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Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery

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Background. Cognitive effects of brain surgery for the removal of intracranial tumors are still under investigation. For many basic sensory/motor or language-based functions, focal, albeit transient, cognitive deficits have been reported low-grade gliomas (LGGs); however, the effects of surgery on higher-level cognitive functions are still largely unknown. It has recently been shown that, following brain tumors, damage to different brain regions causes a variety of deficits at different levels in the perception and interpretation of emotions and intentions. However, the effects of different tumor histologies and, more importantly, the effects of surgery on these functions have not been examined.

Methods. The performance of 66 patients affected by high-grade glioma (HGG), LGG, and meningioma on 4 tasks tapping different levels of perception and interpretations of emotion and intentions was assessed before, immediately after, and (for LGG patients) 4 months following surgery.

Results. Results showed that HGG patients were generally already impaired in the more perceptual tasks before surgery and did not show surgery effects. Conversely, LGG patients, who were unimpaired before surgery, showed a significant deficit in perceptual tasks immediately after surgery that was recovered within few months. Meningioma patients were substantially unimpaired in all tasks.

Conclusions. These results show that surgery can be relatively safe for LGG patients with regard to the higher-level, more complex cognitive functions and can provide further useful information to the neurosurgeon and improve communication with both the patient and the relatives about possible changes that can occur immediately after surgery.

Keywords: brain neoplasm, gliomas, meningioma, surgery, emotions, mentalization.

The preservation of critical cognitive functions during brain surgery for tumor removal is commonly linked to the possibility of directly mapping these functions by means of direct stimulation during surgical procedures, but this is possible only for a limited number of simpler cognitive functions (defined as eloquent) with well-circumscribed representations. Brain surgery has become more precise and effective in mapping and preserving, for example, basic sensorimotor functions (eg,[1,2]) or cognitive skills in the so-called eloquent areas such as those linked to language (eg.[3,4]) or at most visuospatial skills (eg,[5]) and a few other nonlinguistic cognitive functions (see[6] for review). There are, however, a number of other cognitive functions (eg, those linked to reasoning or manipulating/interpreting internal or external information) that are linked to more complex systems and are much more difficult to map on line during surgery given their more distributed representations, which often imply interaction between different brain structures. For these functions, instead of direct mapping, a monitoring approach (ie, comparing pre- and postsurgery performance and monitoring any changes through time) may be preferable, especially comparing the immediate pre- and postsurgery cognitive picture (when the correlation between procedure and dysfunction is more evident).

Brain surgery can sometimes have consequences on the emotional and relational world of patients that can make their social interactions problematic and influence their

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Table 1. Sociodemographic characteristics and composition of the sample of patients

	High-grade Glioma	Low-grade Glioma	Meningioma
Number of patients	29	21	16
Mean age (SD)	55.76 (12.48)	35.62 (11.75)	57.94 (11.08)
Mean education (SD)	11.28 (4.39)	13.19 (3.31)	10.81 (4.02)
Mean lesion vol cm^3 (SD)	115.24 (55.03)	71.84 (61.67)	87.74 (67.49)
Lateralization:			
Left	10	10	9
Right	19	11	7
Location:			
Frontal ($n = 29$)	9	14	6
Temporal ($n = 19$)	11	6	2
Parietal ($n = 18$)	9	1	8
Task completion rate:			
Emotion recognition: PRE	29/29 (100%)	21/21 (100%)	16/16 (100%)
POST	24/29 (82.7%)	19/21 (90.5%)	16/16 (100%)
Theory of Mind: PRE	28/29 (96.6%)	19/21 (90.5%)	15/16 (93.7%)
POST	23/29 (79.3%)	18/21 (85.7%)	15/16 (93.7%)
Alexithymia: PRE	25/29 (86.2%)	21/21 (100%)	16/16 (100%)
POST	22/29 (75.7%)	20/21 (95.2%)	16/16 (100%)
Self Maturity: PRE	17/29 (58.6%)	20/21 (95.2%)	13/16 (81.2%)
POST	16/29 (55.2%)	19/21 (90.5%)	15/16 (93.7%)
Patients' impairments by location:[a]			
	Frontal	Temporal	Parietal
Emotion Recognition:	12/29 (41.38%)	15/19 (78.95%)	3/18 (16.67%)
Theory of Mind:	7/26 (26.92%)	10/19 (52.63%)	0/18 (0%)
Alexithymia:	21/29 (72.41%)	2/16 (12.50%)	3/17 (17.65%)
Self Maturity:	12/26 (46.15%)	2/12 (16.67%)	3/16 (18.75%)

Abbreviations: POST, after surgery; PRE, before surgery; SD, standard deviation; vol, volume.
[a]Adapted from Campanella et al, 2014: number of patients (%) obtaining a score of clinical relevance (see Methods) either before or after surgery (or both) in each of the 4 experimental tasks in relation to the location of the lesion.

behavior in different ways to the point of apparently changing their personality. A deficit in recognizing the emotions of others, for example, or their intentions might lead to misunderstandings and inappropriate reactions during social interactions. Similarly, difficulty in reasoning and rationally evaluating their own or other peoples' emotions and behaviors might lead to analogous outcomes.

In a recently published paper,[7] we showed that tumors located in different brain regions can indeed generate a wide spectrum of difficulties. This work was aimed at making evidence available to the surgeon about the changes that are likely to occur with damage at specific sites. Four tasks were employed to investigate different aspects of the patient's ability to correctly perceive emotions and intentions or to reason/abstract ("mentalize") about them. In particular, more perceptual tasks (implying the ability to recognize the emotions or the intentions from facial cues; see Methods) were more often affected in patients with temporal lobe lesions. On the other hand, more evaluative tasks (implying the ability to mentalize or reason upon emotions and intentions) were more often affected by frontal lobe lesions (see Discussion).

In that study, due to the many potential variables that had to be analyzed, it was necessary for reasons of statistical power to select only the most important variables; therefore, attention was mainly focused on lesion location. The aim of the present work is to provide evidence for the direct effects of surgery and histology (this time regardless of precise lesion location for the same reasons of statistical power) to help the surgeon predict possible, less immediate outcomes of the operation on more cognitive/behavioral aspects of life in the presence of different types of tumors. Indeed, not much is known about the consequences of brain surgery over the higher-level, less eloquent cognitive functions, which have an important role in how we regulate our emotions and behaviors. This becomes particularly important for those brain tumors (eg, low-grade gliomas [LGGs]) having longer life expectancy.

With regard to the effects of different brain tumors on cognition, it is generally acknowledged that fast and slowly growing brain tumors have different cognitive impacts. While aggressive high-grade gliomas (HGGs) are associated with reduced cognitive abilities,[8,9] LGGs typically do not to show cognitive deficits for many years; in fact, the presence of a LGG is revealed only by the onset of seizures in 80%–90% of cases.[10,11] However, neuropsychological impairments may also be present in LGG patients, but these are often detectable only with deeper and more extensive cognitive assessment.[12,13]

Regarding the effects of surgery, reduced cognitive abilities are minimal in the case of meningioma,[14,15] while the picture is more complex in glioma patients. For LGG patients, the available evidence suggests that surgery can have a significant and immediate impact on cognitive functions (at least in eloquent areas), but these deficits are largely transitory and tend to (almost) disappear within a few months.[16,17] For HGG patients, data on effects of surgery are more scarce and less consistent, with some studies suggesting no effect from surgery[18] and some suggesting beneficial effects.[19]

Materials and Methods

Participants

A cohort of 66 patients with ages ranging between 18 and 75 years, who underwent surgery to remove a brain tumor, were included in the study. Inclusion criteria were the presence of brain lesions in the left or right frontal, parietal, or temporal lobes. Patients with probable gliomatosis cerebri or recurring or multiple distinct lesions were excluded. Patients whose clinical and/or cognitive picture prevented evaluation were also excluded. All participants underwent surgery after the first diagnosis, and none of them had previously undergone radio- or chemotherapy. Histologies included HGG ($n = 29$), LGG ($n = 21$), and meningioma ($n = 16$). Twenty-nine participants had a frontal lesion, 19 had a temporal lesion, and 18 had a parietal lesion. Mean age was 49.9 years (SD = 15.3), and the average education level was 11.8 years (SD = 4.1) years. Not all participants completed all 4 experimental tasks for varying reasons that were mainly linked to the presence (or onset) of severe language, attention, or executive function problems limiting their ability to properly complete all tasks. This was particularly true for the Temperament and Character Inventory (TCI) questionnaire, a long and demanding task that yielded a higher drop-off rate. All participants' sample characteristics are detailed in Table 1. The study was approved by the ethical committee of A.O.U. S. Maria della Misericordia of Udine, and all patients gave their written consent for participation.

Neuropsychological Assessment

Participants received a preoperative evaluation (usually on the day before surgery) and a second evaluation postoperatively (usually within the week after surgery). Together with the social cognition tasks, participants also received a baseline neuropsychological evaluation on both occasions to assess the main cognitive domains: language, attention, executive function, memory, and perception (see Table 2).

Lesion Volume Evaluation and Surgery

For lesion volume calculationm, 3D reconstruction was performed by tracing lesion boundaries on each slice of the horizontal plane from preoperative T1 and (when available) T2 MRI sequences. Reconstructed lesion boundaries included all areas of altered MRI signal in the available scans including edema, which is known to have cognitive effects.

From the surgical point of view, complete resection was performed of the meningiomas, which are benign, extra-axial, well-circumscribed lesions. For the LGG participants, who have a longer life expectancy and in which a higher percentage of resection is linked to a significant increase in survival,[11] a radical/aggressive surgical approach (usually coupled with brain mapping in the awake surgery condition) was adopted to allow the maximum extent of resection. This was calculated in terms of percentage of the total volume, using the standard current procedure, by subtracting the postoperative lesion volume from the preoperative lesion volume based on T2 MRI sequences.[11] Postoperative control scans were obtained on the LGG participants at 4 months following surgery, when the acute effects of surgery had resolved and the neuroanatomical picture was stable. For HGG participants, the extent of resection was not calculated at 4 months because radiotherapy, chemotherapy, or regrowth of the lesion may have added substantial artifacts to the MRI signal. Surgery for the HGG participants, however, was ALSO aimed at the maximum extent of resection possible, mainly including the contrast-enhancing part of the lesion, in line with the most recent literature on surgical management of HGG.[20] A tradeoff needs to be made for HGG patients, however, between maximal resection and a more conservative approach to reduce the risk of (even temporary) sequelae. Any postoperative cognitive deficit would have a negative impact on the quality of residual life for these patients whose life expectancy is shorter and have less time to recover.

Experimental Investigation

The experimental part of the study consisted of 4 tasks investigating different aspects of social cognition and involving the recognition or evaluation of one's own or other people's emotions or intentions. Two of the tasks (emotion recognition and theory of mind) involved the more perceptual processes of recognition of emotions and intentions, while the other 2 (alexithymia and personality) questionnaires involved more direct evaluation and reasoning about emotions and intentions (mentalization). A detailed description of each task is found in Campanella et al, 2014.[7]

Perceptual Tasks

Emotion Recognition (Ekman Faces). In this task, a display shows 6 faces of the same person expressing 6 basic emotions[21]: happiness, sadness, anger, surprise, fear, and disgust. Participants were asked to point to the face depicting the facial emotion requested. There were an overall number of 36 stimuli (6 emotions for each of 6 selected models). A separate group of 20 control individuals provided reference performance. The controls were matched for age and education to the participants. Mean age and education were, respectively, 47.2 years (SD = 13.8) and 13.1 years (SD = 4.0); no significant differences were found ($t = 0.653$, $z = 0.515$ for age; $t = -1.351$, $P = .180$ for education) compared with the 2 groups. Given the limited number of controls, the cutoff for any clinically relevant score was strictly set at 2 SD below the average raw score of (28.99/36).

Perceptual Theory of Mind (the Eyes Test). The Italian version of the revised "Reading the Mind in the Eyes" test[22] was

Table 2. Neuropsychological profile for patient groups included in the study. Raw number and percentage of patients showing clinically relevant scores are reported

		Language		Executive Functions		Attention				Perception			
		Token Test[a] (cutoff = 26,5)		FAB[b] (cutoff = 13,4)		Visual Search[a] (cutoff = 32)		Stars Cancellation[c] (cutoff = 51)		BORB subtest 8: Foreshort. Views[d] (cutoff = 16)		Benton Facial Recognition Test[e] (cutoff = 19)	
Histology		PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
HGG ($n = 29$)	Raw no.	7/28	5/22	12/22	9/17	5/28	2/22	3/28	5/25	0/21	0/22	3/20	4/25
	Percentage	25%	22.72%	54.54%	52.94%	17.86%	9.09%	10.71%	20%	0%	0%	15%	16%
LGG ($n = 21$)	Raw no.	0/21	3/21	3/19	5/19	0/21	7/20	1/20	2/20	0/21	1/21	1/21	5/21
	Percentage	0%	15%	15.79%	26.32%	0%	35%	5%	10%	0%	4.76%	4.76%	23.81%
Meningioma ($n = 16$)	Raw no.	0/16	0/14	1/13	3/13	1/16	3/14	0/14	0/14	0/14	0/13	0/16	0/15
	Percentage	0%	0%	7.69%	23.08%	6.25%	21.43%	0%	0%	0%	0%	0%	0%
		Visuospatial Skills		Long-term Memory				Short-term Memory					
		Rey Figure[f] (Immediate) (cutoff = 28,88)		Rey Figure[f] (Delayed) (cutoff = 9,47)		Narrative Memory[g] (cutoff = 8)		Digit Span Forward[h] (cutoff = 3,75)		Digit Span Backward[i] (cutoff = 3)		Corsi Spatial Span[h] (cutoff = 3,5)	
Histology		PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
	Raw no.	6/18	5/13	5/18	3/13	7/19	5/15	4/28	4/23	10/27	10/23	8/21	9/17
HGG ($n = 29$)	Percentage	33.33%	38.46%	27.77%	23.08%	36.84%	33.33%	14.28%	17.39%	37.04%	43.48%	38.09%	52.94%
	Raw no.	1/14	4/14	5/14	5/14	1/17	2/16	0/20	1/19	0/20	4/19	0/17	2/16
LGG ($n = 21$)	Percentage	7.14%	28.57%	35.71%	35.71%	5.88%	12.5%	0%	5.26%	0%	21.05%	0%	12.5%
	Raw no.	2/13	3/11	2/13	3/11	0/13	0/12	1/14	0/13	2/14	3/13	2/12	3/12
Meningioma ($n = 16$)	Percentage	15.38%	27.27%	15.38%	27.27%	0%	0%	7.14%	0%	14.28%	23.08%	16.66%	25%

Abbreviations: FAB, frontal assessment battery; BROB, birmingham object recognition battery; HGG, high-grade glioma; LGG, low-grade glioma; no., number; POST, after surgery; PRE, before surgery.

[a]Spinnler H, Tognoni G (1987) *It J Neurol Sci* 8:1–120.
[b]Appollonio I, *et al.*, (2005) *Neurol Sci* 26:108–116.
[c]Halligan PW, *et al.*, *Neuropsychol Rehabil*. 1991;1:5–32.
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[f]Caffarra P, *et al., Neurol Sci* 2002;22:443–7.
[g]Novelli G. *et al., Arch Neurol, Psich Psicol* **47**, 477–505 (1986).
[h]Orsini A. *et al., It J Neurol Sci* **8**, 539–548 (1987).
[i] Qualitative evaluation.

administered. Participants have to identify which of 4 words (describing complex mental states and intentions) best matches the intention expressed by a photograph of the eye region of a person. A total of 36 stimuli are presented. Scores are expressed as normalized *z* scores obtained from the healthy population.[23] Any score within the lower third (ie, *z* score <1) of the reference population performance was considered clinically relevant.[24]

Evaluative Tasks

Toronto Alexithymia Scale. The Italian version[25] of the Toronto Alexithymia Scale (TAS-20)[26] was administered. Participants are asked to rate, on a 5-point Likert scale, how they generally feel about 20 items capturing difficulties in identifying or describing feelings or in introspective thinking. According to universally accepted cutoff scores for alexithymia, raw scores <51 indicate the absence of alexithymia, scores of 52–60 indicate possible alexithymia, and scores >61 indicate severe alexithymia. Therefore, any score above 51 was considered as a clinically relevant score.

Temperament and Character Inventory. The Italian translation[27] of the Temperament and Character Inventory (TCI[28]) was administered. The TCI is a complex, 240 yes/no questions personality inventory. Beside identifying 4 temperamental profiles (acquired environmental stimulus-response association patterns), it also provides a measure of the development of the character (defined as self maturity) by combining measures of self directedness (self-efficacy and self-esteem) and cooperativeness (compassion, empathy, and tolerance). Low levels (ie, raw scores<58) of the self maturity factor, which corresponds to the lower third (ie, <1 SD) of the reference healthy population, are associated[28] with the presence of a personality disorder. This cutoff was thus set for scores to be considered clinically relevant.

Data Handling

For each task, data were entered separate ANCOVA designs, with surgery (presurgical vs postsurgical performance) as a within-subject variable and histology as between-subject factor. Other variables, potentially modulating the performance of participants in the tasks, were entered into the design as covariates to control for their influence. These were age, education, and lesion volume. Tukey test post hoc analysis was then performed to investigate the sources of possible significant main effects and interaction. ANCOVA results are summarized in Table 4.

To provide an assessment of general cognitive level, the percentage of participants obtaining (in the baseline neuropsychological tasks), a score in the range of clinical relevance (impaired or borderline scores) was computed and averaged across tasks for each participant group (HGG, LGG, and meningioma). Statistical significance was calculated by means of chi squares. The effect of histology was computed comparing the average performance before surgery across the groups of participants, and then post hoc chi-square contrasts were performed (Bonferroni correction: $P = .05/3$, $P = .017$). The effects of surgery were evaluated by means of 3 separate chi squares comparing the performance before and after surgery (Bonferroni correction: $P = .05/3$, $P = .017$) for each group. With a similar statistical approach, the effect of lesion location (regardless of histology or surgery) was calculated by means of chi squares comparing the number of participants obtaining a score of clinical relevance either before or after surgery (or both) across the 3 main lesion locations (frontal vs temporal vs parietal lobes; see Table 3).

Results

Lesion Volume and Extent of Resection

The average volume of lesions calculated with this procedure was 71.84 cm^2 for LGG, 115.24 cm^2 for HGG, and 87.75 cm^2 for meningiomas (see Table 1). For LGG, the extent of resection was equal to 89.4%.

Neuropsychological Baseline

Comparing the preoperative performance of participants across groups (see Table 2) revealed a highly significant effect of the histological type ($\chi^2_{(df=2)} = 20.22$; $P < .001$). The direct comparisons showed that HGG participants had a worse preoperative cognitive functioning level than the LGG and meningioma participants ($P < .001$ in both cases), while LGG and meningioma participants did not differ from each other ($P = .99$). Regarding the effects of surgery, while the HGG and meningioma participants did not change their cognitive level with surgery ($P = .99$ and $P = .334$, respectively), LGG participants showed a significant increase in cognitive deficit rate ($P = .010$).

Lesion Location Effects

As reported in Table 3, both perceptual tasks (tasks 1–2) were maximally affected by lesions in the temporal lobes, while both evaluative tasks (tasks 3–4) were maximally affected by lesions located in the frontal lobes (see[7] for a deeper and detailed analysis of the precise lesion location effects on these tasks).

Acute Effects of Surgery

Perceptual Tasks: Emotion Recognition and Perceptual Theory of Mind (The Eyes Test). In the 2 more perceptual tasks, despite a significant influence of education, lesion volume, and more inconsistently of age (see Table 4), none of these covariates interacted with the surgery factor and thus seemed not to influence the outcomes of surgery. On the other hand, a significant main effect of histology was found for both tasks. HGG participants generally showed more difficulties in the tasks of emotion recognition ($P = .005$) and perceptual theory of mind ($P = .002$) with respect to participants with meningiomas. The LGG participants, on the other hand, showed no difficulty in Emotion Recognition in general compared with the meningioma participants ($P = .474$). They performed similarly to the HGG participants in perceptual theory of mind and obtained lower scores than the meningioma participants ($P = .002$).

Table 3. Location effect analysis: number of patients (%) obtaining a score of clinical relevance (see Methods) either before or after surgery (or both) in each of the 4 experimental tasks in relation to the location of the lesion

Task:	Frontal	Temporal	Parietal	Omnibus Test ($\chi^2_{(df=2)}$)	Post Hoc Contrasts (Fisher Exact)		
					FRO vs TEM	FRO vs PAR	TEM vs PAR
Emotion Recognition:	12/29 (41.38%)	**15/19 (78.95%)**	3/18 (16.67%)	$\chi^2 = 14.807$ $P < .001$	$\chi^2 = 6.58$ $P = .011$	$\chi^2 = 3.12$ $P = .072$	$\chi^2 = 14.35$ $P < .001$
Theory of Mind:	7/26 (26.92%)	**10/19 (52.63%)**	0/18 (0%)	$\chi^2 = 12.995$ $P = .001$	$\chi^2 = 3.09$ $P = .074$	$\chi^2 = 5.76$ $P = .017$	$\chi^2 = 12.98$ $P < .001$
Alexithymia:	**21/29 (72.41%)**	2/16 (12.50%)	3/17 (17.65%)	$\chi^2 = 20.875$ $P < .001$	$\chi^2 = 14.81$ $P < .001$	$\chi^2 = 12.88$ $P < .001$	$\chi^2 = 0.17$ $P = .530$
Self Maturity:	**12/26 (46.15%)**	2/12 (16.67%)	3/16 (18.75%)	$\chi^2 = 5.018$ $P = .081$	$\chi^2 = 3.24$ $P = .069$	$\chi^2 = 3.07$ $P = .079$	$\chi^2 = 0.02$ $P = .643$

Abbreviations: FRO, frontal; PAR, parietal; TEM, temporal.

Table 4. Results of ANCOVA over the 4 experimental tasks. Bold indicates significant results

			Variables	*F*	*P*	η^2
Perceptual Tasks	Emotion, Recognition (Ekman faces)	Covariates	Age	0.691	.410	0.013
			Education	**6.871**	**.011**	**0.115**
			Lesion volume (cm^3)	3.741	.058	0.066
		Main Effects	**Histology**	**4.842**	**.012**	**0.155**
			Surgery	0.037	.849	0.001
		Interactions	Surgery × age	0.338	.564	0.006
			Surgery × education	0.002	.961	0.000
			Surgery × lesion vol	1.827	.182	0.033
			Surgery × histology	**3.852**	**.027**	**0.127**
	Theory of Mind (The Eyes Test)	Covariates	**Age**	**20.468**	**<.001**	**0.295**
			Education	**5.779**	**.020**	**0.105**
			Lesion volume (cm^3)	**5.381**	**.025**	**0.099**
		Main Effects	**Histology**	**3.357**	**.043**	**0.120**
			Surgery	0.240	.626	0.005
		Interactions	Surgery × age	0.005	.942	0.000
			Surgery × education	0.314	.578	0.006
			Surgery × lesion vol	0.595	.444	0.012
			Surgery × histology	**3.286**	**.046**	**0.118**
Evaluative Tasks	Alexithymia (TAS-20)	Covariates	Age	2.568	.115	0.047
			Education	0.323	.572	0.006
			Lesion Volume (cm^3)	**8.037**	**.007**	**0.134**
		Main Effects	Histology	2.784	.071	0.097
			Surgery	0.912	.344	0.017
		Interactions	Surgery × age	0.233	.631	0.004
			Surgery × education	1.351	.250	0.025
			Surgery × lesion vol	0.133	.717	0.003
			Surgery × histology	1.033	.363	0.038
	Self Maturity (TCI Questionnaire)	Covariates	Age	0.199	.658	0.005
			Education	0.029	.865	0.001
			Lesion volume (cm^3)	1.792	.188	0.043
		Main Effects	Histology	0.342	.712	0.017
			Surgery	0.808	.374	0.020
		Interactions	Surgery × age	2.742	.106	0.064
			Surgery × education	0.008	.927	0.000
			Surgery × lesion vol	0.372	.545	0.009
			Surgery × histology	2.778	.074	0.122

Abbreviations: vol, volume.

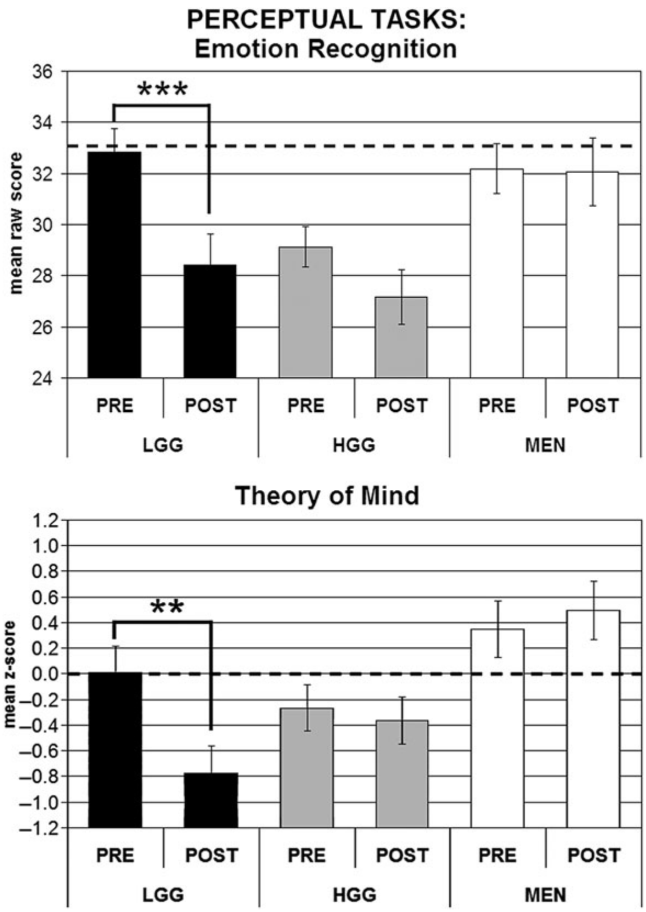

Fig. 1. Only participants with low-grade glioma suffered acute effects of surgery in the more perceptual tasks involving perceptual recognition of emotions or intentions. Dashed line indicates the reference population's mean. Error bars indicate standard error. ***$P < .001$; **$P < .01$.

Most importantly, there was a significant interaction between surgery and histology for both perceptual tasks, showing that the different types of tumors reacted differently to acute effects of resection regardless of any intervening variable (see Fig. 1). In particular, post hoc tests revealed that both HGG ($P = .258$) and meningioma ($P = .999$) participants were unaffected by surgery and maintained the same level of performance after surgery as before. The only group showing significant surgery effects was LGG participants, who clearly worsened their performance (unimpaired before surgery) after the operation ($P < .001$ and $P = .009$, respectively). This result was also evident at the single case level (see Table 5): the percentage of participants showing clinically relevant scores jumped for LGG participants from 9.5% to 42.1% for emotion recognition and from 5.3% to 33.3% for theory of mind after surgery.

Evaluative Tasks: Toronto Alexithymia Scale and Temperament and Character Inventory. The performance in more evaluative tasks (see Table 4) showed that, among the possible covariates considered, only lesion volume significantly influenced the performance of participants but only for the alexithymia scores and not for the self maturity factor in the TCI personality inventory. None of the other variables was significantly associated with the scores or interacted with the surgery factor in any of the 2 tasks. A trend was present toward a significant main effect of histology but only in the alexithymia questionnaire and with no significant differences among the scores for the different types of tumor. No interaction with surgery was found in either task, suggesting that all participants maintained stable scores after surgery. Indeed, looking at data at the single case level (see Table 5), clinically relevant scores were equally distributed across histologies both before and after surgery.

Low-grade Glioma Participant Follow-up

A follow-up evaluation was considered important for LGG participants since their preoperative performance was largely unimpaired on all tasks, but immediately after surgery they (unlike the participants with meningioma) suffered an evident drop in performance in the perceptual tasks. Moreover, unlike the participants with HGG, the LGG participants were free from adjuvant treatments such as chemo- or radiotherapy, which are known to produce additional impact on the cognitive system.[29,30] Most of the LGG participants (14/21) were still available for the follow-up evaluation approximately 4 months after surgery.

Perceptual Tasks: Emotion Recognition and Perceptual Theory of Mind (The Eyes Test)

Four months after surgery, a significant effect of condition was found in both perceptual tasks, (See Supplementary Table S1). Post hoc tests revealed that LGG participants significantly recovered their emotional recognition ($P = .003$) and theory of mind ($P = .047$) abilities with respect to their immediate postsurgical performance and returned to their preoperative level of functioning.

Evaluative Tasks: Toronto Alexithymia Scale and Temperament and Character Inventory

As regards the alexithymia scores, in the follow-up, LGG patients showed a mild but consistent reduction of their scores, with respect to both before ($P = .068$) and immediately after surgery ($P = .084$) conditions (see Supplementary Table S1). Self Maturity scores in the TCI questionnaire, instead, did not show any variation in the follow-up testing, remaining stable across sessions.

Discussion

This study evaluated the impact of brain surgery on the higher-level cognitive functions regulating social cognition and influencing everyday behavior, social interactions, and the quality of life of people affected by brain tumors of different histologies. In a recent work,[7] we showed that tumors in different brain locations impaired different aspects of affect cognition and personality in brain tumor patients (with anterior temporal

Table 5. Mean scores and frequency (raw number and percentage) of clinically relevant scores (see Methods) in the 4 tasks before and after surgery

	Task	Histology	Reference Mean[a]	Before Surgery		After Surgery	
				Mean Score (SE)	No. of deficits (%)[b]	Mean Score (SE)	No. of Deficits (%)[b]
Perceptual Tasks	Emotion Recognition (Ekman faces)[1]	HGG ($n = 29$)		**29.125*** (0.798)	14/29 (48.3%)	**27.167*** (1.076)	15/24 (62.5%)
		LGG ($n = 21$)	33.600	32.842 (0.897)	2/21 (9.5%)	**28.421*** (1.210)	8/19 (42.1%)
		Meningioma ($n = 16$)		32.187 (0.977)	2/16 (12.5%)	32.062 (1.318)	3/16 (18.7%)
	After surgery	HGG ($n = 29$)		−0.264 (0.178)	6/28 (21.4%)	−0.361 (0.182)	6/23 (26.1%)
	After surgery	LGG ($n = 21$)	0.000	0.010 (0.207)	1/19 (5.3%)	**−0.773*** (0.212)	6/18 (33.3%)
	After surgery	Meningioma ($n = 16$)		0.349 (0.221)	1/15 (6.7%)	0.497 (0.226)	0/15 (0%)
Evaluative Tasks	Alexithymia (TAS-20)[3]	HGG ($n = 29$)		43.636 (2.207)	5/25 (20%)	45.273 (2.476)	6/22 (27.3%)
		LGG ($n = 21$)	44.700	45.550 (2.315)	6/21 (28.6%)	47.400 (2.597)	7/20 (35%)
		Meningioma ($n = 16$)		49.062 (2.588)	5/16 (31.3%)	47.312 (2.903)	6/16 (37.5%)
	Self Maturity (TCI inventory)[4]	HGG ($n = 29$)		65.733 (2.591)	3/17 (17.6%)	64.000 (2.857)	2/16 (12.5%)
		LGG ($n = 21$)	64.000	66.611 (2.366)	5/20 (25%)	63.000 (2.608)	7/19 (36.8%)
		Meningioma ($n = 16$)		62.461 (2.784)	4/13 (30.8%)	63.461 (3.068)	5/15 (33.3%)

Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; No., number; SE, standard error.
[a]Task1: 20 healthy control subjects; Task2-3-4: healthy Italian population standardization scores.
[b]Number of patients scoring below the cutoff of "clinical relevance":Emotion Recognition: < 2 SD below mean control sample score (20 subj).Theory of Mind: < 1 SD below the mean population.Alexithymia: > 51 (cut-off for possible alexithymia).Self Maturity: < 58 (cut-off for suspect personality disorder).
*Asterisks indicate significant differences compared with the reference population in each condition (single sample T-test). Significance level was set at $P = .008$ ($P = .05/6$), after Bonferroni correction for multiple comparisons (6 comparisons for each task).

lesions [amygdala and insula] causing deficits in facial emotion recognition; posterior temporal lesions [particularly at the temporoparietal junction] causing difficulties recognizing the intentions of others from their eye-gaze; lesions to medial prefrontal regions [particularly anterior cingulate cortex] leading to alexithymia; and lesions to lateral prefrontal cortex leading to increased risk of personality disorder). A general lobe analysis was also performed here to confirm the same location effects (see Table 3). However, our analysis did not consider the location and histology factors together due to the uneven distribution of lesion histologies across the different anatomical locations (see Table 1). While HGG participants were indeed homogeneously distributed across the 3 anatomical locations, LGG and meningiomas were clearly not. This would have made the statistical design largely unreliable and any result potentially misleading.

The main results indicated that surgery had an immediate, acutely negative impact on the performance of only the LGG participants, who were largely unimpaired before surgery on all measures. However, the effects of surgery were significant only in the more perceptual task, and no effect was found in the more evaluative tasks needing higher levels of mentalization (ie, reasoning and abstracting upon what is perceived). The negative effects, however, were transient, and the participants generally recovered within a few months after surgery. HGG participants showed generally lower levels of performance in the perceptual tasks and were not impacted by surgery. Finally, participants affected by meningioma exhibited globally intact performance in all tasks and were also unaffected by surgery. The pattern of performance described for the more perceptual tasks was also found when analyzing the performance of participants in the general neuropsychological assessment, which mainly evaluated the functioning of localized cognitive modules.

Effects of Surgery on the Different Tumor Histologies

The present data seem to suggest that the effects of surgery on the higher level cognitive functions examined, might be different according to the different types of histology of brain tumor.

Meningioma

In accordance with previous evidence,[14,31] the performance of meningioma participants was (on the average) unaffected by surgery (which was radical) and remained intact both before and also after the intervention. This is not surprising considering that meningiomas are extra-axial lesions and that their removal usually leaves the underlying brain structures intact. However, in tasks 3 and 4 (involving more abstract/integrative cognitive functions), meningioma participants (see Table 4) obtained overall (even if not significantly) higher average alexithymia and lower self-maturity scores compared with the other etiologies, suggesting some kind of cognitive effect for meningiomas that is possibly due to the presence of edema[32] or parenchymal compression.

High-grade Glioma

HGG participants were impaired compared with meningioma participants (always unimpaired) in the perceptual tasks and compared with the reference population preoperatively in the emotion recognition task alone. Their performance, however, did not change with the operation. The lack of cognitive changes after removal of this type of lesion is probably due to the fact that the cognitive system was already damaged by the aggressive progression of the tumor. The removed tissue, limited to the only compact or necrotic part of the tumor, was therefore unlikely to be functional anymore. In participants with HGG, a tumor with a higher malignancy and faster evolution, the infiltrating portion of the lesion is usually not removed to avoid damaging potentially functional tissue. Conversely, in the case of LGG patients, the infiltrated tissue is approached surgically since these patients have a better chance for recovery and a longer life expectancy and usually do not need further adjuvant chemo- or radiotherapy treatments, which could prevent functional recovery.

Low-grade Glioma

The clearest effects of surgery were observed in LGG participants. Before surgery, the LGG participants showed intact performance in all measures. However in the 2 more perceptual tasks (see next section), their performance worsened dramatically after surgery. The good preoperative performance of LGG participants can be explained by looking at the biology of tumoral invasion in LGG. Due to the slow growth rate, LGGs have been found to induce partial reorganization before surgery,[33,34] with functions in the eloquent areas being redistributed around the lesion. Moreover, LGG activity is infiltrative, allowing the activity to persist even inside the tumoral mass.[35] This could also explain the onset of cognitive damage after tumoral resection. Because a more radical and aggressive surgical strategy is adopted with LGG tumors, a larger extent of resection is obtained than with HGG (based mainly on T2 MRI sequences that might include still-functioning tissue). However, follow-up data showed that the cognitive damage recovers quickly due to brain reorganization mechanisms that were probably already triggered before the surgery itself.[16,17] Postoperative cognitive reorganization has already been demonstrated for more peripheral perceptual/sensory functions,[36] but these data clearly suggest that this is also possible for higher-level cognitive functions.

Effects of Surgery on More Perceptual Versus Integrative Cognitive Functions

From a more cognitive point of view, the fact that only more perceptual tasks were affected by surgery concurs with the general organizational principles of cognitive functions in the brain.[37,38] More peripheral, perceptual-like processes would be more focal, localized, and subserved by fewer structures and thus have less distributed functional representations. This means that a brain lesion (either due to the tumor itself or induced by surgery), is more likely to produce cognitive damage if it occurs in the anatomical site where such function is localized.

Turning to more abstract/integrative functions, data showed that the tasks themselves are sensitive to cognitive alteration. Table 4 illustrates an average percentage of detected, clinically relevant cases (see Methods) equal to roughly 25%–30% for each evaluative task both before and after surgery; this rate was very similar to that obtained for the emotion recognition task. The performance of participants, however, did not change after surgery. This might be due to the fact that acute damage (ie, HGG participants before or LGG participants after surgery) can produce a local alteration to a more widely distributed network of areas likely subserving such complex cognitive functions, and cognitive changes can become visible only with more extensive damage. Indeed, the performance of participants on the alexithymia questionnaire showed that, among the variables considered, only lesion volume was significantly linked to higher scores in alexithymia, in accordance with the possibility that larger lesions in general might have a greater impact over more distributed functions.

A possible alternative view can be that the perceptual tasks were simply more efficient in detecting cognitive impairment than the more evaluative tasks. For example, in our case, both evaluative tasks are in fact explicit tasks in which it is (in principle) easier to mask potential problems by giving a socially acceptable answer. This is a common problem intrinsically linked to the use of self-report measures in general, and future works on the topic could benefit from the use of more implicit measures of, for example, personality traits.[39] However, the overall rate of clinical sensitivity of the 2 types of tasks was absolutely comparable in our sample (see Table 4), limiting the possibility that evaluative tasks were simply less sensitive than implicit perceptual tasks.

Conclusions and Limitations

The surgery in LGG showed that deficits in emotion recognition and perceptual theory of mind were only transient and recovered within a few months. Using the useful distinction between essential (nonremovable) and compensable (removable) structures,[34,40] we can say that perceptual social cognition skills are compensable and can in principle be approached surgically without excessive risk of permanent deficit. This means that these modules, even if more perceptual, are not completely peripheral such as those linked to more basic sensorimotor functions, which are more computationally encapsulated and have fewer alternative ways to reorganize.[41]

Overall, these results overlap quite well with those found, for example, in right posterior parietal functions,[42] both in terms of a worse performance of HGG participants and postoperative cognitive decline for LGG participants. Taken together, moreover, these results fit well with and extend the notion that deeper and more extended assessment of neuropsychological functions in glioma patients can be very useful for detecting cognitive difficulties linked to both the tumor histology and the surgery itself.[13,17,19,34] Finally, these data can represent a useful source of information for the neurosurgeon to evaluate costs and benefits in planning the surgical strategy and, on a patient-related perspective, can improve the communication about possible changes that can occur in the period immediately after the surgery and whether these are expected to be stable or only transient.

Several limitations, however, need to be taken into account in generalizing the present results. First, the sample of patients considered was (albeit fairly large) still limited, and this made it impossible to evaluate and consider all the potentially interesting variables together. In particular, although lesion location was already deeply detailed in our previous work,[7] it was not possible (due to the limited sample size) to consider its interactions in particular with histology and lesion volume because this would have considerably reduced statistical power and reliability of the results. Secondly, we could evaluate only patients with a clinical status and cognitive level sufficient to complete the experimental tasks. This is reflected, for example, in the high drop-off rate of HGG participants in completing the TCI questionnaire and will surely limit the generalizability of these findings. Future work should deal with these limitations by identifying tasks that might be informative when dealing with patients with limited cognitive resources. Future work should also consider the use of blind assessors and take into account the possible influences of the pharmacological therapy (eg, anticonvulsant and corticosteroids) on similar measures of emotion and personality.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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