

Heads-Up Micronavigation Reliability of Preoperative Transcranial Magnetic Stimulation Maps for the Motor Function: Comparison With Direct Cortical Stimulation

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BACKGROUND AND OBJECTIVES: We aimed to assess the reliability of preoperative navigated transcranial magnetic stimulation (nTMS) maps for motor function as visualized intraoperatively with augmented reality heads-up display and to assess its accuracy via direct point-by-point comparison with the gold-standard direct cortical stimulation (DCS).

METHODS: From January 2022 to January 2023, candidates for surgical removal of lesions involving the motor pathways underwent preoperative nTMS assessment to obtain cortical maps of motor function. Intraoperatively and before tumor removal, nTMS maps were superimposed on the cortical surface, and DCS was performed on positive points with increasing current intensity until obtaining a positive response at 16 mA. The outcome of each stimulation was recorded to obtain discrimination metrics.

RESULTS: Twelve patients were enrolled (5 females [42%] vs 7 males [58%], mean age 62.9 ± 12.8 years), for a total of 304 investigated points. Agreement between nTMS and DCS was moderate ($\kappa = 0.43$, $P < .005$), with 0.66 (0.53-0.78) sensitivity, 0.87 (0.82-0.90) specificity, 0.50 (0.39-0.62) positive predictive values, 0.93 (0.89-0.95) negative predictive value, and 0.83 (0.79-0.87) accuracy. A loss of accuracy was observed with higher DCS current intensities.

CONCLUSION: We performed a point-by-point validation of preoperative nTMS maps for motor function using augmented reality visualization. The high negative predictive value and low positive predictive values highlight nTMS reliability to visualize safe cortical zones but not to identify critical functional areas, confirming previous findings of nTMS maps for the language function and suggesting the need for combined use of nTMS maps and DCS for optimal maximal safe resection.

KEY WORDS: Motor area, Neuronavigation, Operative microscope, Transcranial magnetic stimulation, Direct cortical stimulation

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Morbidity rates for lesions at risk for postoperative neurological deficit have been reduced in recent years because of the development of strategies for localizing and preserving essential areas for the execution of neurological functions. To limit postoperative neurological sequelae when

approaching lesions located near highly functional brain areas ("eloquent" locations), an exact knowledge of the extension of such cortical areas is essential.¹ Intraoperative direct cortical stimulation (DCS) is the gold standard for cortical mapping.¹⁻³ Still, preoperative knowledge is required to optimally plan surgical strategies and tactics, and prevent suboptimal prognoses from unsatisfactory tumor removal. Radiological depiction of functional areas via diffusion tensor imaging tractography and functional MRI (fMRI) can help. However, drawbacks concerning these techniques' accuracy and resolution limit their full reliability.^{4,5}

ABBREVIATIONS: DCS, direct cortical stimulation; FN, false negatives; FP, false positives; NPV, negative predictive value; nTMS, navigated transcranial magnetic stimulation; PPV, positive predictive values; RMT, resting motor threshold; TMS+, TMS-positive points; TMS-, TMS-negative points; TN, true negatives; TP, true positives.

A growing body of literature has explored using preoperative navigated transcranial magnetic stimulation (nTMS) for this purpose.⁶⁻¹³ Improvements in risk assessment, extent of resection, and neurological outcomes have been observed using nTMS¹³ both for motor function and language.

Despite these benefits, cortical mapping with nTMS is still undergoing investigation. In previous years, validations of preoperative mapping with nTMS via comparison with intraoperative DCS findings have been performed.^{6,7} Although for language function, a direct comparison of the 2 techniques offered metrics of discrimination to assess the actual reliability of nTMS, investigations on motor function were based on measuring postoperatively the distance between the positive sites found with both techniques² by projecting the positive responses on anatomic brain templates or using dedicated software programs.^{7,14} These indirect comparisons could bear drawbacks, hindering their straightforward applications in every clinical setting.

A direct intraoperative point-by-point comparison of the 2 techniques could offer direct feedback on the utility of nTMS maps, and metrics of discriminations have been scarce so far when investigating the reliability of nTMS mapping for motor function. To achieve this, we used a recently introduced augmented reality tool incorporated in the operative microscope (heads-up display or micronavigation).¹⁵ This technical adjunct has been previously used in other subspecialties and has recently proved helpful in neurosurgery.

This work aims to assess the reliability of a direct intraoperative comparison confronting nTMS maps with direct cortical stimulation using microscope-integrated heads-up neuronavigation.

METHODS

The study was approved by the local ethical committee of our institution (CEAVC 17003/oss). All patients signed a general informed consent and consented the publication of their images. We retrospectively consulted our prospectively collected database of patients harboring intrinsic Rolandic brain lesions and undergoing preoperative nTMS mapping from January 2022 to January 2023. On admission, patients performed brain MRI on a 3-T MRI scanner (Ingenia, Philips Healthcare), including pre- and post-contrast sagittal magnetization-prepared rapid acquisition gradient-echo 3-dimensional (3D) T1-weighted imaging and 3D fluid-attenuated inversion recovery, followed by multiplanar reconstruction in axial, coronal, and sagittal planes, axial T2-weighted turbo spin-echo, axial gradient-echo T2* fast-field echo, and axial diffusion-weighted imaging. Before the examination, subjects received dexamethasone 12 mg/24 hours for 3–5 days. These images were uploaded in Digital Imaging and Communication in Medicine format on the nTMS device and used to construct 3D models using the software (3D Slicer, <https://www.slicer.org/>) associated with the nTMS stimulator (EB Neuro S.p.A.).

nTMS Mapping Protocol

TMS investigations were performed using NetBrain Neuronavigator 9000 (EBNeuro SpA). The mapping was performed the day before

surgery. Motor-evoked potentials (MEPs) were studied using electromyography on the orbicularis oris, biceps brachii/common extensor digitorum, first dorsal interosseus, and anterior tibialis muscles. A butterfly (or figure of 8) coil, consisting of 2 side-by-side ring coils, was used for stimulation. The currents generated reach their greatest intensity at the point where the projections meet the rings (hotspots), thus obtaining a stimulation focused under the center, allowing for maximum precision to be achieved.¹⁶

To allow navigation, a band was applied to the patient's head on which 4 reflective spheres were visible from the navigator's infrared camera and were also present on the coil. The system works like intraoperative neuronavigation: by detecting the spheres, the system calculates the position and orientation of the instruments and shows them on a 3D brain model built with MR images. We then calibrated the navigator by searching for reference points (nasion, inion, preauricular points, and the vertex) on the patient's head and started the search for the stimulation threshold. The best precision was obtained by stimulating at an intensity slightly higher than the resting motor threshold (RMT), ie, the lowest intensity of the stimulus for which TMS can evoke an MEP of at least 50 μ V in a relaxed hand muscle in at least 5 stimulations out of 10.¹⁷ The stimulus intensity equal to 105% of the RMT was set for the actual mapping: we stimulated along the precentral gyrus and the adjacent gyri, maintaining the inclination of the electric field perpendicular to the central sulcus. The stimulations were performed at 2-second intervals and a distance of 2–5 mm, intensifying the density in critical areas. For mapping the facial motor area, we moved about halfway between the hand knob and the lateral Sylvian fissure, extending the stimulation zone anteriorly and posteriorly to the precentral gyrus, accounting for the extension of the facial motor area.¹⁸ Particular attention was paid to the MEP latency: direct stimulation of the facial nerve is frequent because of the anatomic proximity, which results in MEPs with a latency of less than 11 $\pm$ 4 ms.¹⁸ For lower-limb mapping, the stimulation intensity was set at 110% of the threshold (RMT): this was made to account for deep localization in the interhemispheric fissure of the lower-limb cortical representation, where a more intense magnetic field is required to evoke MEP.^{19,20} The search of the lower limb was performed by stimulating the area near the confluence between the interhemispheric fissure and the central sulcus. The points with MEP $\geq$ 50 μ V in one or more monitored muscles were considered positive for nTMS. These points were used to create maps through color coding, with points corresponding to the same muscle being marked with the same color (Figure 1).

The negative points (MEP < 50 μ V or with latency not included between 15 and 30 ms) were not exported. The TMS positivity maps were then coregistered on contrast-enhanced T1-weighted MRI sequences and exported as Digital Imaging and Communication in Medicine files.

Intraoperative Neuronavigation and DCS Comparison

The TMS maps were coregistered with other anatomic sequences useful for surgical purposes directly on the neuronavigation system (Stealth Station 8, Medtronic) via the script incorporated into the device (Figures 2 and 3). Once the patient was under general anesthesia, fixed on a Mayfield head clamp, the neuronavigation was calibrated using the patient's external anatomic landmarks. Subdermal needle electrodes were placed over the target muscles for intraoperative monitoring and DCS.

After the dural opening, nTMS maps were projected on the cortical surface using the heads-up display navigation tools integrated into the operative microscope (Kinevo 900, Carl Zeiss AG) (Figure 3).

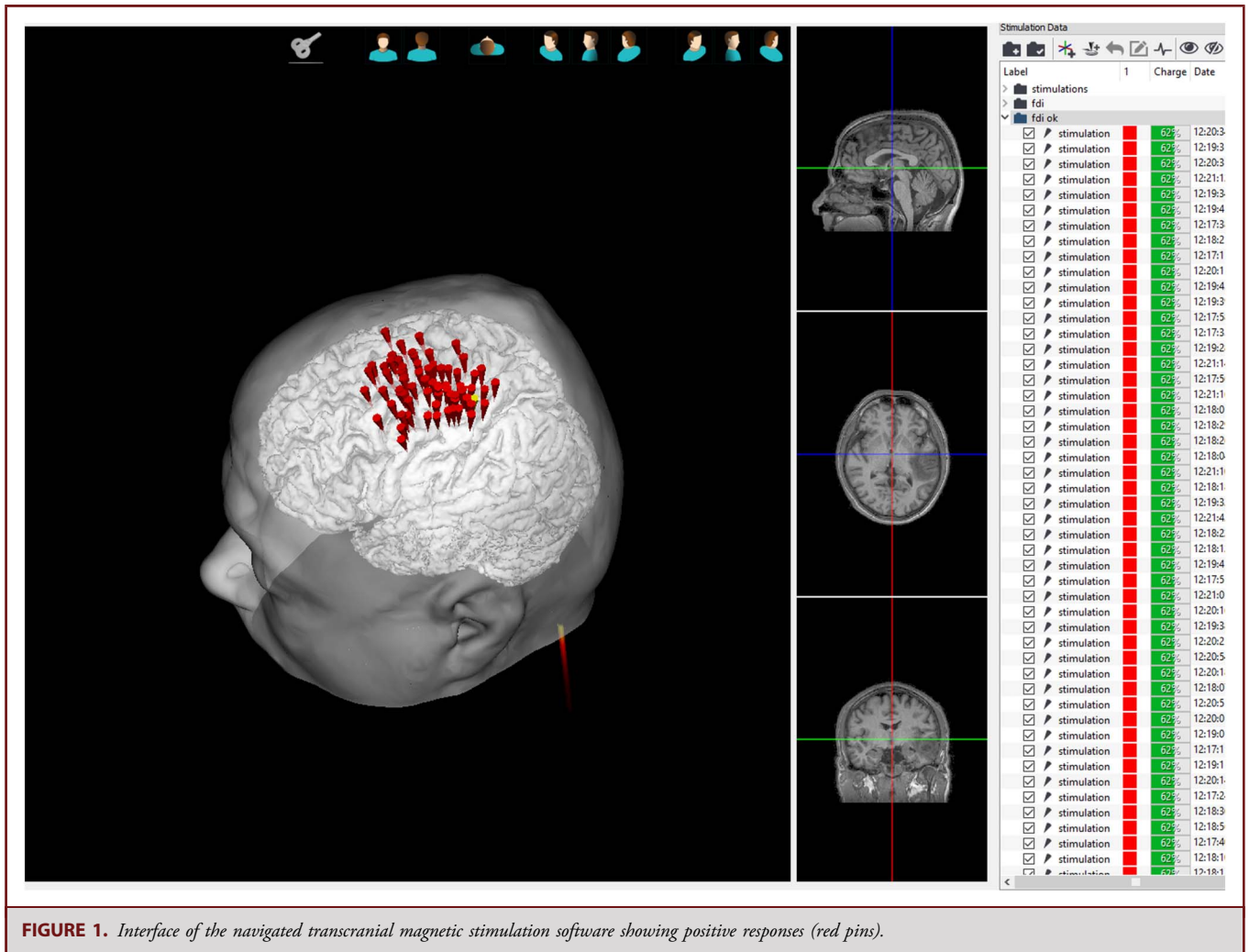


FIGURE 1. Interface of the navigated transcranial magnetic stimulation software showing positive responses (red pins).

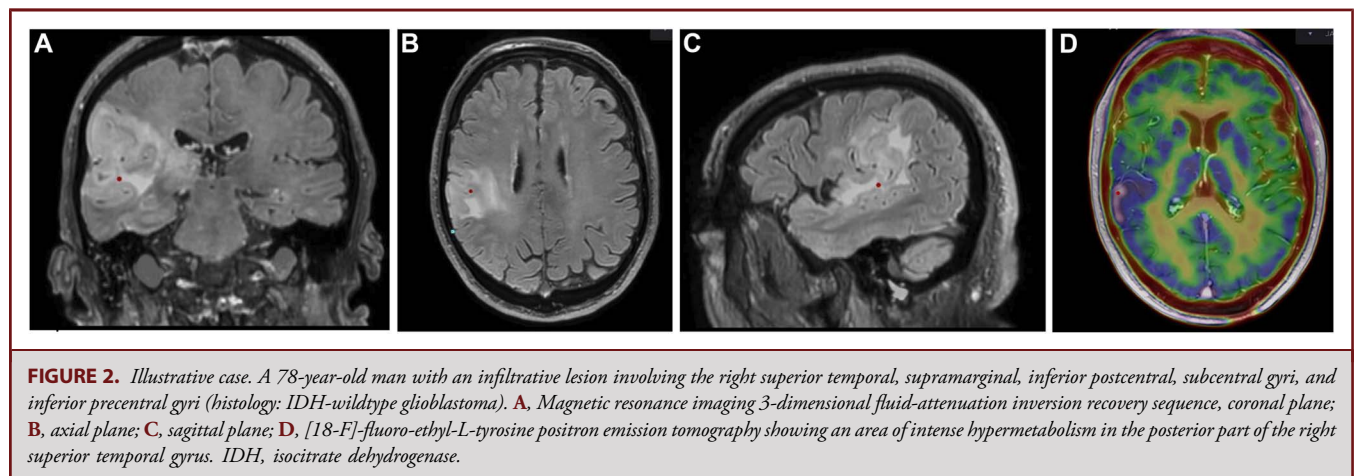


FIGURE 2. Illustrative case. A 78-year-old man with an infiltrative lesion involving the right superior temporal, supramarginal, inferior postcentral, subcentral gyri, and inferior precentral gyri (histology: IDH-wildtype glioblastoma). **A**, Magnetic resonance imaging 3-dimensional fluid-attenuation inversion recovery sequence, coronal plane; **B**, axial plane; **C**, sagittal plane; **D**, [18-F]-fluoro-ethyl-L-tyrosine positron emission tomography showing an area of intense hypermetabolism in the posterior part of the right superior temporal gyrus. IDH, isocitrate dehydrogenase.



FIGURE 3. Intraoperative visualization of nTMS maps provided for the patient presented in Figure 2. On the left: 3-dimensional reconstruction of the brain and nTMS maps: blue points represent positive spots for calculus errors, yellow spots are positive responses for the face muscles, and red spots are positive responses for the upper limb muscles; on the right: augmented reality visualization through the microscope oculars: nTMS positive points are superimposed on the cortical surface. After testing each point with direct cortical stimulation, true-positive responses were marked with numbered labels (white asterisks), and false-negative responses were marked with tags depicting the responding muscle. On the top right is the picture-in-picture view of the standard navigation interface. The navigation probe's point corresponds to the microscope's focal point. nTMS, navigated transcranial magnetic stimulation.

If the positive TMS points were found to overlap (distance <3 mm), they were unified into a single stimulation point. Direct stimulation of these points (TMS+) and the areas of the cortex free from points (TMS-) was then performed.

A monopolar stimulator with a train of 5 stimuli at 0.5–1 Hz and an interstimulus interval of 2–4 ms was used for stimulation. The stimulation took place at increasing current intensity starting from 4 to 5 mA, and, for each stimulated point, the negativity and positivity of the response and possibly the threshold were recorded. A point was considered definitively negative if no responses were obtained at a stimulation intensity of 16 mA. The outcome of each stimulation was recorded for each patient.

Statistical Analysis

TMS and DCS mapping agreements were assessed with Cohen's kappa (κ). Considering DCS as the reference, the results of the stimulation on TMS+ and TMS- points were then labeled as true positives, false positives (FP), true negatives, and false negatives (FN), and discrimination metrics such as sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV), and accuracy with 95% CIs were calculated. Additionally, we tested whether a DCS intensity increase could decrease precision: stimuli of higher intensity could theoretically elicit a response in an increasingly large surrounding area, and applying a stimulus could stimulate nearby points, leading to an incorrect classification of the points. Accordingly, we expected an increase in false-negative results and a decrease in false-positive results related to increasing DCS stimulation intensity. To normalize the data for a better comparison, we calculated the ratio between FN and FP for each stimulation intensity. According to our hypothesis, this FN/FP ratio should grow proportionally with the stimulation intensity, indicating a decrease in the accuracy of the test for higher DCS stimulation values. We then calculated the Pearson correlation coefficient (r) between the average FN/FP ratios and the stimulation intensities to verify this hypothesis, with a threshold for statistical significance of $P = .05$. Statistics were performed with SPSS Statistics 23 (IBM Corp.).

RESULTS

During the period considered, 12 patients underwent surgical treatment for intra-axial lesions at our facility, with a mean age of 62.9 ± 12.8 years (5 females [42%] vs 7 males [58%]) (Table 1).

The minimum DCS stimulation value was 2 mA and the maximum 16 mA. DCS tested 79 TMS-positive (TMS+) and 275 TMS-negative (TMS-) points. Among the TMS+ points, 40 were positive also on DCS (true positives): of these, 0 proved positive at 2-mA stimulation intensity on DCS, 2 at 4 mA, 0 at 5 mA, 8 at 6 mA, 7 at 8 mA, 13 at 10 mA, 3 at 12 mA, 4 at 14 mA, and 3 at 16 mA. In addition, 274 points that were negative on TMS were stimulated by DCS. Of these, 20 were positive for DCS (FN), 1 at 6 mA, 6 at 8 mA, 3 at 10 mA, 2 at 12 mA, 5 at 14 mA, and 1 at 16 mA, while 254 negative points at TMS were also negative for DCS (true negatives). Table 2 summarizes the results sorted by stimulation intensity.

The agreement between TMS and DCS was moderate ($\kappa = 0.43$, $P < .005$), with 0.66 (0.53–0.78) sensitivity, 0.87 (0.82–0.90) specificity, 0.50 (0.39–0.62) PPV, 0.93 (0.89–0.95) NPV, and 0.83 (0.79–0.87) accuracy (see Table 3). After assessing the requirements of relationship linearity, absence of outliers, and normality distribution, the Pearson's correlation between the averaged FN/FP ratio and the stimulation intensities showed a strong positive correlation ($r = 0.86$, $P < .001$), indicating a loss of accuracy of the results with increasing stimulation intensity.

DISCUSSION

In this work, we aimed to validate nTMS maps for motor function by a direct point-by-point intraoperative DCS comparison

TABLE 1. Summary of the Patients Included

Patient	Age, years	Sex	Diagnosis	TMS+ points	TP	TN	FP	FN
1	67	Female	Glioblastoma	8	3	13	5	4
2	33	Male	Diffuse astrocytoma	5	0	17	5	0
3	60	Female	Metastasis (ovarian cancer)	4	4	4	0	0
4	80	Male	Glioblastoma	6	4	22	2	1
5	68	Female	Glioblastoma	6	5	29	1	2
6	71	Male	Metastasis (lung cancer)	11	7	10	4	1
7	66	Male	Metastasis (lung cancer)	7	2	19	5	1
8	69	Female	Diffuse astrocytoma	7	6	14	1	1
9	56	Female	Glioblastoma	5	1	12	4	2
10	53	Male	Glioblastoma	6	4	18	2	1
11	54	Male	Glioblastoma	3	3	36	0	4
12	78	Male	Glioblastoma	11	1	60	10	3

FN, false negatives; FP, false positives; TMS+, transcranial magnetic stimulation positive points; TN, true negatives; TP, true positives.

using a superimposition of TMS maps on the exposed cortical surface. This was achieved with augmented reality integration of navigation tools in the operative microscope interface (the so-called “micronavigation” or heads-up display devices).¹⁵ Although previous attempts of nTMS validation were explicitly performed for motor function by measuring the distance between positive spots observed both on DCS and nTMS² or by confirming the correct identification of the motor strip,¹¹ an intraoperative point-by-point validation was not previously provided for motor function. In fact, previous studies analyzed only the mean distance between DCS and nTMS hotspots (3.4–10 mm), the spatial resolution of nTMS, and the ability to correctly identifying the motor strip and muscles groups.² This allowed us to obtain discrimination metrics previously provided for nTMS language maps but were scarce for motor function. In fact, to the best of our knowledge, only 2 studies provided full discrimination metrics for motor function, with sensitivity: 93%–100%, specificity: 80%–100%, PPV: 66.6%–100%, and NPV: 89.6%–100%.^{2,21,22} Interestingly, our results were similar to previously presented works on language function,

where a larger amount of data concerning discrimination metrics are present, with high NPV and relatively low PPV.²

Also, a more intuitive, direct, and intraoperative validation of nTMS maps seems to be of higher benefit from an operative point of view compared with previous methods using postoperative distance measures, and a direct confirmation of relevant cortical area extension could help modify surgical approaches intraoperatively.

In addition, we observed a loss of accuracy associated with increasing DCS intensity characterized by higher false-negative and lower-false positive results of nTMS maps. Still, despite being relevant, this does not seem to substantially alter the potential role of nTMS in general, as the added value of nTMS appears to rely on its good performances in correctly excluding areas of positive response (NPV: 0.93 [0.89–0.95]), as also elucidated in previous works.² This seems to stress the ancillary role of nTMS in relation to DCS, as the former could help plan the surgical approach and to identify the cortical regions that need to be tested with DCS by displaying safe cortical zones that can be accessed. This feature cannot be routinely replaced by other preoperative mapping tools

TABLE 2. Results Sorted According to Stimulation Intensity Applied on DCS

	2 mA		4 mA		5 mA		6 mA		8 mA		10 mA		12 mA		14 mA		16 mA	
DCS	+	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–
TMS+	0	2	2	21	0	21	8	47	7	44	13	33	3	20	4	16	3	5
TMS–	0	8	0	9	0	0	3	31	6	15	3	11	2	0	5	0	1	0

DCS, direct cortical stimulation; TMS+, transcranial magnetic stimulation positive points; TMS–, transcranial magnetic stimulation negative points.

TABLE 3. Confusion Matrix Depicting the TMS (Expected) vs DCS Results (Observed)

		DCS		Total
		+	–	
TMS	+	40	45	85
	–	18	201	219
Total		58	246	304

DCS, direct cortical stimulation; TMS, transcranial magnetic stimulation.

such as fMRI: despite providing information on the localization of networks pertaining to neurological functions, fMRI is associated with false-negative rates, specifically in neuro-oncologic patients, thus potentially leading to inadvertent removal of functionally relevant brain tissue when relying on the information provided by this tool.⁴ Other tools such as diffusion tensor imaging tractography and the recently introduced Quicktome²³ are limited to subcortical anatomy depiction, and despite offering important information and their constantly improving precision, are associated with technical drawbacks that limit their complete reliability.^{4,5}

This puts nTMS ahead when dealing with patients for whom awake surgery is impossible or contraindicated (for instance, older, noncompliant patients, large lesions requiring extended surgical times, relevant comorbidities, etc.).²⁴

In recent years, augmented reality has been introduced in neurosurgery with interesting findings.¹⁵ However, the reliability of this tool has the same well-known limitations of neuro-navigation,²⁵ with a loss of accuracy in the advanced stages of the operation and the depth of the surgical field¹⁵ while granting higher precision on the brain surface. In our case, augmented reality was used immediately after the dural opening, allowing us to rely on sufficient navigation precision.

Superimposed nTMS maps via augmented reality could facilitate the surgical flow by allowing direct visualization of safe, nTMS-negative zones, thereby providing the surgeon with important information regarding where testing with DCS should be performed at first or exclusively. Also, visualization of nTMS spots inside the microscope oculars frees the surgeons from looking at the same information on other devices (ie, the neuronavigation system screen) and allows the surgical instruments to be kept on the field, thereby offering similar advantages as other operative tools such as the microscope mouthpiece and foot control panel.

Limitations

Some limitations characterize this study, such as the small cohort of enrolled patients. Although much information has been gained concerning the comparison of nTMS and DCS in the current literature, single studies provided an average number of subjects comparable with our cohort.² Another issue concerns the precision and accuracy of DCS and possible overlap between stimulation spots

and distant points, specifically with higher stimulation intensity. To overcome this problem, we grouped nTMS points presenting within a space of 3 mm: this could have led to a loss of accuracy, limiting the spatial resolution of TMS to a 3-mm cutoff.

CONCLUSION

In this work, we assessed the accuracy of augmented reality visualization of preoperative nTMS maps for motor function with a heads-up display incorporated in the operative microscope. The added value of preoperative nTMS maps could reside in their ability to provide information on “safe” cortical areas. The combined use of nTMS and DCS for achieving maximal safe resection is warranted. Confirming our findings with larger cohorts is appropriate with a diffusion of augmented reality employment in neurosurgery.

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The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Accurately identifying eloquent regions of the brain to optimize safe surgical resection of intracranial lesions has been a popular area of research and technological development in the past few years. Many technologies are now commercially available as adjuncts for preoperative and intraoperative mapping or determination of eloquent brain regions, such as awake brain mapping, direct cortical stimulation (DCS), fMRI, and Quicktome. While transcranial magnetic stimulation (TMS) has been investigated as another modality for mapping of the eloquent brain, the authors report the first intraoperative point-by-point comparison of TMS against DCS. They elegantly coupled TMS with augmented reality display through the microscope oculars to streamline the use of this technology, which they have dubbed nTMS, and demonstrated that nTMS had fairly high accuracy at 83% with DCS as the gold standard. The most powerful aspect of nTMS as highlighted by the authors is the negative predictive value (0.93, 0.89-0.95), which can be valuable for operative planning.

However, regardless of the technologies used for mapping of the eloquent brain, the biggest question being asked is can the surgeon trust the technology to keep the patient safe. Despite their strong argument for the accuracy of nTMS, the authors have not completely answered this question of trust. Despite the high accuracy rate and high negative predictive value touted by the authors, 20 of 274 negative nTMS points were false negatives (7.3%). Can we trust a technology with a false-negative rate of 7%? Perhaps there is no good way to answer this question of trust. Afterall, as the authors pointed out, even the gold standard of DCS has questionable accuracy at higher stimulation rates. Simultaneously, can we afford to truly trust any of this technology in mapping eloquent brain? The cost of making a mistake in this arena is frequently too high for the patient. Further research and trials of these technologies are needed to better refine these mapping techniques and operative flow so we can build that trust and minimize patient harm.

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