

Brain tumor surgery guided by navigated transcranial magnetic stimulation mapping for arithmetic calculation

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OBJECTIVE The onco-functional balance represents the primary goal in neuro-oncology. The increasing use of navigated transcranial magnetic stimulation (nTMS) allows the noninvasive characterization of cortical functional anatomy, and its reliability for motor and language mapping has previously been validated. Calculation and arithmetic processing has not been studied with nTMS so far. In this study, the authors present their preliminary data concerning nTMS calculation.

METHODS The authors designed a monocentric prospective study, adopting an internal protocol to use nTMS for preoperative planning, including arithmetic processing. When awake surgery was possible, according to the patients' conditions, nTMS points were used to guide direct cortical stimulation (DCS), i.e., the gold standard for cortical mapping. Navigated TMS-based tractography was used for surgical planning. Statistical analyses on the nTMS and DCS points were performed.

RESULTS From February 2021 to October 2023, 61 procedures for nTMS calculation mapping were performed. The clinical evaluation, including pre- and postoperative evaluations (3 months after surgery), demonstrated a good clinical outcome with preservation of arithmetic function and recovery (92.8% of patients). Between the awake and asleep surgery groups, the postoperative clinical results were comparable at the 3-month follow-up, with > 90% of the patients achieving improved calculation function. The surgical strategy adopted was aimed at sparing nTMS positive points in asleep procedures, whereas nTMS and DCS positive points were not removed in awake procedures. Overall, 62% of the positive points for calculation functions were exposed by craniotomy and 85% were spared during surgery. None of the patients developed nTMS-related seizures. Diffusion tensor imaging fiber tracking based on nTMS positive points for calculation was used. The white matter fiber tracts involved in calculation functions were the arcuate fasciculus (56%) and frontal aslant tract (22%). When nTMS and DCS points were compared in awake surgery (n = 10 patients), a sensitivity of 31.71%, specificity of 85.76%, positive predictive value of 22.41%, negative predictive value of 90.64%, and accuracy of approximately 69% were achieved.

CONCLUSIONS Based on the authors' preliminary data, nTMS can be an advantageous tool to study cognitive functions, aimed at minimizing neurological impairment. The postoperative clinical outcome for patients who underwent operation with nTMS was very good. Considering these results, nTMS has proved to be a feasible method to map cognitive areas including those for calculation functions. Further analyses are needed to validate these data. Finally, other cognitive functions (e.g., visuospatial) may be explored with nTMS.

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KEYWORDS neuro-oncology; nTMS; navigated transcranial magnetic stimulation; preoperative planning; neurocognitive study; calculation; arithmetic functions; tumor; oncology

ABBREVIATIONS AF = arcuate fasciculus; DCS = direct cortical stimulation; DTI = diffusion tensor imaging; FAT = frontal aslant tract; IFOF = inferior fronto-occipital fasciculus; KDE = kernel density estimation; NPV = negative predictive value; nTMS = navigated transcranial magnetic stimulation; PPV = positive predictive value; mTMS = repetitive TMS; SLF-III = third segment of the superior longitudinal fasciculus.

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THE neurocognitive-neuropsychological assessment is pivotal in neurosurgery because it is strictly connected with patients' quality of life.¹⁻⁴ The concepts of functional connectome and brain plasticity are relevant principles in the modern surgical approach.⁴ The onco-functional balance represents the primary goal for neurosurgeons in attempting to achieve a maximal safe resection, considering overall survival and progression-free survival, and preserve the functions⁵ that grant access to postoperative therapies.⁶ The integration of advanced neuroimaging techniques to understand the functional brain architecture and the increasing use of navigated transcranial magnetic stimulation (nTMS) allow a noninvasive characterization of cortical functional anatomy.

A shared protocol for nTMS mapping of motor and language functions to standardize its application and increase its clinical value has previously been published.^{7,8} Nonetheless, cognitive functions include a wide range of brain capabilities, and arithmetic is perhaps one of the most central cognitive functions in our daily life. Arithmetic tasks have been performed with nTMS⁹ and, during awake surgery, DCS for parietal lesions, on either the left or right side.^{10,11} Based on these considerations, the primary aim of this work was to add the calculation function within preoperative mapping using repetitive nTMS (rnTMS) to evaluate the pre- and postoperative clinical outcomes of patients operated on for brain tumors, including awake and asleep procedures. The secondary aim was to evaluate the possible subcortical white matter fiber tracts involved in arithmetic calculations. Lastly, the third aim was to evaluate the correspondence between nTMS and DCS points during awake surgery, to determine nTMS reliability for calculation.

Methods

We designed a monocentric prospective clinical study. We collected data from patients who underwent surgery at the University Hospital of Careggi, Florence, Italy, who presented with focal lesions in eloquent areas for language, calculation, and/or visuospatial functions. Preoper-

ative planning included neuropsychological and logopedic evaluation, MR images, and an nTMS protocol (for nTMS language and calculation) (Fig. 1).

The cognitive evaluation included the Mini-Mental State Examination;⁴⁴ Aachener Aphasia Test;⁴⁵ neuropsychological examination for aphasia;⁴⁶ items for written calculation, addition, subtraction, and multiplication; Oxford Cognitive Screen; Barrage item;⁴⁷ Bells Test;⁴⁸ Wechsler Adult Intelligence Scale, Fourth Edition;⁴⁹ Frontal Assessment Battery;⁵⁰ and Babcock test, Italian version.⁵¹

The nTMS procedure consisted of the picture naming test (D080) for the language task and 44 basic arithmetic operations for the calculation task.

Calculation Mapping

In the preoperative period (approximately 1–2 days before surgery), a full assessment of calculation skills was performed.¹² All results were adapted, based on the patient's age and scholarship level.

Patients presenting with calculation disturbances, hindering test performance, were excluded because adequate calculation abilities were necessary to identify errors and, therefore, nTMS positive spots and mapping. Conventionally, we considered the highest threshold of 40% error on testing to consider patients eligible for nTMS mapping.

Calculation abilities included simple fact retrieval, rule-based processing, and mental and written calculation in all 4 operations. The calculation functions tested consisted of calculation skills, counting skills, number comprehension, and numeric transcoding. For the calculation tasks, all numeric stimuli were presented visually as Arabic numbers on a tablet screen, set 20–30 cm from the patient's view, on a white background and gray frame to reduce visual fatigue. Each slide lasted 4 seconds, with an interpicture interval of 0.5 seconds. The patients' abilities in addition, subtraction, and multiplication were studied. The same test was performed to train patients during nTMS mapping and before awake procedures. Moreover, the test was repeated intraoperatively for cortical and subcortical mapping during the awake procedure. The task adminis-

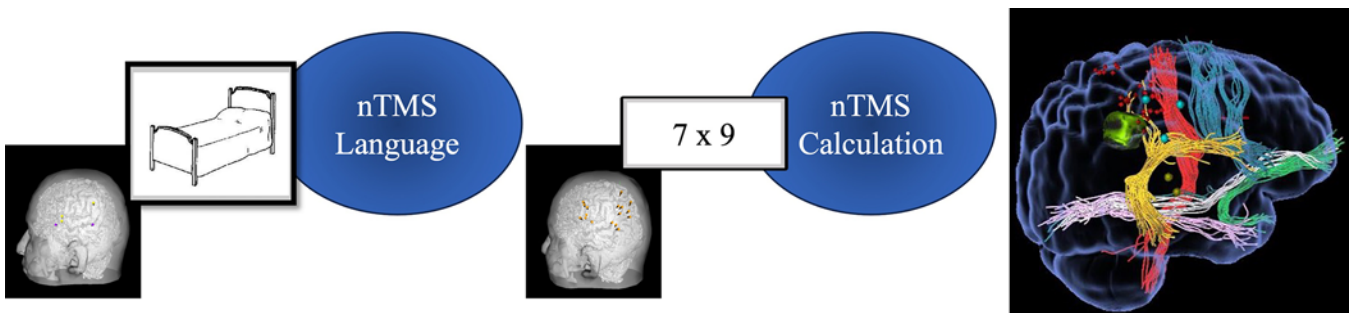


FIG. 1. **Left:** The language task consisted of the picture naming test, whereas the calculation task required simple single-step arithmetic operations (44 addition, subtraction, and multiplication problems). In the nTMS map obtained for each patient, the colored dots represent nTMS mapping dots for either language or calculation functions. **Right:** Case 84. Preoperative planning for a 28-year-old male patient harboring a right parietal lesion (green sphere) whose characteristics were compatible with a low-grade glioma. Tractography and nTMS positive points were integrated in the intraoperative image. The tracts are represented as follows: red, corticospinal tract; yellow, AF; green, optic radiations; white, IFOF; pink, inferior longitudinal fasciculus; and light blue, FAT. The nTMS positive points (dots) are represented as follows: red, motor function (mapping of the right and left hemispheres); yellow, language function; and light blue, calculation function. Figure is available in color online only.

tration procedure was a block of addition, multiplication, and subtraction problems presented to the patient, in random order, with the use of electrostimulation alternated and repeated 3 times.

Preoperative MRI and rTMS Mapping

We performed preoperative MRI using a 3T MRI scanner (Ingenia 3T, Philips Medical Systems). Diffusion tensor imaging (DTI) sequences were used for subcortical tract reconstruction, with chromatic code for each one.

Preoperative language and calculation mapping were performed using an nTMS system (Galileo NetBrain Neuronavigator 9000, EB Neuro Corp.) with a cooled figure-of-eight coil and biphasic pulses. Mapping was performed on both hemispheres when possible (limitations mainly due to patient compliance and/or fatigue), for patients harboring lesions on either the right or left hemisphere; otherwise, it was limited to the affected side. Volumetric T1-weighted MRI sequences were used to reconstruct the patient's 3D brain model, and the resting motor threshold of the right first dorsal interosseus muscle, i.e., the lowest TMS intensity able to evoke a motor evoked potential at rest of at least 50 μ V in 5 of 10 stimulations, was computed.

As mentioned above, the picture naming test was used for the language task, and the calculation task required simple single-step arithmetic operations (44 addition, subtraction, and multiplication problems) (Fig. 1). All tests were displayed on a screen (picture presentation time 4 seconds, interpicture interval 1 second) in front of the patient, who answered aloud. Before each rTMS mapping session, the patient performed the baseline task, i.e., completed the task without rTMS perturbation, to remove the incorrect answers from the stimulation sequence. The rTMS perturbation consisted of trains of 5 pulses at 5 Hz with an intensity of 100% of the first dorsal interosseus muscle resting motor threshold, delivered simultaneously using a picture presentation. For rTMS language mapping, 90 trains were applied over the left perisylvian cortices, while calculation functions were mapped onto 70 spots, distributed over parietal, temporal, frontal, and prefrontal cortices. Errors were detected directly online by a speech therapist and verified offline through video recording analysis. A cortical spot was considered positive for either language or calculation if nTMS perturbation induced an error in at least two of three trials.¹³ An MR DT image was used to create an nTMS-based tractogram^{7,14–18} (Fig. 1).

Intraoperative monitoring included motor and somatosensory evoked potentials. A cortical strip for motor cortex stimulation was positioned to map motor functions. During awake surgery, direct cortical stimulation (DCS), based on the Penfield paradigm with bipolar stimulation, was established case by case (working current intensity 0.5–3 mA).

Anesthesiological Parameters for Awake Surgery

An asleep-awake-asleep procedure was adopted. The patient was briefly sedated with a low dose of propofol under total intravenous anesthesia (Schnider model) with

a target effect site concentration of 1–1.5 μ g/ml, dexmedetomidine 0.02–0.08 μ g/kg/hr, and remifentanyl 0.02–0.05 μ g/kg/min, individually adjusted.^{52,53} For scalp nerve block and Mayfield application, lidocaine 2%, bupivacaine 0.5% with epinephrine, and ropivacaine 7.5% were administered. ECG readings, invasive blood pressure, end-tidal CO₂, saturated O₂, urine output, body temperature, and bispectral index (on the contralateral hemisphere) were monitored. During the awake phase and DCS, the bispectral index was maintained at > 90.

Identification of nTMS Positive Points for Calculation

We identified positive points for language and calculation in the F3 gyrus; T1, T2, or T3 gyrus; and angular and supramarginal gyri. In the parietal lobe, we found positive points for calculation and/or neglect in either the right or left hemisphere. In awake surgery, using the neuronavigation system, we identified nTMS positive points for calculation and marked them with sterile tags on the brain cortex. Then we used the Penfield bipolar stimulation technique (current intensity 0.5–3 mA) for calculation mapping on the cortical surface.

The surgical strategy was aimed at exposing and sparing DCS and nTMS positive points in awake surgery, whereas in asleep surgery the identification of nTMS positive points, considered functionally active, was possible with the neuronavigation system; these points were also spared.

Statistical Analysis

We proposed a statistical evaluation considering the 3D brain location involved with a specific cognitive function. We collected nTMS positive and negative point spatial coordinates (x, y, z) from the neuronavigational system. The Neuronavigation Microscope Integration (NMI) system routinely used consists of a microscope (Kinevo 900, Zeiss) combined with the StealthStation (Medtronic). During the cortical mapping in awake surgery, we highlighted DCS positive and negative points in the neuronavigational system and collected the spatial coordinates (x, y, z). These sets of coordinates were essential for the subsequent analyses, performed using specific scripts written in Python. The use of coordinates allowed us to compare the distributions of DCS and nTMS points statistically. We built up a statistical distribution into the Euclidean space, using the kernel density estimation (KDE) process, setting $\sigma = 5$ mm (confidence level set at $\alpha = 0.95$), which gave us a distance radius from DCS points of 14 mm, comparable with previous work.¹⁹ We finally obtained a spatial distribution of nTMS and DCS points, with marginal probability densities f_{XY} , f_{XZ} , and f_{YZ} .

The mathematic statistical model is explained in the Supplementary Material.

Ethics Approval

The study was approved by the ethics committee CEAVC (Comitato Etico Area Vasta Centro), section of the Regional Ethics Committee of the Region of Tuscany, in compliance with the Declaration of Helsinki.

Results

During the period between February 2021 and October 2023, among > 500 patients operated on for focal lesions at the neurosurgical department of the University Hospital of Careggi, we enrolled 87 patients in whom to perform nTMS cognitive mapping. One patient was excluded because their parenchymal alteration was histologically classified as a focal cortical dysplasia and radiological follow-up was chosen. Three patients were lost to follow-up. In total, 83 patients with a mean $\pm$ SD age of 51.4 ± 14.8 years (median 52 years) were included. The sex distribution was comparable (1:1 male/female). The histological diagnoses included 72 primitive neoplasms, 14 recurrences, and 6 vascular lesions (42 glioblastoma, 14 WHO 2021 grade 3 glioma, 13 WHO 2021 grade 2 glioma, 8 metastases, and 6 vascular lesions). The majority of the procedures were asleep (48, 58%), whereas 35 (42%) were awake. Table 1 summarizes the patients' characteristics.

Around 35% of lesions had multiple lobar locations. Overall, 64% (53/83) of our patients took antiepileptic drugs in the preoperative period, whereas 36% were not being treated. The cognitive nTMS procedure was completely safe; no patient developed nTMS-related epilepsy, the risk of which is 0.5%–1%.⁷ All enrolled patients were tested preoperatively for language function.

Sixty-one patients were considered for nTMS calculation mapping. Twenty-two patients were excluded because their calculation functions were impaired by cerebral lesions (> 80% errors at baseline).

Evaluating the clinical utility of nTMS preoperative planning for language and calculation functions, we considered surgical strategy variations and adaptations and the postoperative clinical outcome (follow-up period up to 3 months).

Evaluation of Preoperative and Postoperative Clinical Conditions

All operations were performed by the same senior neurosurgeon (A.D.P.), and tumor resection was based on postoperative MRI, evaluated by an expert neuroradiologist, and classified as follows: 0 represents no residual tumor (gross total resection; 75% of patients), 1 represents $\leq$ 5% residual tumor (20% of patients), and 2 represents 5%–20% residual tumor (5% of patients).

Surgical Strategy

When nTMS points were located at tumor margins, they were considered functionally active and spared in either awake or asleep surgery. In a few cases in which nTMS points were located on the tumor cortical surface, they were removed, and a clinically accurate evaluation was performed. In asleep surgery, nTMS guided excision functionally, whereas in awake procedures nTMS points were used to identify DCS positive points.

Overall, 62% of nTMS positive points for calculation were exposed in the craniotomies performed and 85% were spared. Most of our patients (92.8%) were discharged at a mean of 5 ± 7 days after surgery, but 5% needed a rehabilitation program in a hospitalized structure. Only 2% had a prolonged hospital stay. Clinical results were re-

corded immediately after surgery and at 1 and 3 months after surgery.

Clinical Outcome for Calculation Function

Calculation function was tested preoperatively in 61 patients. Their postoperative evaluation was comparable to their preoperative one (19% of patients had a postoperative deficit compared with 18% with a preoperative deficit).

Among patients with normal arithmetic function (82%), only 12% developed a transient impairment immediately after surgery, and 98% of these had recovered function by the 3-month follow-up (2% had a moderate deficit).

In patients with a preoperative functional impairment (18%), a postoperative deficit was maintained in 54.5% of them. At the 3-month follow-up, 10% (6/61) of patients had a slight impairment. Between the awake and asleep surgery groups, postoperative clinical results were comparable at the 3-month follow-up: calculation function improved in > 90% of our patients. Global recovery was seen in 92.8% of patients (Fig. 2).

Calculation, i.e., the capability of performing basic arithmetic operations, relies the frontoparietal network²⁰ that may be lesioned by the tumors (35% of the lesions included in our study involved more than one lobe).

Where awake surgery was possible, nTMS points were used to guide DCS to identify the functionally active area. DTI reconstruction of the arcuate fasciculus (AF), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus, and frontal aslant tract (FAT) was driven by nTMS language-positive points.

In Fig. 3, we highlight 1 particular case of a patient with a left fronto-opercular lesion, for whom nTMS identified 16 positive points for calculation. The terminations of the third segment of the superior longitudinal fasciculus (SLF-III) were mapped by C4, C5, C6, C7, C10, and C11. Navigated TMS calculation positive points were concentrated in the frontotemporal regions, in the supramarginal and angular gyri of the parietal lobe (Fig. 3B and C). The tumor was completely lying on the AF. Two language-specific nTMS points mapped to AF, and the anterior cluster of nTMS calculation-positive points completely corresponded to the anterior indirect segment of AF (i.e., SLF-III).²¹

We identified two clusters of nTMS calculation points: the anterior one (frontotemporal) corresponding to the verbal representation of numbers, and the posterior one (parietal) corresponding to the quantitative representation of numbers. This case inspired us to obtain more detailed information about arithmetic processing and the white matter fiber tracts underlying this complex and fascinating function (Fig. 3).

Navigated TMS-Based Tractography and Calculation Mapping

We focused our attention on 10 patients who underwent nTMS calculation mapping and a corresponding evaluation with DCS during awake surgery. (One more patient was included to check the white matter subcortical circuits, but the awake procedure was aborted due to the patient's lack of compliance. The final percentages are

TABLE 1. Patient characteristics

Patient No.	Sex	Age, yrs	Lesion	Antiepileptic Treatment	Awake Surgery	nTMS
1	F	71	Lt temporoinsular GBM	Yes	Yes	C
2	F	59	Rt parietal GBM	Yes	Yes	L/N
3	F	67	Lt temporoinsular G2	Yes	Yes	L/C
4	M	54	Lt temporoinsular G3	Yes	Yes	L
5	M	58	Rt frontal GBM	No	No	L
6	M	56	Lt parietal metastasis (pulmonary)	Yes	Yes	L
7	M	42	Lt temporoinsular GBM (recurrence)	Yes	Yes	L
8	F	43	Rt parieto-occipital GBM	Yes	Yes	L/C/N
9	F	62	Lt temporoparietal GBM	Yes	Yes	L/C
10	M	29	Rt frontal G3	Yes	Yes	L/C
11	F	54	Rt frontal G3	Yes	Yes, failed	L/C
12	M	50	Lt insular cavernoma	Yes	Yes	L/C
13	F	40	Rt frontal G2	Yes	Yes	L/C
14	M	38	Rt temporal G2	Yes	Yes	L/C
15	M	52	Lt frontal G2	Yes	Yes	L/C
16	M	42	Rt frontal G2 (recurrence)	No	Yes	L/C
17	F	39	Lt temporoinsular GBM	No	Yes, failed	L/C
18	F	65	Lt parietal GBM	Yes	Yes, failed	L/C
19	M	48	Lt temporal GBM	Yes	Yes, failed	L/C
20	M	53	Lt frontal GBM	Yes	Yes	L/C
21	F	28	Lt frontotemporal GBM	Yes	Yes, failed	L/C
22	F	47	Lt frontal cavernoma	Yes	Yes	L/C
23	F	38	Lt frontal G3 (recurrence)	Yes	Yes	L
24	F	62	Lt parietal metastasis (NSCLC)	No	No	L
25	M	67	Lt frontal G3 (recurrence)	No	No	L/C
26	M	39	Lt temporal G3	Yes	Yes	L/C
27	F	40	Lt temporoinsular G3 (recurrence)	Yes	No	L/C
28	M	54	Lt parietal GBM	Yes	No	L
29	F	60	Lt frontal GBM	No	Yes	L/C
30	M	64	Lt temporoinsular GBM	Yes	Yes	L
31	F	49	Lt parietal G2 (recurrence)	No	Yes	L/C
32	M	68	Lt parietal GBM	No	Yes, failed	L/C/N
33	M	78	Lt temporoinsular GBM	Yes	No	L/C
34	M	46	Lt frontal GBM (recurrence)	Yes	No	L/C
35	F	42	Lt frontal large-B-cell lymphoma	Yes	Yes	L/C
36	F	30	Lt frontotemporal metastasis (recurrence, pulmonary)	Yes	Yes	L/C
37	F	72	Lt frontal GBM (recurrence)	Yes	No	L
38	M	78	Lt temporal GBM	Yes	No	L
39	M	36	Lt parietal GBM	No	No	C
40	F	63	Lt parietal GBM	Yes	Yes	L/C/N
41	M	79	Lt frontal metastasis (recurrence, breast tumor)	No	No	L
42	M	30	Rt frontotemporal G2	Yes	Yes	L
43	M	55	Lt parietal GBM	No	No	L/C
44	F	67	Lt frontoparietal GBM	No	No	L/C
45	F	45	Lt temporoinsular GBM	Yes	Yes	L/C
46	F	62	Lt temporoinsular GBM	No	Yes	L
47	M	14	Lt parietal G2	No	No	L
48	F	48	Rt temporo-parieto-occipital GBM	No	Yes	L/N
49	F	60	Rt parietal GBM	No	Yes	L

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TABLE 1. Patient characteristics

Patient No.	Sex	Age, yrs	Lesion	Antiepileptic Treatment	Awake Surgery	nTMS
50	M	59	Lt frontotemporal GBM	Yes	No	L/C
51	F	52	Lt temporoparietal GBM	Yes	No	L/C
52	M	47	Rt temporal G2 (recurrence)	Yes	No	L
53	M	31	Lt temporal G3	Yes	Yes	L/C
54	F	69	Rt frontoparietal metastasis (NSCLC)	No	No	L/C
55	M	32	Lt parietal G3	No	Yes	L/C/N
56	M	47	Rt frontoparietal G3 (recurrence)	Yes	No	L/C
57	F	48	Lt parietal GBM	Yes	No	L/C
58	F	57	Lt parieto-occipital G2	Yes	No	L/C
59	F	68	Rt fronto-temporo-insular cavernoma	Yes	No	L/C
60*	M	22	Lt frontal cortical dysplasia	Yes	No	L
61	F	58	Lt fronto-temporo-insular GBM	Yes	No	L
62	M	70	Rt frontal GBM	No	No	L/C
63	F	72	Lt frontal GBM	Yes	No	L/C
64	F	59	Rt frontal cavernoma	Yes	No	L/C
65	F	55	Rt frontal G3	Yes	No	L/C
66	M	72	Rt temporal G2	Yes	No	L/C
67	M	52	Rt temporoparietal GBM	Yes	No	L/C
68	M	20	Rt frontoparietal GBM	No	No	L/C
69	F	43	Lt temporoparietal G3	No	Yes	L/C
70	F	58	Rt frontoparietal GBM	No	No	L/C
71	F	66	Lt frontal GBM	Yes	No	L/C
72	F	68	Lt frontal metastasis (recurrence, breast tumor)	Yes	No	L/C
73	F	77	Rt parietal metastasis (pulmonary)	No	No	L/C
74†						
75†						
76†						
77	M	32	Lt frontal G3	No	No	L
78	M	46	Lt temporal GBM	Yes	Yes	L/C
79	M	41	Rt frontal metastasis (pulmonary)	No	No	L/C
80	F	32	Lt frontal AVM, S-M III	Yes	No	L/C
81	M	58	Rt parietal GBM	Yes	No	L
82	F	30	Lt temporal G3	No	Yes	L/C
83	F	72	Lt parietal GBM	No	No	L/C/N
84	M	28	Rt parietal G2	Yes	Yes	L/C/N
85	M	54	Rt frontal GBM	Yes	No	L/C/N
86	F	71	Rt frontal GBM (recurrence)	Yes	No	L/C/N
87	M	32	Lt temporal G2	Yes	No	L/C/N

C = calculation; GBM = glioblastoma; G2 = glioma grade 2; G3 = glioma grade 3; L = language; N = neglect; NSCLC = non-small cell lung cancer; S-M III = Spetzler-Martin grade III.

* Although this patient received epileptic surgery, he was excluded because his parenchymal alteration was histologically classified as a focal cortical dysplasia and radiological follow-up was chosen.

† Lost to follow-up.

calculated based on 9 patients because in 2 cases the identification of white matter fiber tracts was not certain.) For the selected patients, tractographies were acquired using the StealthViz software (Medtronic) to identify regions of interest at the cortical level based on the location of the

nTMS positive points for calculation. The reconstructed subcortical tracts, intercepted at the cortical level by the nTMS calculation positive points, were then compared by an experienced neuroradiologist in our department, who found that in 5 patients (56%) the identified bundle coin-

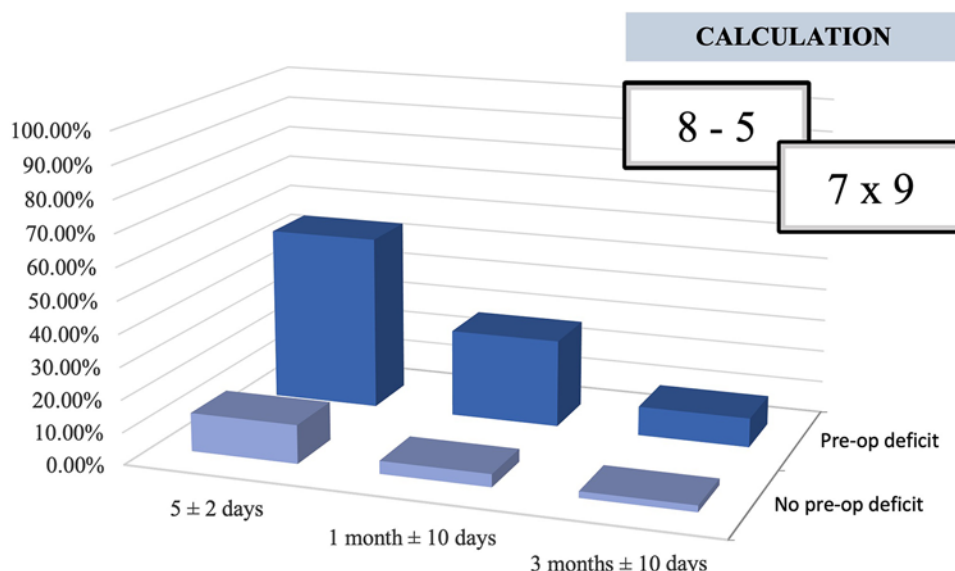


FIG. 2. Summary of clinical data (concerning calculation) obtained immediately after surgery and up to 3 months of follow-up. The *dark blue columns* show patients with preoperative deficits (11/61, 18%). At 5 ± 2 days of follow-up, 54.5% of patients had calculation impairment. At 30 ± 10 days of follow-up, 27.3% of patients had calculation impairment. At 90 ± 10 days of follow-up, 9.09% of patients had calculation impairment. The *light blue columns* show patients with normal calculation processing (50/61, 82%). At 5 ± 2 days of follow-up, 12% of patients had calculation impairment. At 30 ± 10 days of follow-up, 4% of patients had calculation impairment. At 90 ± 10 days of follow-up, 2% of patients had calculation impairment. Figure is available in color online only.

cided with the AF, and in 2 patients (22%) it coincided with the FAT. In 2 patients (22%) the identification was not certain, and in 1 patient (11%) the bundle was identified as both a possible AF and uncinate fasciculus. In the remaining patient (11%) the bundle was identified as both a possible FAT and IFOF.

Therefore, we believe that the role of AF and FAT in calculation may be valuable. Nevertheless, further analyses are needed to confirm this preliminary consideration (Fig. 4).

DCS and nTMS Correspondence

For all our patients, to validate the nTMS points by comparing them with DCS, we considered 35 awake procedures (42%). The standardized protocol of acquiring coordinates (x, y, z) for nTMS and DCS points was performed adequately in 10 cases. Therefore, the following results refer to the awake surgical procedures. The correspondence between nTMS and DCS showed low sensitivity (31.71%) and positive predictive value (PPV) (22.41%). Conversely, the specificity (85.76%) and negative predictive value (NPV) (90.64%) were higher than or comparable to the values for language. Accuracy is estimated at about 69%. These results are summarized in Tables 2 and 3. Finally, a spatial distribution of nTMS and DCS points, with marginal probability densities f_{XY} , f_{XZ} , and f_{YZ} , was estimated (Fig. 5).

Nevertheless, our preliminary results are based on a small sample of patients; therefore, further analyses are needed to validate our data.

Discussion

Our work evaluated the following main objectives:

1) the clinical utility of nTMS preoperative planning for arithmetic functions, considering both surgical strategy and variations and postoperative clinical outcome; 2) the possible white matter fiber tracts underlying arithmetic functions; and 3) nTMS and DCS during awake procedures to validate nTMS for arithmetic cortical mapping.

As far as we know, only one publication has applied nTMS for calculation mapping⁹ in patients with parietal lesions, leading to tumor resection performed blinded to nTMS positive points and demonstrating that removing calculation-positive sites correlated with a worsening of the postoperative outcome. However, correlation to DCS or extent of resection was not performed.

For the first time, in this work, nTMS has been used to explore and spare arithmetic abilities and to understand the clinical outcome of patients operated on with nTMS preoperative functional mapping. We documented a clinical improvement of calculation in > 90% of our patients. Navigated TMS preoperative planning is useful for patients not eligible for awake surgery but who would benefit from an intraoperative functional guided surgery. No nTMS-induced epilepsy occurred in the patients. The surgical strategy was based on nTMS points in either awake or asleep surgery. Whereas the frontoparietal network is described for mathematical cognition, we analyzed the white matter fiber tracts underlying the calculation circuits and documented a major involvement of the AF and the FAT, which suggests that the linguistic circuits (dorsal stream especially) may play a role in elaborating arithmetic processing (as a quantitative representation of numbers). Navigated TMS for arithmetic functions, compared with DCS (the gold standard) in awake surgery, showed a high NPV (90.64%) and specificity (85.76%), whereas low PPV and sensitivity were documented in our study.

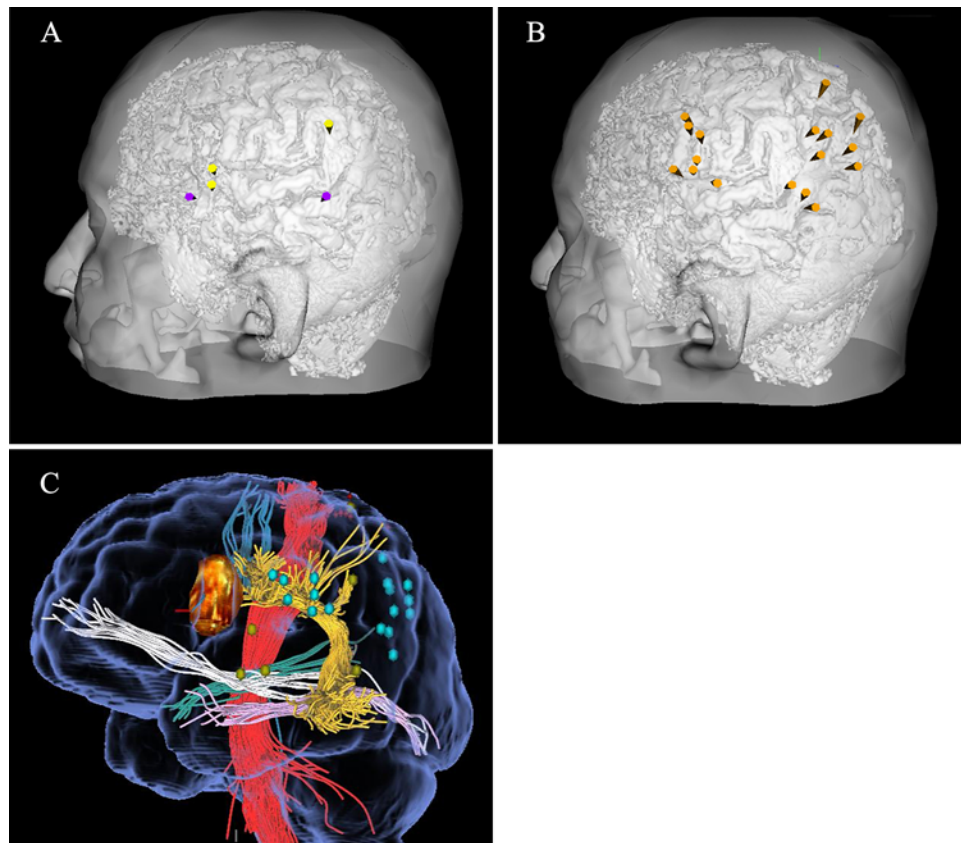


FIG. 3. Case 35. **A:** Illustrative case of a 42-year-old female patient harboring a left fronto-opercular lesion whose nTMS mapping identified language positive points and two clusters of positive points for calculation, located in the cortical frontotemporal regions and the supramarginal and angular gyri of the parietal lobe, respectively. **B:** Positive points for calculation. The anterior cluster (frontotemporal) corresponds to the verbal representation of numbers, and the posterior cluster (parietal) corresponds to the quantitative representation of numbers. **C:** The terminations of the SLF-III were mapped by C4, C5, C6, C7, C10, and C11. Figure is available in color online only.

Finally, as a future perspective, the rehabilitation program for patients with postoperative neurological deficits may be modulated with nTMS.

Navigated TMS is a noninvasive, reliable technique of cortical stimulation used for preoperative mapping that has shown a high concordance with cortical DCS-based mapping results, especially for nonrelevant cortical sites^{19,22,23} and preservation of functionality. Based on its transient inhibitory and excitatory effects, the stimulation of a cortical site can be linked to task performance. Referring to motor functions, the reliability of nTMS motor mapping compared with DCS is highly accurate.^{24,25} A recent review²⁶ considered the results of nTMS compared with DCS for language mapping. Repetitive nTMS is used to suppress part of the (sub-)cortical network responsible for language production, i.e., the induction of a “virtual lesion paradigm.”²⁷ DCS language mapping protocols included the Penfield paradigm with bipolar stimulation. Tractography based on nTMS data has a higher reliability than the anatomical data.^{28,29} Several studies have compared nTMS and DCS with statistical analyses^{27,30} showing a high sensitivity (approximately 100%) and NPV (57%–100%). Therefore, the reliability of nTMS for language mapping is not considered as accurate as that for motor mapping,

although the high NPV helps surgeons to avoid cortical functional areas during surgery. However, as opposed to DCS-based mappings, subcortical structures, which represent the main limitation of neuroplasticity, cannot be stimulated directly by nTMS.^{1,31–33} Moreover, the impact of tumor-induced functional reorganization and plasticity makes it difficult to define single tumors as clearly eloquent for a specific cognitive function.^{29,34} For instance, regarding tumors that are located within language-eloquent areas, the risk of surgery-related aphasia is one of the main factors that can limit the extent of resection and must be considered during patient counseling.³⁵

Consequently, awake surgery still remains the gold standard to preserve language functionality. In the scientific community, which type of intraoperative tests is better to use is still under discussion.^{36,37}

Calculation

Despite a historical focus on motor and language mapping, other cognitive functions contribute significantly to patient quality of life (e.g., vision, spatial awareness, memory, attention, judgment, emotion, and calculation) following surgery and may be mapped intraoperatively.³⁸ Noninvasive brain stimulation (at a cortical level) provides

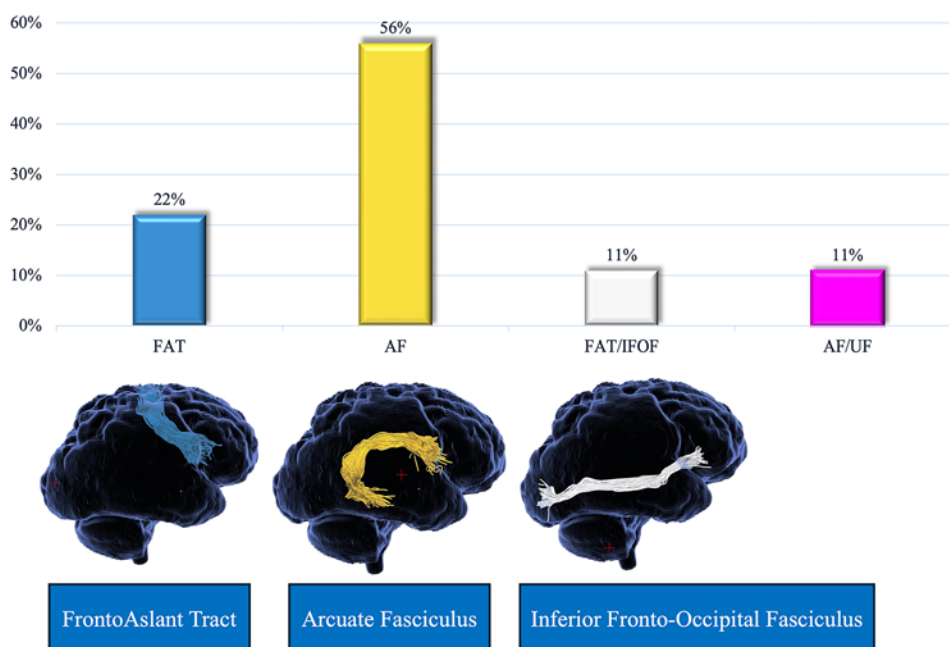


FIG. 4. White matter circuits underlying the calculation functions in our case series. The reconstructed subcortical tracts, intercepted at the cortical level by nTMS positive points for calculus function, were compared by an experienced neuroradiologist in our department. The comparison showed in that 5 patients (56%) the identified bundle coincided with the AF, and in 2 patients (22%) it coincided with the FAT. In 2 patients (22%) the identification was not certain, and in 1 patient (11%) the bundle was identified as both a possible AF and uncinate fasciculus (UF). In the remaining patient (11%), the bundle was identified as both a possible FAT and possible IFOF. White matter fiber tracts involved in language function also participate in math-related functions, based on the connectome and inter-/intra-hemispheric pathways. Further analyses are needed to better understand the role of white matter fiber tracts in elaborating and integrating multiple functions. Figure is available in color online only.

a potential tool for affecting brain functions and can also be used to enhance cognitive performance.³⁹

Calculation With rnTMS

To the best of our knowledge, the use of rnTMS to map calculation function in healthy volunteers⁴⁰ allows a specific categorization of calculation errors, based on anatomical location, showing that nTMS seems to be a feasible way to locate cortical calculation function. The only experience with rnTMS use in patients with parietal lesions⁹ correlated with postoperative clinical outcome, demonstrating that rnTMS could be a valid tool for arithmetic processing mapping. The most relevant works considering nTMS and calculation processing were collected by Krieg.⁷ The noninvasive rnTMS protocol, normally used for language preoperative mapping, is applied and can be implemented in the cognitive evaluation.

TABLE 2. Results comparing DCS and nTMS points for calculation

	DCS Positive	DCS Negative	Total
nTMS positive	26 (TP)	90 (FP)	116
nTMS negative	56 (FN)	542 (TN)	598
Total	82	632	

FN = false negative; FP = false positive; TN = true negative; TP = true positive.

Calculation Mapping in Awake Surgery

For the first time, awake surgery allowed the intraoperative mapping of the cortical areas involved in multiplication and subtraction using an electrostimulation study in a patient with a left parietal glioma.¹⁰ Then, the role of the parietal lobe and, more precisely, the right parietal lobe in testing calculation function was described in several papers. Della Puppa^{2,11,12} in particular identified intraoperative sites for calculation in parietal surgery using bipolar electrostimulation. Furthermore, the role of the right parietal lobe was established with subcortical mapping of calculation function.

In previous works, the classification of nTMS points has been performed in different ways, respecting the gold

TABLE 3. Statistical results comparing nTMS and DCS calculation points

	%
Sensitivity	31.71
Specificity	85.76
PPV	22.41
NPV	90.64
False-negative rate	68.29
False-positive rate	14.24
Accuracy	68.55

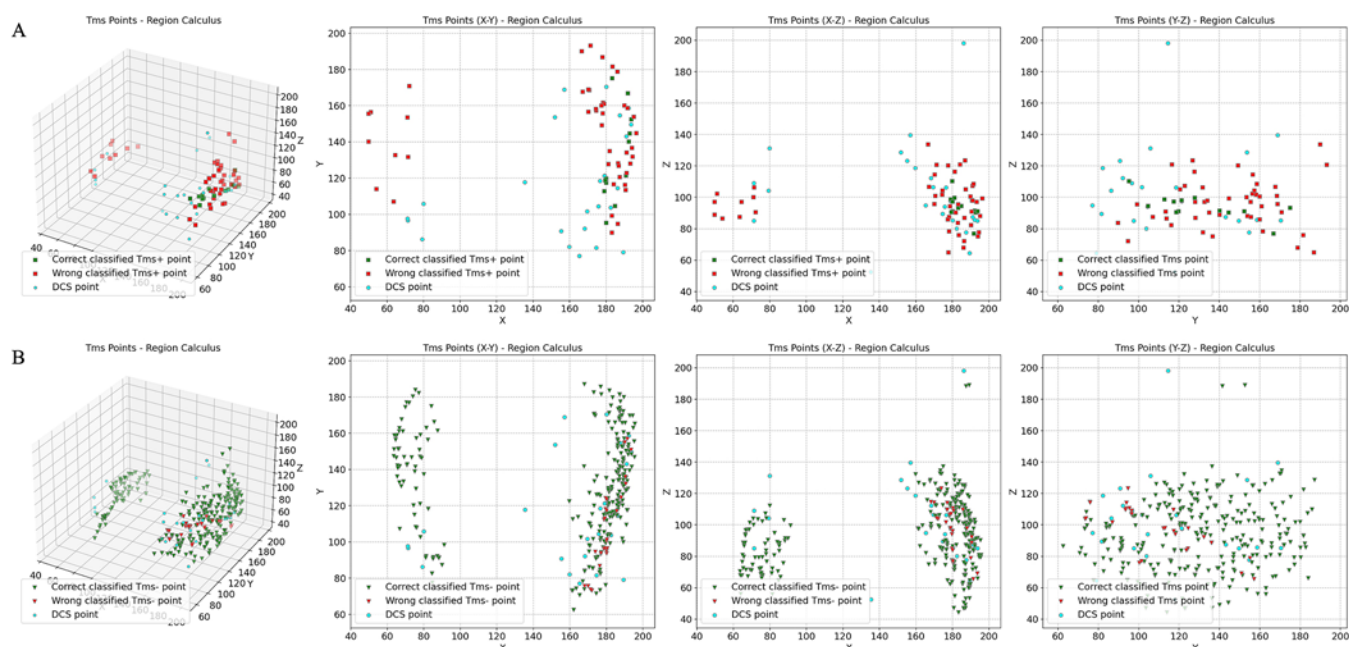


FIG. 5. Cumulative data of each patient who underwent an awake surgical procedure with calculation testing intraoperatively ($n = 10$). Whole spatial distributions of nTMS and DCS positive points (A) and nTMS and DCS negative points (B), with marginal probability densities f_{XY} , f_{XZ} , and f_{YZ} (95% CI; KDE, setting $\sigma = 5$ mm). Figure is available in color online only.

standard DCS. Picht et al.²² used a simple parcellation system, evaluating a TMS point as valid if a DCS point also fell within the same parcellation area. Tarapore et al.¹⁹ used a more granular classification system, coregistering the data of all patients on the same atlas and normalizing them on a grid, formed by 10×10 -mm square sectors, and considering a TMS point correct if there was a corresponding DCS point within the same sector, increasing the specificity, compared with the previously mentioned study. In our case, we did not use a specific parcellation scheme or predefined grids to perform the stimulations on the patients. Conversely, an innovative, reproducible, and objective approach was tested. Our statistical analyses allowed us to calculate statistical values based on the coordinates of 3D nTMS and DCS cortical points: 31.71% sensitivity, comparable to values for nTMS language mapping^{19,27} (10%–100%²⁷ and 90%¹⁹–90.2%²²), 85.76% specificity (13.3–98%²⁷ and 23.8%²²–98%¹⁹), 22.41% PPV (17%–75%²⁷ and 35.6%²²–69%¹⁹), and 90.64% NPV (57%–100%²⁷ and 83.9%²²–99%¹⁹).

Based on the previous considerations, our study is one of the first to investigate arithmetic processing using nTMS, with 61 patients achieving a clinical improvement after surgery. A good functional recovery was possible (92.8% of patients). Clinical worsening was seen in approximately 10% of patients (either with or without preoperative deficits). All documented deficits were transient. The subcortical circuits (white matter fiber tracts) are still under analysis, and based on our preliminary results in DTI, we saw a direct involvement of the AF and FAT, whose role is essential for language but may also underlie arithmetic functions. Comparison between nTMS and DCS demonstrated an accuracy of approximately 69%,

and the high NPV and specificity are comparable to those of nTMS language mapping.

Complications

Six awake procedures were aborted due to intraoperative issues (i.e., fatigue, reduced compliance of patients, intraoperative seizure during DCS, and 1 case of a respiratory problem that led anesthesiologists to intubate the patient). We noticed that patients harboring frontal lesions needed more time to start interacting with the speech therapist and perform intraoperative tests, probably because of brain shift caused by the initial CSF release. Functional boundaries were respected, limiting the extent of resection, to avoid any neurological impairment.

Limitations

In this study, we included only 61 procedures of nTMS calculation mapping. A larger number of patients need to be included in future studies to validate our data. Six awake procedures in which calculation could be tested intraoperatively were aborted due to intraoperative issues.

The adopted strategy of the coordinates (x , y , z) for nTMS and DCS points in awake procedures was elaborated to overcome the limits of the parcellation system proposed by many eminent authors,^{7,8,22,41–43} since we did not use a grid on the cortical surface to map cortical areas. We normally rely on mapping the peritumoral area, based on anatomical data, using the “virtual lesion paradigm.”²⁷ The innovative implementation of statistical analyses allowed us to consider 3D nTMS points on the cortical surface. Further data are necessary to validate our preliminary results.

Conclusions

Our study represents a preliminary promising experience to implement the use of nTMS in the preoperative mapping of arithmetic cognitive functions. Navigated TMS mapping for calculation may impact the postoperative clinical outcome, leading to tractography creation and subcortical pathway visualization. Finally, nTMS might be predictive of safe points, guiding surgical strategy.

However, so far our results confirm the superiority of the gold standard DCS in identifying functional areas. Further analyses may be useful to enlarge our data and study other cognitive functions (e.g., visuospatial).

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Disclosures

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

Author Contributions

Conception and design: Bonaudo, Capelli, Enderage Don, Grippo, Della Puppa. Acquisition of data: Bonaudo, Pedone, Capelli, Gori, Baldanzi, Fedi, Troiano, Maiorelli, Masi, Martinelli, Capialbi, Enderage Don, Campagnaro, Amadori, Fainardi, Carrai, Grippo. Analysis and interpretation of data: Bonaudo, Pedone, Capelli, Fedi, Martinelli, Pieropan, Enderage Don, Della Puppa. Drafting the article: Bonaudo, Capelli, Fedi, Castaldi, Enderage Don, Fainardi. Critically revising the article: Bonaudo, Martinelli, Pieropan, Castaldi, Amadori, Fainardi, Grippo, Della Puppa. Reviewed submitted version of manuscript: Bonaudo, Castaldi, Battista, Campagnaro, Muscas, Amadori, Fainardi, Grippo, Della Puppa. Approved the final version of the manuscript on behalf of all authors: Bonaudo. Statistical analysis: Bonaudo, Capelli, Pieropan, Enderage Don. Administrative/technical/material support: Bonaudo, Baldanzi, Pieropan, Carrai. Study supervision: Bonaudo, Pieropan, Della Puppa.

Supplemental Information

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