.5 (9.1)	3 (10%)	2 (6%)	26 (84%)
M-WCST, number of perseverative mistakes	51.5 (11.3)	5 (16%)	1 (3%)	25 (81%)
TMT-B, time to completion	53.0 (11.7)	3 (10%)	1 (3%)	27 (87%)
TMT, ratio (B/A)	51.3 (10.5)	4 (13%)	1 (3%)	26 (84%)
Clox1, number of criteria	42.7 (11.2)	5 (16%)	6 (19%)	20 (65%)
SCWT (Card-III), time to completion	42.7 (11.0)	8 (26%)	5 (16%)	18 (58%)
SCWT (interference)	51.0 (8.1)	0 (0%)	1 (3%)	30 (97%)

SD: standard deviation; SCWT: the Stroop Color and Word Test; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Task; DS: Digit Span; M-WCST: Modified Wisconsin Card Sorting Test.

Table 4. Differences in cognitive functioning between non-severely mental fatigued patients and severely mental fatigued patients.

Neuropsychological test	Non-severely mental fatigued patients ($n = 14$), mean *t*-scores (SD)	Severely mental fatigued patients ($n = 17$), mean *t*-scores (SD)	*p* Value
Attention			
SCWT (Card-I), time to completion	36.5 (10.7)	28.7 (12.6)	0.131
SCWT (Card-II), time to completion	43.9 (9.9)	34.6 (14.0)	0.043
TMT-A, time to completion	54.5 (7.9)	52.4 (12.4)	0.591
Memory			
RAVLT, immediate recall	50.6 (14.5)	44.8 (12.4)	0.340
RAVLT, delayed recall	46.6 (11.4)	45.1 (10.9)	0.937
DS, total score	58.8 (12.5)	51.4 (9.6)	0.046
Executive functioning			
M-WCST, number of matching categories	51.1 (5.2)	50.0 (11.5)	0.255
M-WCST, number of perseverative mistakes	50.1 (11.6)	52.6 (11.3)	0.415
TMT-B, time to completion	58.5 (6.3)	48.5 (13.2)	0.014
TMT, ratio (B/A)	56.1 (7.1)	47.2 (11.2)	0.014
Clox1, number of criteria	45.3 (10.7)	40.7 (11.4)	0.220
SCWT (Card-III), time to completion	46.0 (9.6)	40.1 (11.7)	0.070
SCWT (interference)	51.3 (9.0)	50.8 (7.7)	0.564

SD: standard deviation; SCWT: the Stroop Color and Word Test; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Task; DS: Digit Span; M-WCST: Modified Wisconsin Card Sorting Test.

Table 5. Differences in employment status between non-severely mental fatigued patients and severely mental fatigued patients.

	Non-severely mental fatigued patients (n= 14)	Severely mental fatigued patients (n= 17)	
Employment status	Mean (SD)	Mean (SD)	p Value
Currently employed, yes	13 (93%)	12 (71%)	0.185
Employed average hours/ week	32.1 (7.9)	18.2 (14.7)	0.013
Change in employment status after diagnosis, yes	1 (7%)	9 (53%)	0.009

SD: standard deviation.

Discussion

The aim of this pilot study was to assess the experienced mental fatigue in patients with LGG in relation to cognitive functioning in the domains of attention, memory, executive functioning, and employment status. We found that 55% of the patients reported severe mental fatigue, 75% of patients had mild or major cognitive impairments in at least one test in the domain of attention, and 53% of patients had a change in employment status due to LGG.

The high prevalence of severe mental fatigue in our study is in agreement with a previous study, which assessed the effects of a multifaceted cognitive rehabilitation program on cognitive functioning and mental fatigue in patients with LGG. In this study, patients also demonstrated relatively high scores on the mental fatigue subscale of the MFI-20 [32]. Other articles which intended to examine fatigue in patients with LGG predominantly used unidimensional fatigue measurement instruments or subscales to measure the severity of experienced fatigue [33,34]. Although these instruments are considered to have robust psychometric characteristics to support their use, they are insufficient to gain insight into fatigue as a multidimensional concept [9,35]. However, fatigue measurement still relies on patient reported outcomes and therefore multidimensional measurements only gain insight in the subjective experience of fatigue in different domains. Mental fatigue might therefore not always correspond to the most closely related objective measurement of cognitive functioning [36]. Therefore, we objectively measured cognitive functioning and examined whether cognitive functioning differed between severely fatigued patients and non-severely fatigued patients in the mental domain of fatigue.

The outcomes of the present study showed that patients had cognitive problems predominantly in the domains of attention, whereas a minority of patients showed deficits in memory or executive functioning. Our results are in line with previous studies, that documented cognitive deficits in similar domains in patients with LGG [11,37]. However, our findings concerning impairment in executive functions do not match prior research. Other studies reported major impairment in executive functioning in at least 50% of the patients [38,39]. We observed major impairment in executive functions in only 19% of the patients. One possible explanation for this discrepancy is the differences in the studied glioma populations. Most of the patients that we included had an IDH mutant type glioma. None of the patients had a IDH-wild type glioma. The severity of neurocognitive impairment seems to be different between these IDH subgroups [40]. IDH-wildtype gliomas are associated with poorer neurocognitive performance in the domains of verbal learning and memory, processing speed and executive functioning compared to patients with IDH-mutant gliomas [40]. This explanation is further supported by a conclusion from a recent study that IDH mutated gliomas are associated with relatively good performance in memory function and a possible lower risk of impairment in executive functioning [41]. Together, this supports the hypothesis that patients with IDH-mutant tumors have a more favorable cognitive profile compared to patients with IDH-wildtype tumors. Another explanation is the composition of the test battery of cognitive tests. Unfortunately, there is no standardization of using a specific cognitive test battery in glioma patients [42]. The three key executive functions are: inhibition, working memory, and cognitive flexibility. However, executive functioning consists of a very broad spectrum of (high)cognitive skills that enable people to control and regulate their behavior and functions that are necessary for decision making [22,39]. Different cognitive tests measure different "elements" of executive functioning, which makes the comparison of different studies difficult.

By studying the relationship between cognitive functioning and fatigue, we found that severely mentally fatigued LGG patients demonstrated lower scores on all cognitive domains compared to non-severely fatigued LGG patients. The relationship between higher levels of self-reported mental fatigue and impaired cognitive functioning might be explained by the cognitive coping-hypothesis, which states that mental fatigue may develop due to increased cognitive efforts that patients with brain injury have to deliver to compensate for their information processing deficits [17]. Our study is in line with this hypothesis. A broad interpretation of the central fatigue theory can also be a (partial) explanation for the relationship between cognitive impairments and fatigue. Studies in LGG patients concluded that impairment in cognitive functioning and fatigue cannot be explained by tumor location alone [43], as in our study, but also depends on widespread changes in the strength and spatial organization of brain networks [44,45].

Fatigue is a negative predictor of return to work in patients that survived a diagnosis of cancer [46–48]. We also found that LGG patients with severe mental fatigue differed from patients without severe mental fatigue in employment status. Severe mental fatigue patients worked significantly less hours per week and/or had more changes in their employment status after diagnosis. This is in line with a recent study on return to work in glioma patients, in which mental fatigue was significantly associated with unemployment [49].

Glioma patients experience increased levels of depression, with reported rates between 15% and 48% [50,51]. In our study, 36% of the patients was depressed. Glioma patients with a depression have poorer outcomes with respect to quality of life and even on survival time [52]. Depression has been associated with increased levels of general fatigue [53], but in our study, we did not find a difference in the proportion of depressed patients between the non-severe mental fatigue patients and the severe mental fatigue patients.

Some limitations of this study need to be mentioned. This study only focused on the domains of executive functioning, memory, and attention. Cognitive impairment in glioma patients has also been reported with regard to visuoconstruction, processing speed, and verbal memory [54]. As our study does not capture the full scope of cognitive functioning, results obtained by our study might be an underestimation of the true impaired cognitive functions in patients with LGG. Future studies must therefore include additional cognitive domains. In addition, we would

like to emphasize that due to a small sample size results must be interpreted with caution and that the results are tentative and suggestive only. Also, the approach used to identify patients could have selected patients with more severe complaints.

In conclusion, although far from being conclusive, our study demonstrates that LGG patients show high rates of fatigue, especially in the mental domain. The high rates of mental fatigue were associated with impairments in cognitive functioning and changes in employment status. Despite the increased awareness of cancer-related fatigue in LGG patients, understanding of underlying mechanisms is still limited. We recommend a routine screening for all LGG patients and development of vocational rehabilitation programs specifically tailored to the needs of LGG patients, which focus on coping with cognitive impairment and mental fatigue.

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