Higher-order cognitive functions in low-grade glioma patients: relationship with tumor location and tumor volume

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Master Thesis - Clinical Neuropsychology

S3129810

July 3, 2021

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Abstract

Objective: The author's aim was twofold: (1) to investigate higher-order cognitive functions, namely EF and SC, in patients with low-grade gliomas (LGG) and (2) to examine the relationship between higher-order cognitive functions and both tumor location and tumor volume in LGG patients. ***Method:*** Patients were assessed with tests measuring EF (Zoo Map Test, Key Search Test, Trail Making Test, Letter Fluency) and an important aspect of SC, namely emotion recognition (Facial Expressions of Emotion Stimuli and Tests). Comparative tests and correlation coefficients were used to examine the relationship between higher-order cognitive functions and both tumor location and tumor volume. ***Results:*** In total, 73 patients with LGG were included. Approximately one fifth of patients show impairments in EF and SC compared to norms. Patients with larger tumor volume show significantly lower scores on total emotion recognition, as well as for the expressions 'Disgust' and 'Fear'. Furthermore, there were no significant differences between tumor locations, i.e. frontal, temporal and tumors located elsewhere, for mean scores on tests for EF and SC. Additionally, there were no significant differences in mean scores on tests for EF and SC between tumors located in the left versus the right hemisphere, except for the expression 'Surprise'. ***Conclusions:*** This is the first study that reports a significant part of LGG patients to be impaired on higher-order cognitive functions. Furthermore, this is also the first study that that investigated the associations between tumor volume and emotion recognition in patients with LGG: larger tumor volume was associated with poorer recognition of emotions. However, no direct association between tumor location and higher-order cognitive functions was found, supporting the network perspective on cognition. Considering the importance of higher-order cognitive functions for daily life functioning, awareness of EF and SC is of great relevance for management of LGG patients.

Introduction

Low-grade gliomas (LGG) are brain tumors that often arise in young to middle aged adults (Forst et al., 2014). Gliomas are graded from I to IV based on morphology and molecular features as specified in the World Health Organization (WHO) classification. Grade II tumors are generally referred to as LGG's, whereas grade III and grade IV often include high-grade gliomas (Louis et al., 2016; Rasmussen et al., 2017). Although patients with LGG have a better survival than patients with high-grade gliomas, it is estimated that approximately 70% of patients with LGG eventually will progress to grade III and IV tumors within 5 to 10 years after diagnosis (Larsen et al., 2017). The care of LGG consists of tumor resection often followed by radiotherapy and chemotherapy (van der Weide et al., 2020).

Gliomas can have impact on cognitive functioning of patients. Studies suggest that most cognitive decline is attributable to the tumor itself, with additional effects of surgery, radiotherapy, chemotherapy and concomitant medication such as anti-epileptic drugs (Habets et al., 2019; Miotto et al., 2011; Schiff, 2017). Impairments in higher-order cognitive functions, namely executive functions (EF) and social cognition (SC), can have adverse effects on daily life functioning (Goebel et al., 2018; Miotto et al., 2011; Rijnen et al., 2020; van der Linden et al., 2020). EF comprise cognitive capacities necessary for goal-oriented behavior, planning and carrying out activities in an effective way (Cristofori et al., 2019; Zgaljardic et al., 2010; Lezak, 1995). Impairments in EF have been observed prior to surgery (Habets et al., 2019; Miotto et al., 2011; Rijnen et al., 2020), but also after initial tumor resection in patients with low- and high-grade gliomas (Rijnen et al., 2020; van der Linden et al., 2020). Besides EF, another important aspect of higher-order cognitive functions is the recognition of facial emotions. Limited studies show impairments in emotion recognition in patients with different types of brain tumors (Campanella et al., 2014; Goebel et al., 2018). However, literature in emotion recognition in LGG patients is lacking.

Possible factors that influence higher-order cognitive functions are tumor location and tumor volume (Campanella et al., 2014; Habets et al., 2014; Hendrix et al., 2017; Tucha et al., 2000). Tumor location has been related to neurocognitive decline, as damage to different brain regions may affect neurocognitive outcomes differently (Corti et al., 2020). Limited and mixed results were found for the relationship between EF and tumor location. Rijnen et al. (2020) found executive impairments in patients with LGG both before and after surgery, irrespective of tumor location. However, Habets et al. (2019) found involvement of the left frontal and parietal cortex and left white matter structures for EF in patients with diffuse gliomas prior to treatment. Besides these studies, no research has been conducted into the relationship between

tumor location and EF in patients with LGG. Furthermore, there is limited evidence for a relationship between tumor location and emotion recognition in patients with LGG. Campanella et al. (2014) showed impairments in emotion recognition in brain tumor patients with temporal and frontal lesions. However, they investigated a variety of different brain tumors, i.e., high-grade gliomas, low-grade gliomas, meningiomas and metastases, whereas research on the relationship between tumor location and emotion recognition in LGG patients is lacking. Furthermore, the relationship between brain laterality and higher-order cognitive functions in LGG patients remains unclear as existent literature yielded mixed findings in the involvement of hemispheres in EF and emotion recognition in healthy individuals, mixed brain tumor diagnoses and other neurological disorders (Campanella et al., 2014; Cipolotti et al., 2016; Gainotti, 2019; Rodway et al., 2003; Sinha et al., 2020; Tavor et al., 2014; Unger et al., 2016).

In addition to tumor location, tumor volume is also a factor that may be associated with higher-order cognitive functions in LGG patients. Various studies showing larger tumor volume to be associated with worse cognitive functioning, including EF, for different types of tumor diagnoses (Hendrix et al., 2017; Russell et al., 2005; Tucha et al., 2000; Vogt, 2015). However, the relationships between tumor volume and both EF and emotion recognition have not yet been examined in LGG patients.

More research is needed to determine the relationship between higher-order cognitive functions and both tumor location and tumor volume in LGG patients. This study seeks to improve our knowledge to the current research and may raise more awareness for higher-order cognitive impairments in these patients. The aim of the present study is twofold. First, to investigate higher-order cognitive functions in patients with LGG. Secondly, to examine the relationship between higher-order cognitive functions and both tumor location and tumor volume.

Methods

Participants and procedure

The present study is part of a larger prospective study in which LGG patients were included who receive proton therapy at the Proton Therapy Center in Groningen. Only patients with favorable prognosis based on tumor and patient characteristics can be offered proton therapy in the Netherlands (Weide et al., 2020). LGG patients admitted to the University Medical Center Groningen (UMCG) between November 2017 and January 2021, included for proton therapy, with confirmed WHO grade I, II or III gliomas were included in this study. Exclusion criteria were age younger than 18 years, patients with meningiomas, neurological or severe psychiatric disorders, alcohol or drug abuse, indicative performance on a test for symptom validity and insufficient command of the Dutch language.

Patients underwent neuropsychological assessment preceding proton therapy at the UMCG. They completed a full battery of standardized neuropsychological tests, covering a wide range of cognitive functions. The administration time of the complete test battery was approximately 2.5 hours. Furthermore, sociodemographic data (age, sex, educational level) and clinical data (WHO tumor grade, tumor location and tumor volume) were collected. Educational level was scored according to the Dutch classification system of Verhage (1964). All patients provided written informed consent.

Measurement instruments

Executive functions

The Zoo Map Test is part of the Behavioral Assessment of the Dysexecutive Syndrome (BADS), intended to measure planning ability as part of EF. The participant is instructed to plan a route along a number of given destinations, while some restrictive rules need to be kept in mind. The total score ranges from below 0 to 16 (Wilson et al., 2004).

The Key Search Test, also part of the BADS, is intended to measure the ability to plan a strategy to solve a problem. The participant is instructed to draw a line to show where they would search to find a key lost in a field, with a maximum score of 16 (Wilson et al., 2004).

The Trail Making Test (TMT) is a test consisting of Condition A (psychomotor speed) and Condition B (switching attention). In condition B, the participant alternately has to connect numbers and letters in ascending sequence (Reitan, 1958). Time on Condition B is used as measure for cognitive flexibility.

The Dutch version of the Controlled Oral Word Association Test (COWAT), Letter Fluency, is a test intended to measure executive control. The participant is required to list as

many words as possible with a given letter within one minute, while complying to restrictive rules. The score is the number of accurately produced words from three different starting letters, within 3 minutes (Schmand et al., 2008).

Social cognition

The Ekman 60 faces test of the Facial Expressions of Emotion Stimuli and Tests (FEEST) investigates recognition of facial expressions of emotion. Participants are shown 60 static photos, each showing one of the six basic emotions: anger, disgust, fear, happiness, sadness and surprise. The stimuli are presented for five seconds, then the subject is asked to choose which emotion label best describes the emotion shown. The scores range from 0 to 60; for each of the six emotions a maximum score of 10 (Young, 2002).

Statistical analysis

The analyses were conducted in Statistical Package for the Social Sciences (SPSS), Version 23.0. Neuropsychological test data were checked for normal distribution by using quantile-quantile (Q-Q) plots. Parametric statistical tests were used for normally distributed data, otherwise a nonparametric alternative was applied. For each test, the patients' scores were compared to published normative data as used in clinical practice. Performances below the tenth percentile or a profile score ≤ 2 in case of the Zoo Map Test and Key Search Test were considered to be impaired (Lezak et al., 2004).

One-way analyses of variance (ANOVAs) and Kruskal-Wallis H tests were used to investigate the relationship between tumor location and both EF and SC. Mean scores on the different tests were compared for three separate groups: frontal, temporal and 'other' tumors. Patients with parietal, occipital, insular and tumors located elsewhere (as shown in Table 1) were grouped as 'other' for the analysis into tumor location.

The relationship between tumor extensions and both EF and SC into frontal and temporal lobes was examined by comparing mean scores on the different tests for frontal versus non-frontal tumor extensions and temporal versus non-temporal tumor extensions, using independent t-tests and Mann-Whitney *U* tests. Tumor extensions into other brain areas are visually determined by radiotherapists based on Magnetic Resonance Imaging **(**MRI), without an associated amount of minimum volume. Patients with tumors located completely in the frontal lobe were excluded from the analysis of frontal versus non-frontal tumor extensions. Likewise, patients with tumors located completely in the temporal lobe, were excluded from the analysis of temporal versus non-temporal tumor extensions.

Additionally, the relationships between lateralization and both EF and SC were examined by comparing mean scores on the different tests for tumors located in the right versus the left hemisphere, using independent t-tests and Mann-Whitney *U* tests. Patients with midline tumors were excluded from the analysis into lateralization.

Correlational analyses were performed to examine the relationship between tumor volume and both EF and SC. Tumor volume was defined as the target volume for radiotherapy: the area residual tumor with resection cavity, including a margin of non-malignant brain tissue. Associations between measures for cognitive functions and tumor volume were tested with Spearman's rank correlations for nonparametric data.

Effect sizes (Cohen's *d*) were calculated for all between-groups comparisons (Cohen, 1988). The overall alpha level (*p*) was set at .05, two-sided.

Results

A total of 73 LGG patients were included for analysis. Table 1 shows the sociodemographic and clinical characteristics of the patient group.

Table 1
Sociodemographic and clinical characteristics of LGG patients

Characteristic	LGG (n=73)
Sex, number of women (%)	34 (46.6)
Age in yrs, mean ± SD	41.2 ± 12.4
Educational level, mean ± SD	5.1 ± 1.0
Diagnosis	
Oligodendroglioma, n (%)	37 (50.7)
Astrocytoma, n (%)	34 (46.6)
Pilocytic astrocytoma, n (%)	1 (1.4)
Ependymoma, n (%)	1 (1.4)
WHO tumor grade[a]	
Grade I, n (%)	1 (1.4)
Grade II, n (%)	56 (76.7)
Grade III, n (%)	15 (20.5)
Tumor location[b]	
Frontal, n (%)	46 (63.0)
Temporal, n (%)	12 (16.4)
Parietal, n (%)	9 (12.3)
Insular, n (%)	3 (4.1)
Elsewhere[c], n (%)	3 (4.1)
Tumor extension[d]	
Frontal, n (%)	54 (74)
Temporal, n (%)	26 (35.6)
Parietal, n (%)	14 (19.2)
Occipital, n (%)	7 (9.6)
Insular, n (%)	24 (32.9)
Hippocampus, n (%)	17 (23.3)
Lateralization	
Left-sided, n (%)	37 (50.7)
Right-sided, n (%)	34 (46.6)
Bilateral, n (%)	2 (2.7)
Treatment before proton therapy	
Surgery, n (%)	67 (91.8)
Chemotherapy, n (%)	4 (5.4)
Radiotherapy, n (%)	0 (0%)
Tumor volume in cc, mean ± SD	118.2 ± 83.7

Note. LGG = lower-grade glioma; Educational level = 7-point scale 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] Indicated as the location of the main bulk of tumor.
[c] Corpus callosum, brain stem, thalamus, basal ganglia, cerebellum.
[d] Indicated as tumor extension into a brain structure.

EF and SC

Table 2 shows the percentage of the total group of LGG patients who were impaired on tests for EF and emotion recognition. 20-40% of LGG patients were impaired on tests for

EF. Furthermore, 26% of patients were impaired on a test for emotion recognition, i.e., the FEEST.

Tumor location

Table 2 also shows the differences between the group of frontal, temporal and other tumors for mean scores on tests for EF and SC. Kruskal-Wallis tests showed no statistically significant differences between groups in mean scores on the Zoo Map Test, Key Search Test, TMT-B and the six subscales of the FEEST. Furthermore, there was no statistically significant difference in mean scores on Letter Fluency and total mean score on the FEEST between groups, as determined by one-way ANOVAs.

Table 2

Performance on tests for EF and SC and comparisons between frontal, temporal and 'other' tumors of LGG patients

	Total (n = 73)		Frontal [a] (n = 46)	Temporal [a] (n = 12)	Other [b] (n = 15)	χ^2/F[c]	p
Measure	Impaired, n (%)	M (SD)	M (SD)	M (SD)	M (SD)		
Executive functions							
Zoo Map Test	29 (39.7)	12.1 (3.7)	12.3 (3.8)	12.4 (2.9)	11.1 (4.2)	1.03	.599
Key Search Test	17 (23.3)	13.1 (2.9)	13.3 (2.9)	12.9 (3.3)	12.6 (3.0)	0.73	.639
TMT-B	15 (20.5)	77.3 (42.3)	71.1 (41.1)	86.2 (45.0)	89.9 (42.4)	3.76	.153
Letter Fluency	16 (21.9)	32.3 (12.4)	32.3 (11.9)	31.9 (16.7)	32.6 (10.8)	0.01	.989
Emotion recognition (FEEST)							
Anger	9 (12.3)	7.7 (1.5)	7.6 (1.4)	7.7 (2.1)	8.2 (1.1)	1.78	.410
Disgust	13 (17.8)	6.9 (2.2)	7.1 (2.1)	6.3 (2.0)	6.6 (2.5)	1.54	.463
Fear	8 (11.0)	5.9 (2.4)	6.4 (2.3)	4.8 (2.2)	5.4 (2.7)	4.39	.111
Happiness	5 (6.8)	9.9 (0.4)	9.9 (0.4)	9.8 (0.4)	9.9 (0.3)	0.77	.682
Sadness	14 (19.2)	6.7 (2.1)	7.0 (2.0)	5.7 (2.0)	6.4 (2.3)	4.74	.094
Surprise	5 (6.8)	9.0 (1.4)	9.0 (1.4)	8.5 (1.6)	9.3 (1.1)	2.74	.254
Total score	19 (26)	46.1 (6.4)	47.0 (6.0)	42.8 (8.1)	45.9 (5.6)	2.07	.134

Note. M = Mean; SD = Standard Deviation. TMT = Trail Making Test; FEEST = Facial Expressions of Emotion Stimuli and Tests.
[a] Indicated as the location of the main bulk of tumor.
[b] Indicated as parietal, occipital and insular and tumors located elsewhere (as defined in Table 1).
[c] One-way ANOVA: Letter Fluency, total score on the FEEST; Kruskal-Wallis H test: Zoo Map Test, Key Search Test, TMT-B, subscales of the FEEST (Anger, Disgust, Fear, Happiness, Sadness, Surprise).
*Significant p value < .05

Table 3 and 4 present differences in mean scores on tests for EF and SC between frontal versus non-frontal and temporal versus non-temporal tumor extensions. For the analysis of frontal versus non-frontal tumor extensions, we examined non-frontal tumors that do or do not extend to the frontal brain lobe. Results indicated that scores of patients with frontal tumor extensions were not significantly different from scores of patients with non-frontal tumor extensions. Likewise, for the analysis of temporal versus non-temporal tumor extensions, we examined non-temporal tumors that do or do not extend to the temporal brain lobe. Scores of patients with temporal tumor extensions were significantly higher than scores of patients with

non-temporal tumor extensions on the FEEST subscales 'Anger' and 'Surprise'. Scores on other tests did not significantly differ between patients with temporal and non-temporal tumor extensions. Effect sizes were low to moderate for differences between these patients.

Table 3
Comparison of EF and SC between patients with frontal versus non-frontal tumor extensions

	Frontal *(n=8)*	Non-frontal *(n=18)*			
Measure	M (SD)	M (SD)	*t/U*[a]	*p*	*d*[b]
Executive functions					
Zoo Map Test	10.7 (4.0)	12.5 (3.0)	43.00	.211	.61
Key Search Test	12.6 (2.6)	12.8 (3.4)	68.00	.821	.00
TMT-B	93.6 (37.7)	82.4 (43.6)	47.00	.333	.51
Letter Fluency	32.6 (12.2)	32.2 (14.9)	-.064	.949	.03
Emotion recognition (FEEST)					
Anger	8.3 (2.3)	7.9 (1.4)	46.50	.259	.52
Disgust	6.9 (2.3)	6.5 (2.2)	61.00	.679	.16
Fear	4.6 (2.9)	5.4 (2.3)	.733	.471	.30
Happiness	9.9 (0.4)	9.9 (0.3)	67.50	.959	.01
Sadness	5.5 (1.8)	6.5 (2.3)	48.50	.249	.47
Surprise	9.1 (1.8)	8.8 (1.3)	45.00	.154	.56
Total score	44.3 (7.4)	44.9 (7.0)	.21	.838	.09

Note. M = Mean; SD = Standard Deviation. TMT = Trail Making Test; FEEST = Facial Expressions of Emotion Stimuli and Tests.
[a] Independent t-test: Letter Fluency, total scores on the FEEST and one subscale of the FEEST (Fear); Mann-Whitney U: Zoo Map Test, Key Search Test, TMT-B, five subscales of the FEEST (Anger, Disgust, Happiness, Sadness, Surprise).
[b] Cohen's *d*, effect size.
*Significant p value < .05.

Table 4
Comparison of EF and SC between patients with temporal versus non-temporal tumor extensions

	Temporal *(n=14)*	Non-temporal *(n=46)*			
Measure	M (SD)	M (SD)	*t/U*[a]	*p*	*d*[b]
Executive functions					
Zoo Map Test	12.5 (3.4)	12.07 (3.8)	305.50	.767	.04
Key Search Test	13.0 (2.4)	13.1 (3.1)	283.00	.560	.15
TMT-B	72.0 (31.2)	74.8 (43.6)	292.50	.905	.11
Letter Fluency	33.6 (12.8)	32.0 (11.4)	-.437	.664	.13
Emotion recognition (FEEST)					
Anger	8.6 (0.8)	7.5 (1.4)	161.50	**.005****	.76
Disgust	7.1 (2.2)	7.0 (2.2)	314.50	.993	.00
Fear	5.9 (2.7)	6.3 (2.3)	.557	.579	.16
Happiness	9.9 (0.3)	9.9 (0.4)	309.00	.825	.03
Sadness	7.4 (1.9)	6.8 (2.1)	265.00	.366	.23
Surprise	9.5 (1.6)	8.9 (1.2)	177.50	**.008****	.67
Total score	48.4 (4.8)	46.4 (6.1)	-1.114	.270	.36

Note. M = Mean; SD = Standard Deviation. TMT = Trail Making Test; FEEST = Facial Expressions of Emotion Stimuli and Tests.
[a] Independent t-test: Letter Fluency, total scores on the FEEST and one subscale of the FEEST (Fear); Mann-Whitney U: Zoo Map Test, Key Search Test, TMT-B, subscales of the FEEST (Anger, Disgust, Happiness, Sadness, Surprise).
[b] Cohen's *d*, effect size.
**Significant p value < .01

Table 5 presents differences in mean scores on tests for EF and SC between tumors located in the left versus the right hemisphere. Results indicated that scores of tumors located in the left hemisphere were not significantly different from scores of tumors located in the right hemisphere, with the exception of the subscale 'surprise' of the FEEST: scores of patients with tumors located in the left hemisphere were significantly lower than scores of patients with tumors located in the right hemisphere. Effect sizes were low to moderate for differences between these patients.

Table 5
Comparison between patients with tumors located in the left- versus right hemisphere and correlation coefficients for tumor volume and tests for EF and SC

	Left *(n=37)*	Right *(n=34)*				Tumor volume *(n=73)*
Measure	M (SD)	M (SD)	*t/U*[a]	*p*	*d*[b]	*r*
Executive functions						
Zoo Map Test	12.3 (3.3)	12.1 (4.1)	597.50	.875	.04	-.17
Key Search Test	12.8 (3.0)	13.2 (2.9)	563.00	.558	.14	.03
TMT-B	76.3 (40.7)	75.9 (44.4)	587.50	.773	.07	.23
Letter Fluency	29.7 (12.6)	34.9 (11.0)	-1.76	.083	.42	-.09
Emotion recognition (FEEST)						
Anger	7.6 (1.5)	7.7 (1.6)	580.50	.703	.09	-.09
Disgust	6.8 (2.2)	7.0 (2.1)	-.38	.704	.09	**-.31****
Fear	6.2 (2.0)	5.9 (2.6)	.57	.574	.14	**-.28***
Happiness	9.9 (0.3)	9.9 (0.4)	600.00	.786	.03	-.12
Sadness	6.9 (1.9)	6.6 (2.3)	581.00	.712	.09	-.16
Surprise	8.7 (1.3)	9.2 (1.5)	425.00	**.019***	.54	.00
Total score	46.1 (6.0)	46.3 (7.0)	-.14	.892	.03	**-.29***

Note. M = Mean; SD = Standard Deviation. TMT = Trail Making Test; FEEST = Facial Expressions of Emotion Stimuli and Tests.
Tumor volume in cc.
[a] Independent t-test: Letter Fluency, total scores on the FEEST and two subscales of the FEEST (Disgust and Fear); Mann-Whitney U: Zoo Map Test, Key Search Test, TMT-B, subscales of the FEEST (Anger, Happiness, Sadness, Surprise).
[b] Cohen's *d*, effect size.
*Significant p-value < .05
** Significant p-value <.01

Tumor volume

Spearman correlations between tumor volume and scores on tests for EF and SC are also displayed in Table 5. A significant and weak correlation was found between tumor volume and the total score on the FEEST, indicating patients with larger tumors show lower total scores on the FEEST. Additionally, significant and weak correlations were found between tumor volume and the emotions 'Disgust' and 'Fear', indicating patients with larger tumors show lower scores on 'Disgust' and 'Fear' of the FEEST.

Discussion

The present study aimed to better understand the relationship between higher-order cognitive functions and both tumor location and tumor volume in patients with LGG. We found approximately one fifth of LGG patients to be impaired on so called higher-order cognitive functions, namely EF and SC. Interestingly, larger tumor volume was found to be related with poorer emotion recognition. No relationship between tumor location and higher-order cognitive functions was found. Furthermore, there was no relationship between hemispheric laterality and higher-order cognitive functions, except for the expression 'Surprise': patients with tumors located in the left hemisphere were worse in recognizing the expression 'Surprise' than patients with tumors located in the right hemisphere.

First of all, it needs to be emphasized that a part of the LGG patients in the present study, who have relatively favorable expected long-term survival and therefore an indication for proton therapy, nonetheless show impairments in EF and SC. We found a significant part of LGG patients to be impaired on EF, which is in accordance with earlier studies (Habets et al., 2019; Miotto et al., 2011; Rijnen et al., 2020). Furthermore, we were the first study that found a significant part of LGG patients to show impairments in emotion recognition. The impairments in higher-order cognitive functions can have a negative impact on daily life functioning (Rigon et al., 2018; Schiebener et al., 2014; Spikman et al., 2013; Zgaljardic et al., 2010). Accordingly, we must consider the higher-order cognitive performance of patients with LGG before receiving proton therapy.

Contrasting with earlier studies, no association between tumor location and both EF and emotion recognition was found. Many different structures within the fronto-parietal network have been associated with EF performance in healthy and brain injured patients, partly depending on the type of EF task (Cristofori et al., 2019; Hendrix et al., 2017; Milap et al., 2014; Tucha et al., 2003). Additionally, a number of studies report specific brain areas, i.e. the prefrontal cortex, temporal lobe, amygdala, insula, to be associated with emotion recognition (Campanella et al., 2014; Fang et al., 2016; Hornak et al., 2003; van de Riet et al., 2009). However, other research demonstrated that EF and emotion recognition are not merely associated with distinct brain areas but also with white matter networks, supporting a network perspective on cognition in which cognitive functions are carried out by the operations of functional networks comprised by interacting network nodes (Campanella et al., 2014; Cristofori et al., 2019; Medaglia et al., 2017; Rijnen et al., 2020; Tavor et al., 2014). Moreover, since LGGs are slow-growing tumors, the areas infiltrated by the tumor may undergo functional plasticity. Consequently, these infiltrated areas may not be significant to the neural network

responsible for higher order cognitive functions, possibly explaining the lack of a relationship between tumor location and higher-order cognitive functions (Barzilai et al., 2019).

With regard to lateralization, the current study did not demonstrate clear evidence for a relationship between brain laterality and both EF and SC. We did find a relationship between brain laterality and a specific aspect of emotion recognition; patients with tumors located in the left hemisphere were significantly worse in recognizing the expression 'Surprise', compared to patients with tumors located in the right hemisphere. Two dominant hypotheses have been proposed to explain emotion lateralization: the 'Valence hypothesis' assumes a dominance of the left hemisphere for positive emotion processing and of the right hemisphere for negative emotion processing (Reuter-Lorenz & Davidson, 1981). In contrast, the 'Right hemisphere hypothesis' (Gainotti, 1972) posits a general dominance of the right hemisphere for processing of emotions, in accordance with findings from several studies showing clear evidence of a prominent role of the right hemisphere in facial emotion recognition (Gainotti, 2019; Sinha et al., 2020; Tavor et al., 2014; Unger et al., 2016). Findings of the present study do not comply with one of the hypotheses. More recent research shows an involvement of both hemispheres in the process of emotion recognition (Campanella et al., 2014; Killgore & Yurgelun-Todd, 2007; Liang et al., 2019; Prete et al., 2015), suggesting a complex emotional perception system that encompasses processes included by both the 'Right hemisphere hypothesis' and the 'Valence hypothesis'. Besides emotion recognition, recent research also shows that executive processes rely on distributed neural networks with involvement of both hemispheres (Kim et al., 2017; Prasad, 2018; Zgaljardic et al., 2010). This may explain the findings of no hemispheric dominance for higher-order cognitive functions in LGG patients.

Regarding tumor extensions, no relationship was found between tumor extensions into the frontal lobe and higher-order cognitive functions. However, we found that patients with non-temporal tumors, who do not have extensions into the temporal lobe, were worse in recognizing the expressions 'Anger' and 'Surprise' compared to patients with non-temporal tumors who do have extensions into the temporal lobe. The fact that patients with pure non-temporal tumors were worse in recognizing emotions, combined with the finding that there was no difference in performance on emotion recognition between temporal and non-temporal tumor locations, suggests that damage in the temporal lobe possibly is not significant for emotion recognition.

With regard to tumor volume, this is the first study that found tumor volume to be related to deficits in emotion recognition in patients with LGG. Specifically, larger tumor volume was associated with poorer recognition of the expressions 'Disgust' and 'Fear'. There is a dearth of

direct evidence in support of the relationship between tumor volume and social cognition. However, earlier studies do show a clear relationship between tumor volume and other cognitive functions, i.e., memory, attention, executive functions, psychomotor speed (Hendrix et al., 2017; Russell et al., 2005; Tucha et al., 2000; Vogt, 2015). In contrast with these studies, the current study did not find any associations of EF and tumor volume. Nevertheless, it should be noted that 74% of the tumors of patients in our study were located in the frontal lobe, suggesting that particularly frontal tumor volume might be relevant for SC.

Some limitations of our study have to be taken into account. First, due to a relatively large number of patients with tumors located in the frontal lobe, a lack of statistical power could be explained for the absence of significant differences in higher-order cognitive function outcomes between different tumor locations and tumor extensions. Second, we examined a highly selected patient group receiving proton therapy. This has to be taken into account when generalizing results, since LGG patients selected for proton therapy have favorable tumor and patient characteristics (Weide et al., 2020). Lastly, in our study it is unknown how much tumor volume is belongs to the tumor extension, i.e. even exceptionally small amounts of tumor volume can be defined as a tumor extension, making it difficult to draw conclusions about these findings.

In conclusion, our study shows approximately one fifth of LGG patients to be impaired on so called higher-order cognitive functions, namely EF and SC. Importantly, this is the first study that investigated the associations between tumor volume and emotion recognition in patients with LGG: larger tumor volume was associated with poorer recognition of emotions. However, no direct association between tumor location and higher-order cognitive functions was found, supporting the network perspective on cognition (Medaglia, 2017; McIntosh, 2000; Pessoa, 2012).

The results of the present study are of importance for clinical practice. Neuropsychological examination at an early stage is crucial to inform and alert LGG patients and clinicians about the status of higher-order cognitive functions, even though a relatively favorable prognosis. Moreover, it is important to be alert to LGG patients with a large tumor volume, considering the particular effects on social cognition. Therefore, awareness of higher-order cognitive functions in relation to tumor volume is of great relevance for management of the patient.

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