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Cognitive awareness after treatment for high-grade glioma

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ABSTRACT

Objective: In patients with brain lesion, awareness of cognitive deficits is an important aspect of disease awareness. Glioblastoma (GBM) and anaplastic astrocytoma (AA) can cause cognitive deficits, but, to date, awareness of these deficits has not been documented. This study aimed to test cognitive awareness in these patients after the end of treatment.

Methods: Fifty patients with GBM or AA were assessed using the Multiple Ability Self-Report Questionnaire (MASQ), State-Trait Anxiety Inventory (STAI), Self Rating Depression Scale (SRDS), and memory, attention, mental speed, abstract reasoning, and flexibility neuropsychological tests. Cognitive awareness was calculated as the concordance between the composite score of neuropsychological performance (PEC) and the total MASQ score. The controls were 48 healthy subjects. Analysis of variance and regression analysis compared subject groups and explored variables predicting perceived abilities.

Results: Patients with GBM or AA showed similar attention, memory, and executive deficits compared with controls. Cognitive awareness was fair/full in 64% of patients. In the entire patients group, the worst MASQ scores were associated with neuropsychological deficits, anxiety, depression, and glioma location in the right hemisphere . In patients with fair/full awareness, MASQ scores were related to affective status and neuropsychological performance, whereas, in those with scarce/no awareness, they were related only to affective status.

Conclusions: After treatment, many patients with GBM or AA are aware of their cognitive deficits. Anxiety, depression, and right hemisphere tumour exacerbate the perceived difficulties. This neurocognitive approach expands the behavioural phenotypes of high-grade gliomas and may have therapeutic implications over the course of the disease.

1. Introduction

High-grade gliomas (HGGs) can cause cognitive deficits that alter quality of life (QoL) more severely than physical and motor deficits [1–5]. At the onset of the disease, cognitive function may be normal, but over the course of the disease, patients may show cognitive deficits that worsen the clinical picture and reduce their cooperation with treatment [6]. Impairment of mental speed, attention, problem-solving ability, and memory is a frequent symptomology of cerebral gliomas, resulting from ipsilateral or contralateral brain lesions [1,2,7]. Brain lesions undetected by radiological examinations, mass effects [8,9], radiotherapy, and chemotherapy can cause acute and short- or long-term cognitive deficits [6–11], whereas depression can exacerbate all symptoms [12]. However, patients with HGG may maintain adequate cognitive function until advanced stages of the disease [2,5], whereas patients with low-grade glioma (LGG) may have impaired or normal function for many years after surgery and radiotherapy [6]. Awareness of one's cognitive abilities is a component of self-awareness, reflecting psychological characteristics and personality traits as well as brain function. Self-awareness is a state of consciousness that can change as a consequence of environmental, relational, and inner stimuli and responses, supported by limbic and para-limbic networks that include the medial prefrontal, anterior cingulate, medial parietal, and posterior cingulate cortices and related brain structures [13]. Anosognosia for cognitive deficits, such as those involving memory, reasoning, and inhibitory control, is often associated with frontal lobe lesions, whereas anosognosia for motor and sensory deficits is attributed to parietal lobe damage [14–17]. Awareness of one's cognitive abilities has been distinguished

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from metacognition, which represents "the aspect of information processing that monitors, interprets, evaluates and regulates the contents and processes of its organization" [18] and is related to right prefrontal areas [19].

Patients with dementia, traumatic brain injury, or cerebral infarction showed reduced awareness of the disease [20]. However, surgical resection of unilateral or bilateral prefrontal LGGs did not cause awareness changes for cognitive abilities [21], whereas resection of LGGs in the right inferior parietal lobule did not alter movement awareness [22]. The degree of tumour malignancy and speed of progression may influence brain reorganization [23]. Slow-growing tumours facilitate brain connectivity and compensatory functional mechanisms, which explains the lack of correlation between cognitive deficits and tumour site unlike acute brain injury [3].

In patients with malignant brain tumours, disease awareness may be influenced by defensive psychological mechanisms that prevent them from seeing a prospect of low hope and autonomy [24]. These patients may also underestimate their own psychological distress and its impact on cognitive functions [25].

Anderson and Tranel [20] defined cognitive awareness as the concordance between self-assessment and objective measures of a given function, while Prigatano and Altman [26] calculated the correlation between patients' self-assessment and family members' ratings. Based on Anderson and Tranel's model [20], 39% of patients with epilepsy appeared to be aware of their cognitive abilities, but 47% and 53% of those with low awareness, respectively, overestimated and underestimated their cognitive abilities, with a significant influence of depression and anxiety on self.rating [27]. In short, patients with HGG may present with cognitive deficits but also normal function until the advanced stages of the disease. Awareness of cognitive deficits, to date, is undocumented, despite its importance for disease awareness and clinical implications. This study compared perceived cognitive abilities and neuropsychological performance in patients with HGG after the end of treatment in order to determine their awareness of cognitive deficits and explore the effect of clinicopathological and psychological variables on perceived abilities.

2. Material and methods

2.1. Participants

Fifty adult patients with supratentorial glioblastoma (GBM) (n = 23) or anaplastic astrocytoma (AA) (n = 27), treated with surgery, radiotherapy, and chemotherapy, and a Karnofsky Performance Status (KPS) score [28] >70 and able to cooperate on neuropsychological testing, were serially selected after their informed consent. The mean interval between surgery and neuropsychological evaluation was 35 months (range: 1–439 months). Cognitive function was assessed by clinical examination before surgery, highlighting mild to moderate deficits. Glioblastomas and AAs had a similar distribution in the anterior or posterior areas of the left and right hemispheres [chi^2 (3) = 3.51, p = 0.31]. Compared with previous examinations, computed tomography (CT) or magnetic resonance imaging (MRI) showed increased tumour mass in 15 patients [five GBM, 10 AA; chi^2 (1) = 1.38, p = 0.24]. Forty-eight healthy controls were selected from hospital staff and visitors, excluding patients' relatives. Patients and controls were similar in female-to-male ratio, but differed in age [F(2,95) = 22.61, p < 0.001] and years of schooling [F(2,95) = −6.48, p = 0.002], [(controls were younger than patients with GBM or AA and had more years of schooling than GBM patients (p = 0.006)] (Table 1).

2.2. Neuropsychological tests and questionnaires

Attentional Matrices [29], Trail Making Test (TMT A and B) [30], Raven Colored Progressive Matrices (RCPM) [31], and Short Story [32] were used to assess selective attention, mental speed, flexibility, abstract reasoning, and episodic memory. The Multiple Ability Self-Report Questionnaire (MASQ) [33], the State-Trait Anxiety Inventory (STAI) [34], and the Self Rating Depression Scale (SRDS) [35] assessed perceived cognitive ability, anxiety, and depression.

2.3. Data analysis

A composite performance score (PEC) was calculated as the arithmetic mean of z-scores from neuropsychological tests. PEC scores and total MASQ scores were classified into four ranks (very impaired, partially impaired, fair, and very good scores) [26]. Based on Anderson and Tranel's model [20], awareness was calculated as the concordance between the MASQ score and the PEC score: full (no discrepancy), discrete [one-level discrepancy, e.g., combination of the very impaired MASQ score with the partially impaired PEC score], scarce (two-level discrepancy), or no awareness (three-level discrepancy). Analysis of variance (ANOVA), with age and years of schooling as covariates and significance level at p < 0.01, compared test scores obtained by patients and controls. Pearson's correlation and chi^2 tests and multiple stepwise regression analyses explored the relationship between perceived cognitive ability (expressed by the MASQ total score) and demographic (age, schooling, gender, marital status) and clinicopathological variables (interval from surgery, histological type, tumour site in left or right anterior or posterior brain areas, tumour progression), neuropsychological performance, and affective status. Factor analysis was used to reduce the number of the scores provided by the neuropsychological tests, STAI, and SRDS. The Statistical Package for Social Science 20.0/2020 was used for statistical analyses.

Table 1
Demographic, clinical, ad pathological features.

	All patients n = 50	Patients with glioblastoma n = 23	Patients with anaplastic astrocytoma n = 27	Controls n = 48	p values*
Females/males	24/50	8/15	16/11	26/22	NS
Married	42	19	23	38	NS
Age	48.06 ± 11.54	52.52 ± 10.09	44.26 ± 11.51	34.96 ± 10.24	<0.001
Schooling (years)	9.84 ± 4.57	9.43 ± 4.22	10.19 ± 4.91	12.75 ± 3.76	p = 0.002
Interval between surgery and assessment (months)	34.72 ± 65.43	29.43 ± 89.60	39.22 ± 35.26		NS
Tumour progression	15 (30%)	5 (22%)	10 (37%)		NS
Tumour location					
Anterior left	11 (22%)	4 (17%)	7 (26%)		NS
Anterior right	12 (24%)	8 (35%)	4 (15%)		NS
Posterior left	17 (34%)	8 (35%)	9 (33%)		NS
Posterior right	10 (20%)	3 (13%)	7 (26%)		NS

* Demographic characteristics compared between patients with glioblastoma or anaplastic astrocytoma and controls.

3. Results

3.1. Perceived cognitive abilities

MASQ scores showed no differences with respect to gender, marital status, histologic type, or presence of tumour progression. Patients with right hemisphere HGGs showed higher scores (more severe cognitive difficulties) than patients with left hemisphere HGGs ($t = -2.063$, $p = 0.045$), whereas there were no differences between patients with anterior and posterior HGGs.

3.2. Neuropsychological performance

The multivariate ANOVA comparing patients with GBM or AA and controls showed a significant overall influence of schooling (Pillai value $= 0.39$, $F = 11.40$, $p < 0.001$) and group (Pillai value $= 0.37$, $F = 4.11$, $p < 0.001$). Subsequent univariate ANOVA revealed significant differences between the groups for RCPM ($F = 4.72$, $p = 0.01$), Attentional Matrices ($F = 9.80$, $p < 0.001$), TMTA ($F = 6–03$, $p = 0.003$), TMTB ($F = 9.27$, $p < 0.001$), and Short Story ($F = 19.18$, $p < 0.001$); Bonferroni's post hoc test showed that, compared to controls, patients with GBM or AA were significantly impaired but did not differ from each other (Table 2).

3.3. Affective status

STAI and SRDS scores showed a significant influence for the group (Pillai value $= 0.25$, $F = 4.48$, $p < 0.001$): patients with GBM or AA were significantly more anxious (STAI1: $F = 13.15$, $p < 0.001$; STAI2: $F = 9.31$, $p < 0.001$) and depressed SRDS: $F = 10.40$, $p < 0.001$) than controls but did not differ between them.

The comparison between controls and patients divided by tumour site also showed a significant influence for the group (Pillai value $= 0.17$, $F = 2.90$, $p < 0.001$). Compared to controls, patients with left or right hemisphere HGG were more anxious (STAI1: $F = 8.22$, $p = 0.001$; STAI2: $F = 5.74$, $p = 0.004$) and depressed (SRDS: $F = 5.57$, $p = 0.005$) (Table 2) but did not differ between them.

Table 2
Scores of neuropsychological tests and questionnaires.

	All patients	Patients with glioblastoma	Patients with anaplastic astrocytoma	Controls	p values*
Raven Colored Progressive Matrices	25.94 ± 6.39	25.17 + 6.62	26.59 + 6.23	31.88 ± 4.34	0.011
Attentive Matrices	43.28 ± 11.87	42.13 + 11.89	44.26 + 11.99	55.50 ± 3.38	<0.001
Trail Making Test A	127.44 ± 110.58	140.96 + 92.10	115.93 + 124.97	39.27 ± 15.87	0.003
Trail Making Test B	315.24 ± 240.91	357.39 + 250.51	279.33 + 231.03	94.17 ± 30.25	<0.001
Short Story	8.71 ± 3.81	8.34 + 4.33	8.98 + 3.37	16.17 ± 4.26	<0.001
State Trait Anxiety Inventory 1	43.44 ± 13.16	44.04 + 14.41	42.93 + 12.26	30.52 ± 11.62	<0.001
State Trait Anxiety Inventory 2	42.72 ± 12.88	43.30 + 13.36	42.22 + 12.69	32.21 ± 11–06	<0.001
Self Rating Depression Scale	38.02 ± 10.56	37.78 + 11.63	38.22 + 9.79	29.33 ± 7.96	<0.001
Multiple Ability Self Report Questionnaire	79.08 ± 27.84	84.38 + 33.80	74.56 + 21.18	–	NS

* Comparisons between patients with glioblastoma or anaplastic astrocytoma and controls with the exception of the Multiple Ability Self Report Questionnaire which was completed by patients only.

3.4. Cognitive awareness

Cognitive awareness was fair or full in 64% of patients, with no differences between patients with left or right GBM or AA and between patients with or without tumour progression (Tables 3 and 4). Patients with different levels of awareness (full, fair, scarce, or no awareness) were also similar in anterior and posterior tumour location, interval between neuropsychological assessment and surgery, age, gender, marital status, and level of anxiety and depression. Compared to patients with scarce/no awareness, those with fair/full awareness had more years of schooling ($t = -1.9$, $p = 0.05$) and better AM ($t = -2.45$, $p = 0.018$), TMTB ($t = 2.72$, $p = 0.028$), and Short Story ($t = -3.08$, $p = 0.003$) scores.

3.5. Variables predicting perceived cognitive abilities

Factor analysis of STAI, SRDS and neuropsychological test scores yielded two factors (Cognition, Affectivity) (Table 5). In the whole group of patients, MASQ total scores correlated with Cognition ($r = -0.28$, $p = 0.05$) and Affectivity ($r = 0.49$, $p < 0.001$) scores and with age ($r = 0.29$, $p = 0.04$), but not with years of schooling or the interval between neuropsychological assessment and surgery. Specifically, MASQ total scores were correlated with STAI1 ($r = 0.30$, $p = 0.03$), STAI2 ($r = 0.53$, $p < 0.001$), and SRDS ($r = 0.58$, $p < 0.001$) scores. Stepwise multiple regression analysis revealed that the MASQ total score was predicted by Affectivity ($r^2 = 0.24$, $F = 15.32$, $p < 0.001$) and Cognition ($r^2 = 0.32$, $F = 10.91$, $p < 0.001$) scores and tumour location ($r^2 = 0.40$, $F = 10.33$, $p < 0.001$): more severe neuropsychological deficits, depression and tumour location in the right hemisphere were associated with worse perceived cognitive abilities. Further analysis showed that the MASQ language score was related to Affectivity ($r^2 = 0.11$, $F = 6.04$, $p = 0.018$) and Cognition ($r^2 = 0.26$, $F = 5.30$, $p = 0.023$) and tumour location ($r^2 = 0.19$, $F = 5.56$, $p = 0.007$); verbal memory score was related to Affectivity ($r^2 = 0.14$, $F = 7.61$, $p = 0.008$) and Cognition ($r^2 = 0.22$, $F = 6.77$, $p = 0.003$) scores. The total MASQ score was predicted by the Cognition score ($r^2 = 0.36$, $F = 8.17$, $p = 0.002$) and Affectivity score ($r^2 = 0.18$, $F = 6.69$, $p = 0.015$) in patients with fair/full awareness but only by the Affectivity score ($r^2 = 0.37$, $F = 9.35$, $p = 0.008$) in those with scarce/no awareness.

Table 3
Cognitive awareness in patients with glioblastoma or anaplastic astrocytoma.

	All patients	Patients with glioblastoma	Patients with anaplastic astrocytoma
Multiple Ability Self Report Questionnaire			
Very impaired	12 (24%)	8 (35%)	4 (15%)
Partly altered	9 (8%)	3 (13%)	6 (22%)
Fair	16 (32%)	6 (26%)	10 (37%)
Very good	13 (26%)	6 (26%)	7 (26%)
Composite performance score			
Very impaired	12 (24%)	5 (22%)	7 (26%)
Partly impaired	14 (28%)	6 (26%)	8 (30%)
Fair	12 (24%)	8 (35%)	4 (14%)
Very good	12 (24%)	4 (17%)	8 (30%)
Awareness			
None	6 (12%)	2 (9%)	4 (15%)
Scarce	12 (24%)	6 (26%)	6 (22%)
Fair	19 (38%)	8 (35%)	11 (41%)
Full	13 (26%)	7 (30%)	6 (22%)

Table 4
Cognitive awareness in patients with high-grade glioma stratified by detected progression status.

	None	Scarce	Fair	Full
No detected progression	6	8	13	8
Detected progression	2	4	5	4

Table 5
Cognition and affectivity in patients with high-grade glioma.

	Cognition	Affectivity
Raven Colored Progressive Matrices	0.63	
Attentive Matrices	0.82	
Trail Making Test A	-0.82	
Trail Making Test B	-0.86	
Short Story	0.70	
State Trail Anxiety Inventory 1		0.87
State Trait Anxiety Inventory 2		0.95
Self Rating Depression Scale		0.86
Explained variance		
Total 68.78%	37.52%	31.26%

4. Discussion

It is known that patients with HGG may show cognitive deficits but also normal functions until advanced stages of the disease. Awareness of cognitive deficits is not documented, although it may have implications for disease awareness in these patients. This study addressed this issue by assessing perceived cognitive ability and neuropsychological performance in patients with GBM or AA after the end of treatment. Compared to healthy subjects, patients with HGG in the left or right hemisphere showed significant deficits in attention, mental speed, flexibility, abstract reasoning and memory and symptoms of anxiety and depression, in line with the results of previous studies [1–3]. Cognitive awareness, as expressed by the concordance between neuropsychological performance and perceived abilities [20], was fair/full in 64% of patients. This percentage is in the upper range of cognitive awareness observed in patients with vascular, degenerative or traumatic brain injury (31%–75%) [20] and lower than that described in patients with epilepsy (74%) [27], suggesting that the type of brain lesion may influence this type of awareness. Of note, patients with GBM or AA, with or without radiological evidence of tumour progression, showed similar levels of awareness. It is possible that the satisfactory clinical condition (expressed by a KPS score > 70), with active collaboration in the study, outweighed the effects of pathological variables. In patients with fair/full awareness, affective status had a slight influence on perceived cognitive ability. In contrast, it was the only predictor of perceived abilities in patients with scarce/no awareness. Psychological distress also showed a significant impact on the perceived cognitive difficulties of brain tumour patients prior to surgery [36] and may even be exacerbated by the deficit of awareness that reduces self-mastery [37]. Anxiety and depression have also contributed to a negative perception of one's cognitive abilities in patients with epilepsy [27], highlighting the impact of affective status on self-efficacy and self-esteem in different neurological conditions. Of note, in patients with HGG, lack of awareness may reflect psychic defences that help cope with disability and hopelessness [24,25].

The Cognition factor, derived from test scores of attention, mental speed, memory, flexibility and abstract reasoning, showed a significant influence on perceived cognitive abilities. In patients with fair/full consciousness, perceived abilities were significantly related to this factor, explaining 36% of the variance in the total MASQ score, outweighing the effect of the Affectivity factor, while, in the whole group of patients, it explained 22%–32% of MASQ scores. Patients with fair/full awareness had more years of schooling and scored better on tests of attention, flexibility and memory than patients with scarce/no awareness. Indeed, memory and executive functions are important for behaviour control and, together with culture and schooling, contribute to cognitive reserve, counterbalancing the causes of impaired awareness. Patients with HGGs in the right hemisphere reported worse cognitive abilities than patients with HGGs in the left hemisphere, although these groups were similar in neuropsychological performance and affectivity status. It is possible that the overestimation of one's cognitive deficits in patients with HGGs in the right hemisphere reflects a general impairment of self-perception, which is known to be primarily associated with this hemisphere [38]. In contrast, localization of HGGs in posterior or anterior brain areas was associated with similar levels of awareness, probably due to similar direct or indirect pathophysiological effects on the frontal lobes [17,19–21]. These results should take into account some limitations. Fair or good clinical conditions make the study patients not representative of all patients with HGG. In an unselected population, cognitive awareness might be influenced by performance status, tumour progression, medical treatments or systemic diseases. In addition, a sample size of 50 patients does not allow for the assessment of particular variables, such as antiepileptic drugs, steroids, tumour extension, time to tumour progression and disease duration that might influence cognitive function and health status.

5. Conclusions

Many patients with HGG are aware of their cognitive difficulties. Although awareness does not imply good QoL, it is important for patient cooperation in examinations and treatments that improve physical and psychological well-being. Knowing the patient's awareness is particularly important for clinical decisions that address risks and benefits after tumour progression. This neurocognitive approach to cognitive awareness may contribute to the behavioural phenotyping of HGGs. As this is the first study of cognitive awareness in these patients, further investigation is needed to assess its characteristics and predictors over the course of the disease.

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Ethical approval

The study was approved by the institutional Review Board. All of the research procedures were conducted according to the Declaration of Helsinki of 2013 concerning the ethical principles for medical research involving human subjects. The subjects gave their informed consent to all the evaluations.

CRediT authorship contribution statement

Anna Rita Giovagnoli: Conceptualization, Methodology, Study coordination, Data curation, Formal analysis, Writing. **Rute Flavia Meneses:** Neuropsychological assessment, Writing – review & editing. **Chiara Paterlini:** Neuropsychological scoring and database. **Antonio Silvani:** Neurological assessment and treatment. **Amerigo Boiardi:** Neurological assessment and treatment, Supervision.

Availability of data and material

Data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflict of interests/Competing interests

The authors declare no conflict of interest.

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