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EFFECTS OF STANDARD OF ART TREATMENT

Cognitive outcome after awake surgery for tumors in language areas

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Abstract In surgery for tumors of the dominant hemisphere, the attention devoted to quality of resection and preservation of language function has not been accompanied by comparable interest in preservation of cognitive abilities which may affect quality of life. We studied 22 patients undergoing awake surgery for glioma removal in the language areas of the brain. Besides monitoring tumor variables (size, location, histology, edema), we used a multifaceted battery of tests to investigate mood, cognition, and language in an attempt to assess the burden of disease and treatment, and the relationships between these three dimensions. Baseline assessment showed that 45% of the patients were depressed and 23% anxious; some cognitive and language impairment was noted for 59 and 50%, respectively. A general decline in postoperative cognitive performance (significant for memory and attention only) and language function (significant for picture naming) was observed, whereas depression was unchanged and anxiety decreased. Tumor histology, but not demographic variables or extent of resection, correlated with postoperative cognitive changes: patients undergoing surgery for high-grade tumors were more likely to improve. No correlation was observed between scores for mood, cognition, and language function. A subset of patients with low-grade glioma was followed up for 3–6 months; although some improvement was observed they did not always regain their preoperative performance. In conclusion, we believe that cognitive assessment performed in conjunction with language testing is a necessary step in the global evaluation of brain tumor patients both before and after surgery.

Keywords Glioma · Surgical treatment · Cognition · Mood · Language

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Introduction

The most reliable method of cortical mapping is currently intraoperative electrical stimulation [1, 2]. It was once thought that no electrically identified areas should be removed if postoperative complications were to be avoided. This limitation was later restricted to brain areas "essential" for language functions, the assumption being that postoperative language deficits would not occur after removal of cortex that does not respond to electrical stimulation [3, 4]. This notion is gaining wider acceptance, but support from detailed comprehensive assessment and objective evaluation of postsurgical cognitive complications remains insufficient.

Mounting clinical evidence has reinforced questions about the use of testing procedures that involve other cognitive abilities besides language. Despite attempts to intraoperatively identify critical functions and preserve preoperative skills, studies which used appropriate diagnostic tools still resulted in high cognitive impairment, which cannot be overlooked. Furthermore, several recent reports have pointed to the frequent occurrence of attention and memory deficits and the pivotal role they play in preserving good quality of life (QoL) [5–7].

The objective of this study was to determine the effect of awake surgery on cognitive function other than language ability and to examine differences between pre and post-operative performance status.

Materials and methods

This prospective study included 22 consecutive patients undergoing awake surgery for glioma of the left hemisphere at the Neurosurgical Unit of Verona University. To minimize the possible effect of confounding factors on cognitive outcome, Karnofsky performance score (KPS) $\geq$70 was taken as an indication for awake surgery; exclusion criteria were multifocal lesions and long-lasting epilepsy and/or antiepileptic therapy. The only pharmacological treatment was corticosteroid therapy (dexamethasone, maximum dose 16 mg/day). Antiepileptic drugs (levetiracetam or oxacarbazepine) were started as prophylaxis for surgery after baseline test administration and were withdrawn before re-testing during the postoperative period. The mean duration of clinical history was five months (range, 1–9). Patient demographics are listed in Table 1. A microsurgical technique was performed in all cases.

Language function was assessed by means of subtests selected from a battery of tests for aphasic deficits (BADA) [8]. The task types were: phonemic discrimination; word repetition; picture naming (nouns and verbs); auditory and visual word-to-picture matching (nouns and verbs); auditory and visual sentence-to-picture matching; writing to dictation; and reading aloud. Impairment in each subtest was measured as error percentage. In the picture-naming task, >30% errors was taken as an exclusion criterion [3].

All patients completed a comprehensive neuropsychological battery of tests that measure intellectual and executive function, memory, praxis, gnosis, and mood (depression and anxiety). Cognitive domains were investigated by use of a variety of tests (Table 2a). The mean score for each domain was calculated from the sum of the means of the *z*-score for each test in that domain. The characteristics of the tests and the scoring procedures have been described elsewhere [6] (Table 2a, b) [9–17].

Postoperative and follow-up changes were analyzed by domain and by test (Table 2a) as follows:

Table 1 Patient characteristics and tumor variables

Variable	Patients (N = 22) no. (%)
Age (years)	
≥65	2 (9)
<65	20 (91)
Sex	
Male	10 (45)
Female	12 (55)
Tumor grade	
High-grade	8 (36)
Low-grade	14 (64)
Tumor classification[a]	
Grade II	
Astrocytoma pilocitic	2
Oligodendroglioma	8
Oligoastrocytoma	4
Grade III	
Astrocytoma	4
Oligodendroglioma	1
Oligoastrocytoma	1
Glioblastoma	2
Location	
Parietal	9 (41)
Frontal	8 (36)
Temporal	5 (23)
Size (cm)	
≤3.5	9 (41)
>3.5	13 (59)
Edema	
Yes	11 (50)
No	11 (50)
Removal	
Total	17 (77)
Subtotal	5 (23)
Mapping	
Positive	18 (81)
Negative	4 (19)

[a] II second grade, III anaplastic

- Unimpaired/impaired affective, neuropsychological, and language performance at baseline evaluation was analyzed according to demographic and tumor variables (age, sex, tumor location, histology, edema, size) by means of χ^2 tests ($p \leq 0.05$).
- Analysis of variance (ANOVA) ($p < 0.05$) was used to assess the effect of mood on neuropsychological performance.
- Pre and post-operative scores for affective, neuropsychological, and language measures were compared by test (Wilcoxon sum rank test; $p \leq 0.05$) and patient (McNemar; $p \leq 0.05$). Patients whose condition

Table 2 **a** Cognitive tests, **b** psychological questionnaires

(a) Cognitive tests

Neuropsychological domain	Neuropsychological tests
Handedness	Edinburgh handedness inventory (EHI) [9]
Intelligence	Raven colored matrix (Raven 47) [10]
Executive functions	Word fluency (FAS) [10]
	Trail-making test (TMT—A and B) [11]
Memory	Verbal digit span (span) [10]
	15 Rey word list, immediate recall (RWL-IR) [10]
	15 Rey word list, delayed recall (RWL-DR) [10]
	Rey–Osterrieth complex figure (ROCF) [13]
Language	Picture object naming [12]
	BADA subtests of language [8]
Praxis	Copy design [12]
	Limb praxis [15]
	Orofacial praxis [15]
Gnosis	Body part naming (BPN) [15]
	Finger naming (FN) [15]

(b) Psychological questionnaires

Affective state	Psychological questionnaire
Depression	Beck depression inventory (BDI) [16]
Anxiety	State and trait of anxiety inventory (STAI state and trait) [17]

worsened were further analyzed according to demographic, tumor, and treatment (mapping and extent of resection) variables (χ^2; $p < 0.05$).

– Analysis of variance (ANOVA) ($p < 0.05$) was used to assess the effect of language deficit (picture naming) on neuropsychological performance according to test and domain.

Cortical mapping was performed by use of electrocorticography and electrocortical stimulation with a bipolar forceps delivering a biphasic current (pulse frequency 50 Hz; duration 0.2 ms). Current intensity was determined on a case-by-case basis by progressively increasing the amplitude in 2 mA increments, starting at 2 mA until an after-discharge was elicited.

Intraoperative tasks for each patient were chosen on the basis of lesion location and performance on preoperative neuropsychological assessment. Automatic series (counting) and picture object naming tests were administered to all patients; if impairment was observed for a patient in a specific BADA subtest, further tasks were administered to keep these more specific language functions under control during the operation. The types of error examined were: latency; speech arrest; phonemic paraphasia; perseveration; and semantic error by Ojemann's procedure [3].

Extent of removal was classified on the basis of postoperative magnetic resonance imaging (MRI), as described in detail elsewhere [6].

Whenever possible, follow-up data were obtained 3–6 months postoperatively, using the same evaluation criteria for patients with low-grade glioma who did not receive radiotherapy or chemotherapy. Cognitive decline was not sufficiently severe for any patient to suggest the need for a rehabilitation cognitive program.

Results

Affective measures

Nine out of 22 patients (41%) complained of depressive mood before surgery. Mood remained unchanged for seven (32%) patients and improved for two (9%) after treatment. Among the 13 (59%) patients without depression, two (9% of the sample) became clinically depressed. Five (24%) patients experienced preoperative anxiety, which subsided after surgery for three. Although comparison of pre and postoperative mean scores for affective measures revealed no significant change in depression, a statistically significant decrease in anxiety scores was noted (Table 3).

Depression and anxiety did not correlate with damage in any impaired test domain preoperatively, but postsurgical depression was related to impaired verbal memory (ROW-RD) and orofacial praxis ($\chi^2 = 6.11$, $p <$ *0.05 and $\chi^2 = 10.47$, $p < 0.005$, respectively). Changes in depression and anxiety between pre and post-operative testing were noted but they did not seem to affect neuropsychological test performance.

Baseline cognitive and language characteristics

In preoperative assessment, nine (41%) patients scored normal in all tests. A deficit in at least one task was

Table 3 Time course of mood disorders ($N = 22$)

Questionnaire	Impaired patients no. (%)		Raw mean score[a]		p value[b]
	Preop	Postop	Preop	Postop	
BDI	9 (45)	9 (41)	11.1 ± 7.4	11.9 ± 8.1	−0.9
STAI-Y state	0	0	44.9 ± 4.7	43.4 ± 5.3	0.62
STAI-Y trait	5 (23)	2 (14)	48.2 ± 6.1	45.1 ± 10	<0.05

[a] Mean ± SD

[b] Wilcoxon sum rank test

observed for 13 (59%): seven (32%) scored below normal in one test; two (9%) scored below normal in two tests; two (9%) performed poorly in three; and two (9%) performed poorly in four to seven tests (Table 4).

The tasks most frequently impaired were visuospatial memory (ROCF), verbal memory (RLW-DR), and word fluency (FAS) (Tables 5, 6). Comparison of patients with and without impairment revealed no significant correlation with tumor characteristics and demographic variables.

In assessment of neuropsychological domains, 14 (63%) patients scored normal before surgery. Of the eight patients for whom performance was defective, seven (32% of the sample) had only one impaired domain and one (5%) was impaired in two or more domains (Table 7). Visuospatial memory was the most frequently impaired domain. Impaired and unimpaired patients did not differ in tumor characteristics.

In language function assessment, 11 (50%) patients fared poorly in at least one task. Specifically, before surgery five (23%) patients scored below normal on picture naming, seven (32%) on comprehension, and three (13%) on reading. None had writing deficits (Table 8). No significant correlation between the presence/absence of language deficits and tumor characteristics and demographic variables was found when patients with and without language deficits were compared.

Table 4 Time course of number of impaired tasks

No. of impaired tasks	Patients no. (%)		
	Preop ($N = 22$)	Postop ($N = 22$)	Follow-up ($N = 11$)
0	9 (41)	7 (32)	5
1	7 (32)	3 (14)	1
2	2 (9)	2 (9)	1
3	2 (9)	4 (17)	2
≥4	2 (9)	6 (27)	2

Intraoperative results

The cortical stimulation range for obtaining a functional response was 4–10 mA. All 22 patients completed a picture-naming task, four a reading task, and two a comprehension task. Positive sites were found during picture naming for 18 patients, during reading in two, and during comprehension in one.

Postoperative cognitive and language function

Comparison of pre and postoperative scores in individual tests revealed significant deterioration of FAS (word fluency), TMT-B (attention), verbal span (working memory), and RLW-IR (verbal memory) (Table 5). When the comparison focused on cognitive domains, a significant difference was found for executive functions, verbal memory, and praxis.

Patients were classified by comparing the number of impaired tasks or domains before and after surgery. Of the 22 patients, 12 (54%) worsened and four (18%) improved. Of the 13 patients for whom at least one cognitive task was impaired before surgery, six (46%) worsened and four (31%) improved. Of the nine who scored normal before surgery, two (22%) worsened. In general, patients with a large number of impaired tasks were more likely to improve after surgery. In the neuropsychological domain, ten patients (45%) worsened and one (5%) improved. In the former group, cognitive loss involved executive function and memory, irrespective of whether analysis focused on single tasks (FAS, word fluency; TMT-B, attention; digit

Table 5 Time course of cognitive function by number of impaired neuropsychological tasks and mean scores ($N = 22$)

Test	Impaired patients no. (%)		Mean score[a]		p value[b]
	Preop	Postop	Preop	Postop	
Raven 47	0	0	30.66 ± 3.7	31.31 ± 2.9	n.s.[c]
FAS	4 (18)	11 (50)	24.5 ± 11.7	16.1 ± 13.3	<0.05
TMT-B	2 (9)	6 (27)	134.19 ± 78	195.47 ± 111	<0.05
Digit span	0	3 (13)	5.2 ± 0.8	4.4 ± 1.1	<0.05
RWL (IR)	2 (9)	4 (18)	32.5 ± 9.5	27.1 ± 14.7	<0.05
RWL (DR)	5 (22)	7 (32)	6.4 ± 3.3	4.3 ± 3.2	n.s.
ROCF	6 (27)	5 (22)	14.4 ± 5.3	16.2 ± 5.7	n.s.
Copy design	0	1 (4)	12.2 ± 0.5	12 ± 0.4	n.s.
Limb praxis	0	1 (4)	19.2 ± 0.6	19.6 ± 0.4	n.s.
Orofacial praxis	0	1 (4)	19.6 ± 0.4	18.1 ± 4.7	n.s.
BPN	2 (9)	2 (9)	11.5 ± 1.2	10.5 ± 2.9	n.s.
FN	2 (9)	3 (13)	4.6 ± 1.1	4.6 ± 0.8	n.s.

[a] Mean ± SD
[b] Wilcoxon sum rank test
[c] Not significant

Table 6 Time course of cognitive functions by number of impaired neuropsychological tasks and mean scores ($N = 11$)

Test	Impaired patients no.			Mean score[a]			p value[b]		
	Preop	Postop	Follow-up	Preop	Postop	Follow-up	Preop vs postop	Preop vs follow-up	Postop vs follow-up
Raven 47	0	0	0	32.0 ± 3.2	31.09 ± 3.49	32.7 ± 2.9	n.s.[c]	n.s.	n.s.
FAS	4	3	5	22.51 ± 14.7	11.76 ± 6.8	17.7 ± 12.8	n.s.	n.s.	n.s.
TMT-B	2	3	2	129 ± 74.7	213.2 ± 118.4	166.4 ± 97.7	<0.05	n.s.	n.s.
Digit Span	0	3	3	5.25 ± 1.04	4.18 ± 1.48	4.55 ± 1.2	<0.05	n.s.	n.s.
RWL (IR)	2	1	0	35.34 ± 11.04	31.5 ± 13.2)	36.2 ± 7.6	<0.05	n.s.	n.s.
RWL (DR)	5	1	3	6.72 ± 3.5	5.21 ± 3.18	6.49 ± 3.8	n.s.	n.s.	n.s.
ROCF	6	1	2	13.59 ± 6.8	14 ± 4.7	15.5 ± 7.8	n.s.	n.s.	n.s.
Copy design	0	2	0	11.9 ± 0.15	10.86 ± 3.62	11.9 ± 0.3	n.s.	n.s.	n.s.
Limb praxis	0	1	0	19.45 ± 0.6	17.18 ± 5.7	19.5 ± 0.4	n.s.	n.s.	n.s.
Orofacial praxis	0	1	0	19.45 ± 0.54	17.48 ± 5.8	19.75 ± 0.35	n.s.	n.s.	n.s.
BPN	2	1	0	11.18 ± 1.6	9.36 ± 4.08	11.64 ± 0.9	n.s.	n.s.	n.s.
FN	2	3	0	4.27 ± 1.4	4.7 ± 0.6	4.82 ± 4	n.s.	n.s.	n.s.

[a] Mean ± SD

[b] Wilcoxon sum rank test

[c] Not significant

Table 7 Time course of number of impaired neuropsychological domains

No. of impaired domains	Patients no. (%)		
	Preop ($N = 22$)	Postop ($N = 22$)	Follow-up ($N = 11$)
0	14 (63)	9 (41)	9
1	7 (32)	4 (18)	2
2 or more	1 (5)	9 (41)	–

span, working memory; RLW-RI and RLW-RD, verbal memory immediate, and delay recall) or domains.

Tumor histology was the only variable significantly associated with performance changes ($\chi^2 = 6.15$; $p = 0.046$); patients operated for high-grade tumors were noted to improve more than those with low-grade tumors.

In postoperative language assessment, six (27%) out of 22 patients fared worse in picture-naming tests and three (13%) each in reading and writing comprehension tests. Significant deterioration was observed for postoperative mean scores for picture naming (Table 8). Language results (picture naming) did not affect performance in other cognitive tasks, both when the comparison involved tasks and when it focused on domains.

Follow-up cognitive and language function

Eleven of the 14 patients with low-grade glioma were assessed at early follow-up (3-6 months). Improvement was observed in five out of six patients who had worsened during the early postoperative period. No significant differences were observed between preoperative and follow-up scores or between postoperative and follow-up scores (Table 6).

A general trend toward improvement in language tests between postoperative and follow-up assessment emerged, but the difference was significant for picture naming only (Table 9).

Discussion

A primary objective of awake surgery and brain mapping is to achieve maximum resection with minimum clinical side effects in eloquent areas. Although these techniques are of proved effectiveness in preserving language ability, their usefulness in sparing other cognitive functions, whether related or unrelated to language, is still uncertain, because although great effort is devoted to preservation of language functions, there is no firm evidence verifying the safety of awake surgery with regard to cognitive functions and to preservation of QoL. We have addressed this issue.

Affective characteristics

Psychological distress (i.e., depression and anxiety) is known to be greater in brain tumor patients than in the normal population. In our setting (hospitalized patients awaiting an awake procedure), the prevalence of depression and anxiety was 41 and 24%, respectively, in

Table 8 Time course of language functions according to number of impaired subfunctions and mean scores ($N = 22$)

Test	Impaired patients no. (%)		Mean scores[a]		p value[b]
	Preop	Postop	Preop	Postop	
Picture naming	5 (22)	11 (50)	59.68 ± 4.42	50.68 ± 18.05	<0.05
Comprehension[c]	7 (31)	10 (45)	5.09 ± 10.72	6.35 ± 10.98	n.s.[d]
Reading[c]	3 (13)	6 (27)	1.95 ± 5.59	9.62 ± 24.43	n.s.
Writing[c]	0	3	0.0 ± 0.0	6.4 ± 15.46	n.s.

[a] Plus–minus values are means ± SD

[b] Wilcoxon sum rank test

[c] Scores are expressed as percentages; higher values mean greater impairment

[d] Not significant

Table 9 Time course of language functions according to number of impaired subfunctions and mean scores ($N = 11$)

Test	Impaired patients no.			Mean score[a]			p value[b]		
	Preop	Postop	Follow-up	Preop	Postop	Follow-up	Preop vs postop	Preop vs follow-up	Postop vs follow-up
Picture naming	3	5	3	59 ± 5.17	46.64 ± 22.6	58.64 ± 7.08	<0.01	n.s.	<0.01
Comprehension[c]	2	6	4	8.2 ± 14.28	9.58 ± 14.18	6.5 ± 14.5	n.s.[d]	n.s.	n.s.
Reading[c]	2	3	1	4 ± 8	9.9 ± 20.2	2.14 ± 5.66	n.s.	n.s.	n.s.
Writing[c]	0	2	0	0.0 ± 0.0	7.75 ± 18.69	0.0 ± 0.0	n.s.	n.s.	n.s.

[a] Plus–minus values are means ± SD

[b] Wilcoxon sum rank test

[c] Scores are expressed as percentages; higher values mean greater impairment

[d] Not significant

agreement with previous studies [18, 19]. Neither depression nor anxiety was found to affect cognitive scores: depression remained unchanged whereas anxiety improved. Notably, although our patients were scheduled for awake surgery, a more stressful procedure than traditional surgery because it demands patient collaboration during the operation, they did not have higher anxiety scores than those awaiting traditional surgery for brain tumors [18, 19].

Language outcome

Our data confirm that picture naming declined immediately after surgery but had recovered at follow-up [6, 20]. The same trend—a decline in performance on immediate postoperative testing followed by regained preoperative performance at long-term follow-up—was observed for the other language skills.

Cognitive performance and QoL

In awake surgery, great care is devoted to sparing language abilities and to verifying that the technique indeed achieves this objective. Much less attention has been devoted to preserving other cognitive functions, although damage to executive skills, attention, working memory, and praxis among others, will inevitably affect QoL. Moreover, evaluation of non-linguistic cognitive functions has received insufficient emphasis in clinical practice, as demonstrated by widespread use of the KPS for assessment of QoL, despite its known inadequacy, because it is simple to manage and designed to measure physical performance. In other words, there are no established standards for evaluation of deficits in domains other than language, even though it has been convincingly shown that cognitive problems affect QoL more than physical ones [21, 22]. Baseline cognitive evaluations have seldom been reported [6, 23, 24]. Some studies have demonstrated that, on the basis of additional preoperative evaluation, it is the effect of the tumor on cognition, rather than those of the surgery, that seems to be more prevalent in the immediate postoperative phase, especially for verbal and visual-spatial memory, attention, and executive functions. These observations suggest that detailed neuropsychological testing is highly informative for brain tumor patients.

However, the postoperative effect of any treatment is not only scarcely observed in patients undergoing general anesthesia, but also when mapping cognitive areas was an objective of the operation. Teixidor et al. found that working memory (WM) declined in the immediate postoperative period in 90.4% of patients undergoing awake surgery, and recovered at 3 months follow-up for 35% of patients [25]. For our sample also, damage to verbal working memory was the prevalent dysfunction, but the incidence was significantly lower (13%). Wu et al. [26] compared a group of patients with insular glioma operated under an awake procedure with a group of patients undergoing general anesthesia. They used a wide range of cognitive tests for pre and postoperative assessment and performed mapping only for language sites. Interestingly, besides language impairment they also detected other cognitive dysfunctions at the postoperative control: insular patients were mostly impaired in the word fluency test, whereas while the controls were more impaired in TMT-B; however, the timing of postoperative assessment differed substantially (range, 8–205 days). Braun et al. [24] used alternative methods of brain mapping, preoperative functional MRI (fMRI) and neuronavigation, to detect working memory areas, in addition to administering a complex range of neuropsychological tests pre and postoperatively, to verify results at fMRI. They found worsening in one patient for whom the WM site was removed, because it was close to the tumor location as detected by fMRI; for all other patients, for whom the WM sites were far from the tumor location, working memory was generally preserved but other cognitive deficits were present.

Our results provide additional evidence that the tumor is the main single factor associated with cognitive impairment (13/22, 59%) and that surgery may further interfere with cognitive function in the acute postoperative period: six of the 13 subjects with impaired preoperative performance in cognitive tests worsened and four improved; only two of the nine subjects with normal preoperative performance deteriorated in the immediate postoperative period. In other words, surgery seems to have a relatively unpredictable effect on cognitive function, especially for patients who are already impaired. Consistent with previous observations [5, 6, 25–27], attention, verbal fluency, working memory, and verbal memory were the only significantly impaired functions.

We were able to follow some patients with low-grade glioma for a reasonable length of time after surgery. Their cognitive performance improved within months but remained below their preoperative levels, especially for verbal working memory.

Deficits on cognitive and language tasks

Cognitive functions can be impaired before and after surgery for tumor removal in language areas. In our sample, word fluency (FAS), verbal working memory (digit span), and immediate recall of word list (RWL-IR) were significantly poorer in postoperative assessment, as previously observed in other studies of a subset of patients with low-grade glioma, irrespective of tumor location [6, 25]. Surprisingly, here we found that language deficits (picture-naming test) did not significantly correlate with performance in any single cognitive task. It is quite possible, however, that poor performance in these three tests did not result (at least not entirely) from impairment of purely non-linguistic cognitive abilities (e.g., executive functions in the case of word fluency), but rather from a subtle language deficit. Normal performance in verbal memory (RWL) and word fluency (FAS) tests and in the digit span test requires normal language ability. Yet this cannot be the whole story because the TMT-B test, a nonverbal measure of executive function, was also impaired postoperatively. Performance in this test should prompt attention to the possibility that awake surgery may affect cognitive ability, at least in the immediate postoperative period. Further studies are needed to establish long-term prognosis for these impairments. The data reported in Table 5 clearly illustrate that accurate intraoperative testing of cognitive and language functions is warranted.

Conclusion

Our findings are preliminary; nonetheless, they provide evidence of a subclinical disease burden which cannot be captured by simple neurological observation alone. In patients with tumors in language areas, detailed neuropsychological assessment with systematic evaluation of performance in cognitive non-language tasks can track functional impairments which may affect QoL. From these additional clinical data, new knowledge can be obtained about surgical treatment for improving patient performance, optimizing operative planning, and minimizing cognitive sequelae.

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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