ISSN 1220-8841 (Print)
ISSN 2344-4959 (Online)

ROMANIAN NEUROSURGERY

Vol. XXXV | No. 1 March 2021

Navigated transcranial magnetic stimulation mapping in patients with language-eloquent brain lesions

George E. D. Petrescu,
Roxana Radu,
Andrei Giovani,
Cristina Gorgan,
Felix M. Brehar,
Radu M. Gorgan

DOI: 10.33962/roneuro-2021-002

Romanian Neurosurgery (2021) XXXV (1): pp. 14-19
DOI: 10.33962/roneuro-2021-002
www.journals.lapub.co.uk/index.php/roneurosurgery

Navigated transcranial magnetic stimulation mapping in patients with language-eloquent brain lesions

George E. D. Petrescu[1,2], Roxana Radu[1,2], Andrei Giovani[1], Cristina Gorgan[3], Felix M. Brehar[1,4], Radu M. Gorgan[1,4]

[1] Neurosurgery Department, "Bagdasar-Arseni" Emergency Hospital, Bucharest, ROMANIA
[2] PhD student, "Carol Davila" University of Medicine and Pharmacy, ROMANIA
[3] Neurology Department, "Bagdasar-Arseni" Emergency Hospital, Bucharest, ROMANIA
[4] Neurosurgery Department, "Carol Davila" University of Medicine and Pharmacy, ROMANIA

ABSTRACT

Introduction: The surgical resection of brain lesions located in language-eloquent areas harbours a great risk for determining new functional deficits. Navigated transcranial magnetic stimulation represents a novel non-invasive cortical mapping method that can be used preoperative to determine language-eloquent areas.

Materials and methods: We retrospectively reviewed a prospectively maintained database of patients that underwent preoperative cortical mapping using nTMS between March 2017 and June 2020. Patients older than 18 years old with brain lesions situated in a presumed language eloquent area, that underwent surgical resection of the brain lesion were included in the study. Various parameters such as error rate, number of language-negative sites were assessed.

Results: Fourteen patients were included in the study. There were 10 males and 4 females in total. Most of the tumours were in the temporal and frontal lobes (five and four cases, respectively). The histopathological diagnosis was glioblastoma in seven cases, in one case there was an anaplastic astrocytoma and there were two cases of low-grade gliomas. There were three cases of brain metastasis and one cavernoma. The median (range) tumor volume was 25.01 cm3 (0.89 – 86.55 cm3). Gross-total resection (GTR) was achieved in seven cases. The error rate was significantly higher in patients that continued to have an impaired language function after surgical resection ($p = 0.016$), while the perilesional error rate was higher in patients with preoperative aphasia ($p = 0.019$).

Conclusion: Our findings suggest that a lower tumour volume to perilesional negative stimuli ratio is associated with an extended surgical resection of brain tumours located in language-eloquent areas and that patients that presented with aphasia and have a high error rate have a worse functional prognosis. Through nTMS preoperative cortical mapping of language-eloquent areas, the neurosurgeon has more insight regarding the cortical function and can maximize the surgical resection, while avoiding the onset of new functional deficits.

Keywords
navigated transcranial magnetic stimulation, language areas cortical mapping, brain tumours

Corresponding author:
George E. D. Petrescu

"Carol Davila" University of Medicine and Pharmacy, Romania

gedpetrescu@gmail.com

ISSN online 2344-4959
© Romanian Society of Neurosurgery

First published March 2021 by London Academic Publishing www.lapub.co.uk

INTRODUCTION

The surgical resection of brain lesions located in language-eloquent areas harbors a great risk for determining new functional deficits. Since a complex network is involved in speech and language processing, and there is a high individual variability regarding the cortical representation of language areas, cortical mapping of eloquent areas should be performed in order to decrease this risk (1). Moreover, brain tumors can disrupt and reorganize the normal functional areas (2, 3). The "gold-standard" method for the mapping of language areas is direct cortical stimulation (DCS) under awake surgery (4). However, not all patients can tolerate or have contraindications for an awake craniotomy (5). Navigated transcranial magnetic stimulation (nTMS) represents a preoperative, non-invasive method used for cortical mapping of motor and language eloquent areas (6, 7). By using navigated repetitive TMS (nrTMS) pulses, language areas can be mapped in patients with brain tumors, as well as in healthy individuals, without adverse events (3).

In this study we present our experience with nTMS cortical mapping for language-eloquent brain lesions.

MATERIALS AND METHODS

Patient cohort

We retrospectively reviewed a prospectively maintained database of patients that underwent preoperative cortical mapping using nTMS between March 2017 and June 2020. The inclusion criteria were: (1) patients with brain lesions situated in a presumed language eloquent area; (2) patients that underwent surgical resection of the brain lesion; (3) age > 18 years old. Patients that had nTMS contraindications (e.g.: frequent generalized epileptic seizures, cranial implants) or did not undergo surgical resection or underwent only a stereotactic biopsy procedure were excluded from the study.

nTMS language mapping

Cortical mapping was performed by using the Nexstim Navigated Brain Stimulation System 5 (Nexstim Oy, Helsinki, Finland) according to the established protocol (8), as previously described (9). Briefly, the brain MRI and the patients' head were co-registered, and a motor mapping was performed to determine the resting motor threshold (RMT). Afterwards, using the NexSpeech Software (Nexstim Oy, Helsinki, Finland) the patients performed a baseline object-naming task without TMS stimuli, in order to evaluate each patients' vocabulary and misidentified pictures were removed. The baseline procedure was repeated twice. The remaining pictures were used for the object-naming task performed with nrTMS pulses. The following parameters were used for the language mapping: picture display time (PDT): 700 ms, interpicture interval (IPI): 2500 ms and picture-to-trigger (PTT) interval: 0 ms. The navigated repetitive TMS (nrTMS) pulses were applied in bursts of 5 pulses with 5 Hz frequency, with an intensity of 100% of the RMT. Individual adjustments were performed, when needed, based on the preexisting neurological deficits. Every site was stimulated three times. The results were analyzed blinded to the location of the TMS stimuli and compared with the baseline. The language errors were defined in the following categories: no response, performance error, semantic error and other. Errors due to muscle stimulation were discarded.

Surgical planning

The brain MRI scans with the annotated language errors were included in the intraoperative neuronavigation system (SonoWand Invite - SonoWand AS, Trondheim, Norway, or Medtronic Stealth S8 – Medtronic, Minneapolis, USA). The surgical planning took into account the results from the brain mapping, in order to select the optimal entry point and trajectory, with the goal of avoiding postoperative neurological deficits and maximizing the surgical resection.

Brain lesion evaluation

The brain MRI used for the mapping procedure was used the calculate to volume of the brain lesion with the aid of the 3D Slicer 4.10.0 Software (10, 11). Based on the histopathological diagnosis, the tumors were classified in two categories: (1) tumors with slow growth rate (low grade gliomas) and tumors with fast growth rate (high grade gliomas, metastases).

Language mapping analysis

In order to better evaluate the language function and the mapping results, a series of variables were assessed: number of language errors, number of no-response errors, number of language-negative sites, error rate (ER) = language errors/total stimuli * 100, perilesional error rate (PER) = perilesional language errors/perilesional stimuli * 100. The tumor volume to language-negative sites ratio was calculated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics, version 25 (IBM Corp., Armonk, N.Y., USA). The t-test was used for continuous variables with parametric distribution and the Mann-Whitney U test for the non-parametric ones. $p < 0.05$ was considered statistically significant.

Results

Patient cohort

Fourteen patients met the inclusion criteria with a mean (SD) age of 51.5 (13.9) years. There were 10 males and 4 females in total. All patients were right-handed, with the left hemisphere being considered the dominant one. Most of the tumors were located in the temporal and frontal lobes (five and four cases, respectively). Two tumors were in the fronto-temporal lobes and one in each of the following: parietal lobe, fronto-parietal and temporo-parietal. The histopathological diagnosis was glioblastoma in seven cases, in one case there was an anaplastic astrocytoma and there were two cases of low-grade gliomas. There were three cases of brain metastasis and one cavernoma. According to the growth rate classification, there were 11 fast-growing tumors and 2 slow-growing tumors (the cavernoma case was excluded from this classification). Gross-total resection (GTR) was achieved in seven cases, while in the others a subtotal resection (STR) was performed. The median (range) tumor volume was 25.01 cm3 (0.89 – 86.55 cm3). Cohort characteristics are summarized in Table 1.

Table 1. Cohort characteristics

	No.
Age – mean (SD)	51.5 (13.9)
Tumor location	
Temporal	5
Frontal	4
Fronto-temporal	2
Fronto-parietal	1
Parietal	1
Temporo-parietal	1
Histopathology	
High-grade glioma	8
Metastasis	3
Low-grade glioma	2
Cavernoma	1
Extent of resection	
GTR	7
STR	7

Table 1 summarizes the characteristics of the patient cohort. GTR = gross-total resection; STR = subtotal resection.

Language function analysis and cortical mapping results

Preoperatively, seven patients presented with aphasia. Short-term following the surgical resection, there was an improvement of function in four cases. None of the patients had new language functional deficits following surgery. No adverse events were encountered during the preoperative mapping procedure. Figure 1 illustrates the results of a language mapping procedure using nTMS.

The error rate was significantly higher in patients that continued to have an impaired language function after surgical resection ($p = 0.016$), while the perilesional error rate was higher in patients with preoperative aphasia ($p = 0.019$). Although, the perilesional error rate was increased in tumors with fast-growing rate compared to those with slow-growing rate, the result was not statistically significant ($p = 0.058$). The results of the language mapping analysis are depicted in Table 2 and Table 3.

Regarding the extent of resection, a lower ratio between tumor volume and number of perilesional negative stimuli (cm3/stimuli) was associated with an extended resection ($p = 0.004$).

Table 2. Patient characteristics and language mapping results

Pt. No.	Age	Sex	Tumor Location	Pathology	Preoperative aphasia	ER	Perilesional ER	EOR
1	65	Ma	TP	GBM	Yes	12%	25%	GTR
2	18	Ma	F	Cav.	No	8%	17%	GTR
3	70	Fe	P	Met.	No	8%	16%	GTR
4	62	Ma	T	GBM	Yes	8%	21%	STR

5	46	Ma	FP	GBM	No	13%	19%	GTR
6	54	Ma	F	GBM	Yes	26%	33%	STR
7	61	Fe	T	GBM	Yes	6%	16%	STR
8	59	Ma	T	Met.	Yes	17%	22%	GTR
9	43	Ma	T	LGG	No	4%	8%	STR
10	59	Ma	T	AA	No	9%	14%	GTR
11	32	Fe	FT	LGG	No	13%	12%	STR
12	45	Ma	F	Met.	No	8%	22%	GTR
13	58	Ma	FT	GBM	Yes	16%	22%	STR
14	49	Fe	F	GBM	Yes	37%	42%	STR

Table 2 presents the patients' characteristics and results of language mapping analysis. AA = anaplastic astrocytoma; Cav. = cavernoma; EOR = extent of resection; ER = error rate; F = frontal; Fe= female; FP = fronto-parietal; FT = fronto-temporal; GBM = glioblastoma; LGG = low-grade glioma; Ma = male; Met. = metastasis; P = parietal; T = temporal; TP = temporo-parietal.

Table 3. Language mapping analysis

	mean (SD) / median (range)	p value
Persistent aphasia	**Error rate**	
Yes	23.39% (11.82)	0.016
No	10.55% (5.92)	
Preoperative aphasia Yes No	**Perilesional error rate** 25.72% (8.63) 15.40% (4.64)	0.019
Tumor type (n = 13) Fast growth rate Slow growth rate	**Perilesional error rate** 22.75% (8.12) 10.10% (2.68)	0.058
Extent of resection GTR STR	**Vol/ Perilesional Neg. Stim.** 0.97 (0.22-5.28) 10.10 (2.39-28.85)	0.004

Table 3 depicts the results of the language mapping analysis. GTR = gross-total resection; STR = subtotal resection; Vol/ Perilesional Neg. Stim. = ratio between tumor volume and number of perilesional negative stimuli (cm3/stimuli).

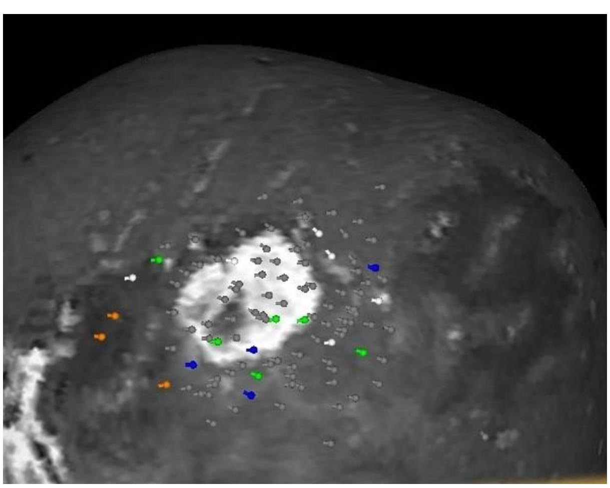

Figure 1 illustrates the results of the nTMS language mapping in a patient with a left temporal glioblastoma. white dots – no response error, blue dots – semantic error, green dots – performance error, orange dots – muscle stimulation, gray dots – negative stimuli. Color figure available only online.

Discussion

Numerous objections have been addressed to the classical localizationist theory of speech and language processing, that relies on modular, static structures (such as Broca's and Wernicke's areas) and instead a dynamic model consisting of networks between cortical and subcortical structures has been proposed (12-14). This concept supports the idea that brain has the ability to reorganize following brain injury, if the connection between axons is spared (13).

Although DCS remains the current "gold-standard" for language mapping, nrTMS can aid the surgeon in the preoperative surgical planning and has similar results to DCS regarding language-negative sites (5, 15-17). In our study, although the GTR group had a higher number of negative stimuli than the STR group, the difference was not statistically significant ($p = 0.21$). Therefore, we took into account the tumor volume and the negative stimuli that were situated perilesional. The tumor volume to perilesional negative stimuli ratio (cm3/ stimuli) was significantly lower in the GTR group, meaning that a higher number of negative stimuli were attributed per tumor volume, and thus creating a clearer and more reliable map of the language-negative areas, which consequently lead to a greater extent of resection. Even though nTMS is not as reliable as DCS, compared to functional MRI (fMRI) it has a greater sensitivity, but it is less specific (15, 16, 18). One of the advantages of nTMS over fMRI in language mapping is represented by the fact that fMRI relies on task-induced metabolic changes and it well known that brain tumors, and especially high-grade gliomas, have the tendency to alter the local metabolic activity and vasculature (15, 19, 20).

In our cohort, even though there was no statistically significant difference, the error rate and the perilesional error rate were higher in patients with fast-growing brain tumors. The lack of significance might be due to the fact, that in our study there were few patients with lesions with slow growth rate. In their study, Schwarzer et al. had an increased ER in fast-growing lesions but, again, there was no statistically significant difference (1). However, the authors found a statistically significant difference regarding the baseline error rate between patients with lesions with fast growth rate and patients with vascular malformations (1). This could be explained through the plasticity of the brain, in reaction to the displacement caused by the brain lesion (2). Nevertheless, contradictory data regarding which lesion type (slow or fast-growing) induces an extensive reorganization exist (1, 21).

The perilesional error rate was significantly higher in patients that presented with aphasia (25.72% vs. 15.40%, $p = 0.019$) and the ER was increased in patients that had mild or no improvement of aphasia following surgery (23.39% vs. 10.55%, $p = 0.016$). Schwarzer et al. also reported an increased error rate in patients with severe aphasia and altered cognition and proposed a baseline error rate lower than 28% as more probable to correctly determine the true language-positive sites (1).

The current study is limited by a relatively small cohort size and the histological heterogeneity of the lesions included in the study.

Conclusions

Our findings suggest that a lower tumor volume to perilesional negative stimuli ratio is associated with an extended surgical resection of brain tumors located in language-eloquent areas and that patients that presented with aphasia and have a high error rate have a worse functional prognosis. Through nTMS preoperative cortical mapping of language-eloquent areas the neurosurgeon has more insight regarding the cortical function and is able to maximize the surgical resection, while avoiding the onset of new functional deficits.

Conflicts of Interest

The authors declare no potential conflict of interest.

References

1. Schwarzer V, Bährend I, Rosenstock T, Dreyer FR, Vajkoczy P, Picht T. Aphasia and cognitive impairment decrease the reliability of rnTMS language mapping. Acta Neurochirurgica. 2018;160(2):343-56.
2. Kosla K, Pfajfer L, Bryszewski B, Jaskolski D, Stefanczyk L, Majos A. Functional rearrangement of language areas in patients with tumors of the central nervous system using functional magnetic resonance imaging. Pol J Radiol. 2012;77(3):39-45.
3. Rösler J, Niraula B, Strack V, Zdunczyk A, Schilt S, Savolainen P, et al. Language mapping in healthy volunteers and brain tumor patients with a novel navigated TMS system: Evidence of tumor-induced plasticity. Clinical Neurophysiology. 2014;125(3):526-36.
4. Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, Van Effenterre R, et al. Contribution of intraoperative electrical stimulations in surgery of low-grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(6):845.
5. Picht T, Krieg SM, Sollmann N, Rosler J, Niraula B, Neuvonen T, et al. A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery. 2013;72(5):808-19.
6. Picht T. Current and potential utility of transcranial magnetic stimulation in the diagnostics before brain tumor surgery. CNS Oncology. 2014;3(4):299-310.
7. Lefaucheur J-P, Picht T. The value of preoperative functional cortical mapping using navigated TMS. Neurophysiologie Clinique/Clinical Neurophysiology. 2016;46(2):125-33.
8. Krieg SM, Lioumis P, Makela JP, Wilenius J, Karhu J, Hannula H, et al. Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. Acta Neurochir (Wien). 2017;159(7):1187-95.
9. Petrescu G, Gorgan C, Giovani A, Brehar FM, Gorgan RM. Preoperative mapping of the eloquent cortical areas using navigated transcranial magnetic stimulation combined with intraoperative neuronavigation for intracerebral lesions. Romanian Neurosurgery. 2018;32(1):16-24.
10. 3D Slicer [Available from: https://www.slicer.org/].
11. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magnetic Resonance Imaging. 2012;30(9):1323-41.
12. De Benedictis A, Duffau H. Brain Hodotopy: From Esoteric Concept to Practical Surgical Applications. Neurosurgery. 2011;68(6):1703-23.

13. Duffau H. The error of Broca: From the traditional localizationist concept to a connectomal anatomy of human brain. Journal of Chemical Neuroanatomy. 2018;89:73-81.
14. 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 and Language. 2014;131:1-10.
15. Sebastian I, Nico S, Theresa H, Stefanie M, Noriko T, Thomas O, et al. Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study. Journal of Neurosurgery JNS. 2015;123(2):314-24.
16. Jeltema H-R, Ohlerth A-K, de Wit A, Wagemakers M, Rofes A, Bastiaanse R, et al. Comparing navigated transcranial magnetic stimulation mapping and "gold standard" direct cortical stimulation mapping in neurosurgery: a systematic review. Neurosurgical Review. 2020.
17. Motomura K, Takeuchi H, Nojima I, Aoki K, Chalise L, Iijima K, et al. Navigated repetitive transcranial magnetic stimulation as preoperative assessment in patients with brain tumors. Scientific Reports. 2020;10(1):9044.
18. Babajani-Feremi A, Narayana S, Rezaie R, Choudhri AF, Fulton SP, Boop FA, et al. Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation. Clinical Neurophysiology. 2016;127(3):1822-36.
19. Holodny AI, Schulder M, Liu W-C, Wolko J, Maldjian JA, Kalnin AJ. The Effect of Brain Tumors on BOLD Functional MR Imaging Activation in the Adjacent Motor Cortex: Implications for Image-guided Neurosurgery. American Journal of Neuroradiology. 2000;21(8):1415.
20. Ulmer JL, Krouwer HG, Mueller WM, Ugurel MS, Kocak M, Mark LP. Pseudo-Reorganization of Language Cortical Function at fMR Imaging: A Consequence of Tumor-Induced Neurovascular Uncoupling. American Journal of Neuroradiology. 2003;24(2):213.
21. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain. 2007;130(4):898-914.