Neurol Sci (2013) 34:1551–1557
DOI 10.1007/s10072-012-1283-7

ORIGINAL ARTICLE

Practical assessment of preoperative functional mapping techniques: navigated transcranial magnetic stimulation and functional magnetic resonance imaging

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Received: 22 September 2012 / Accepted: 17 December 2012 / Published online: 25 December 2012

Abstract Preoperative brain mapping is vital to improve the outcome of patients with tumors located in eloquent areas. While functional magnetic resonance imaging (fMRI) remains the most commonly used preoperative mapping technique, navigated transcranial magnetic stimulation (nTMS) has recently been proposed as a new preoperative method for the clinical and surgical management of such patients. This study aims at evaluating the impact of nTMS as a routine examination and its ultimate contribution to patient outcome. We performed a preliminary prospective study on eight patients harboring a cerebral lesion in eloquent motor areas. Each patient underwent preoperative cortical brain mapping via both fMRI and nTMS; then, we assessed the reliability of both methods by comparing them with intraoperative mapping by direct cortical stimulation (DCS). This study suggests that nTMS was more accurate than fMRI in detecting the true cortical motor area when compared with DCS data, with a mean of deviation ± confidence interval (CI) of 8.47 ± 4.6 mm between nTMS and DCS and of 12.9 ± 5.7 mm between fMRI and DCS ($p < 0.05$). The results indicated that within the limits of our statistical sample, nTMS was found to be a useful, reliable, and non-invasive option for preoperative planning as well as for the identification of the motor strip; in addition, it usually has short processing times and is very well tolerated by patients, thereby increasing their compliance and possibly improving surgical outcome.

Keywords Preoperative functional mapping · Navigated transcanial magnetic stimulation · Functional magnetic resonance imaging · Direct cortical stimulation · Brain tumor · Neurosurgery

Introduction

It is widely accepted that tumor mass reduction should be as maximal as possible for all gliomas, and especially for low-grade gliomas (LGGs), where extent of resection has been shown to have a clear impact on recurrence-free survival [1–7]. Maximizing tumor resection in eloquent areas presents additional challenges, since it might impact on patient quality of life, because of associated risks of post-operative motor deficits. Minimizing this risk is extremely important, since a low Karnofsky Performance Status score usually prevents access to further adjuvant treatments.

To this end, it is mandatory to have accurate knowledge of the location of the tumor and of the nearby functional brain tissue before resection. However, while functional cartography of peritumoral motor areas via direct cortical stimulation (DCS) has become the intraoperative gold standard [8–14], no such standard as yet exists for preoperative functional mapping, which is traditionally performed by functional magnetic resonance imaging (fMRI) [15].

The limitations of this technique are widely recognized [16–20]. These are often described in terms of the so-called

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"get-what-you-(barely)-see" limits of the BOLD effect, which refers to the fact that acquired images do not always correspond to anatomical reality [21]. Even so, thanks to more accurate image acquisition and statistical data processing, the sensitivity and the specificity of fMRI motor area localization have recently increased to 88 and 87 %, respectively [22], with a 92 % correspondence to DCS mapping data [23]. However, fMRI results are often unsatisfactory since this level of accuracy is still considered suboptimal [17, 24, 25].

Navigated transcranial magnetic stimulation (nTMS)—so far mostly used for the treatment of tinnitus, depression or chronic pain—has recently been suggested as an alternative method of functional preoperative brain mapping [25–28]. This study aims to test this experimental literature on the ground. We chose a small but representative sample of routine surgical patients to evaluate nTMS as a practical, everyday tool in the hands of doctors and surgeons. In doing so, we compared nTMS versus fMRI with the intraoperative DCS to evaluate the reliability of nTMS as a practical tool in the pre- and intra-operative assessment of tumors in eloquent areas.

Methods and patients

Study design

The aim of our study was to assess the reliability of preoperative mapping techniques and compare it with the present intraoperative gold standard. Our patients underwent cortical functional mapping preoperatively by fMRI and nTMS and intraoperatively by DCS. nTMS performance was compared with DCS and then referred to fMRI. To assess the usability of nTMS, we also conducted a survey among patients and surgeons. Furthermore, we evaluated whether nTMS can improve patient outcome, measured as increased tumor extent of resection (quantified by post-op CT and MRI scan) and better neurological score after surgery.

Ethics

All patients signed an informed consent form and agreed to all the preoperative and operative procedures required to perform this study.

Patients

This prospective study was conducted on 8 patients, 4 males and 4 females (mean age of 42.6 years, ranging 20–72), who were consecutively enrolled from March to September 2011. The main inclusion criterion was the presence of an expansive cerebral lesion located in the precentral gyrus or just nearby; all patients underwent a contrast-enhanced brain MRI. Patients were all right-handed and three out of eight lesions were located in the dominant hemisphere. The exclusion criterion was the presence of either a pacemaker device or deep brain stimulation electrodes. (Patient details in Table 1).

Preoperative fMRI

All MRI studies were performed according to a codified protocol, under controlled conditions. MRI scans were performed with a Achieva 3T clinical magnetic resonance system (Philips Healthcare BV, Best, Netherlands); a total of 192 scans were acquired after subjects were instructed to perform three sets of alternating tongue movements, finger tapping and foot extensions of roughly 20 s each and at a self-paced rate of ~ 2 Hz. The 3D data set was then transferred to the nTMS system as DICOM files.

Preoperative nTMS

This study employed an eXimia Navigation system (Nexstim NBS System 4.0, Helsinki, Finland), which combines the TMS procedure introduced by Barker et al. [29] with an optical navigation machine. This machine includes a navigated brain system where the scalp stimulation sites and the underlying brain anatomy are correlated in real time through a frameless stereotactic system (FSS) that is fixed, through a jointed mechanical arm, to both the stimulation coil and the patient's head. During the TMS session, we first co-registered the anatomical MRI data of the patient head in order to reach an alignment accuracy of <2 mm. Then, we determined the resting motor threshold (rMT), which refers to the intensity of stimulation needed to elicit electromyography (EMG) responses of 50 mV in at least five of 10 trials. This required the determination of the motor hotspot by eliciting the strongest compound muscle action potential (CMAP) in the abductor pollicis brevis (APB) muscle, and thereby stimulating the hand knob, a reliable landmark of precentral gyrus [30]. We subsequently mapped the functional areas using an output stimulus of 110 % of rMT for the upper extremities and 130 % for the lower extremities.

To execute EMG, we attached self-adhesive electrodes (Ambu® Neuroline 720) over the skin of three muscles of reference, namely the APB, the flexor carpi radialis (FCR), and the tibialis anterior (TA).

Intraoperative DCS

All patients underwent intraoperative cortical mapping. This was performed with the assistance of a neurophysiologist.

Table 1 Summary of patients

Case	Tumor location	Histology	Resection	Preop. musc. strength	Postop. musc. strength	rmt (%)	Peeling depth (mm)
1	Precentral-D	Astrocytoma[a]	Subtotal	5/5	5/5	36	20
2	Precentral-L	Oligodendroglioma	Subtotal	5/5	5/5	40	20
3	Central-D	Oligodendroglioma[b]	Total	3/5 HP	3/5 HP	85	20
4	Postcentral-D	Glioblastoma	Total	4/5 HP	4/5 HP	36	20
5	Postcentral-L	Metastasis[c]	Total	4/5 HP	4/5 HP	32	20
6	Precentral-L	Glioblastoma	Total	3/5 UEP	4/5 UEP	71	20
7	Postcentral-D	Cavernosus Angioma	Total	5/5	5/5	38	20
8	Precentral-D	Gliobastoma	Total	5/5	4/5 LEP	35	20

Muscle Strength (graded according to the Medical Research Council Scale)

HP hemiparesis, *LEP* lower-extremity paresis, *nTMS* navigated transcranial magnetic stimulation, *Peeling depth* the brain surface peeling setup from the scalp surface, *rMT* resting motor threshold in percentage stimulator output, *UEP* upper-extremity paresis

[a] Fibrillary, [b]Anaplastic, [c]Ovarian adenocarcinoma

After opening the dura, we used a monopolar anodal probe stimulator and disposable bipolar needle electrodes to identify the motor strip; data were recorded by an intraoperative navigation system (Stealth Station®, Medtronic, Italy).

Surgery

The study involved four different surgeons, randomly combined in groups of two for each surgery. nTMS hotspots were displayed on an intraoperative navigation system to assess their impact on surgical strategies and on the identification of the motor strip.

Statistical analysis

Data processing involved the calculation of the mean, standard deviation, and confidence interval for the distances of the three sets (nTMS-DCS, fMRI-DCS, and nTMS-fMRI) using a t test with $p < 0.05$.

Results

Preoperative mapping

All eight patients underwent preoperative mapping. Motor cortex mapping required a mean of 179 ± 32.12 stimulations per case. No procedure was interrupted or discontinued because of patients feeling discomfort or pain; some of them defined the elicitation of the motor area as a tingling sensation or as mild shock-waves along the extremities. We were able to identify the precentral gyrus and to produce a cartography of the peritumoral motor area in all cases. We used a peeling depth of 20 mm with an maximum electric field of 70 and 125 V/m, on average, for the upper and lower extremities.

Intraoperative mapping

We performed direct cortical stimulations (of up to 7 mA) on seven of eight patients; in one case DCS did not elicit MEPs because of technical issues. During cortical stimulation, one patient had a focal motor seizure at the contralateral upper extremity, subsequently diffused to the whole hemisoma; this was controlled by local irrigation with cold saline solution and systemic administration of Diazepam. The seizure occurred at the end of the cortical stimulation, which was then interrupted as enough data had already been gathered. The patient, who was a young male without history of seizures, suffered no postictal neurological deficits.

Data analysis: comparison of nTMS, fMRI and DCS

A comparison among nTMS, fMRI, and DCS was possible in all but one (12.5 %) of our cases, i.e. where DCS did not elicit MEPs. The data obtained include hotspots (the largest MEPs elicited by nTMS), intraoperatively acquired cortical points (where DCS triggered MEPs), and the coordinates of the center of the fMRI area; all three mapping methods were displayed simultaneously on individually calculated 3D head models (Fig. 1).

The pair-wise Euclidian distance between DCS coordinates and nTMS hotspots (between DCS coordinates and the centroid of the fMRI activation area, and between nTMS hotspots and fMRI) were all manually adjusted on the 3D head model at a depth equivalent to cortical surface (i.e. at the depth of DCS) and were subsequently calculated with the eXimia NBS system.

These distances were calculated in terms of their mean, standard deviation, and confidence interval (the latter by t test with confidence level of =95 %). The results on Table 2 show that for each muscle nTMS hotspots correspond more closely to DCS than do fMRI data. fMRI-DCS distance varied very little between upper and lower

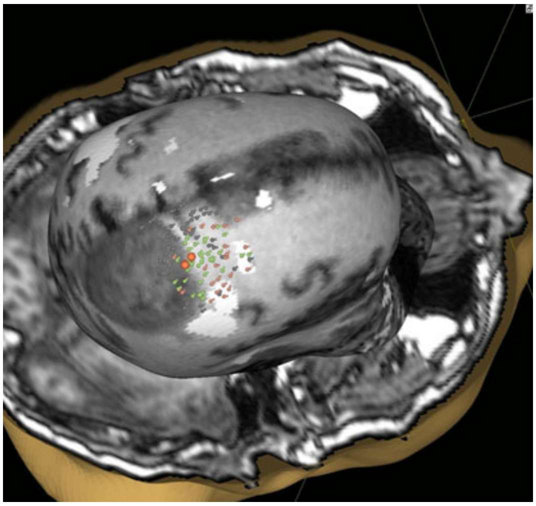

Fig. 1 Navigated transcranial magnetic stimulation (nTMS) screenshot image showing DCS hotspots (*orange spheres*), fMRI BOLD signals (*white areas*), and nTMS hotspots (*pink pins* for the APB muscle and *green pins* for the FCR muscle). *Gray pins* mark non-significant stimuli of up to 50 μV (color figure online)

extremities (FCR: 13.9 ± 6.3; APB: 11.6 ± 4; TA: 12 ± 9.9). It should be noted, however, that the TA muscle could not be examined by DCS in two cases as the craniotomy made the stimulation of the cortex impossible, thereby precluding any comparison with nTMS hotspots or fMRI. Here, we prioritized surgical obligations at the expense of statistical comprehensiveness.

We also calculated the distance between nTMS and fMRI to determine how the distribution of functional motor areas is cartographically arranged with regard to DCS mapping. When comparing images with hotspots, there seems to be a spatial correspondence between the two preoperative techniques. This is true for FCR and TA, but not for APB, probably owing to the impact of the illustrative case on our APB statistics (FCR: 8.8 ± 4.7; TA: 7.3 ± 3.5; APB: 24.3 ± 14.8) (Table 2).

Patients

On the first day after surgery, we observed neurological decline in one case. This was probably associated with a hypodensity of the supplementary motor area, as shown on the postoperative CT scan. We evaluated the extent of resection with MRI, by analyzing T1 (before and after contrast medium injection) T2 and PD weighting sequences (Table 2). During nTMS mapping, the rMT % appeared to change markedly as motor impairment got worse (see patient no. 3 and 6 in Table 1); furthermore, patient no. 3, who displayed one of the two highest rMT values, was the only patient on AEDs (Levetiracetam).

Illustrative case

We found striking discrepancies between fMRI and nTMS in one case. This patient was a 51-year-old male with a right postcentral glioblastoma and a preoperative hemiparesis of grade 4/5 (MRC scale). While performing preoperative cortical mapping by nTMS, we noticed a gap between nTMS hotspots and fMRI (Fig. 2). The surgeon was timely informed, and the patient had no additional postoperative neurological deficits. Comparing nTMS and fMRI results with DCS-processed data confirmed what was preoperatively observed in macroscopic view: nTMS-DCS was 6.9 ± 3.6 mm (range 3.1–14.4 mm) and fMRI-DCS was 14.8 ± 4.8 mm (range 9.7–20.5 mm). This case suggests that nTMS may have a positive impact on patient outcome.

Feedback

We conducted a qualitative analysis into how neurosurgeons and patients felt about nTMS. It emerged that intraoperative visualization of nTMS hotspots improved surgeon confidence in identifying the motor strip as well as in planning pre- and intra-operative surgical strategies. Patient feedback was always positive; the technique was described as quick, comfortable, and painless. When asked to compare the two procedures, 5 of 8 patients expressed a clear preference for nTMS, while the rest were undecided. It is worth noting that all the patients felt generally at ease at every stage of the procedure and as a result appeared to be personally involved in its success. This allowed for greater compliance to treatment.

Table 2 Difference between preoperative and intraoperative motor area mapping—shown per muscle groups (mm)

	FCR			APB			TA		
	nTMS–DCS	fMRI–DCS	nTMS–fMRI	nTMS–DCS	fMRI–DCS	nTMS–fMRI	nTMS–DCS	fMRI–DCS	nTMS–fMRI
Min	3.10	5.34	3.07	2.03	5.47	5.82	3.45	4.52	5.21
Max	14.71	25.28	17.47	12.55	16.79	49.08	10.44	21.34	10.10
Mean	7.94	13.97	8.86	9.45	11.64	24.33	7.76	12.00	7.30
CI	4.24	6.37	4.75	5.19	4.00	14.81	3.66	9.94	3.76

APB abductor pollicis brevis muscle, *DCS* direct cortical stimulation, *FCR* flexor arpi radialis, *fMRI* functional magnetic imaging, *nTMS* navigated transcranial magnetic stimulation, *TA* tibial anterior muscle

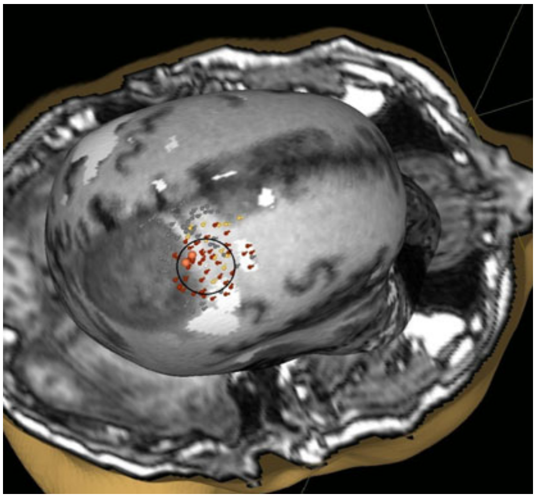

Fig. 2 Navigated transcranial magnetic stimulation (nTMS) screenshot image showing our illustrative case: DCS hotspots (*orange spheres*), nTMS hotspots (*gray, red, yellow pins*), and the fMRI BOLD signal (*white area*). Note that the hand area identified as functional by both nTMS and DCS is not matched by the fMRI BOLD signal (color figure online)

Discussion

nTMS-fMRI

This study suggests that nTMS was more accurate than fMRI in detecting the true cortical motor area when compared with DCS data, with a mean of deviation ± confidence interval (CI) of 8.47 ± 4.6 mm between nTMS and DCS, and of 12.9 ± 5.7 mm between fMRI and DCS with $p < 0.05$ (0.0498). The mean deviation between nTMS data and DCS is consistent with the conclusions of similar studies, where this is reported to be around 9 mm [31] or 10 ± 5.6 of SEM [28]. Our results seem to validate previous studies, where the fMRI-DCS deviation is reported to be much higher than that between nTMS and DCS (16 mm [31] and 15 ± 7.6 of SEM [28], respectively). This study also suggests that the deviation between the two techniques does not vary much between upper and lower extremities, as apparent by comparing the data for the FCR muscle (8.8 mm) and the TA muscle (7.3 mm); this differs from what found in Krieg et al. [25] where the deviation between the two methods is much larger in the lower extremities (9.8 mm vs. 14.7 mm).

The greater nTMS-fMRI difference observed for the APB muscle (24.3 mm) may simply be ascribed to the false-negative value obtained by fMRI in our illustrative case (see Sect. 3.5). In particular, this case depicts how the reliability of the BOLD effect—the basic principle of fMRI—is often imperfect. This is due not only to the fact that the metabolic activation of the brain parenchyma (associated with the BOLD effect) is not essential in motor functions [17, 26], but to the BOLD response itself, which can be affected by a number of different factors [16, 17]. These factors include impaired task performance, loss of autoregulation of tumor vasculature (associated with close hypervascular, high-grade tumor [32], edema or direct infiltrative growth into functional cortex [24]), and brain plasticity [34] (although this is often overrated [33]). While it is always difficult to determine the contribution of each of the confounding factors, the false-negative case we reported may have been due to some combination thereof, such as high-tumor grade, large edema, and blood vessel modifications.

In our experience, nTMS seemed to have some advantages over fMRI: as our illustrative case shows, nTMS can be more reliable in supporting intraoperative DCS data; moreover, nTMS is a more handy and practical preoperative technique as it allows easier functional mapping in patients who are young, claustrophobic, non-collaborative, or with titanium plates and because it eliminates the problem of fMRI movement artifacts. Furthermore, the length of the procedure is shorter. The whole nTMS procedure was performed by non-specialist doctors in 30–90 min (with an average of 53 min, including first-use training times). Instead, fMRI was executed in 30–40 min by specialized personnel and required data processing and reading times by radiologists, which increased the overall duration of the procedure (from 125 to 135 min). In light of this experience, we found nTMS to be quicker and easier to use, especially considering the relatively short learning curve and prompt data delivery.

nTMS-DCS

The key performance criterion for transcranial navigation is spatial accuracy, namely the correspondence between predicted and actual locations; the gap between nTMS and DCS, therefore, is a strong challenge to nTMS as a reliable mapping method [25, 26, 28, 31, 35]. It is important that this gap, however inferior to the one between fMRI and DCS, should be reduced. To do so, it is best to reconsider these techniques in light of their physical limitations and intrinsic differences.

One of the possible causes for this gap may be the internal sources of error of the NBS system, resulting in an accuracy limit of approximately 5.73 mm. The mean deviation we registered between nTMS and DCS can therefore be partly attributed to the three sets of system errors identified by the manufacturers [36]. Second, as shown in Picht et al. [26], the discrepancy between nTMS and DCS is also affected by the number of DCS stimulations. When this is < or =10, DCS mapping has limited coverage of nTMS hotspots or of the true cortical areas, thus resulting in asymmetric procedural comparisons vis-àvis nTMS. The number of DCS responses in our cases ranged from 6 to 10 (never >10), so it is reasonable to assume that the deviation between the two methods would have been smaller otherwise. A third confounding factor is the likely presence of more foci per muscle representation area, which might have been taken into account with a center-of-gravity approach [37]. This factor is often neglected because the prioritization of surgery time conflicts with the number of DCS stimulations needed to identify the centers of individual muscle representations. Fourth, there is as yet no clear understanding of the actual physiology and spatial anatomic resolution of either nTMS [38] or DCS [39, 40]. Finally, although DCS mapping is performed after durotomy, there may still be a few millimeters of inaccuracy resulting from intraoperative brain shift.

Considerations

The accuracy of the system depends on both technical and methodological issues. First, to minimize the former, we recommend keeping the co-registration error of the neuronavigation system and real patient position as low as possible, i.e. up to 2 mm. Second, to improve methodological reproducibility, it is important to ensure a consistently high enough number of DCS responses to achieve minimum nTMS-DCS distance [26]. These guidelines may help to reduce the gap between nTMS and DCS down to the limit of accuracy of the machine (5 mm), as only achieved in a handful of studies [25, 26, 35].

Conclusions

nTMS mapping was successfully performed in all of our cases. Our results suggest that this preoperative technique can provide data in closer agreement with intraoperative DCS mapping than fMRI, although our statistical limitations preclude any definitive conclusions. Precision and speed made nTMS data particularly valuable to pre- and intra-operative decision-making, as it helped to accelerate and improve the localization of the functional motor areas. The procedure allows for better patient compliance; it is noninvasive, painless, and easy to perform as it requires minimal patient cooperation. This makes it practical to use with patients who are less collaborative because of age or medical conditions. Our preliminary results indicate that the use of nTMS, if associated with DCS, may have a positive impact on both pre-surgical and surgical planning as well as on patient outcome. However, the advantages found in this small-scale usability test should not eclipse the statistical constraints that the prioritization of surgical access and timing often imposed on data collection. Despite the utility and usability merits of nTMS, larger studies will be needed to offset against the impact of surgical exigencies on the study of nTMS as a preoperative functional mapping technique.

Acknowledgments We would like to thank the engineers at Tekmed Istruments SPA Milan for their professional assistance.

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