The Relationship between Mental Fatigue, Information Processing Speed and Complex Attention in Patients with Low Grade Glioma

Master thesis Clinical Neuropsychology

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Abstract

Objective: The author's aim was twofold: (1) to investigate the prevalence and severity of different facets of fatigue and impairments in simple information processing speed, response inhibition and divided attention in patients with low grade glioma (LGG) and (2) to examine the relationship between mental fatigue and these three cognitive functions in patients with LGG. ***Method***: Patients with LGG were assessed with neuropsychological tests measuring simple information processing speed (VTS RT-S1 and RT-S2), response inhibition (VTS RT-S3) and divided attention (VTS DT-S1). Different facets of fatigue were measured with a multidimensional fatigue scale, the Dutch Multifactor Fatigue Scale (DMFS). Descriptive statistics and between group comparisons were performed. ***Results***: In total, 124 patients with LGG were included. Approximately forty percent of LGG patients reported severe mental fatigue and a high impact of their fatigue on daily life. A quarter reported severe physical fatigue. Regarding cognitive functioning, simple information processing speed was impaired in 1-3% of patients, while frequencies of impairment in response inhibition and divided attention were 21% and 27% respectively. Furthermore, at group level no significant differences were found in mean performance on simple information processing speed, response inhibition and divided attention between severely mental fatigued patients and non-severely mental fatigued patients. However, we found that the percentage of patients with impaired divided attention was significantly higher in the severely mental fatigued group compared to the non-severely mental fatigued group. ***Conclusions***: Patients with low grade glioma show high rates of fatigue, especially in the mental domain. Complex attention was impaired in around a quarter of patients with LGG, while simple information processing speed remained relatively intact. As we only found a relationship between impaired divided attention and severe mental fatigue, results imply that the higher the cognitive load of a test, the larger the difference in performance between severely fatigued and non-fatigued patients. Considering the importance of mental fatigue and complex attention for daily functioning, and following the results of the present study, it is recommended to assess both constructs and its relationship thoroughly in order to develop rehabilitation programs specifically tailored to the needs of patients with LGG.

Introduction

Low grade gliomas (LGG) are primary diffusely infiltrative brain tumors of glial origin that often arise in young adults (Claus et al., 2015; Smits & Jakola, 2019). Gliomas are classified from grade I to IV based on morphological and molecular features as specified in the World Health Organization (WHO) Classification of Tumours of the Central Nervous System. Grade II gliomas are regarded as low grade, whereas grades III and IV include high grade gliomas (Louis et al., 2007; Louis et al., 2016). It is estimated that approximately 70% of LGG undergo anaplastic progression into a higher-grade glioma within 5-10 years (Furnari et al., 2007). However, due to new and improved treatment options (commonly a combination of surgical resection, radiation therapy and/or chemotherapy), the median life expectancy of LGG patients has increased in recent decades, ranging from 4 to 13 years (van den Bent, 2014; Schomas et al., 2009; van der Weide et al., 2020). Consequently, this led to increased attention for patients' quality of life, as patients with LGG often report a large array of complaints, such as fatigue, cognitive problems and symptoms of depression and anxiety (Wefel et al., 2008).

Fatigue in patients with cancer is the most prevalent and important cause of loss of quality of life for both the patient and caregiver (Gustafsson et al., 2006; Mock et al., 2000). However, fatigue and its associated factors have not been extensively studied in patients with LGG. Reported frequencies vary from 39% to 77%, depending on the definition and instrument used (van Coevorden-van Loon, 2017). Fatigue in LGG patients is often investigated as a unitary construct and measured with a limited number of items from a quality of life scale. However, fatigue after brain injury is a multidimensional phenomenon with various modes of expression (e.g., mental, physical, emotional and experienced impact on daily life) and should therefore be comprehensively assessed with a multidimensional instrument (Pattyn et al., 2018; Struik et al., 2009). While these different components of fatigue are of great influence on quality of life, specifically mental fatigue has shown to be debilitating in patients with brain injury (Kluger et al., 2013). Mental fatigue is described as a sustained feeling of exhaustion and lack of mental energy and initiative after performing mentally demanding activities (Johansson & Rönnbäck, 2014). Unfortunately, only two studies have used a multidimensional instrument to assess mental fatigue in patients with LGG. Van Coevorden-van Loon et al. (2021) found high rates on all subscales of the Multidimensional Fatigue Inventory-20 (MFI-20), and specifically mental fatigue (subscales are mental fatigue, physical fatigue, reduced activity and reduced motivation). However, the MFI-20 is not specifically designed for patients with brain injury and this study only included a small group of LGG patients (n=31) of whom the majority received a combination of treatments more than three months before assessment (resection, radiation therapy and/or chemotherapy). Gehring et al. (2009) also found high scores on the MFI-20, but did not study fatigue as a primary outcome and excluded subscales. Research on other aspects of fatigue, such as physical and emotional influences, is even more limited in patients with LGG. It is crucial to conduct more extensive research on fatigue as a multidimensional construct in this patient group, as these different facets of fatigue presumably require different types of treatment.

A possible factor underlying fatigue in glioma patients is cognitive impairment. While patients with glioma often experience impairment in physical and emotional functioning, specifically deficits in neurocognitive functioning negatively affects daily functioning and quality of life (Habets et al., 2019). Impairments are possible in all cognitive domains, but attentional deficits are suggested to be the most common (30% of LGG patients) (van Coevorden-van Loon et al., 2021; Ek et al., 2010; Gehring et al., 2010; Habets et al., 2019; van Kessel et al., 2017). However, the available literature is very heterogeneous regarding the neuropsychological tests used, making it difficult to compare results between studies (van Coevorden-van Loon et al., 2015; van Kessel et al., 2017). Related to this complication is the fact that many studies classify the subtests differently, do not report results of subtests or specify which neuropsychological tests were used. Furthermore, not all cognitive tests may be appropriate to use in this patient group. Short assessments and simple screenings are not sufficient to detect the often subtle cognitive deficits in patients with LGG. Sensitive and wide-ranged tests are therefore required to detect these milder neurocognitive deficits in LGG patients (van Kessel et al., 2017). The majority of studies on cognitive functioning in LGG patients used the Trailmaking Test (TMT) and Stroop Color-Word Test (SCWT) to measure processing speed, attention and inhibition, an element of executive functioning. However, these tests also tap into other cognitive domains and processes. For instance, the TMT requires visual search strategies and motor speed; and the SCWT requires verbal speed. A test that disentangles the confounding effects of peripheral slowness and central slowness and that permits distinguishing reaction and motor times may be more appropriate to measure simple information processing speed and attention (Spikman & van Zomeren, 2010). The Vienna Test System (VTS) Reaction Time (RT) and Determination Test (DT) allows for this disentanglement, but has not yet been applied to measure simple information processing speed, response inhibition and divided attention in patients with LGG.

Another factor that may be considered an underlying mechanism of fatigue is psychological symptoms. Studies suggest that patients with LGG experience increased levels of depression (15%-48%) and anxiety (21%) (Alessandra et al., 2021; Mainio et al., 2006;

Rooney et al., 2011). Although not extensively studied in patients with LGG, depression, and to a lesser degree anxiety, have been found to have relatively high correlations with fatigue in several patient populations, including cancer patients (Brown & Kroenke, 2009; Day et al., 2015). It is therefore suggested to control for these psychological factors when investigating fatigue and cognitive functioning in patients with LGG

Regarding mental fatigue and cognitive functioning, only a singular study has examined this relationship in patients with LGG. Van Coevorden-van Loon et al. (2021) showed that mentally fatigued patients perform worse than non-mentally fatigued patients on various attention, inhibition and mental flexibility tasks (SCWT card II and III; TMT-B). However, results were inconsistent in cognitive domains and may not be generalizable to the whole LGG population, as results are based on a small group of patients with mostly WHO grade II IDH-mutant tumors (n=31). Furthermore, simple information processing speed was not examined.

The relationship between mental fatigue and cognitive functioning has been better established in patients with traumatic brain injury (TBI). A recent systematic review stated that several studies have demonstrated that mental fatigue is related to slower information processing speed and problems in attention in mild TBI patients (Johansson, 2021). Some studies found worse performance on more demanding attentional tasks to be related to mental fatigue (Hattori et al., 2009), but this relationship is also found with automatic and simple attention measures in mild TBI patients (Johansson et al., 2009). However, other studies on mild to severe TBI only find complex attention to be associated with mental fatigue (Stuss, 1989; Ziino & Ponsford, 2006). For instance, Möller et al. (2014) found decreased performance for a mild TBI group who reported more mental fatigue than controls in a demanding divided attention task. However, they did not find this decrease to be present for less demanding tests involving simple information processing speed and automatic attention. These inconsistencies in results demonstrate a complex relationship between mental fatigue, information processing speed and attention that is not yet understood.

More research is needed on the role of different facets of fatigue, attentional functioning and the relationship between both factors in LGG patients. Therefore, the aim of the present study is twofold. First, to investigate the prevalence and severity of different facets of fatigue and impairments in simple information processing speed, response inhibition and divided attention in LGG patients. Secondly, to examine the relationship between mental fatigue and these three cognitive functions in LGG patients.

Method

Patients and procedure

This study is part of a larger research project in which LGG patients were included who receive proton therapy in the UMCG Proton Therapy Center in Groningen, the Netherlands. Patients with confirmed WHO grade I, II and III gliomas, who were treated between November 2017 and February 2022, were eligible for inclusion in the present study. Exclusion criteria were age under 18, diagnosis with any additional neurological disease and/or psychiatric disorder, alcohol or drugs abuse, indicative performance on a symptom validity test during neuropsychological assessment and insufficient mastery of the Dutch language.

All patients completed a battery of standardized neuropsychological tests at the UMCG, before the start of proton therapy. The battery contained tests measuring a wide range of cognitive domains and has an administration time of approximately 150 minutes. Self-report questionnaires were completed during the visit or could be completed later and returned by postal mail. Demographical data and tumor characteristics were obtained during the assessment or from patients' medical reports. The study was approved by the Medical Ethical Committee of the UMCG. All participants provided written informed consent and were treated in accordance with the Declaration of Helsinki.

Measurement instruments

Speed of information processing

Two simple information processing tasks (RT-S1 and RT-S2) of the computerized Vienna Test System (VTS) (Prieler, 2008) were used to assess the ability to react under simple stimulus constellations by measuring reaction time and motor time separately. During the task, participants need to place their dominant index finger on a rest key and react as quickly as they can to optical (RT-S1) or acoustic (RT-S2) stimuli by pressing a response key. Both tasks consisted of five practice trials and 28 test trials. Two scores were calculated for each participant: (1) the mean reaction time (RT), that is the mean time between the appearance of the stimulus and lifting the index finger and (2) the mean motor time (MT), the mean time between lifting the index finger and pressing the response key. Times in milliseconds are converted to percentiles adjusted for age group. Only the RT was used in the present study. The RT-S1 and RT-S2 have shown to have good reliability and validity (Prieler, 2008).

Response inhibition

Response inhibition was measured with the RT-S3 of the VTS (Prieler, 2008), which assesses the ability to react to a critical stimulus combination, including an inhibitory element. During the task, participants are asked to place their dominant index finger on a rest key and react as quickly as they can to a certain stimulus combination (optical and acoustic), while inhibiting responses to other simultaneous or sequentially presented stimuli combinations. Equivalent to the information processing tasks, the RT and MT are calculated for each participant in milliseconds. These scores are converted to percentiles adjusted for age group. Only the RT was used in the present study. The RT-S3 has shown to have good reliability and validity (Prieler, 2008).

Divided attention

Divided attention was measured with the Determination Test-S1 (DT-S1) of the VTS (Neuwirth & Benesch, 2007). The DT-S1 assesses the ability to react under complex multi-stimuli conditions, having to sustain continuous and diverse responses in a fast pace, making it necessary for the participant to divide their attention. Participants had to react to different auditory and visual signals by pressing the corresponding buttons or foot pedals. The speed of the presentation of the stimuli was automatically adapted to the participant's response to make the subjective difficulty of the test sufficiently high. The test takes four minutes, and the outcome is the number of accurate responses, which is converted to a percentile adjusted to age group. The DT-S1 has shown to have good reliability and validity (Neuwirth & Benesch, 2007).

Fatigue

Different facets of fatigue were measured with the Dutch Multifactor Fatigue Scale (DMFS) (Visser-Keizer et al., 2015). The DMFS is a multidimensional scale designed to measure fatigue in patients with brain injury and is subdivided into five scales: (1) mental fatigue, addressing precursors and consequences of mental fatigue (range 7-35) (Mental-f); (2) physical fatigue, addressing physical fitness and precursors and consequences of physical fatigue (range 6-30) (Physical-f); (3) signs and direct consequences of fatigue, addressing emotional and physical symptoms that directly co-occur with fatigue (range 9-45) (Signs-f); (4) impact of fatigue, addressing the impact of fatigue patients experience on their life in general (Impact-f) and (5) coping with fatigue, addressing the ability of patients to signal fatigue and use this signal to adapt to fatigue (Coping-f). The scale consists of 38 items and each item is scored on a five-point Likert scale (1 = totally disagree to 5 = totally agree). Scores on the subscales were compared to a norm group based on 129 healthy control participants and are converted to percentile ranges. All subscales have a sufficient to good reliability and validity.

Depression and anxiety

The Hospital and Depression Scale (HADS) (Zigmond & Snaith, 1983) was used to compare reports of depression (HADS-D) and anxiety (HADS-A) between severely mental fatigued and non-severely mental fatigued patients. Higher scores indicate higher symptom frequency. Three thresholds are recommended: ≥ 7 for a mild indication; ≥ 11 for a moderate indication and ≥ 15 for a severe indication (with a maximum of 21). We used a cut-off of ≥ 7 to define increased levels of depression and anxiety.

Statistical analysis

Statistical analyses were conducted using SPSS software, version 23.0 (SPSS Inc. Armonk, NY, USA). Educational level was recorded with the Dutch classification system of Verhage (1964), ranging from 1 (no primary school) to 7 (university). Test data were assessed for normality using quantile-quantile (Q-Q) plots, non-parametric alternatives were applied in case of not-normally distributed scores. Test performances were examined in contrast to normative data as used in clinical practice and performances below the tenth percentile were considered impaired (Lezak et al., 2004).

Scores on the DMFS Mental-f subscale were dichotomized into two patient groups as ‘non-severe mental fatigue’ (0-88 percentile) and ‘severe mental fatigue’ (89-100 percentile). Differences between groups on demographical, clinical and psychological factors were analyzed with Mann-Whitney *U* and Pearson Chi-Squared tests. Differences in mean percentiles of cognitive performance between the two mental fatigue groups were investigated using Mann-Whitney *U* tests. Additionally, Pearson Chi-squared tests were performed to compare the percentages of impaired performance between the severely mental fatigued group and non-severely mental fatigued group. Effect sizes (*r* and *phi*) were calculated. The overall alpha level was set at 0.05, two sided.

Results

Participant characteristics

In total, 124 patients were included in this study. Table 1 shows the sociodemographic and tumor characteristics of all patients.

Table 1

Sociodemographic and tumor characteristics of LGG patients.

Characteristic	patients (n=124)
Sex, number of women (%)	59 (47.6%)
Age in years, mean (SD)	42.1 (12.5)
Educational level, mean (SD)	5.2 (1.0)
Diagnosis	
Oligodendroglioma, n (%)	60 (48.4%)
Astrocytoma, n (%)	62 (50.0%)
Pilocytic astrocytoma, n (%)	1 (0.8%)
Ependymoma, n (%)	1 (0.8%)
WHO tumor grade[a]	
Grade I, n (%)	1 (0.8%)
Grade II, n (%)	99 (79.8%)
Grade III, n (%)	24 (19.4%)
Histopathology	
IDH-mutated	119 (96%)
IDH-wildtype	2 (1.6%)
Unknown	3 (2.4%)
Lateralization[b]	
Left-sided, n (%)	66 (53.2%)
Right-sided, n (%)	54 (43.5%)
Bilateral, n (%)	4 (3.2%)
Tumor location[c]	
Frontal, n (%)	82 (66.1%)
Temporal, n (%)	24 (19.4%)
Parietal, n (%)	22 (17.7%)
Occipital, n (%)	6 (4.8%)
Insular, n (%)	9 (7.3%)
Other[d], n (%)	11 (8.9%)
Type of surgery	
Basic craniotomy, n (%)	51 (41.1%)
Advanced craniotomy (awake craniotomy or intraoperative neurophysiological monitoring), n (%)	53 (42.7%)
Unknown	12 (9.7%)
Other treatments	
Chemotherapy, n (%)	4 (2.6%)
Radiotherapy, n (%)	0 (0.0%)

Comorbidity	
Depressive symptoms (HADS-D)	
Mild (score 8-10)	17 (13.7%)
Moderate (score 11-14)	7 (5.6%)
Severe (score 15-21)	1 (0.8%)
Anxiety symptoms (HADS-A)	
Mild (score 8-10)	12 (9.7%)
Moderate (11-14)	1 (0.8%)
Severe (15-21)	0 (0.0%)

Note. Educational level is according to Verhage classification system, ranging from 1 (no primary school) to 7 (university); WHO = World Health Organization.
[a] Indicated as the highest glioma grade within the tumor according to WHO 2006.
[b] Laterality of the main bulk of the tumor.
[c] Presence of tumor may overlap in multiple location domains.
[d]Corpus callosum, cingulate gyrus, brain stem, thalamus, basal ganglia and cerebellum.

Fatigue: prevalence and severity

Mean scores and the prevalence of severe fatigue per DMFS subscale are shown in Table 2.

No significant differences were found between severely mental fatigued patients and non-severely mental fatigued patients in terms of sex, educational level, type of glioma, WHO tumor grade, lateralization and location of the tumor (all $p > 0.05$). Importantly, there were also no significant differences in increased depression or anxiety scores between the two fatigue groups (HADS-D: $X^2 = 0.55$ (1, 113), $p = .460$; HADS-A: $X^2 = 1.19$ (1, 99), $p = .276$). However, there was a significant difference in terms of age (fatigued M = 45.0 years [SD = 11.4 years]; non-fatigued M = 40.2 years [SD = 12.9 years]; $Z = -2.308$; $p = .021$).

Table 2

Fatigue characteristics of the patients, measured with the DMFS (n=124).

DMFS subscales	Score, mean (SD)	Severe fatigue[a], n (%)
Mental-f	20.9 (5.9)	51 (41.1%)
Physical-f	15.3 (5.3)	31 (25.0%)
Impact-f	27.4 (10.1)	47 (37.9%)
Signs-f	24.0 (6.8)	43 (34.7%)
Coping-f	14.1 (3.5)	19 (15.3%)

Note. DMFS, Dutch Multifactor Fatigue Scale; Mental-f, Mental fatigue; Physical-f, Physical fatigue; Impact-f, Impact of fatigue; Signs-f, Signs and direct consequences of fatigue; Coping-f, Coping with fatigue. Mean, in raw scores. SD, standard deviation.
[a] Severe fatigue is defined as scores above the 89^{th} percentile.

Cognitive impairment: prevalence and severity

In simple information processing speed, impairments were observed in 0.8-3.2% of the patients for RT-S1, RT-S2 and the summary score of these two tests. Regarding response inhibition, 21.1% of patients demonstrated impaired scores on the RT-S3. In the domain of divided attention, 26.7% of patients showed impairment on the DT-S1 accuracy score. Overall results and frequencies of impaired scores are detailed in Table 3.

Table 3

Cognitive functioning in LGG patients: percentiles and percentages of impaired scores.

Neuropsychological test	N	M (SD)	Impaired, n (%)
Simple information processing speed			
VTS RT-S1, mean reaction time	124	61.7 (26.6)	4 (3.2%)
VTS RT-S2, mean reaction time	123	65.1 (29.1)	2 (1.6%)
Summary score of RT-S1 and RT-S2	123	63.2 (24.8	1 (0.8%)
Response inhibition			
VTS RT-S3, mean reaction time	123	35.7 (26.6)	26 (21.1%)
Divided attention			
VTS DT-S1, accuracy score	120	31.1 (26.6)	32 (26.7%)

Note. VTS, Vienna Test System. Summary score of RT-S1 and RT-S2, mean of RT-S1 and RT-S2 percentiles per patient. M, mean in percentiles. SD, standard deviation in percentiles. Impaired, scores below tenth percentile.

Cognitive functioning and mental fatigue

Mann-Whitney *U* tests showed no significant differences in mean scores on all neuropsychological tests between severely mental fatigued patients and non-severely mental fatigued patients (Table 4).

Additionally, Chi-squared tests were performed with an added impaired and non-impaired group. In simple information processing speed and response inhibition, there were no significant differences in the percentages impaired between the severely mental fatigued and non-severely mental fatigued group. However, on divided attention the percentage impaired in the severely mental fatigued group (38.8%) is significantly higher than in the non-severely mental fatigued group (16.2%). Overall results are detailed in Table 5; results on divided attention are displayed with a graph (Figure 1).

Table 4

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

Neuropsychological test	Severely mental fatigued patients (n=51), mean percentiles (SD)	Non-severely mental fatigued patients (n=70), mean percentiles (SD)	*p* value [a]	*r* [b]
Simple information processing speed				
VTS RT-S1, mean reaction time	59.5 (25.6)	62.5 (27.7)	0.461	-0.067
VTS RT-S2, mean reaction time	64.1 (29.1)	65.6 (28.8)	0.880	-0.014
Summary score of RT-S1 and RT-S2	61.8 (24.6)	63.8 (25.0)	0.644	-0.042
Response inhibition				
VTS RT-S3, mean reaction time	30.6 (25.1)	38.1 (26.1)	0.117	-0.143
Divided attention				
VTS, DT-S1, accuracy score	26.5 (24.5)	34.9 (27.6)	0.076	-0.164

Note. VTS, Vienna Test System.
[a]Mann-Whitney *U* tests. [b]*r*, effect size. **p* value <05.

Table 5

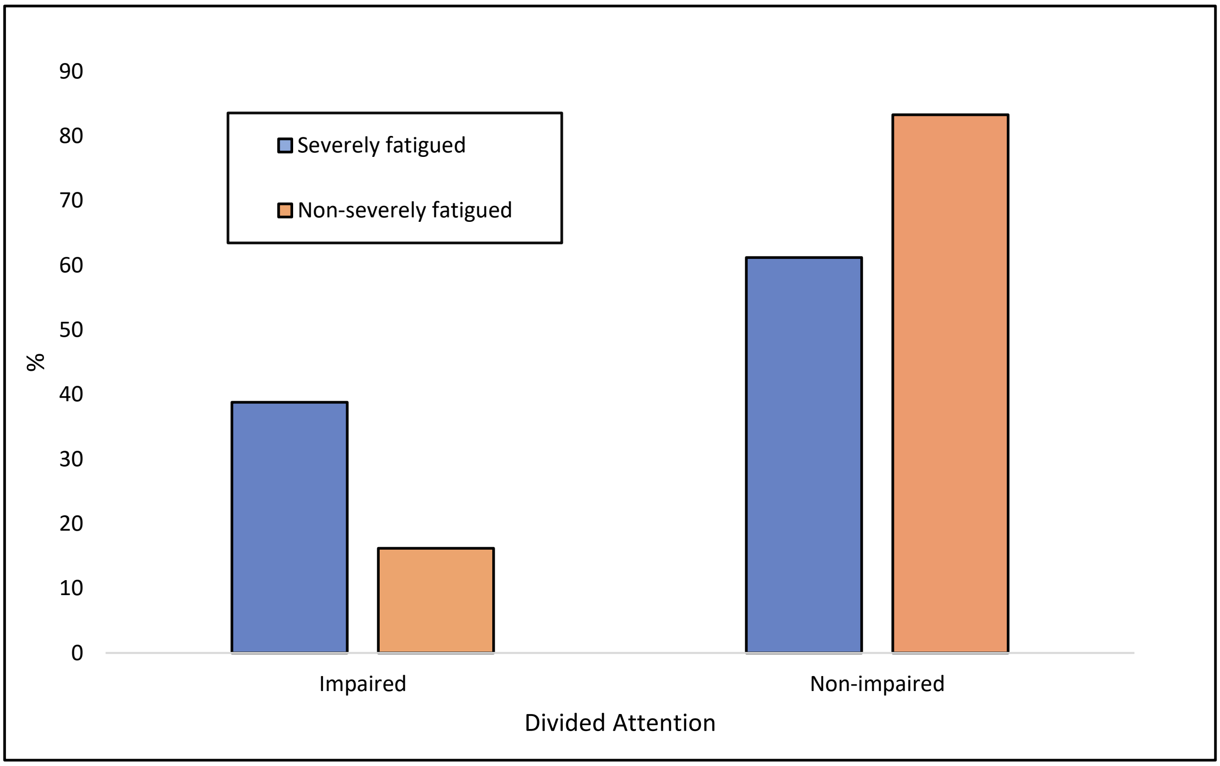
Chi-squared test results of impaired and non-impaired neuropsychological performance between severely mental fatigued and non-severely mental fatigued patients (n=120).

	Severely mental fatigued, n (%) (n=51)	Non-severely mental fatigued, n (%) (n=69)	X^{2a}	*p value*	Φ^b
Simple information processing speed			1.364	0.243	0.107
Impaired[c]	1 (2.0%)	0 (0.0%)			
Response inhibition			0.764	0.382	0.080
Impaired[c]	13 (25.5%)	13 (18.8%)			
Divided attention			7.628	**0.006***	0.255
Impaired [c]	19 (38.8%)	11 (16.2%)			

Note. Information processing, summary score of RT-S1 and RT-S2; Response inhibition, RT-S3 mean reaction time; Divided attention, DT-S1 accuracy score.
[a] Pearson Chi-squared test value. [b] *Phi*, effect size. [c]Impaired, scores below the tenth percentile. *Significant *p* value <.05.

Figure 1

Percentages of impaired and non-impaired neuropsychological performance in divided attention between severely mental fatigued and non-severely mental fatigued patients.



Note. Divided attention, VTS DT-S1 accuracy score. Impaired, scores below the tenth percentile.

Discussion

The present study aimed to better understand different facets of fatigue, simple information processing speed, response inhibition and divided attention in patients with LGG. Secondly, the relationship between mental fatigue and these three cognitive functions was investigated. Approximately forty percent of LGG patients reported severe mental fatigue and a high impact of their fatigue on daily life. Regarding attentional functioning, simple information processing speed seemed to be relatively intact, while approximately one fifth to one fourth of LGG patients perform impaired on response inhibition and divided attention tasks. Furthermore, we found significantly more patients with an impairment in divided attention in the severely mental fatigued group compared to the non-severely mental fatigued group.

The outcomes of the present study showed that multiple aspects of fatigue are present in many LGG patients. Severe mental fatigue was found to be frequent in patients with LGG (41%) and 38% of all patients experienced a high impact of fatigue on daily life. Physical fatigue was also present in a quarter of LGG patients. A previous study has found comparable percentages on mental and physical fatigue in patients with LGG with a multidimensional fatigue scale (MFI-20) (van Coevorden-van Loon et al., 2021). As mentioned before, this study has some limitations. Results are based on a small group of IDH-mutant LGG patients (n=31) and they used a scale not designed for patients with brain injury, such as the DMFS. Other studies examining fatigue in patients with LGG used unidimensional fatigue scales or subscales (Cheng et al., 2010; van Coevorden-van Loon et al., 2017; Struik et al., 2009; Taphoorn et al., 1994). The present study is therefore the first that has used a multidimensional fatigue scale specifically designed for patients with brain injury in a relatively large LGG sample. The high rates on the subscales show that it is important to consider different types of fatigue in LGG patients even before having received radiation- and chemotherapy.

Regarding neurocognitive functioning, the present study found clear deficits on response inhibition (21%) and divided attention (27%), whereas barely any patients showed impairment on simple information processing speed (1-3%). These results imply that simple or automatic variants of information processing and attention remain relatively intact in LGG patients, while complex aspects of attention are more frequently affected. Accordingly, it seems that the higher the cognitive load of a task, the more LGG patients perform impaired. This is an important find, because it suggests that impairments in divided attention in LGG patients do not result from reduced information processing speed per se, but rather from problems processing competing stimuli, inefficient sharing of resources or switching of attention between tasks. Studies found cognitive deficits in patients with LGG, although these were often subtle and not severe in nature (Laack et al., 2005; Correa et al., 2008). Taking the results of the present study into account, it seems that the complex VTS tests are appropriate measures for detecting those milder and complex impairments. The present study is the first study that investigated simple information processing speed and complex variants of attention with these VTS tests in LGG patients. Furthermore, due to the disentanglement of reaction times and motor times, the VTS controls for motor slowness, resulting in a clean measure of information processing speed and attention. Other articles examining neurocognitive functioning in LGG patients also found the domain attention to be most frequently affected (van Coevorden-van Loon et al., 2021; Habets et al., 2019; van Kessel et al., 2017). However, these studies did not investigate simple information processing speed with such a ‘simple’ test; and have not used a measurement that equals in complexity regarding divided attention. This difference in test selection makes it difficult to compare the results of the present study to other articles.

By studying the relationship between cognitive functioning and mental fatigue, we found no significant differences at group level in mean performance on simple information processing speed, response inhibition and divided attention between the two mental fatigue groups. However, when investigating the composition of the more and less severely fatigued group more closely, we found significantly more patients with an impairment in divided attention in the severely mental fatigued group compared to the non-severely mental fatigued group. To explain the relationship between these two factors, the coping hypothesis has been proposed. This hypothesis states that patients have to increase their cognitive efforts to compensate for their information processing and attention deficits, resulting in mental fatigue (van Zomeren et al., 1984). This would mean that performance on cognitive tests would not differ between fatigued and non-fatigued patients. Although this hypothesis is in accordance with the results on simple information processing speed and response inhibition, it is not for divided attention. These findings imply that when a task becomes too complex and exceeds a fatigued person’s capacity of cognitive load, compensation is not possible and a drop in performance will be visible. Accordingly, it may be that the influence of mental fatigue becomes more visible when a test is more resource demanding. Another possible explanation for this relationship is based on a central fatigue hypothesis stating that injury in certain brain regions (e.g. basal ganglia, thalamus, prefrontal cortex and/or connecting pathways) results in complex attention deficits, while may in turn lead to mental fatigue (Chaudhuri & Behan, 2000). The present study indicates that it is important to consider the association between mental fatigue and complex attention in patients with LGG, as both factors have a large (and possibly entangled) influence on daily functioning (Ziino & Ponsford, 2006).

Studies indicate that patients with LGG experience increased levels of depression (15%-48%) and anxiety (21%). In our study, frequencies of increased levels of depression and anxiety were 20.1% and 10.5% respectively. Although an association between fatigue and psychological symptoms has been found in several patient groups, we did not find a difference in the proportion of patients with an increased depression or anxiety score between the severely mental fatigued group and the non-severely mental fatigued group.

Some limitations have to be taken into account. First, our sample only included patients with LGG who were eligible for proton therapy and thus have a favorable prognosis. Our results may not be applicable to more severely impaired patients who have to restrain from comprehensive neuropsychological testing and proton therapy. Second, almost all patients included had an IDH-mutant type glioma, only a few patients had an IDH-wildtype glioma. In comparison to IDH1-mutant gliomas, patients with IDH1-wildtype gliomas show reduced neurocognitive functioning in multiple domains, including processing speed (Wefel et al., 2016). As a result, the cognitive impairments that we found may be underestimating deficits when compared to the whole LGG population. Lastly, the severely mental fatigued group was significantly older than the non-severely mental fatigued group. However, we controlled for age by using the percentiles of the VTS tests, which are based on age groups. Also, the absolute differences in years between groups were small, so we do not expect this to have had a large influence on the results.

In conclusion, our study shows high rates of different facets of fatigue in patients with LGG, especially in the mental domain. Regarding neurocognitive functioning, we found deficits in response inhibition and divided attention in a significant proportion of patients with LGG, while simple information processing speed remained relatively intact. Although no significant differences between severely mental fatigued patients and non-severely mental fatigued patients were found at group level on the three cognitive functions, we found a significant higher percentage of patients with deficits in divided attention in the severely mental-fatigued group compared to the non-severely mental fatigued group.

For future research it is recommended to use tests such as the VTS, as these have shown to be sensitive in patients with LGG and are not dependent on motor speed, search strategies and visuo-motor skills. Furthermore, although awareness of cancer-related fatigue is increasing, there is still a lack of knowledge of the mechanisms underlying mental fatigue and its relationship with neurocognitive functioning. Improving our knowledge on this relationship is necessary to investigate strategies to treat mental fatigue and cognitive impairment and improve quality of life and chances of returning to work (van Coevorden-van Loon et al., 2021). Emphasizing the importance of attentional functioning and mental fatigue, we recommend assessing these constructs thoroughly in LGG patients in order to develop rehabilitation programs specifically tailored to the needs of this patient group.

References

Alessandra, L., Marcel, K., Christiane, von S., Daniel, H., Michael, S., & Marion, R. (2021). Psychooncological distress in low-grade glioma patients—a monocentric study. *Acta Neurochirurgica, 1-10*, 1–10. https://doi.org/10.1007/s00701-021-04863-7

van den Bent, M. J., Weller, M., Wen, P. Y., Kros, J. M., Aldape, K., & Chang, S. (2017). A clinical perspective on the 2016 who brain tumor classification and routine molecular diagnostics. *Neuro Oncology*, *19*(5), 614–624. https://doi.org/10.1093/neuonc/now277

van den Bent, M. (2014). Practice changing mature results of rtog study 9802: another positive pcv trial makes adjuvant chemotherapy part of standard of care in low-grade glioma. *Neuro Oncology*, *16*(12), 1570–1574.

Brown, L.F., Kroenke, K. (2009) Cancer-related fatigue and its associations with depression and anxiety: a systematic review. Psychosomatics. 50(5):440–447.

Chaudhuri, A., & Behan, P. O. (2000). Fatigue and basal ganglia. *Journal of the Neurological Sciences*, *179*(1), 34–42. https://doi.org/10.1016/S0022-510X(00)00411-1

Cheng, S., Siddiqui, T. G., Gossop, M., Stavem, K., Kristoffersen, E. S., & Lundqvist, C. (2020). Health-related quality of life in hospitalized older patients with versus without prolonged use of opioid analgesics, benzodiazepines, and z-hypnotics: a cross-sectional study. *BMC geriatrics*, *20*(1), 425. https://doi.org/10.1186/s12877-020-01838-8

Claus, E. B., Walsh, K. M., Wiencke, J. K., Molinaro, A. M., Wiemels, J. L., Schildkraut, J. M., Bondy, M. L., Berger, M., Jenkins, R., & Wrensch, M. (2015). Survival and low grade glioma: the emergence of genetic information. *Neurosurgical focus*, *38*(1), E6. https://doi.org/10.3171/2014.10.FOCUS12367

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. M. P., Heijenbrok-Kal, M. H., Horemans, H. L. D., Boere, R., de Bat, R. A. K. M., Vincent, A. J. P. E., 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*, 1–7.

Correa, D.D (2008). Cognition in brain tumor patients. *Curr Neurol Neurosci Rep* **8**, 242-248.

Day, J., Berntzen, B., Harden, S., Williams, S., Peoples, S., Erridge, S., & Grant, R. (2015).

Pcsm-03 physical disability and anxiety are independent predictors of fatigue in stable primary brain tumour patients. *Neuro-Oncology, 17*(Suppl_5), 176.

Ek, L., Almkvist, O., Wiberg, M. K., Stragliotto, G., & Smits, A. (2010). Early cognitive impairment in a subset of patients with presumed low-grade glioma. *Neurocase*, *16*(6), 503–11. https://doi.org/10.1080/13554791003730634

Furnari, F. B., Fenton, T., Bachoo, R. M., Mukasa, A., Stommel, J. M., Stegh, A., Hahn, W. C., Ligon, K. L., Louis, D. N., Brennan, C., Chin, L., DePinho, R. A., & Cavenee, W. K. (2007). Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes & Development*, *21*(21), 2683–710.

Gehring, K., Sitskoorn, M. M., Gundy, C. M., Sikkes, S. A. M., Klein, M., Postma, T. J., van den Bent, M., Beute, G. N., Enting, R. H., Kappelle, A. C., Boogerd, W., Veninga, T., Twijnstra, A., Boerman, D. H., Taphoorn, M. J. B., & Aaronson, N. K. (2009). Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *Journal of Clinical Oncology*, *27*(22), 3712–3722.

Gustafsson, M., Edvardsson, T., & Ahlström Gerd. (2006). The relationship between function, quality of life and coping in patients with low-grade gliomas. *Supportive Care in Cancer*, *14*(12), 1205 1212.

Habets, E. J. J., Hendriks, E. J., Taphoorn, M. J. B., Douw, L., Zwinderman, A. H., Vandertop, W. P., Barkhof, F., De Witt Hamer, P. C., & Klein, M. (2019). Association between tumor location and neurocognitive functioning using tumor localization maps. *Journal of Neuro-Oncology*, *144*(3), 573–582. https://doi.org/10.1007/s11060 019-03259-z

Hattori, N., Swan, M., Stobbe, G.A., Uomoto, J.M., Minoshima, S., Djang, D. Krishnananthan, R. & Lewis, D.H. Differential SPECT Activation Patterns Associated with PASAT Performance May Indicate Frontocerebellar Functional Dissociation in Chronic Mild Traumatic Brain Injury. J. Nucl. Med. 2009, 50, 1054–1061.

Johansson, B. (2021). Mental fatigue after mild traumatic brain injury in relation to cognitive tests and brain imaging methods. *International Journal of Environmental Research and Public Health*, *18*(11). https://doi.org/10.3390/ijerph18115955

Johansson, B., Berglund, P. &; Rönnbäck, L. (2009) Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. *Brain Inj*,23, 1027–1040.

Johansson, B. & Rönnbäck, L. (2014) Long-Lasting Mental Fatigue after Traumatic Brain Injury—A Major Problem Most Often Neglected Diagnostic Criteria, Assessment, Relation to Emotional and Cognitive Problems, Cellular Background, and Aspects on Treatment. *Trauma. Brain Inj.*

van Kessel E., Baumfalk A.E., van Zandvoort M.J.E., 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. J Neurooncol 134(1):9–18. https://doi.org/10.1007/s11060-017-2503-z

van Kessel, E., Emons, M.A.C., Wajer, I.H., van Baarsen, K.M., Broekman, M.L., Robe P.A., Snijders, T.J., Van Zandvoort, M.J.E. (2019) Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. *Neurooncol Pract.***Fout! De hyperlinkverwijzing is ongeldig.**

van Kessel, E., Huenges Wajer, I.-repo/dai/nl/412715309, Ruis, C., Seute, T., Fonville, S., De Vos, F., Verhoeff, J., Robe, P., van Zandvoort, M., Snijders, T., Helmholtz, I., Experimental, P. (onderzoeksprogramma P. F., Leerstoel, D., & Leerstoel, Z. (2021). Cognitive impairments are independently associated with shorter survival in diffuse glioma patients. *Journal of Neurology*, *268*.

Kluger, B.M., Krupp, L.B., Enoka, R.M. (2013). Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*; 80: 409–416.

Laack, N. N., Brown, P. D., Ivnik, R. J., Furth, A. F. M. S., Ballman, K. V., Hammack, J. E., Arusell, R. M., Shaw, E. G., & Buckner, J. C. (2005). Cognitive function after radiotherapy for supratentorial low-grade glioma: a north central cancer treatment group prospective study. *International Journal of Radiation Oncology, Biology and Physics*, *63*(4). https://doi.org/10.1016/j.ijrobp.2005.04.016

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004). *Neuropsychological assessment* (4th ed.). New York, NY: Oxford University Press.

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

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*(5), 547–547. https://doi.org/10.1007/s00401-007-0278-6

Mainio, A., Tuunanen, S., Hakko, H., et al. (2006). Decreased quality of life and depression as predictors for shorter survival among patients with low-grade gliomas: a follow-up from 1990 to 2003. *Eur Arch Psychiatry Clin Neurosci*.;256(8):516–521.

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. (2000) Practice Guidelines for Cancer-Related Fatigue. *Oncology* Nov;14(11A):151-61. PMID: 11195408.

Möller, M.C., de Boussard, C.N., Oldenburg C. & Bartfai, A. (2014) An investigation of attention, executive, and psychomotor aspects of cognitive fatigability, *Journal of Clinical and Experimental Neuropsychology*, 36:7, 716-729, DOI: 10.1080/13803395.2014.933779

Neuwirth, W., & Benesch, M. (2007). Manual DT: Determination test, Version 33.00. *Mödling: Schuhfried GmbH,*

Pattyn, N., Van Cutsem, J., Dessy, E., & Mairesse, O. (2018). Bridging Exercise Science, Cognitive Psychology, and Medical Practice: Is "Cognitive Fatigue" a Remake of "The Emperor's New Clothes"?. *Frontiers in psychology*, *9*, 1246. https://doi.org/10.3389/fpsyg.2018.01246

Prieler, J. (2008). *Manual RT: Reaction test, Version 31.*

Rooney, A.G., Carson, A., Grant, R. (2011). Depression in cerebral glioma patients: a systematic review of observational studies. (2011) *J Natl Cancer Inst*. 103(1):61–76.

Schomas, D. A., Laack, N. N. I., Rao, R. D., Meyer, F. B., Shaw, E. G., O'Neill, B. P., Giannini, C., & Brown, P. D. (2009). Intracranial low-grade gliomas in adults: 30 year experience with long-term follow-up at mayo clinic. *Neuro-Oncology*, *11*(4), 437–45. https://doi.org/10.1215/15228517/2008102

Smits A, Jakola A.S. (2019). Clinical presentation, natural history, and prognosis of diffuse low-grade gliomas. *Neurosurg Clin North Am*, 30:35-42.

Spikman, J.M., & van Zomeren, E. (2010). Assessment of attention. *The Handbook of Clinical Neuropsychology* (2nd ed.,). Oxford University Press. https://10.1093/acprof:oso/9780199234110.003.05

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), 73–8. https://doi.org/10.1007/s11060-008-9738-7.

Stuss, D. T., Stethem, L. L., Hugenholtz, H., Picton, T., Pivik, J., & Richard, M. T. (1989). Reaction time after head injury: fatigue, divided and focused attention, and consistency of performance. *Journal of Neurology, Neurosurgery, and Psychiatry*, *52*(6), 742–8.

Taphoorn, M.J.B., Schiphorst, A.K., Snoek, F.J., Lindeboom, J., Wolbers, J.G., Karim, A.B.M.F., Huijgens, P.C. and Heimans, J.J. (1994), Cognitive functions and quality of life in patients with low-grade gliomas: The impact of radiotherapy. *Ann Neurol.*, 36: 48 54. https://doi.org/10.1002/ana.410360111

Verhage, F. (1964). *Intelligentie en leeftijd bij volwassenen en bejaarden - Research database - University of Groningen*. 2–5.

Visser-Keizer, A. C., Hogenkamp, A., Westerhof-Evers, H. J., Egberink, I. J. L., & 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.

Wefel, J. S., Witgert, M. E., & Meyers, C. A. (2008). Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychology Review*, *18*(2), 121 131. https://doi.org/10.1007/s11065-008-9058-x

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. (2020). 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

Ziino, C.; Ponsford, J. (2006) Selective attention deficits and subjective fatigue following traumatic brain injury. *Neuropsychology*, 20, 383–390.

Zigmond, A.S. & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand*;.Jun;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x. PMID: 6880820.

van Zomeren A.H., van Brouwer W.H., Deelman B.G.. Attentional deficits: the riddles of selectivity, speed and alertness. In: *Closed head injury. Psychological, social and family consequences*; 1984. p. 398–415.