Brain mapping: a novel intraoperative neuropsychological approach

Miran Skrap, MD,¹ Dario Marin, PsyD,² Tamara Ius, MD, PhD,¹ Franco Fabbro, MD, PhD,² and Barbara Tomasino, PhD²

¹Unità Operativa di Neurochirurgia, A.O.S. Maria della Misericordia, Udine; and ²IRCCS “E. Medea,” San Vito al Tagliamento (PN), Italy

OBJECTIVE Awake surgery and mapping are performed in patients with low-grade tumors infiltrating functional brain areas for which the greater the resection, the longer the patient survival. However, the extent of resection is subject to preservation of cognitive functions, and in the absence of proper feedback during mapping, the surgeon may be less prone to perform an extensive resection. The object of this study was to perform real-time continuous assessment of cognitive function during the resection of tumor tissue that could infiltrate eloquent tissue.

METHODS The authors evaluated the use of new, complex real-time neuropsychological testing (RTNT) in a series of 92 patients. They reported normal scoring and decrements in patient performance as well as reversible intraoperative neuropsychological dysfunctions in tasks (for example, naming) associated with different cognitive abilities.

RESULTS RTNT allowed one to obtain a more defined neuropsychological picture of the impact of surgery. The influence of this monitoring on surgical strategy was expressed as the mean extent of resection: 95% (range 73%–100%). At 1 week postsurgery, the neuropsychological scores were very similar to those detected with RTNT, revealing the validity of the RTNT technique as a predictive tool. At the follow-up, the majority of neuropsychological scores were still > 70%, indicating a decrease of < 30%.

CONCLUSIONS RTNT enables continuous enriched intraoperative feedback, allowing the surgeon to increase the extent of resection. In sharp contrast to classic mapping techniques, RTNT allows testing of several cognitive functions for one brain area under surgery.

<http://thejns.org/doi/abs/10.3171/2015.10.JNS15740>

KEY WORDS glioma; brain mapping; cognitive functions; neuropsychology; awake surgery; surgical technique

DIRECT electrical stimulation (DES) mapping is a well-known technique for identifying brain functions in an eloquent brain area during surgery.^{3,8,13,16,26,27,29,40} It can minimize permanent postoperative deficits while maximizing the extent of resection, especially in cases of infiltrative tumors such as low-grade gliomas (LGGs), in which the greater the resection, the longer the patient survival.^{9,10,19,20,25,29,34,35}

In routine mapping, DES usually provides a high percentage of positive responses for relatively simple functions in sensorimotor areas at both cortical and subcortical levels^{3,11,12,18,29} and for simple language tasks such as counting. For more complex tasks such as object naming,^{3,11,12,18,29} as well as tasks testing extralinguistic functions, the inter-

pretation of DES effects is more complex. The percentage of positive responses significantly decreases for extralinguistic tasks, especially in subcortical mapping and in nondominant-hemisphere mapping, which, in general, are performed in rare cases only.^{7,14,15,17,21,32,32,41,44}

Preoperative diffusion tensor imaging (DTI) serves as orientation during surgical planning, but intraoperative confirmation with DES in the white matter is needed. However, DES does not offer the same guarantee of response in the white matter as in the cortex. In fact, few studies have reported the exact percentage of positive responses during subcortical DES for critical-function mapping outside the sensorimotor areas or Broca's area.^{1,10,20,22}

Consequently, the concept of “negative mapping” was

ABBREVIATIONS DES = direct electrical stimulation; DTI = diffusion tensor imaging; EOR = extent of resection; fMRI = functional MRI; LGG = low-grade glioma; MEP = motor evoked potential; RTNT = real-time neuropsychological testing; SSEP = somatosensory evoked potential.

SUBMITTED April 1, 2015. **ACCEPTED** October 19, 2015.

INCLUDE WHEN CITING Published online February 5, 2016; DOI: 10.3171/2015.10.JNS15740.

defined owing to possible low DES positivity.³⁵ Several factors could be responsible for negative mapping, such as a smaller craniotomy, individual variability, anatomical distortions, functional reorganization due to a tumor mass, an inappropriate task for the target area, and a network of areas subserving cognitive functioning that cannot be affected by the small area where DES exerts its electrical interference.²⁸

Thus, in the absence of DES-induced responses, the surgeon cannot rely on proper feedback during the procedure and may be less prone to perform an extensive resection, even if negative mapping is correlated with a better clinical result.³⁵ The lack of positive DES responses does not necessarily imply a lack of function in the target area; therefore, the patient could experience postoperative dysfunction. Because of the possible dissonance between intraoperative mapping and postoperative outcome and in order to obtain a real-time view of what happens to cognitive functioning during the resection of tumor tissue that may infiltrate functionally preserved tissue, we used a novel approach consisting of more complex, continuous real-time neuropsychological testing (RTNT) performed during tumor resection.

While DES gives on/off responses on a relatively few simple tasks, RTNT offers supplementary information about different cognitive functions. Moreover, the resection can be continued without feedback between 2 DES phases. As compared with the DES used in the past, RTNT offers continuous feedback. In addition, it is likely to trigger the functioning of larger networks and thus reflects a dynamic view of brain functions. It also reduces the uncertainty associated with negative mapping and the temporal gaps between sequential DES phases throughout a resection. Furthermore, in RTNT many tasks can be continuously rotated, while DES allows testing of just a few simple tasks because of time constraints. Lastly, RTNT allows assessment of several cognitive functions for a particular brain area in surgery, while only 1 function can be tested during DES.

In this study, we present our experience with continuous RTNT during surgery for LGGs. We describe patient performance during surgery, reversible intraoperative neuropsychological dysfunction or oscillations, the influence of such monitoring on surgical strategy, and clinical and surgical outcomes.

Methods

Patients

RTNT was performed in a consecutive series of patients (and is still used at our institution). The criteria we used to perform RTNT are the same as those used for awake surgery. However, since RTNT is demanding, which can be one of the limitations of this technique, we used an additional inclusion criterion: presurgical neuropsychological performance should be > 85% in terms of accuracy.

We selected 92 patients—65 subjects with low-grade gliomas, 23 with anaplastic gliomas, and 4 with cavernomas—all right-handed, native Italian speakers (Table 1). The 4 patients with cavernomas served as a comparative group.

The local ethics committee approved the study. All patients gave written consent.

Presurgical Evaluation

Seven to 10 days prior to craniotomy, all patients underwent diagnostic evaluation including functional MRI (fMRI), anatomical and diffusion tensor imaging (DTI) as previously described,^{42,43} and neuropsychological testing (Supplementary Table S1).

Surgery

All patients underwent awake surgery as previously described.¹⁹ All patients were fixed to a Mayfield frame and remained awake from the beginning of the surgery. They were slightly sedated during exposure and closure of the surgical field.^{19,38} Anatomical imaging, fMRI, and DTI data were sent to the navigator system (StealthStation, Medtronic), and they proved particularly useful during cortical mapping immediately after opening the dura mater. Standard tags were used to identify functions on the brain surface. Guided by the navigator, we placed colored tags along the medial border of the lesion through the tumor mass for spatial orientation during the advanced stage of tumor resection, when brain shifts usually occur. Surgery was performed under cortical and subcortical white matter DES, according to the intraoperative technique previously described by Duffau et al.¹⁰ and based on the methodology of Berger and Ojemann.^{2,4,29,30} Motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) were also recorded during surgery to continuously monitor the integrity of motor and somatosensory pathways (64-channel Eclipse Neurovascular Workstation, Axon Systems Inc.; 32-channel video polygraphic station, Brain Quick SystemPlus, MicroMed). Continuous electrocorticography was performed to detect discharge phenomena and rule out the possibility that the patient's decrement in performance or oscillatory performance was caused by the concomitant presence of short focal seizures.

Surgical Strategy and RTNT and DES

Before resection, DES was performed as described in the literature. RTNT was started at the beginning of the resection and ended at the beginning of hemostasis. During surgery, at intervals, DES was performed in the classic way. In such cases we temporarily stopped the RTNT. If DES evoked a positive effect, the surgeon usually stopped the resection. If DES produced a negative response, we restarted the RTNT, which remained the only feedback on the patient's performance and was evaluated by the neuropsychologist.

The battery of tasks included in RTNT was created as follows. Tasks were selected from published neuropsychological batteries available in the Italian normative data. We included tasks encompassing a wide range of cognitive functions to have an exhaustive intraoperative neuropsychological battery. Some tasks are common for both right- and left-hemisphere lesions, testing 1) orientation, 2) memory and attention, 3) automatic series, and 4) fluency (Supplementary Table S1). For patients with left-

TABLE 1. Summary of demographic and tumor details in 92 patients who underwent RTNT

Parameter	LGG	Anaplastic Glioma	Cavernoma	Total
No. of cases	65	23	4	92
Sex				
Male	36	14	3	53
Female	29	9	1	39
Mean age in yrs	42.2 ± 11.5	51.98 ± 15.12	42.83 ± 10.03	45.67 ± 13.18
Mean education in yrs	12.83 ± 3.9	11.57 ± 2.58	13.83 ± 5	12.74 ± 3.91
Side of tumor				
Lt	39	15	4	58
Rt	26	8	0	34
Tumor location				
Precentral	29	12	1	42
Retrocentral	8	4	1	13
Temporal	10	5	1	16
Insular	18	2	1	21
Symptoms at presentation				
None, incidental finding	3	0	0	3
Headache	4	2	1	7
Neurological deficits	5	3	0	8
Generalized seizure	38	9	2	49
Motor seizure	12	9	1	22
Viscerosensory seizure	3	0	0	3

hemisphere lesions, we used tasks testing 1) naming, 2) repetition, 3) reading, and 4) comprehension.

From our extensive list of tasks (Supplementary Table S1), we selected a series of tasks according to lesion localization, fMRI and DTI results, and preoperative neuropsychological profile. Task sequence follows a fixed order with regard to an area (Fig. 1). We created a fixed task order for lesions of the left frontal, left Broca's, left premotor, left temporoinsular, left parietal, right frontal, right premotor, right temporoinsular, and right parietal area. For example, for surgery involving the left temporal cortex, the sequence of RTNT includes object naming, phonemic discrimination, word reading, word repetition, nonword reading, nonword repetition, phonological discrimination, digit span, lexical decision, action naming, and picture description (Supplementary Table S2).

The sequence of tasks was repeated (presenting a different stimuli list for each sequence) until the end of the resection. Intraoperatively, however, task order and selection could suddenly change according to the principles of differential diagnosis (Supplementary Table S3). For example, in each test for a patient who underwent surgery in the left temporal lobe, 10–15 items were presented (for instance, 15 pictures for naming, 10 words for reading, 10 pseudowords for repetition) for about 30 seconds for each task, in a rotating manner. In this way task assessment and task switching were quick and dynamic for immediate dysfunction detection. As soon as the patient exhibited a decrement, the neurosurgeon was immediately informed and carried on with the surgical technique already described. In 1–2 minutes the RTNT allowed the assessment of object naming, word reading, and pseudoword repetition.

When this sequence was completed and if patient performance was within the normal range, we restarted testing using the first task and followed the same sequence but with different items. On the contrary, if a patient showed a decrement—for instance, if the patient's object naming performance decreased (in the example, the score was 10/15-anomia)—we performed in-depth testing. Following the principles of differential diagnosis (Supplementary Table S3), we assessed whether the decrease was confined to object naming, so we used action naming (in the example, the score was 10/15-anomia), reading of words and pseudowords (score 9/10 for each task), phonology (phonological discrimination: 15/16), picture description (showing that the anomies also impacted fluency: 2/4-anomia), lexicon (lexical decision: 18/20), and repetition (word: 10/10 and nonword: 10/10). We restarted with object naming (in the example, the score was 12/15-anomia) and action naming (13/15-anomia), picture description (3/4-anomia), digit span (5/9), and lexical decision (19/20), and we again administered object naming. If the performance was restored (14/15) we continued with a second sequence of the RTNT phase (Supplementary Table S3). This protocol was, of course, subject to real surgical timing. If everything runs smoothly, a sequence like the one described lasts about 7–8 minutes.

The possible deterioration in performance usually occurred in a gradual way. An interesting feature was the often temporary nature of the deterioration, with a recovery in performance after some minutes (Fig. 2). Considering that tissue traumatism due to manipulation or patient fatigue may have caused this oscillation, we adopted a more dynamic surgical strategy. To assess the effect of surgical

FIG. 1. Case 12. Images obtained in a patient with an LGG in the temporoinsular area with the left inferior frontooccipital fasciculus passing close to the lesion (A). The patient performed RTNT (B). *Black circle* indicates the point of manipulation where the patient exhibited oscillatory performance, that is, decreased performance followed by recovery. The sequence of tasks was rotated during resection (C); note the repetition of a sequence of tasks (same color, same test). Figure is available in color online only.

manipulation, we briefly interrupted the surgery, giving the patients short breaks, or we moved to another part of the surgical field by using the “stop-and-go” surgical approach as done for intramedullary tumors.³ With this approach, patients were able to rest and restart performing the tasks, and we were able to continue the procedure in the same area if the patients recovered.

Using the logic of neuropsychological differential diagnosis with different tests, we could either confirm or exclude that testing was affected by manipulation or fatigue. This is fairly similar to standard neuropsychological testing outside the operating room, when fatigue can affect patient performance as well.

The limit used to stop surgery temporarily or definitively coincided with a decrease in performance to 70% of baseline levels. The 30% threshold was established by examining a preliminary group of patients in whom we tested the feasibility of our technique before actually starting the present study. Thus this threshold was correlated to follow-up performance. For example, for the object

naming task, 1) we identified patients with pathology at the follow-up examination and calculated their mean performance, which was around 75%; and 2) we identified their RTNT level of performance on the same task and calculated their mean accuracy, which was around 70%. Consequently, we considered this level of performance as a warning to stop surgery. In the present series of patients, we set the threshold at the same value on the basis of our initial experience and verified whether it worked by correlating RTNT performance with the follow-up performance.

Deterioration usually occurred when the resection was very close to the tumor boundary. The above-described strategy provided us with ongoing confirmation that we could continue with a resection. In contrast, with a negative DES response, we lacked the confidence necessary to continue with an aggressive and somewhat blind surgery in an eloquent area. DES in the same areas did not produce a similar response. During RTNT, each subject viewed the stimuli (Presentation, Neurobehavioral Systems Inc.) via

FIG. 2. Cases 4 and 21. Two different patterns of performance during object naming, in which the patients either named the items correctly or did not. In the patient in Case 21 (**A left**), the deterioration was often just temporary, with recovery in the impaired performance after some minutes (reversible neuropsychological deficit), whereas in the patient in Case 4 (**B left**), the decrement was more stable. These patterns were confirmed by neuropsychological testing at 1 week (1w) after surgery and at follow-up (F up), showing no decrement in the patient in Case 21 (**A right**) as compared with a temporary decrement in the patient in Case 4 (**B right**) at 1 week after surgery. Pre = presurgery.

a monitor at a distance of 30 cm. Audio from the patients and the neuropsychologist was recorded. The intraoperative information has provided feedback to the surgeon.

Statistical Analysis

Nonparametric statistics were applied (Wilcoxon test, 2-tailed, α level < 0.05) to compare the patient's accuracy pre- versus intraoperatively, preoperatively versus 1 week postoperatively, and preoperatively versus follow-up.

Results

Postsurgical Evaluation

All patients underwent standard diagnostic MRI with tumor volume analysis¹⁹ and neuropsychological testing.

Neuropsychological Performance, RTNT, and Follow-Up

To determine each patient's performance accuracy, the reference level (100%) was set at his or her preoperative performance. Scores were thus normalized. To correlate the impact of each test on the follow-up level of performance, we grouped the tests into 3 categories: Group 1, absent or minimal intraoperative dysfunction with complete recovery at the end of surgery; Group 2, intraoperative dysfunction still present at 1 week after surgery and complete recovery achieved 6 months after surgery; and Group 3, intraoperative dysfunction and some deficits at 6 months after surgery.

At 1 week postsurgery, scores were very similar to those

detected with RTNT, proving the validity of the RTNT technique as a predictive tool. The majority of scores were still > 70% of the baseline performance, which indicated a decrease < 30%. For example, for a critical function such as naming, significant improvement was found in the left-hemisphere LGG group at follow-up (from 79% at 1 week postsurgery to 86% at the 6-month follow-up). Results of tests that were the most critical in our sample appear in Tables 2–6.

Task Sequence and Duration

Mean duration of testing during the resection was 43 ± 21 minutes, and the mean number of tasks administered was 16 ± 21 . A mean of 3.9 ± 1.4 tasks were administered during 10 minutes. For example, as can be seen in Supplementary Table S3, the total time needed for resection of an LGG in the left temporal lobe was 55.40 minutes.

Comparative Study With a Cavernoma Group

The patients with a cavernoma had very high performance scores (Table 4). The cavernomas were localized according to presurgical fMRI in language-related areas at both cortical and intrasulcal levels. Lesion size ranged from 12 to 22 cm³ including the hemosiderin layer. Localization was the left insula, postcentral area, and precen-tral area. Two patients had generalized seizures, 1 patient had motor seizures, and 1 patient had headaches. In all 4 cases but 1, the thin layer of hemosiderin was removed ac-

TABLE 2. Real-time neuropsychological testing data for 39 patients with left-hemisphere LGG*

Group	Tasks	Presurgery	Intraop	Presurgery-Intraop (Z, p value)	1 Wk Postop	Presurgery-1 Wk Postop (Z, p value)	FU	Presurgery-FU (Z, p value)
1	Orientation	100	93	-1.604, 0.109	100	0.000, 1.000	100	0.000, 1.000
	Phonological discrimination	100	87	-1.342, 0.180	97	-1.342, 0.180	97	-1.414, 0.157
	Oral apraxia	99	80	-1.000, 0.317	91	-1.572, 0.116	97	-1.069, 0.285
	Mental rotation	89	62	-1.826, 0.068	80	-1.633, 0.102	80	-1.633, 0.102
	Theory of mind	86	64	-1.604, 0.109	66	-1.633, 0.102	65	-1.414, 0.157
	Finger agnosia	100	85	-1.342, 0.180	80	-1.414, 0.157	87	-1.342, 0.180
	Word-pseudoword repetition	100	82	-3.296, 0.001	96	-1.342, 0.180	97	-1.342, 0.180
2	Digit span	100	87	-2.639, 0.008	90	-1.684, 0.092	92	-0.356, 0.722
	Auditory comprehension	100	90	-2.201, 0.028	87	-1.857, 0.063	89	-1.841, 0.066
	Ideomotor apraxia	99	100	0.000, 1.000	92	-3.063, 0.002	98	-0.598, 0.550
	Phonological fluency	100	58	-2.763, 0.006	65	-3.492, 0.000	94	-1.843, 0.065
	Pseudoword reading	99	100	-1.604, 0.109	89	-2.624, 0.009	91	-1.214, 0.225
	Differences	100	75	-2.000, 0.046	90	-2.000, 0.046	90	-2.000, 0.046
	Object naming	97	78	-3.659, 0.000	79	-3.356, 0.001	86	-2.318, 0.020
3	Verb naming	96	73	-2.201, 0.028	78	-3.160, 0.002	86	-2.044, 0.041
	Picture description	95	63	-3.059, 0.002	66	-3.307, 0.001	81	-2.677, 0.007
	Word reading	99	94	-2.201, 0.028	92	-2.805, 0.005	91	-2.201, 0.028

FU = follow-up.

* Patients were divided into 3 groups according to their pattern of performance. Results from the Wilcoxon nonparametric test and the percentage of accuracy in performance are reported. Boldface type indicates significant changes. Patient performance at some tasks testing language-related functions was altered at the 6-month follow-up and belonged to Group 3.

TABLE 3. Real-time neuropsychological testing data for 15 patients with left-hemisphere anaplastic glioma*

Group	Real-Time Tasks	Preop	Intraop	Preop-Intraop (Z, p value)	1 Wk	Preop-1 Wk (Z, p value)
1	Oral apraxia	99	100	0.000, 1.000	97	-1.069, 0.285
	Ideomotor apraxia	93	100	-1.000, 0.317	91	-0.507, 0.612
	Orientation	100	87	-1.342, 0.180	100	0.000, 1.000
	Phonological discrimination	100	72	-1.414, 0.157	—	—
	Auditory comprehension	100	90	-1.604, 0.109	—	—
	Object naming	90	70	-1.362, 0.173	80	-0.774, 0.439
	Digit span	100	93	-1.633, 0.102	93	-0.447, 0.655
	Repetition	99	84	-1.461, 0.144	87	-1.069, 0.285
	Word Reading	96	78	-1.604, 0.109	95	-0.405, 0.686
	Picture description	88	63	-2.023, 0.043	83	-0.535, 0.593
2	Phonological fluency	100	52	-2.201, 0.028	78	-2.046, 0.041

* Patients were divided in 2 groups according to their pattern of performance. Results from the Wilcoxon nonparametric test and the percentage of accuracy in performance are reported. Boldface type indicates the significant changes detected between pre- and intraoperative testing, and preoperative and 1-week testing. The follow-up ended at 1 week since later anaplastic patients received radio- or chemotherapy, which can worsen cognitive functioning. For this reason, we avoided adding an additional variable in our patient series. We decided to exclusively focus on RTNT performance correlated to resection and to follow up performance for those patients for whom no other uncontrollable variables (such as the cognitive decline related to chemotherapy and radiation) were present at the follow-up testing.

cording to negative DES and RTNT performance. In that 1 case, the DES response was positive in the hemosiderin layer and thus we left that layer.

Since cavernomas are extraaxial lesions not infiltrating the parenchyma as gliomas do, the comparison with cavernoma patients served as a validation study and enabled us to conclude that RTNT is reliable for measuring intraoperative cognitive changes, as the patients could perform the RTNT with a high degree of proficiency.

Impact on Resection

We compared the value of the extent of resection (EOR) based on our intraoperative protocol with that using our historical database.¹⁹ As reported in our previous study,¹⁹ patients in Series 1 (those who had undergone intraoperative DES alone) had a mean EOR of 77% (range 28%–

100%) and patients in Series 2 (those who had undergone intraoperative DES plus had overlapping fMRI/fiber tracking DTI data on a neuronavigation system) had a mean EOR of 90% (range 49%–100%), whereas patients in the present study had a mean EOR of 95% (range 73%–100%).

Discussion

Mapping and Functions

Maximal resection is currently the first therapeutic option for LGGs to prolong overall survival.^{19,24,34,36,38,39} Given the ability of LGGs to infiltrate eloquent cortical areas and subcortical functional pathways,^{19,23} brain mapping techniques and awake surgery have become mandatory in dealing with such lesions.^{3,9,10,19,20,35} In contrast to the situation for cortical DES, only a few studies concerning language function have documented in detail the per-

TABLE 4. Real-time neuropsychological testing performance of 4 patients with left-hemisphere cavernoma*

Group	Real-Time Tasks	Preop	Intraop	Preop-Intraop (Z, p value)	1 Wk	Preop-1 Wk (Z, p value)	FU	Preop-FU (Z, p value)
1	Orientation	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Object naming	100	99	-1.000, 0.317	98	-1.000, 0.317	98	-1.000, 0.317
	Word reading	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Pseudoword reading	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Oral apraxia	97	97	0.000, 1.000	99	0.000, 1.000	99	0.000, 1.000
	Repetition	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Ideomotor apraxia	100	90	-1.000, 0.317	95	-1.000, 0.317	100	-1.000, 0.317
	Word writing	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Pseudoword writing	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Digit span	100	120	-1.342, 0.180	94	-1.000, 0.317	101	-0.447, 0.655
	Picture description	100	100	-1.000, 0.317	100	-1.000, 0.317	100	0.000, 1.000
	Digit span backward	100	80	-1.000, 0.317	80	-1.000, 0.317	105	-0.447, 0.655
	Digit span	100	105	-1.342, 0.180	103	-1.342, 0.180	130	-1.342, 0.180

* Patients were divided in 3 groups according to their pattern of performance. Results from the Wilcoxon nonparametric test and the percentage of accuracy in performance are reported. No significant changes were detected between pre- and intraoperative testing, preoperative and 1-week testing, and preoperative and follow-up (at 6 months) testing. All tasks were unaltered at 1 week and at 6 months and belonged to Group 1.

TABLE 5. Real-time neuropsychological testing data for 26 patients with right-hemisphere LGG*

Group	Real-Time Tasks	Preop	Intraop	Preop-Intraop (Z, p value)	1 Wk	Preop-1 Wk (Z, p value)	FU	Preop-FU (Z, p value)
1	Orientation	100	98	-1.000, 0.317	97	-1.000, 0.317	100	0.000, 1.000
	Stroop	100	100	0.000, 1.000	100	-1.000, 0.317	100	0.000, 1.000
	Automatic series	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Reading dyslexia	100	95	-1.342, 0.180	96	-1.000, 0.317	100	0.000, 1.000
	Picture description	100	100	0.000, 1.000	100	0.000, 1.000	100	0.000, 1.000
	Calculation	100	97	-1.604, 0.109	96	-1.732, 0.083	96	-1.732, 0.083
	Target detection	99	96	-0.447, 0.655	96	-1.342, 0.180	97	-1.000, 0.317
	Digit span backward	100	85	-1.000, 0.317	82	-1.342, 0.180	100	-1.342, 0.180
	Digit span	100	91	-1.342, 0.180	103	-1.000, 0.317	95	-1.342, 0.180
	Line bisection	100	96	0.000, 1.000	83	-1.000, 0.317	100	0.000, 1.000
	Clock test	91	90	-0.272, 0.785	90	-1.342, 0.180	92	-1.633, 0.102
	Stars cancellation	95	97	-0.447, 0.655	97	-2.014, 0.044	99	-0.213, 0.832
2	Handedness decision/mental rotation	100	92	-2.023, 0.043	92	-2.023, 0.043	96	-1.414, 0.157
	Metaphor comprehension	94	77	-2.803, 0.005	81	-2.375, 0.018	88	-1.890, 0.059

* Patients were divided in 3 groups according to their pattern of performance. Results from the Wilcoxon non-parametric test and the percentage of accuracy in performance are reported. Boldface type indicates the significant changes detected between pre- and intraoperative testing, preoperative and 1-week testing, and preoperative and follow-up testing. None of the tests belonged to Group 3, meaning that patients had completely recovered at the 6-month follow-up testing.

centage of positive responses for subcortical DES^{1,10,20} and extralinguistic functions.^{7,14,15,17,21,31,32,41,44} Consequently, the concept of negative mapping was proposed even if, in the absence of a DES effect, impaired cognitive performance was found at follow-up neuropsychological testing.⁵

Real-Time Neuropsychological Testing and Surgery

Nowadays we accept that the relation between one brain function and a brain area is not 1:1 and, instead, that cognitive processing is subserved by multiple brain networks. Consequently, the brain areas involved in cognitive processing are larger than the small, circumscribed portion of brain on which DES exerts its electrical interference.

Accordingly, RTNT, which is complementary to DES, enables the surgeon to monitor a patient's cognitive performance, reducing the uncertainty associated with negative feedback on DES. A very interesting feature of RTNT, which significantly influenced our surgical strategy, was the oscillation in patient performance, with worsened and then recovered accuracy in a response within a few minutes. We considered this a warning signal, usually manifesting when the resection was close to the lesion border. When this happened, the resection was stopped and resumed in another site. If the patient's performance recovered, we returned to the same area and continued the resection after in-depth testing. Resection was stopped when

TABLE 6. Real-time neuropsychological testing data from 8 patients with right-hemisphere anaplastic glioma*

Group	Real-Time Tasks	Preop	Intraop	Preop-Intraop (Z, p value)	1 Wk	Preop-1 Wk (Z, p value)
1	Orientation	100	98	0.000, 1.000	100	0.000, 1.000
	Digit span	100	100	0.000, 1.000	100	0.000, 1.000
	Reading dyslexia	100	81.81	-1, 0.317	85	-1, 0.317
	Picture description	100	83.6	-1.34, 0.18	100	0.000, 1.000
	Calculation	100	87.2	-1, 0.31	NE	NE
	Target detection	99	82.05	-0.447, 0.655	96	-1.342, 0.180
	Line bisection	83.33	82.05	-0.44, 0.65	100	0.000, 1.000
	Star cancellation	99.38	82.05	-1.6, 0.102	96.29	0.000, 1.000
	Clock test	94.28	82.05	-1.47, 0.141	100	-1, 0.31
	Constructional apraxia	91.96	82.05	-1.89, 0.059	92.85	0.000, 1.000
	Handedness decision/mental rotation	85	65	-1, 0.31	NE	NE
	Metaphor comprehension	92.5	74.61	-1.604, 0.18	80	-1.34, 0.18

NE = not executed.

* Patients were divided in 2 groups according to their pattern of performance. Results from the Wilcoxon nonparametric test and the percentage of accuracy in performance are reported. No significant changes were detected. The follow-up ended at 1 week of testing since later anaplastic patients received radio- or chemotherapy.

the patient's performance dropped to 70% of baseline levels. Importantly, we believe that the issue of the threshold should be carefully considered and, as in our group sample, could be highly dependent on several factors such as lesion localization, presurgical patient status, and the list of tasks used. In our series the 70% threshold worked well, but we think that in the future in improving the battery of tasks, better analysis on the different tasks may influence the defined threshold. With RTNT feedback, the surgeon felt safer continuing the resection in comparison with cases when he had no feedback due to negative DES responses. Similar brain behavior has never been appreciable with DES, which, on the contrary, provides a simple on-off response to usually quite simple tests. Our results with RTNT led us to change the surgical procedure. In the present study, we did not operate on the same site for too long, preferring instead to change the surgical field quite often to temporarily interrupt the manipulation of brain tissue in the same site since we believed that allowing the structure to rest could facilitate the recovery of function. We might observe a similar reaction when traction is applied close to the corticospinal tract or in the medulla. Because of tissue manipulation, the MEPs and SSEPs could be temporarily altered or even disappear, although they could recover after a temporary interruption in the surgery.

In those cases in which DES was negative, the continuous feedback from the patient and the described surgical strategy allowed a larger resection. If compared with the simple responses of the 1-0 type evoked by DES, RTNT does not necessarily give stopping signals but does provide us with more information. We should mainly consider 2 reasons that have permitted increased resection. First, in the standard mapping technique, the negative response obtained with DES, at least in our experience, tends to inhibit major surgical aggressiveness. Without real feedback, the surgeon has simply stopped the resection earlier in apparently healthy tissue. A negative response in RTNT (that is, the patient performs within the normal range) is more informative than the negative response provided by DES (that is, negative mapping). Consequently, in the case of RTNT, the surgeon is less prone to stop resection and often is more confident in carrying it on. Second, in the present RTNT series, we learned that when a transient decrease happens, a recovery can occur after a short period of time (a few or several minutes) and consequently the resection can continue. This has induced us to adopt the stop-and-go technique. Applying the same logic to other fiber tracts, we would probably avoid a false-positive response that would stop surgery too early.

Tests and Brain Areas

Tests belonging to Group 3 might be seen as the most sensible tests for the most critical functions as they still indicated pathology at the follow-up. Most of them are correlated with language functions, as the patients' lesions mainly included the insular, temporal, and/or premotor areas. On the contrary, the tests involving extralinguistic functions on the dominant hemisphere as well as the nondominant hemisphere generally showed a complete recovery at 6 months after surgery. We also noticed a faster recovery in the group with right-hemisphere lesions. More

selective tests may still be used in the future, but the need for awake craniotomy in areas different from the sensorimotor area on the nondominant side may be reconsidered. Clearly, these results are preliminary because they depend on the number of patients who performed a given task and on the lesion site. Nonetheless, this correlation could help determine the predictive value of RTNT. Overall, no task showed a preoperative versus a follow-up change > 25%. As far as the neuropsychological follow-up at 6 months is concerned, with our detailed neuropsychological battery of tasks, we observed a decrease in performance mainly affecting language function that went unnoticed with standard neurosurgical evaluations.

Clinical Results

In this preliminary experience, continuous, more intensive, complex feedback allowed greater resection. From a mean EOR of 90% (range 49%–100%) in our second historical series (that is, Series 2; Series 1 had a mean EOR of 77% [range 28%–100%]),¹⁹ we reached a mean EOR of 95% in the present series (range 73%–100%). It is in effect a modest increase, but several recent volumetric analyses have shown that even small improvements in the resection rate, such as from > 90% to 100%, may provide an advantage both in terms of better overall survival and in terms of anaplastic transformation.^{6,19,33,34,37} More recent studies speak about supratotal resection in which a small difference in tumor resection can influence prognosis.⁶ In principle, it is likely that even the modest improvement in the resection rate in our patient sample could lead to similar clinical advantages. Furthermore, we have to consider the qualitative aspect allowed by this method, which gives the surgeon better and safer feedback. In our opinion, it is difficult to resect infiltrated brain tissue despite negative DES mapping. Thus, it is likely that patients in the present RTNT series will have a different neuropsychological pattern at follow-up, as compared with other patients who did not undergo RTNT. By using this method, we could exert better tumor control and could better predict the patients' clinical follow-up. However, this series is still too small, and we need a greater number of cases to validate this resection method and evaluate its real impact on follow-up.

Conclusions

RTNT allows for ongoing monitoring of cognitive performance during resection of an infiltrative brain tumor in functional tissue. It enables one to evaluate cognitive functions during follow-up, obtaining a more defined neuropsychological picture of the impact of surgery. RTNT in combination with DES allows for continuous feedback, reducing the uncertainty of negative feedback on DES, particularly when operating in the white matter, and thus allowing one to increase the extent of resection.

References

1. Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, et al: Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurgery* 60:67–82, 2007
2. Berger MS: Lesions in functional ("eloquent") cortex and subcortical white matter. *Clin Neurosurg* 41:444–463, 1994

3. Berger MS: Minimalism through intraoperative functional mapping. **Clin Neurosurg** 43:324–337, 1996
4. Berger MS, Ojemann GA: Intraoperative brain mapping techniques in neuro-oncology. **Stereotact Funct Neurosurg** 58:153–161, 1992
5. Bizzi A: Clinico-anatomical correlation in gliomas: a new frontier in clinical neuroscience? **Cortex** 47:1013–1015, 2011
6. Capelle L, Fontaine D, Mandonnet E, Taillandier L, Golmar JL, Bauchet L, et al: Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. **J Neurosurg** 118:1157–1168, 2013
7. Desmurget M, Sirigu A: A parietal-premotor network for movement intention and motor awareness. **Trends Cogn Sci** 13:411–419, 2009
8. Duffau H: Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. **Lancet Neurol** 4:476–486, 2005
9. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Lopes M, et al: Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. **J Neurol Neurosurg Psychiatry** 74:901–907, 2003
10. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Taillandier L, et al: Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. **J Neurosurg** 98:764–778, 2003
11. Duffau H, Capelle L, Sichez JP, Bitar A, Faillot T, Arthuis F, et al: [Surgery of the central nervous system: value of preoperative functional brain mapping by direct electric stimulation.] **Presse Med** 29:421–422, 2000 (Fr)
12. Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, et al: Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. **Brain** 125:199–214, 2002
13. Duffau H, Moritz-Gasser S, Mandonnet E: A re-examination of neural basis of language processing: proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. **Brain Lang** 131:1–10, 2014
14. Fernández Coello A, Duvaux S, De Benedictis A, Matsuda R, Duffau H: Involvement of the right inferior longitudinal fascicle in visual hemianopia: a brain stimulation mapping study. **J Neurosurg** 118:202–205, 2013
15. Gharabaghi A, Fruhmann Berger M, Tatagiba M, Karnath HO: The role of the right superior temporal gyrus in visual search-insights from intraoperative electrical stimulation. **Neuropsychologia** 44:2578–2581, 2006
16. Gil-Robles S, Carvallo A, Jimenez MdelM, Gomez Caicoya A, Martinez R, Ruiz-Ocaña C, et al: Double dissociation between visual recognition and picture naming: a study of the visual language connectivity using tractography and brain stimulation. **Neurosurgery** 72:678–686, 2013
17. Giussani C, Pirillo D, Roux FE: Mirror of the soul: a cortical stimulation study on recognition of facial emotions. **J Neurosurg** 112:520–527, 2010
18. Ilmberger J, Ruge M, Kreth FW, Briegel J, Reulen HJ, Tonn JC: Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis. **J Neurosurg** 109:583–592, 2008
19. Ius T, Isola M, Budai R, Pauletto G, Tomasino B, Fadiga L, et al: Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients: clinical article. **J Neurosurg** 117:1039–1052, 2012
20. Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS: Intraoperative subcortical stimulation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. **J Neurosurg** 100:369–375, 2004
21. Kleinman JT, Sepkuty JP, Hillis AE, Lenz FA, Heidler-Gary J, Gingis L, et al: Spatial neglect during electrocortical stimulation mapping in the right hemisphere. **Epilepsia** 48:2365–2368, 2007
22. Maldonado IL, Moritz-Gasser S, de Champfleury NM, Bertram L, Moulinié G, Duffau H: Surgery for gliomas involving the left inferior parietal lobule: new insights into the functional anatomy provided by stimulation mapping in awake patients. **J Neurosurg** 115:770–779, 2011
23. Mandonnet E, Capelle L, Duffau H: Extension of paralimbic low grade gliomas: toward an anatomical classification based on white matter invasion patterns. **J Neurooncol** 78:179–185, 2006
24. McGirt MJ, Chaichana KL, Attenello FJ, Weingart JD, Than K, Burger PC, et al: Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. **Neurosurgery** 63:700–708, 2008
25. McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A, et al: Independent association of extent of resection with survival in patients with malignant brain astrocytoma. **J Neurosurg** 110:156–162, 2009
26. Moritz-Gasser S, Duffau H: The anatomo-functional connectivity of word repetition: insights provided by awake brain tumor surgery. **Front Hum Neurosci** 7:405, 2013
27. Moritz-Gasser S, Herbet G, Duffau H: Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: a brain electrostimulation study. **Neuropsychologia** 51:1814–1822, 2013
28. Nathan SS, Sinha SR, Gordon B, Lesser RP, Thakor NV: Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. **Electroencephalogr Clin Neurophysiol** 86:183–192, 1993
29. Ojemann G, Ojemann J, Lettich E, Berger M: Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. **J Neurosurg** 71:316–326, 1989
30. Ojemann GA: Functional mapping of cortical language areas in adults. Intraoperative approaches. **Adv Neurol** 63:155–163, 1993
31. Perrine K, Devinsky O, Uysal S, Santschi C, Doyle WK: Cortical mapping of right hemisphere functions. **Epilepsy Behav** 1:7–16, 2000
32. Roux FE, Dufor O, Lauwers-Cances V, Boukhatem L, Brauge D, Draper L, et al: Electrostimulation mapping of spatial neglect. **Neurosurgery** 69:1218–1231, 2011
33. Sanai N, Berger MS: Extent of resection influences outcomes for patients with gliomas. **Rev Neurol (Paris)** 167:648–654, 2011
34. Sanai N, Chang S, Berger MS: Low-grade gliomas in adults. **J Neurosurg** 115:948–965, 2011
35. Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. **N Engl J Med** 358:18–27, 2008
36. Sanai N, Polley MY, Berger MS: Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. **J Neurosurg** 112:1–9, 2010
37. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. **J Neurosurg** 115:3–8, 2011
38. Skrap M, Mondani M, Tomasino B, Weis L, Budai R, Pauletto G, et al: Surgery of insular nonenhancing gliomas: volumetric analysis of tumoral resection, clinical outcome, and survival in a consecutive series of 66 cases. **Neurosurgery** 70:1081–1094, 2012
39. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al: Role of extent of resection in the long-term

- outcome of low-grade hemispheric gliomas. **J Clin Oncol** **26**:1338–1345, 2008
40. Szélenyi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, et al: Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. **Neurosurg Focus** **28**(2):E7, 2010
 41. Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Lévy R, Dubois B, et al: Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. **Science** **309**:2226–2228, 2005
 42. Tomasino B, Marin D, Canderan C, Maieron M, Budai R, Fabbro F, et al: Involuntary switching into the native language induced by electrocortical stimulation of the superior temporal gyrus: a multimodal mapping study. **Neuropsychologia** **62**:87–100, 2014
 43. Tomasino B, Marin D, Maieron M, Ius T, Budai R, Fabbro F, et al: Foreign accent syndrome: a multimodal mapping study. **Cortex** **49**:18–39, 2013
 44. Wager M, Du Boisgueheneuc F, Pluchon C, Bouyer C, Stal V, Bataille B, et al: Intraoperative monitoring of an aspect of executive functions: administration of the Stroop test in 9 adult patients during awake surgery for resection of frontal glioma. **Neurosurgery** **72** (2 Suppl Operative):ons169–ons181, 2013

Disclosures

The authors report no conflict of interest concerning the materi-

als or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Tomasino, Skrap, Marin. Acquisition of data: Tomasino, Skrap, Marin, Ius. Analysis and interpretation of data: all authors. Drafting the article: Tomasino, Skrap, Marin. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: Tomasino. Statistical analysis: Tomasino, Marin, Ius. Study supervision: Tomasino, Skrap.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables 1–3. <http://thejns.org/doi/suppl/10.3171/2015.10.JNS15740>.

Correspondence

Barbara Tomasino, IRCCS “E. Medea,” Polo Regionale del Friuli Venezia Giulia, Via della Bontà, 7, San Vito al Tagliamento (PN) 33078, Italy. email: barbara.tomasino@gmail.com.