rijksuniversiteit groningen

Subjective complaints in patients with lower-grade glioma: Relationships with tumor characteristics and life satisfaction

Miriam Leijzer

Master Thesis – Klinische Neuropsychologie

S3147657

June 2022

Department of Psychology

University of Groningen

Daily supervisor: dr. A.M. Buunk

Examiner: prof. dr. J.M. Spikman

Abstract

Objective: The author's objective was to investigate tumor-related risk factors for depressive complaints, anxiety, fatigue, and cognitive complaints in lower-grade glioma (LGG) patients with relatively favorable prognosis. In addition, relationships between these complaints and life satisfaction, a meaningful part of quality of life (QoL), were examined. ***Method:*** Post-craniotomy and at the start of proton therapy, LGG patients filled in questionnaires measuring depressive complaints and anxiety (Hospital Anxiety and Depression Scale), mental and physical fatigue (Dutch Multifactor Fatigue Scale), cognitive complaints (Behavioural Assessment of the Dysexecutive Syndrome – Dysexecutive Questionnaire; Patient Competency Rating Scale) and life satisfaction (Quality of Life after Brain Injury). Tumor volume, laterality, and location were determined by means of a magnetic resonance imaging scan. Tumor grade was determined by means of a biopsy. Spearman correlations were computed, and between-group comparisons were performed. ***Results:*** Frequencies of complaints were 43.3% for mental fatigue, 25.0% for physical fatigue, 20.8% for depressive complaints, 2.5-14.2% for cognition and 10.8% for anxiety. All subjective complaints were significantly interrelated. Patients with relatively large LGG had significantly more complaints of physical fatigue and cognition compared to patients with relatively small LGG. Tumor laterality, whether the tumor was frontally located, and grade according to the World Health Organization 2007 classification system were not significantly associated with subjective complaints. Higher rates of fatigue, cognitive complaints and anxiety were significantly related to lower life satisfaction. ***Discussion***: In conclusion, considering relatively high rates of especially fatigue and depression, all LGG patients should be screened for at least these complaints possibly reducing QoL. Patients with relatively large tumors should be screened for all subjective complaints. If desired, suffering patients should receive adequate treatment to improve QoL. Future research should investigate additional risk factors and the course of complaints. Thus, patients at-risk can be identified early, monitored and treated, hopefully contributing to higher QoL.

Introduction

Lower-grade gliomas (LGG) are brain tumors that mostly arise in young to middle-aged adults. They manifest as a slow progressing disease but inevitably transform to high-grade gliomas (HGG) (Rijnen et al., 2019; van der Weide et al., 2021). Treatment of LGG is therefore only life-extending and consists of tumor resection often followed by radiotherapy and chemotherapy (Schiff et al., 2019). Gliomas are classified into LGG or HGG for predicting prognosis and choice of therapies according to the World Health Organization (WHO) grading system I to IV based on tumor histology (Louis et al., 2007). Because of a relatively favourable prognosis of LGG patients (Brown et al., 2019), especially compared to that of HGG, the monitoring and management of LGG patients' subjective complaints is of high importance, to maintain sufficient quality of life (QoL).

Research shows that patients with LGG suffer from a variety of symptoms, including anxiety and depressive complaints (Bunevicius et al., 2017; Jarvis et al., 2020; Ley et al., 2022). In LGG patients these complaints are associated with poorer prognosis and shorter survival (Hao et al., 2021; Shi et al., 2018). Spiegel & Giese-Davis (2003) described how depression in cancer patients can result in tumor growth, not only through worse treatment adherence, but through dysregulation of the hypothalamic-pituitary-adrenal axis and immune functioning as well. Hao et al. (2021) identified being female, not having a partner and suffering from hyperlipidaemia as risk factors for depression and anxiety in LGG patients.

In LGG patients fatigue is a common complaint as well (Schei et al., 2020; Struik et al., 2009). Gustafsson et al. (2006) stated that fatigue is the most prominent problem experienced by patients. Patients especially show high rates of mental fatigue, which is associated with cognitive impairments and changes in employment status (van Coevorden-van Loon et al., 2021). Fatigue in LGG patients can emerge both as a disease symptom and as a side-effect of treatment (van Coevorden-van Loon et al., 2017). In addition, higher age is a risk factor for experiencing fatigue in LGG (Struik et al., 2009).

Furthermore, LGG patients suffer from cognitive impairments in various domains (Miotto et al., 2011; Rijnen et al., 2019; van Kessel et al., 2017; van Loon et al., 2015). Research shows that in these patients cognitive impairments are associated with poorer prognosis and shorter survival (van Kessel et al., 2021) and can emerge both as a disease symptom and as a side-effect of treatment (Correa et al., 2019; Klein et al., 2012). Cognitive functioning of LGG patients is mostly assessed using objective measures. The correlation between objective and subjective cognitive functioning is, however, only modest in most patient groups including

LGG patients (Gehring et al., 2015; Klein et al., 2002). Although objective measures contain significant value because the design of the testing environment ensures valid and reliable measures, cognitive complaints represent daily difficulties in a clinically relevant way as well. The calmness and clearness of the standardized testing environment does not expose all difficulties patients may face in daily generally more chaotic situations. Gosselt et al. (2020) showed that LGG patients suffer from cognitive complaints as well. Additionally, it has been proposed that in LGG patients cognitive complaints are more closely related to depression, anxiety, and mental fatigue than to objectively assessed cognitive impairments (Gehring et al., 2015).

The present study is conducted post-craniotomy and at the start of proton therapy. Post-craniotomy complaints assessment is relevant for determining treatment needs. These complaints may be more predictive of long-term complaints than pre-treatment complaints, for example because of relieved intracranial pressure by tumor resection. Proton therapy has distinct advantages compared to conventional radiotherapy on terms of sparing surrounding healthy brain tissue (Olsen et al., 2007) and is in the Netherlands only available to patients with relatively favourable prognosis based on patient and tumor characteristics (van der Weide et al., 2021). Important to investigate is whether these patients experience subjective complaints of depression, anxiety, fatigue, and cognition as well as other LGG patients. In that case, patients should be identified early and treated adequately, to diminish suffering and consequences. Research conducted pre-craniotomy shows that depressive complaints, anxiety, and fatigue negatively impact QoL (Boele et al., 2014; Buvarp et al., 2021; Ley et al., 2022). Furthermore, Coomans et al. (2019) demonstrated that in glioma patients QoL is independently prognostic for overall survival and progression-free survival. Whether the relationship between complaints and QoL persists post-craniotomy is unknown. If so, the importance of adequate treatment of complaints is underlined. To screen, detect early and subsequently monitor and manage subjective complaints in these patients, identifying risk factors is of high importance.

One possible risk factor is tumor volume. Proposedly, larger tumor size results in more complaints of depression, anxiety, and fatigue through biological factors, e.g., increased dysregulation of brain networks. Concerning depression and anxiety, the realization of having a relatively large tumor may be more anxiety- and depression-inducing than having a relatively small tumor. A complex interrelationship between biological, psychological, and social factors may be most likely (Malec et al., 2007). To our knowledge, no research has been performed on the relationship between LGG tumor volume and depression, anxiety, or fatigue. Research has

demonstrated positive relationships between LGG volume and cognitive impairment, post-operative by Luks et al. (2022), and pre-operative specifically concerning cognitive complaints by Schei et al. (2022). Noteworthy, the latter study only used two questions to measure cognitive complaints which gives an incomplete picture of cognitive complaints. Post-craniotomy the relationship between tumor volume and cognitive complaints was not investigated yet.

In addition to volume, tumor laterality may be a factor as well. To this day, no consensus has been reached on the hemispheric lateralization of emotion processing. Two hypotheses supported by extensive research data are at the same time mutually exclusive. The Right Hemisphere Hypothesis states the right hemisphere being dominant in emotion processing, while the Valence Hypothesis states negative emotions to be modulated by the right hemisphere and positive emotions to be modulated by the left hemisphere (Ross, 2021). Interestingly, Mainio et al. (2003) demonstrated right-hemispheric tumors to be associated with pre-operative anxiety in brain tumor patients. The relationship between laterality and fatigue was investigated in HGG, with conflicting results. Hansen et al. (2021) found patients with right-hemispheric glioma to be more affected by fatigue than left-hemispheric glioma patients, while Valko et al. (2015) found left-hemispheric glioma patients to be more affected. Schei et al. (2022) stated that left-hemispheric glioma is associated with more pre-craniotomy cognitive complaints. However, as mentioned earlier, the study failed to form a complete picture of cognitive complaints. Post-craniotomy relationships between tumor laterality and subjective complaints have not been investigated in LGG patients.

Concerning tumor location, patients with frontal lobe LGG may report less complaints than patients with LGG located elsewhere. The frontal lobes are essential in maintaining awareness of the self, including one's problems and difficulties (Stuss & Levine, 2002). Therefore, frontal lobe damage can result in diminished self-awareness, which is the case in fronto-temporal dementia (FTD) (Mendez & Shapira, 2005) and traumatic brain injury (TBI) (Morton et al., 2010). Importantly, diminished awareness of complaints does not mean patients or their caregivers do not suffer because of the complaints (Andrewes et al., 2013). Sasse et al. (2013) showed no significant QoL differences in TBI patients impaired compared to patients not impaired in self-awareness. Research into Alzheimer's disease failed to find a direct relationship between self-awareness and QoL but found depressed mood to be a mediator (Cines et al., 2015). In case patients with frontally located LGG report less subjective

complaints, more objective or proxy measures should be used to screen for these complaints in patients possibly reducing QoL.

Although widely used, the WHO glioma classification system of 2007 (Louis et al., 2007) is solely based on morphological criteria for tumor histology, resulting in high inter-observer variability and variable survival rates within tumor grades (Molinaro et al., 2019). Extensive research showed that gliomas should be classified according to molecular and chromosomal subtypes, like isocitrate dehydrogenase (IDH) and 1p/19q co-deletion (Cancer Genome Atlas Research Network, 2015). The WHO incorporated the findings into the glioma classification system of 2016 (Louis et al., 2016). Interesting to examine would be whether the classification system of 2007 is relevant for risk assessment of subjective complaints in our group of LGG patients, considering it is still widely used.

Various studies have investigated the prevalence and consequences of depressive complaints, anxiety, fatigue, and cognitive complaints in LGG patients. Subjective complaints in relationship to the proposed tumor characteristics and QoL have not yet been studied in these patients post-craniotomy. The aim of the present study was therefore threefold: (1) to determine to what extent depressive complaints, anxiety, fatigue, and cognitive complaints exist in LGG patients with relatively favourable prognosis, (2) to examine whether tumor characteristics of volume, laterality, whether the tumor was frontally location, and grade based on the WHO 2007 classification (Louis et al., 2007) are related to these subjective complaints, and (3) to examine whether the complaints are related to life satisfaction. This might allow for early identification of patients who are at-risk for complaints and therefore possibly lower QoL, with the purpose of treating affected patients adequately.

Method

Patients and procedure

The present study is part of a large prospective research project in the University Medical Center Groningen (UMCG). Brain tumor patients admitted to the UMCG between November 2017 and February 2022 who had an indication for proton therapy were eligible for inclusion in this study. In the Netherlands, only patients with favourable prognosis based on tumor and patient characteristics receive proton therapy (van der Weide et al., 2021). The diagnosis of brain tumor was established by means of a magnetic resonance imaging (MRI) scan. Exclusion criteria were age lower than 18 years, patients with meningiomas, neurological diseases or psychiatric disorders, alcohol or substance abuse, insufficient proficiency of the Dutch language, an indicative performance on a symptom validity test and not having completed the questionnaires.

Patients were assessed post-craniotomy pre-adjuvant therapy with a comprehensive neuropsychological test battery of approximately 2.5 hours, including questionnaires. Additionally, demographical data and tumor characteristics were collected. The Dutch Classification System of Verhage (1964) was used to describe educational level (ranging from (1) primary school to (7) university). The study was approved by the Medical Ethical Committee of the UMCG. All participants completed written informed consent.

Questionnaires

Depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale that detects depression and anxiety states in a medical setting (Zigmond & Snaith, 1983). Items (for example ‘I still enjoy the things I used to enjoy’ and ‘I worry a lot’) are rated on a 4-point scale, resulting in total scores between 0 and 21 for both depression and anxiety. Higher scores represent higher symptom frequency. Patients were classified as having depressive or anxiety complaints if they scored 8 or higher on the subscales, based on the norms of Breeman et al. (2015).

Fatigue

The Dutch Multifactor Fatigue Scale (DMFS) is a 38-item scale consisting of 5 subscales that measure the nature and impact of fatigue and coping with fatigue in the chronic phase after acquired brain injury (Visser-Keizer et al., 2015). Two subscales are used in the present study: (1) mental fatigue (for example ‘Thinking makes me tired’) and (2) physical

fatigue (for example 'I have little energy'). Items are scored from (1) totally disagree to (5) totally agree, resulting in mental fatigue scores between 7 and 35 and physical fatigue scores between 6 and 30. Higher scores indicate more severe fatigue. Patients were classified as being mentally or physically fatigued if they scored above the 88th percentile, based on the norms of Visser-Keizer et al. (2015).

Cognitive complaints

Cognitive complaints were measured by two different questionnaires. The Patient Competency Rating Scale (PCRS) is a 30-item scale that measures perceived degree of competency in several behavioural, cognitive, and emotional situations (Prigatano, 1996). The present study used a proposed selection of 17 items (for example 'Can you remember what you have to do during the day?' and 'Can you continue working, even when you are bored or tired?') focusing on cognitive complaints (Zimmermann et al., 2014). A scoring of (1) impossible to (5) easy results in total scores between 0 and 85. Higher scores represent less cognitive complaints. Based on the dichotomization of Buunk et al. (2017) patients with scores lower than 68 were classified as having cognitive complaints.

The Behavioural Assessment of the Dysexecutive Syndrome – Dysexecutive Questionnaire (BADS-DEX) is a 20-item scale that samples a range of problems commonly associated with the dysexecutive syndrome (Wilson et al., 1996). Items are for example 'I have trouble making decisions or deciding what I want to do' and 'I have trouble understanding what other people mean, except when it comes to simple and clear matters'. The items are rated on a 5-point scale (never to very often), resulting in a total score between 0 and 80. Higher scores indicate more cognitive complaints. Scores above the 75th percentile are interpreted as indicating cognitive complaints, based on the norms of Wilson et al. (1996).

QoL: life satisfaction

The Quality of Life after Brain Injury (QOLIBRI) is a 37-item rating scale that measures QoL (Polinder et al., 2015). The present study used three items focusing on satisfaction with social life. Patients are asked (1) How satisfied are you with your relationship with your partner, (2) How satisfied are you with your relationship with your family, and (3) How satisfied are you with your relationship with your friends or acquaintances? The items are rated on a 5-point scale (very unsatisfied to very satisfied or not applicable). Higher scores indicate more satisfaction. Because of the possibility to answer not applicable no total score was calculated, and each item was analysed separately.

Tumor characteristics

Tumor volume, laterality, and location were determined by means of an MRI scan by the department of Radiotherapy in the UMCG. The department of Pathology determined tumor grade according to the WHO classification of 2007 (Louis et al., 2007) by biopsy, and whether the IDH gene of the tumor was mutated by immunohistochemistry staining, with additionally Next Generation Sequencing in case of a grade II or III glioma. Tumor volume was operationalized as the gross tumor volume (GTV). The GTV is post-craniotomy the extent of the remaining tumor and the surrounding part from where the tumor was removed in cubic centimetres (cc). To compare patients with 'small' and 'large' tumors, a GTV larger than mean (M) + 1.5 standard deviation (SD) was classified as relatively large.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 23.0. To investigate the relationships between (1) all subjective complaints, (2) tumor volume and subjective complaints, and (3) subjective complaints and life satisfaction, Spearman correlations were used. To test for subjective complaints rate differences between patients with (1) relatively small and large tumor volumes, (2) left- and right-hemispheric tumors, (3) frontal lobe and elsewhere located tumors, and (4) grade II and III tumors, an independent two-sample t-test or, in case of non-normally distributed data, a Mann-Whitney U test was performed. Effect sizes were calculated for all between group comparisons. An alpha-level (p) of 0.05 was set for all analyses, with Bonferroni-Holm corrections in case of multiple comparisons.

Results

In Table 1 the sociodemographic and clinical characteristics of the 120 LGG patients included for analysis are displayed. Shapiro-Wilk tests showed that subjective complaints and GTV were not normally distributed.

Table 1
Sociodemographic and clinical characteristics of LGG patients

Characteristic	LGG (n=120)
Sex, number of women (%)	58 (48.3)
Age in years, M ± SD	42.4 ± 12.3
Educational level, M ± SD	5.2 ± 1.0
Diagnosis	
Oligodendroglioma, n (%)	61 (50.8)
Astrocytoma, n (%)	57 (47.5)
Pilocytic astrocytoma, n (%)	1 (0.8)
Ependymoma, n (%)	1 (0.8)
WHO tumor grade[1]	
Grade I, n (%)	1 (0.8)
Grade II, n (%)	93 (77.5)
Grade III, n (%)	26 (21.7)
IDH-mutation	
IDH-mutant, n (%)	117 (97.5)
IDH-wild type, n (%)	2 (1.7)
Tumor location[2]	
Frontal, n (%)	81 (67.5)
Temporal, n (%)	23 (19.2)
Parietal, n (%)	22 (18.3)
Occipital, n (%)	6 (5.0)
Insular, n (%)	9 (7.5)
Elsewhere, n (%)	9 (7.5)
Laterality[3]	
Left-sided, n (%)	64 (53.3)
Right-sided, n (%)	56 (46.7)
Treatment before proton therapy	
Basic craniotomy, n (%)	51 (42.5)
Advanced craniotomy (awake or IONM[4]), n (%)	53 (44.2)
Chemotherapy, n (%)	3 (2.5)
GTV in cc, M ± SD	59.1 ± 51.0
Relatively small tumors, M ± SD	44.1 ± 27.9
Relatively large tumors, M ± SD	172.1 ± 44.4

Note.
[1] Indicated as the highest glioma grade within the tumor according to WHO 2007.
[2] Indicated as the location of at least part of the tumor.
[3] Indicated as the laterality of the main bulk of the tumor.
[4] Intraoperative neuromonitoring.

Subjective complaints

Of all patients, 43.3% reported mental and 25.0% physical fatigue (DMFS score ≥ 88th percentile). Furthermore, 20.8% reported depressive complaints and 10.8% reported anxiety complaints (HADS score ≥ 8). Cognitive complaints (PCRS score ≥ 68; DEX score ≥ 75th

percentile) were reported by 2.5-14.2% of the patients. Table 2 shows interrelationships of all subjective complaints. Higher rates of any subjective complaint are associated with higher rates of any other subjective complaint. Correlation coefficients were moderate to strong.

Table 2

Correlation coefficients for intercorrelations of subjective complaints

	Depression	Anxiety	Mental fatigue	Physical fatigue	Cognition[1]	Cognition[2]
	r	*r*	*r*	*r*	*r*	*r*
Depression	-	**.56****	**.40****	**.29****	**-.37****	**.42****
Anxiety	**.56****	-	**.43****	**.42****	**-.45****	**.48****
Mental fatigue	**.40****	**.43****	-	**.48****	**-.45****	**.54****
Physical fatigue	**.29****	**.42****	**.48****	-	**-.43****	**.45****
Cognition[1]	**-.37****	**-.45****	**-.45****	**-.43****	-	**-.61****
Cognition[2]	**.42****	**.48****	**.54****	**.45****	**-.61****	-

Note. *r* = Spearman's Correlation
[1] Cognition based on the PCRS.
[2] Cognition based on the BADS-DEX.
** Significant *p*-value <.01

Tumor volume and subjective complaints

Table 3 shows comparisons of subjective complaints rates between LGG patients with relatively small and large (≥ 135.6 cc) tumor volumes. Mann-Whitney U tests showed statistically significant differences between groups on physical fatigue and cognitive complaints. Thus, patients with relatively large tumors had more complaints of physical fatigue and cognitive functioning. Effect sizes were small. Spearman's correlations between subjective complaints and tumor volume were not significant and are displayed in Table 3 as well.

Table 3

Subjective complaints comparisons between LGG patients with relatively small and large tumor volumes, and correlation coefficients for tumor volume and subjective complaints

	Total (*n* = 120)	Small[1] (*n* = 106)	Large[1] (*n* = 14)	*U*[2]	*p*	*r*[3]	Tumor volume
Subjective complaints	M (SD)	M (SD)	M (SD)				*r*[4]
Depression	5.0 (3.4)	5.1 (3.5)	4.4 (2.5)	689.0	.66	.04	-.06
Anxiety	3.1 (2.9)	2.9 (2.8)	4.6 (3.3)	502.0	.047	.18	-.01
Mental fatigue	21.0 (5.8)	20.7 (6.0)	23.3 (3.6)	533.5	.096	.15	.01
Physical fatigue	15.3 (5.3)	14.8 (5.2)	19.1 (5.2)	399.0	**.005***	.25	.09
Cognition[5]	75.7 (7.3)	76.2 (7.0)	70.9 (9.0)	395.5	.04	.19	-.1
Cognition[6]	17.6 (9.8)	16.6 (9.5)	24.6 (8.7)	400.5	**.006***	.25	.05

Note. M = Mean; SD = Standard Deviation.
[1] Indicated as a tumor volume < or ≥ M + 1.5 SD
[2] Mann-Whitney U test statistic.
[3] Effect size.
[4] Spearman's Correlation.
[5] Cognition based on the PCRS.
[6] Cognition based on the BADS-DEX.
* Significant after Bonferroni-Holm correction.

Tumor location and subjective complaints

Table 4 shows comparisons of subjective complaints between LGG patients with left- and right-sided tumors. Table 5 shows subjective complaints comparisons between LGG patients with frontal and non-frontal tumors. None of the Mann-Whitney U analyses showed significant group mean differences.

Table 4

Subjective complaints comparisons between LGG patients with left- and right-sided tumors

	Left-sided (*n* = 64)	Right-sided (*n* = 56)	*U*[1]	*p*	*r*
Subjective complaints	M (SD)	M (SD)			
Depression	4.9 (3.3)	5.1 (3.6)	1773.5	.92	.01
Anxiety	2.9 (2.7)	3.4 (3.0)	1587.5	.28	.10
Mental fatigue	21.2 (6.1)	20.6 (5.5)	1661.5	.59	.05
Physical fatigue	14.9 (5.4)	15.8 (5.3)	1598.0	.38	.08
Cognition[2]	75.8 (6.6)	75.5 (8.1)	1679.0	.89	.01
Cognition[3]	18.2 (9.6)	16.8 (10.0)	1641.5	.51	.06

Note. M = Mean; SD = Standard Deviation; *r* = Effect size.
[1] Mann-Whitney U test statistic.
[2] Cognition based on the PCRS.
[3] Cognition based on the BADS-DEX.

Table 5

Subjective complaints comparisons between LGG patients with frontal and non-frontal tumors

	Frontal (*n* = 81)	Non-frontal (*n* = 39)	*U*[1]	*p*	*r*
Subjective complaints	M (SD)	M (SD)			
Depression	4.8 (3.3)	5.4 (3.6)	1419.5	.37	.08
Anxiety	3.0 (3.0)	3.3 (2.6)	1400.5	.31	.09
Mental fatigue	20.5 (5.8)	21.9 (5.8)	1345.5	.22	.11
Physical fatigue	15.6 (5.6)	14.7 (4.8)	1445.5	.52	.06
Cognition[2]	75.8 (7.0)	75.5 (8.0)	1498.0	.99	.00
Cognition[3]	18.2 (9.8)	16.3 (9.7)	1377.0	.30	.09

Note. M = Mean; SD = Standard Deviation; *r* = Effect size.
[1] Mann-Whitney U test statistic.
[2] Cognition based on the PCRS.
[3] Cognition based on the BADS-DEX.

Tumor grade and subjective complaints

Table 6 shows comparisons of subjective complaints between LGG patients with grade II and III tumors. Mann-Whitney U tests showed no significant group mean differences for any subjective complaint.

Table 6

Subjective complaints comparisons between LGG patients with grade II and grade III tumors

	Total (*n* = 119)	Grade II[1] (*n* = 93)	Grade III[1] (*n* = 26)	*U*[2]	*p*	*r*
Subjective complaints	M (SD)	M (SD)	M (SD)			
Depression	5.0 (3.4)	4.7 (3.2)	6.1 (3.9)	957.5	.10	.15
Anxiety	3.1 (2.9)	2.8 (2.6)	4.2 (3.3)	886.5	.04*	.19
Mental fatigue	21.0 (5.8)	20.5 (6.0)	22.5 (5.1)	952.5	.11	.15
Physical fatigue	15.3 (5.3)	14.8 (5.0)	17.0 (6.1)	933.0	.09	.16
Cognition[3]	75.7 (7.3)	75.9 (7.5)	74.8 (7.0)	1012.5	.40	.08
Cognition[4]	17.6 (9.8)	16.9 (9.6)	19.4 (10.3)	1017.0	.25	.10

Note. M = Mean; SD = Standard Deviation; *r* = Effect size.
[1] Indicated as the highest glioma grade within the tumor according to WHO 2007.
[2] Mann-Whitney U test statistic.
[3] Cognition based on the PCRS.
[4] Cognition based on the BADS-DEX.
* Non-significant after Bonferroni-Holm correction.

Subjective complaints and life satisfaction

Table 7 shows Spearman's correlation coefficients of subjective complaints and life satisfaction. Significant small and moderate negative correlations were found for fatigue, cognitive complaints measured by the BADS-DEX, and anxiety and satisfaction with relationships with family and friends. Furthermore, significant and small to moderate positive correlations were found for cognitive complaints measured by the PCRS and satisfaction with relationships with family and friends. Thus, higher rates of anxiety, fatigue and cognitive complaints were related to lower satisfaction with relationships with family and friends.

Table 7

Correlation coefficients for subjective complaints and QoL

	Relationship with partner	Relationship with family	Relationship with friends
Subjective complaints	*r*	*r*	*r*
Depression	-.11	-.16	-.14
Anxiety	-.07	**-.34****	**-.35****
Mental fatigue	-.13	**-.20***	-.18
Physical fatigue	-.05	**-.34****	**-.28****
Cognition[1]	.09	**.35****	**.25****
Cognition[2]	-.04	**-.34****	**-.22***

Note. *r* = Spearman's Correlation
[1] Cognition based on the PCRS.
[2] Cognition based on the BADS-DEX.
* Significant p-value <.05
** Significant p-value <.01

Discussion

The present study focused on subjective complaints of LGG patients with relatively good prognosis, post-craniotomy. Relationships between subjective complaints and tumor characteristics, and life satisfaction were investigated. Almost half of the patients reported mental fatigue, one fourth physical fatigue and one fifth depressive complaints. Percentages of cognitive complaints and anxiety were lower (between 2.5 and 14.2%). Relatively large tumor volume was identified as risk factor for higher rates of physical fatigue and cognitive complaints. Subjective complaints were independent of tumor laterality, whether the tumor was frontally located, and grade according to the WHO classification of 2007 (Louis et al., 2007). Furthermore, patients with higher rates of fatigue, cognitive complaints and anxiety had lower life satisfaction.

This study shows that in LGG patients with relatively good prognosis fatigue is as common as in other LGG patients (Schei et al., 2020; Struik et al., 2009). Especially mental fatigue was frequently reported. Such a debilitating symptom can have considerable impact on patients' and caregivers' daily life (Mock et al., 2000), while already having to cope with a highly impactful disease. Screening for and managing mental fatigue is therefore of high importance. According to the cognitive coping hypothesis, accomplishing tasks is more effortful and energy-intensive for patients with brain injury. Patients tire more easily and need more time to recover from fatigue (Johansson et al., 2022). Van Coevorden-van Loon et al. (2017) proposed that the same mechanism contributes to mental fatigue in LGG patients. Therefore, LGG patients suffering from fatigue should be advised and guided in how to organize their daily lives in order to deal with fatigue.

Depressive complaints were frequently reported as well in our patient group, in accordance with studies in other LGG patient groups (Bunevicius et al., 2017; Jarvis et al., 2020; Ley et al., 2022). Although there is no consensus on causing factors of depression in LGG, the impact is obvious, and Renovanz et al. (2017) showed that psychological needs were the highest need of support for glioma patients. In addition, considering that depression in LGG patients can induce tumor growth (Spiegel & Giese-Davis, 2003) and worsen survival (Shi et al., 2018), patients affected should be identified and treated early and adequately.

Cognitive complaints and anxiety had hardly been studied in LGG patients, and not yet in a post-craniotomy setting. The only other study on cognitive complaints in LGG patients showed higher rates than ours. However, patients in their study reported most cognitive complaints during driving and working (Gosselt et al., 2020), situations which the patients in

our study usually do not face at time of assessment. Driving is often prohibited due to epilepsy at tumor presentation, and most patients are not working for they are at the start of an intensive medical trajectory. Two pre-craniotomy studies performed on anxiety rates in LGG patients found higher rates than the present study (Bunevicius et al., 2017; Ley et al., 2022). However, patient's anxiety may be linked to the approaching craniotomy (Ruis et al., 2017). Based on our results, the upcoming proton therapy seems to be less anxiety-inducing. Interestingly, this difference is not apparent when comparing depressive complaints rates in our patient group compared to patients pre-craniotomy. In addition, all subjective complaints were significantly interrelated. Apparently, the complaints tend to present together in these patients, which underlines the necessity for identification of and adequate treatment for affected patients.

Research into the relationship between tumor characteristics and subjective complaints in LGG patients is scarce. The present study focused on tumor volume, laterality, whether the tumor was frontally located, and grade based on the WHO classification of 2007 (Louis et al., 2007). It was the first to find that patients with relatively large tumors had significantly more complaints of physical fatigue and cognition post-craniotomy than patients with relatively small tumors. Thus, patients with large tumors should be given extra attention, for they are at-risk for experiencing subjective complaints and lower QoL.

This was the first study that investigated relationships between a wide range of subjective complaints and tumor laterality in LGG. No differences of subjective complaints between left-hemispheric and right-hemispheric LGG patients were found. Both hemispheres were equally involved in subjective complaints of LGG patients. Our results fit into a currently dominant theory that the brain functions in a network, e.g., with respect to fatigue (Qi et al., 2019), depression (Li et al., 2018), cognition (Basset & Sporns, 2017; Medaglia et al., 2015; Mill et al., 2017) and anxiety (Northoff, 2020). Thus, every LGG patient, regardless of tumor laterality, should be screened for having certain subjective complaints.

In addition, patients with frontal LGG did not report lower rates of complaints than patients with non-frontal LGG. Beforehand, we hypothesized frontal location of the tumor to be associated with reporting less subjective complaints, because of diminished self-awareness in FTD (Mendez & Shapira, 2005) and TBI (Morton et al., 2010). However, whether patients with frontal LGG are as aware of their complaints as patients with non-frontal LGG is unknown because no objective or proxy data were included. Still, based on our study there is no reason to believe that patients with frontal LGG have diminished self-awareness. In contrast to the sudden damage caused by TBI, LGG grow slowly, and the plasticity of the brain may have

ensured new pathways to maintain self-awareness. For now, independent of whether LGG is frontally located, patients do experience subjective complaints, especially mental fatigue, and depressive complaints.

In addition, subjective complaint rates of patients with tumor grade classification II or III based on the 2007 WHO classification (Louis et al., 2007) did not differ significantly. Although still widely used, this classification system is solely based on histologic visual criteria and vulnerable to inter-observer variation (Vigneswaran et al., 2015). Since molecular and cytogenetic biomarkers, like IDH and 1p/19q co-deletion, have appeared to be more accurate in treatment decisions and predicting prognosis (Molinaro et al., 2019), these have been incorporated in the renewed WHO classification system of 2016 (Louis et al., 2016). Our results showing no rate differences of complaints between grade II and III glioma patients verify the 2007 classification becoming less relevant. Future research could investigate whether the WHO 2016 classification is useful for screening for subjective complaints in glioma patients.

Importantly, LGG patients with higher rates of fatigue, cognitive complaints and anxiety had lower satisfaction with relationships with family and friends, a meaningful part of QoL. This study is the first to find these relationships post-craniotomy. Research performed pre-treatment had shown QoL to be associated with fatigue (Buvarp et al., 2022) and anxiety (Ley et al., 2022) in LGG patients. Experiencing subjective complaints and lowered QoL can impact survival time as well (Coomans et al., 2019). Interestingly, even subjective complaints that were not often reported (cognitive complaints and anxiety) were significantly related to life satisfaction. None of the subjective complaints were associated with satisfaction with relationship with the partner. These relationships may be less dependent on subjective complaints than relationships with friends and family. Fatigue, cognitive complaints, and anxiety being related to life satisfaction underlines the importance of early identification and treatment of these complaints in LGG patients.

Next to sufficient strengths, for example high power because of a large patient group, the present study had limitations worth nothing. First, the results cannot be generalized to all LGG patients without further ado. The patient group we included is specific, with favorable prognosis, for they were selected for proton therapy. To display, only 2 out of 120 included patients did not have an IDH-mutated LGG, an important prognostic biomarker related to shorter survival (Bunevicius et al., 2020; Etxaniz et al., 2017), higher rates of cognitive impairment (Derks et al., 2019; van Kessel et al., 2019) and more severe fatigue (Buvarp et al., 2021). Interestingly, even in our favorable prognosis patient group rates of fatigue and

depressive complaints were relatively high. Another limitation is that only one aspect of QoL was assessed, namely satisfaction with relationships. For a more complete picture of QoL, more factors can be included in future studies. A third limitation is that the cut-off point for categorizing tumors was based on GTV mean and standard deviation in our patient group, for no objective criteria were available. However, the cut-off used (≥135.6 cc) is only an indication and should not be a deciding factor in any form.

Lastly, this study focused solely on identifying tumor-related risk factors for subjective complaints. Naturally, other factors may be risk factors as well. By identifying protective factors complaints may even be prevented. Possible protective factors for all subjective complaints are lifestyle factors like eating healthy and physical activity (Johansson et al., 2021; Kelly et al., 2020), or having a strong social support network (Eizaguirre et al., 2020; Orlas et al., 2021). On a biological perspective, specific molecular determinants may be related to subjective complaints, in the same way van Kessel et al. (2022) demonstrated molecular determinants to be associated with neurocognitive deficits. Hao et al. (2021) already identified being female, not having a partner, and suffering from hyperlipidaemia as risk factors for anxiety and depression in LGG patients. For experiencing fatigue higher age was found to be a risk factor (Struik et al., 2009). Future research should proceed in creating risk profiles, in order to efficiently screen and early identify at-risk patients.

In conclusion, the present study showed high rates of subjective complaints, mainly fatigue and depressive complaints, in LGG patients having a relatively good prognosis. Moreover, this study identified a relatively large tumor volume as a risk factor for experiencing physical fatigue and cognitive complaints. Subjective complaint rates were independent of tumor laterality, whether the tumor was frontally located, and tumor grade based on the WHO classification of 2007 (Louis et al., 2007). We believe that all LGG patients should be screened for experiencing subjective complaints, at least fatigue and depression, considering these complaints are common and can negatively impact QoL. If unrealistic, at least patients with relatively large tumor volumes should be screened, and for all subjective complaints. LGG patients experiencing subjective complaints should be treated timely and adequately, for example by psychosocial interventions (Ownsworth et al., 2014), rehabilitation (Kim et al., 2012) or cognitive rehabilitation (Gehring et al., 2009). For patients experiencing mental fatigue psychoeducation can already be effective. Becoming aware of their limitations and gaining knowledge on mental fatigue can help them manage their daily activities. For example, activity balance is crucial (Johansson et al., 2022).

This study investigated subjective complaints in LGG patients on one specific moment in the medical trajectory, namely post-craniotomy, at the start of proton therapy and with the possibility of chemotherapy afterwards. Future research could, in addition to creating risk profiles for LGG patients being affected by subjective complaints, investigate how the complaints change over time and by adjuvant therapy. Consequently, important assessment moments can be determined. Early identification, adequate monitoring and effective treatment of patients being affected by the complaints will hopefully contribute to higher QoL.

Reference list

Andrewes, H. E., Drummond, K. J., Rosenthal, M., Bucknill, A., & Andrewes, D. G. (2013). Awareness of psychological and relationship problems amongst brain tumour patients and its association with carer distress. *Psycho-oncology*, *22*(10), 2200–2205. https://doi.org/10.1002/pon.3274

Bassett, D. S., & Sporns, O. (2017). Network neuroscience. *Nature neuroscience*, *20*(3), 353–364. https://doi.org/10.1038/nn.4502

Boele, F. W., Zant, M., Heine, E. C. E., Aaronson, N. K., Taphoorn, M. J. B., Reijneveld, J. C., Postma, T. J., Heimans, J. J., & Klein, M. (2014). The association between cognitive functioning and health-related quality of life in low-grade glioma patients. *Neuro-Oncology Practice*, *1*(2), 40–46. https://doi.org/10.1093/nop/npu007

Breeman, S., Cotton, S., Fielding, S., & Jones, G. T. (2015). Normative data for the Hospital Anxiety and Depression Scale. *Quality of life research: An international journal of quality of life aspects of treatment, care and rehabilitation*, *24*(2), 391–398. https://doi.org/10.1007/s11136-014-0763-z

Brown, T. J., Bota, D. A., van Den Bent, M. J., Brown, P. D., Maher, E., Aregawi, D., Liau, L. M., Buckner, J. C., Weller, M., Berger, M. S., & Glantz, M. (2019). Management of low-grade glioma: a systematic review and meta-analysis. *Neuro-oncology practice*, *6*(4), 249–258. https://doi.org/10.1093/nop/npy034

Bunevicius, A., Deltuva, V. P., & Tamasauskas, A. (2017). Association of pre-operative depressive and anxiety symptoms with five-year survival of glioma and meningioma patients: a prospective cohort study. *Oncotarget*, *8*(34), 57543–57551. https://doi.org/10.18632/oncotarget.15743

Bunevicius, A., Miller, J., & Parsons, M. (2020). Isocitrate Dehydrogenase, Patient-Reported Outcomes, and Cognitive Functioning of Glioma Patients: a Systematic Review. *Current Oncology Reports*, *22*(12), 120. https://doi.org/10.1007/s11912-020-00978-9

Buunk, A. M., Spikman, J. M., Veenstra, W. S., van Laar, P. J., Metzemaekers, J., van Dijk, J., Meiners, L. C., & Groen, R. (2017). Social cognition impairments after aneurysmal subarachnoid haemorrhage: Associations with deficits in interpersonal behaviour, apathy, and impaired self-awareness. *Neuropsychologia*, *103*, 131–139. https://doi.org/10.1016/j.neuropsychologia.2017.07.015

Buvarp, D., Rydén, I., Sunnerhagen, K. S., Olsson Bontell, T., Gómez Vecchio, T., Smits, A., & Jakola, A. S. (2021). Preoperative Patient-Reported Outcomes in Suspected Low

Grade Glioma: Markers of Disease Severity and Correlations with Molecular Subtypes. *Journal of clinical medicine*, *10*(4), 645. https://doi.org/10.3390/jcm10040645

Cancer Genome Atlas Research Network, Brat, D. J., Verhaak, R. G., Aldape, K. D., Yung, W. K., Salama, S. R., Cooper, L. A., Rheinbay, E., Miller, C. R., Vitucci, M., Morozova, O., Robertson, A. G., Noushmehr, H., Laird, P. W., Cherniack, A. D., Akbani, R., Huse, J. T., Ciriello, G., Poisson, L. M., Barnholtz-Sloan, J. S., … Zhang, J. (2015). Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. *The New England journal of medicine*, *372*(26), 2481–2498. https://doi.org/10.1056/NEJMoa1402121

Cines, S., Farrell, M., Steffener, J., Sullo, L., Huey, E., Karlawish, J., & Cosentino, S. (2015). Examining the Pathways Between Self-Awareness and Well-Being in Mild to Moderate Alzheimer Disease. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*, *23*(12), 1297–1306. https://doi.org/10.1016/j.jagp.2015.05.005

Coomans, M., Dirven, L., K Aaronson, N., Baumert, B. G., van den Bent, M., Bottomley, A., Brandes, A. A., Chinot, O., Coens, C., Gorlia, T., Herrlinger, U., Keime-Guibert, F., Malmström, A., Martinelli, F., Stupp, R., Talacchi, A., Weller, M., Wick, W., Reijneveld, J. C., Taphoorn, M., … EORTC Quality of Life Group and the EORTC Brain Tumor Group. (2019). The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials. *European journal of cancer*, *116*, 190–198. https://doi.org/10.1016/j.ejca.2019.05.012

Correa, D. D., DeAngelis, L. M., Shi, W., Thaler, H. T., Lin, M., & Abrey, L. E. (2007). Cognitive functions in low-grade gliomas: disease and treatment effects. *Journal of neuro-oncology*, *81*(2), 175–184. https://doi.org/10.1007/s11060-006-9212-3

Derks, J., Kulik, S., Wesseling, P., Numan, T., Hillebrand, A., van Dellen, E., de Witt Hamer, P. C., Geurts, J., Reijneveld, J. C., Stam, C. J., Klein, M., & Douw, L. (2019). Understanding cognitive functioning in glioma patients: The relevance of IDH mutation status and functional connectivity. *Brain and behavior*, *9*(4), e01204. https://doi.org/10.1002/brb3.1204

Eizaguirre, M. B., Ciufia, N., Roman, M. S., Martínez Canyazo, C., Alonso, R., Silva, B.,

Pita, C., Garcea, O., & Vanotti, S. (2020). Perceived fatigue in multiple sclerosis: The importance of highlighting its impact on quality of life, social network and cognition. *Clinical Neurology and Neurosurgery*, *199*, 106265. https://doi-org.proxy-ub.rug.nl/10.1016/j.clineuro.2020.106265

Etxaniz, O., Carrato, C., de Aguirre, I., Queralt, C., Muñoz, A., Ramírez, J.L., Rosell, R., Villà, S., Diaz, R., Estival, A., Teixidor, P., Indacochea, A., Ahjal, S., Vilà, L., & Balañà, C. (2017). IDH mutation status trumps the Pignatti risk score as a prognostic marker in low-grade gliomas. *Journal of Neuro-Oncology*, *135*(2), 273–284. https://doi.org/10.1007/s11060-017-2570-1

Gehring, K., Sitskoorn, M. M., Gundy, C. M., Sikkes, S. A., Klein, M., Postma, T. J., van den Bent, M. J., Beute, G. N., Enting, R. H., Kappelle, A. C., Boogerd, W., Veninga, T., Twijnstra, A., Boerman, D. H., Taphoorn, M. J., & Aaronson, N. K. (2009). Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, *27*(22), 3712–3722. https://doi.org/10.1200/JCO.2008.20.5765

Gehring, K., Taphoorn, M. J., Sitskoorn, M. M., & Aaronson, N. K. (2015). Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neuro-oncology practice*, *2*(1), 20–31. https://doi.org/10.1093/nop/npu035

Gosselt, I. K., Scheepers, V., Spreij, L. A., Visser-Meily, J., & Nijboer, T. (2020). Cognitive complaints in brain tumor patients and their relatives' perspectives. *Neuro-oncology practice*, *8*(2), 160–170. https://doi.org/10.1093/nop/npaa078

Gustafsson, M., Edvardsson, T. & Ahlström, G. The relationship between function, quality of life and coping in patients with low-grade gliomas. (2006). *Support Care in Cancer*, *14*(12), 1205–1212. https://doi.org/10.1007/s00520-006-0080-3

Hansen, A., Pedersen, C. B., Minet, L. R., Beier, D., Jarden, J. O., & Søgaard, K. (2021). Hemispheric tumor location and the impact on health-related quality of life, symptomatology, and functional performance outcomes in patients with glioma: an exploratory cross-sectional study. *Disability and rehabilitation*, *43*(10), 1443–1449. https://doi.org/10.1080/09638288.2019.1668486

Hao, A., Huang, J., & Xu, X. (2021). Anxiety and depression in glioma patients: prevalence, risk factors, and their correlation with survival. Irish Journal of Medical Science, *190*(3), 1155–1164. https://doi.org/10.1007/s11845-020-02374-5

Jarvis, C. A., Lin, M., Ding, L., Julian, A., Giannotta, S. L., Zada, G., Mack, W. J., &

Attenello, F. J. (2020). Comorbid depression associated with non-routine discharge following craniotomy for low-grade gliomas and benign tumors – a nationwide readmission database analysis. *Acta Neurochirurgica*, *162*(11), 2671–2681. https://doi.org/10.1007/s00701-020-04559-4

Johansson, B., Andréll, P., Mannheimer, C., & Rönnbäck, L. (2022). Mental fatigue – possible explanations, diagnostic methods and possible treatments. *Lakartidningen*, *119*, 21073.

Johansson, S., Skjerbæk, A. G., Nørgaard, M., Boesen, F., Hvid, L. G., & Dalgas, U. (2021). Associations between fatigue impact and lifestyle factors in people with multiple sclerosis - The Danish MS hospitals rehabilitation study. *Multiple Sclerosis and Related Disorders*, *50*, 102799. https://doi-org.proxy-ub.rug.nl/10.1016/j.msard.2021.102799

Kelly, D. L., Yang, G. S., Starkweather, A. R., Siangphoe, U., Alexander-Delpech, P., & Lyon, D. E. (2020). Relationships Among Fatigue, Anxiety, Depression, and Pain and Health-Promoting Lifestyle Behaviors in Women With Early-Stage Breast Cancer. *Cancer Nursing*, *43*(2), 134–146. https://doi-org.proxy-ub.rug.nl/10.1097/NCC.0000000000000676

Kim, B. R., Chun, M. H., Han, E. Y., & Kim, D. K. (2012). Fatigue assessment and rehabilitation outcomes in patients with brain tumors. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*, *20*(4), 805–812. https://doi.org/10.1007/s00520-011-1153-5

Klein, M., Duffau, H., & De Witt Hamer, P. C. (2012). Cognition and resective craniotomy for diffuse infiltrative glioma: an overview. *Journal of neuro-oncology*, *108*(2), 309–318. https://doi.org/10.1007/s11060-012-0811-x

Klein, M., Heimans, J. J., Aaronson, N. K., van der Ploeg, H. M., Grit, J., Muller, M., Postma, T. J., Mooij, J. J., Boerman, R. H., Imhoff, G.W., va Ossenkoppele, G. J., Dekker, A. W., Jolles, J., Slotman, B. J., Struikmans, H., & Taphoorn, M. J. B. (2002). Effect of radiotherapy and other treatment-related factors on mid to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet*, *377*(9778), 1361–1368. https://doi.org/10.1016/S0140-6736(02)11398-5

Ley, A., Kamp, M. A., von Sass, C., Hänggi, D., Sabel, M. C., & Rapp, M. (2022). Psychooncological distress in low-grade glioma patients—a monocentric study. *Acta Neurochirurgica*, *164*(3), 713–722. https://doi.org/10.1007/s00701-021-04863-7

Li, B. J., Friston, K., Mody, M., Wang, H. N., Lu, H. B., & Hu, D. W. (2018). A brain network model for depression: From symptom understanding to disease intervention. *CNS neuroscience & therapeutics*, *24*(11), 1004–1019. https://doi.org/10.1111/cns.12998

Louis, D. N., Ohgaki, H., Wiestler, O. D., Cavenee, W. K., Burger, P. C., Jouvet, A., Scheithauer, B. W., & Kleihues, P. (2007). The 2007 WHO classification of tumours of the central nervous system. *Acta neuropathologica*, *114*(2), 97–109. https://doi.org/10.1007/s00401-007-0243-4

Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., Ohgaki, H., Wiestler, O. D., Kleihues, P., & Ellison, D. W. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta neuropathologica*, *131*(6), 803–820. https://doi.org/10.1007/s00401-016-1545-1

Luks, T. L., Villanueva-Meyer, J. E., Weyer-Jamora, C., Gehring, K., Jakary, A., Hervey Jumper, S. L., Braunstein, S. E., Bracci, P. M., Brie, M. S., Smith, E. M., Chang, S. M., & Taylor, J. W. (2022). T2 FLAIR Hyperintensity Volume Is Associated With Cognitive Function and Quality of Life in Clinically Stable Patients With Lower Grade Gliomas. *Frontiers in neurology*, *12*, 769345. https://doi.org/10.3389/fneur.2021.769345

Mainio, A., Hakko, H., Niemelä, A., Tuurinkoski, T., Koivukangas, J., & Räsänen, P. (2003). The effect of brain tumour laterality on anxiety levels among neurosurgical patients. *Journal of neurology, neurosurgery, and psychiatry*, *74*(9), 1278–1282. https://doi.org/10.1136/jnnp.74.9.1278

Malec, J. F., Testa, J. A., Rush, B. K., Brown, A. W., & Moessner, A. M. (2007). Self assessment of impairment, impaired self-awareness, and depression after traumatic brain injury. *The Journal of head trauma rehabilitation*, *22*(3), 156–166. https://doi.org/10.1097/01.HTR.0000271116.12028.af

Medaglia, J.D., Lynall, M., & Bassett, D.S. (2015). Cognitive Network Neuroscience. *Journal of Cognitive Neuroscience*, *27*, 1471–1491. https://doi.org/10.1162/jocn_a_00810

Mendez, M. F., & Shapira, J. S. (2005). Loss of insight and functional neuroimaging in frontotemporal dementia. *The Journal of neuropsychiatry and clinical neurosciences*, *17*(3), 413–416. https://doi.org/10.1176/jnp.17.3.413

Mill, R.D., Ito, T., & Cole, M.W. (2017). From connectome to cognition: The search for

mechanism in human functional brain networks. *NeuroImage, 160,* 124-139. https://doi.org/10.1016/j.neuroimage.2017.01.060

Miotto, E. C., Junior, A. S., Silva, C. C., Cabrera, H. N., Machado, M. A., Benute, G. R., Lucia, M. C., Scaff, M., & Teixeira, M. J. (2011). Cognitive impairments in patients with low grade gliomas and high grade gliomas. *Arquivos de neuro-psiquiatria*, *69*(4), 596–601. https://doi.org/10.1590/s0004-282x2011000500005

Mock, V., Atkinson, A., Barsevick, A., Cella, D., Cimprich, B., Cleeland, C., Donnelly, J., Eisenberger, M. A., Escalante, C., Hinds, P., Jacobsen, P. B., Kaldor, P., Knight, S. J., Peterman, A., Piper, B. F., Rugo, H., Sabbatini, P., Stahl, C., & National Comprehensive Cancer Network (2000). NCCN Practice Guidelines for Cancer Related Fatigue. *Oncology (Williston Park, N.Y.), 14*(11A), 151–161.

Molinaro, A. M., Taylor, J. W., Wiencke, J. K., & Wrensch, M. R. (2019). Genetic and molecular epidemiology of adult diffuse glioma. *Nature Reviews Neurology*, *15*(7), 405–417. https://doi.org/10.1038/s41582-019-0220-2

Morton, N., & Barker, L. (2010). The contribution of injury severity, executive and implicit functions to awareness of deficits after traumatic brain injury (TBI). *Journal of the International Neuropsychological Society*, *16*(6), 1089–1098. https://doi.org/10.1017/S1355617710000925

Northoff, G. (2020). Anxiety Disorders and the Brain's Resting State Networks: From Altered Spatiotemporal Synchronization to Psychopathological Symptoms. *Advances in experimental medicine and biology*, *1191*, 71–90. https://doi.org/10.1007/978-981-32-9705-0_5

Olsen, D. R., Bruland, O. S., Frykholm, G., & Norderhaug, I. N. (2007). Proton therapy – a systematic review of clinical effectiveness. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*, *83*(2), 123–132. https://doi.org/10.1016/j.radonc.2007.03.001

Orlas, C. P., Herrera-Escobar, J. P., Hau, K. M., Velmahos, A., Patel, N., Sanchez, S., Kaafarani, H. M. A., Salim, A., & Nehra, D. (2021). Perceived social support is strongly associated with recovery after injury. *The Journal of Trauma and Acute Care surgery*, *91*(3), 552–558. https://doi-org.proxy-ub.rug.nl/10.1097/TA.0000000000003230

Ownsworth, T., Chambers, S., Damborg, E., Casey, L., Walker, D. G., & Shum, D. H. (2015). Evaluation of the making sense of brain tumor program: a randomized controlled trial

of a home-based psychosocial intervention. *Psycho-oncology*, *24*(5), 540–547. https://doi.org/10.1002/pon.3687

Prigatano G. P. (1996). Neuropsychological rehabilitation after brain injury: Scientific and professional issues. *Journal of clinical psychology in medical settings*, *3*(1), 1–10. https://doi.org/10.1007/BF01989285

Polinder, S., Haagsma, J. A., van Klaveren, D., Steyerberg, E. W., & Van Beeck, E. F. (2015). Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. *Population health metrics*, *13*(1), 1–12. https://doi.org/10.1186/s12963-015-0037-1

Qi, P., Ru, H., Gao, L., Zhang, X., Zhou, T., Tian, Y., Thakor, N., Bezerianos, A., Li, J., & Sun, Y. (2019). Neural Mechanisms of Mental Fatigue Revisited: New Insights from the Brain Connectome. *Engineering*, *5*(2), 276–286. https://doi.org/10.1016/j.eng.2018.11.025

Renovanz, M., Hechtner, M., Janko, M., Kohlmann, K., Coburger, J., Nadji-Ohl, M., König, J., Ringel, F., Singer, S., & Hickmann, A. K. (2017). Factors associated with supportive care needs in glioma patients in the neuro-oncological outpatient setting. *Journal of neuro-oncology*, *133*(3), 653–662. https://doi.org/10.1007/s11060-017-2484-y

Rijnen, S. J. M., Gülizar, K., Gehring, K.; Verheul, J. B., Wallis, O., Sitskoorn, M. M., & Rutten, G. M. (2019). Cognitive functioning in patients with low-grade glioma: effects of hemispheric tumor location and surgical procedure. *Journal of Neurosurgery*, *133*(6), 1–12. https://doi.org/10.3171/2019.8.JNS191667

Ruis, C., Wajer, I. H., Robe, P., & van Zandvoort, M. (2017). Anxiety in the preoperative phase of awake brain tumor surgery. *Clinical neurology and neurosurgery*, *157*, 7–10. https://doi.org/10.1016/j.clineuro.2017.03.018

Sasse, N., Gibbons, H., Wilson, L., Martinez-Olivera, R., Schmidt, H., Hasselhorn, M., von Wild, K., & von Steinbüchel, N. (2013). Self-awareness and health-related quality of life after traumatic brain injury. *The Journal of head trauma rehabilitation*, *28*(6), 464–472. https://doi.org/10.1097/HTR.0b013e318263977d

Schei, S., Solheim, O., Jakola, A. S., & Sagberg, L. M. (2020). Perioperative fatigue in patients with diffuse glioma. *Journal of neuro-oncology*, *147*(1), 97–107. https://doi.org/10.1007/s11060-020-03403-0

Schei, S., Solheim, O., Salvesen, Ø., Hjermstad, M. J., Bouget, D., & Sagberg, L. M. (2022).

Pretreatment patient-reported cognitive function in patients with diffuse glioma. *Acta neurochirurgica*, *164*(3), 703–711. https://doi.org/10.1007/s00701-022-05126-9

Schiff, D., Van den Bent, M., Vogelbaum, M. A., Wick, W., Miller, C. R., Taphoorn, M., Pope, W., Brown, P. D., Platten, M., Jalali, R., Armstrong, T., & Wen, P. Y. (2019). Recent developments and future directions in adult lower-grade gliomas: Society for Neuro-Oncology (SNO) and European Association of Neuro-Oncology (EANO) consensus. *Neuro-oncology*, *21*(7), 837–853. https://doi.org/10.1093/neuonc/noz033

Shi, C., Lamba, N., Zheng, L. J., Cote, D., Regestein, Q. R., Liu, C. M., Tran, Q., Routh, S., Smith, T. R., Mekary, R. A., & Broekman, M. (2018). Depression and survival of glioma patients: A systematic review and meta-analysis. *Clinical neurology and neurosurgery*, *36*(15), 8–19. https://doi.org/10.1016/j.clineuro.2018.06.016

Spiegel, D., & Giese-Davis, J. (2003). Depression and cancer: mechanisms and disease progression. *Biological psychiatry*, *54*(3), 269–282. https://doi.org/10.1016/s0006-3223(03)00566-3

Struik, K., Klein M., Heimans J. J., Gielissen M. F., Bleijenberg G., Taphoorn M. J., Reijneveld J. C., Postma T. J. (2009). Fatigue in low-grade glioma. *Journal of Neuro oncology*, *92*(1), 73–78. https://doi.org/10.1007/s11060-008-9738-7

Stuss, D.T., & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual review of psychology*, *53*, 401–433. https://doi.org/10.1146/annurev.psych.53.100901.135220

Valko, P. O., Siddique, A., Linsenmeier, C., Zaugg, K., Held, U., & Hofer, S. (2015). Prevalence and predictors of fatigue in glioblastoma: a prospective study. *Neuro oncology*, *17*(2), 274–281. https://doi.org/10.1093/neuonc/nou127

van Coevorden-van Loon, E. M. P., Coomans, M. B., Heijenbrok-Kal, M. H., Ribbers, G. M., & Van den Bent, M. J. (2017). Fatigue in patients with low grade glioma: systematic evaluation of assessment and prevalence. *Journal of Neuro-Oncology*, *133*(2), 237–246. https://doi.org/10.1007/s11060-017-2454-4

van Coevorden-van Loon, E., Heijenbrok-Kal, M. H., Horemans, H., Boere, R., de Bat, R., Vincent, A., van den Bent, M. J., & Ribbers, G. M. (2021). The relationship between mental fatigue, cognitive functioning, and employment status in patients with low grade glioma: a cross-sectional single-center study. *Disability and rehabilitation*, 1–7. https://doi.org/10.1080/09638288.2021.1991013

van der Weide, H. L., Kramer, M. C. A., Scandurra, D., Eekers, D. B. P., Klaver, Y. L. B., Wiggenraad, R. G. J., Méndez Romero, A., Coremans, I. E. M., Boersma, L., Van Vulpen, M., & Langendijk, J. A. (2021). Proton therapy for selected low grade glioma patients in the Netherlands. *Radiotherapy and Oncology*, *154*, 283–290. https://doi.org/10.1016/j.radonc.2020.11.004

van Kessel, E., Baumfalk, A. E., van Zandvoort, M., Robe, P. A., & Snijders, T. J. (2017). Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *Journal of neuro-oncology*, *134*(1), 9–18. https://doi.org/10.1007/s11060-017-2503-z

van Kessel, E., Berendsen, S., Baumfalk, A. E., Venugopal, H., Krijnen, E. A., Spliet, W. G. M., Van Hecke, W., Giuliani, F., Seute, T., Van Zandvoort, M. J. E., Snijders, T. J., Robe, P. A. (2022). Tumor-related molecular determinants of neurocognitive deficits in patients with diffuse glioma. *Neuro-Oncology*, *23*(6). https://doi.org/10.1093/neuonc/noac036

van Kessel, E., Emons, M. A., Wajer, I. H., van Baarsen, K. M., Broekman, M. L., Robe, P. A., Snijders, T. J., & Van Zandvoort, M. J. (2019). Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. *Neuro-oncology practice*, *6*(6), 463–472. https://doi.org/10.1093/nop/npz008

van Kessel, E., Huenges Wajer, I., Ruis, C., Seute, T., Fonville, S., De Vos, F., Verhoeff, J., Robe, P. A., van Zandvoort, M., & Snijders, T. J. (2021). Cognitive impairments are independently associated with shorter survival in diffuse glioma patients. *Journal of neurology*, *268*(4), 1434–1442. https://doi.org/10.1007/s00415-020-10303-w

van Loon, E. M., Heijenbrok-Kal, M. H., van Loon, W. S., van den Bent, M. J., Vincent, A. J., de Koning, I., & Ribbers, G. M. (2015). Assessment methods and prevalence of cognitive dysfunction in patients with low-grade glioma: A systematic review. *Journal of rehabilitation medicine*, *47*(6), 481–488. https://doi.org/10.2340/16501977-1975

Verhage, F. (1964). Intelligentie en leeftijd: onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. Assen: Van Gorcum.

Vigneswaran, K., Neill, S., & Hadjipanayis, C. G. (2015). Beyond the World Health Organization grading of infiltrating gliomas: advances in the molecular genetics of glioma classification. *Annals of translational medicine*, *3*(7), 95.

https://doi.org/10.3978/j.issn.2305-5839.2015.03.57

Visser-Keizer A. C., Hogenkamp A., Westerhof-Evers H. J., Egberink I. J., Spikman J. M. (2015). Dutch multifactor fatigue scale: a new scale to measure the different aspects of fatigue after acquired brain injury. *Archives of Physical Medicine and Rehabilitation*, *96*(6), 1056–1063. https://doi.org/10.1016/j.apmr.2014.12.010

Wilson, B.A., Alderman, N., Burgess, P.W., Emslie, H.E., & Evans, J.J. (1996). *Behavioural Assessment of the Dysexecutive Syndrome.* Bury St Edmunds: Thames Valley Test Company.

Zigmond, A. S. & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zimmermann, N., Pereira, A.P., & Fonseca, R.P. (2014). Brazilian Portuguese version of the Patient Competency Rating Scale (PCRS-R-BR): semantic adaptation and validity. *Trends in psychiatry and psychotherapy*, *36*(1), 40–51. https://doi.org/10.1590/2237-6089-2013-0021