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REVIEW ARTICLE - NEUROSURGICAL TECHNIQUES

Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report

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Abstract

Introduction Navigated transcranial magnetic stimulation (nTMS) is increasingly used for preoperative mapping of motor function, and clinical evidence for its benefit for brain tumor patients is accumulating. In respect to language mapping with repetitive nTMS, literature reports have yielded variable results, and it is currently not routinely performed for presurgical language localization. The aim of this project is to define a common protocol for nTMS motor and language mapping to standardize its neurosurgical application and increase its clinical value.

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The navigated TMS workshop group; Helsinki Meeting 2016

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Methods The nTMS workshop group, consisting of highly experienced nTMS users with experience of more than 1500 preoperative nTMS examinations, met in Helsinki in January 2016 for thorough discussions of current evidence and personal experiences with the goal to recommend a standardized protocol for neurosurgical applications.

Results nTMS motor mapping is a reliable and clinically validated tool to identify functional areas belonging to both normal and lesioned primary motor cortex. In contrast, this is less clear for language-eloquent cortical areas identified by nTMS. The user group agreed on a core protocol, which enables comparison of results between centers and has an excellent safety profile. Recommendations for nTMS motor and language mapping protocols and their optimal clinical integration are presented here.

Conclusion At present, the expert panel recommends nTMS motor mapping in routine neurosurgical practice, as it has a sufficient level of evidence supporting its reliability. The panel recommends that nTMS language mapping be used in the framework of clinical studies to continue refinement of its protocol and increase reliability.

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Introduction

Navigated transcranial magnetic stimulation (nTMS) has gained increasing acceptance for preoperative mapping of motor and language function in neurosurgical centers across the world [4, 11, 17, 26, 41, 47].

Clinical evidence of its benefit for the patients is growing [10, 19, 26, 38]. Various protocols for motor and language mapping have been published to enhance the specificity and sensitivity of nTMS, [12, 13, 21, 22, 27, 30, 46]. Protocols for language mapping are particularly variable between centers [14, 21, 22, 42, 45]. This variability diminishes comparability of results and hampers its widespread adoption in clinical practice.

This workshop report aims to recommend a common protocol for nTMS mapping that addresses all aspects of its application, including the parameters used, data analyses, and clinical integration. It is a part of a larger project to establish a worldwide cooperation of researchers using nTMS for presurgical delineation of motor and language function and to fully integrate nTMS in clinical standards of care.

This report is not meant to replace existing guidelines on non-invasive stimulation of the brain [33]. It represents an adjunct for previous guidelines focusing on the presurgical use of nTMS in functional cortical mapping, particularly to benefit neurosurgeons and affiliated researchers.

Due to the extensive data already available for the use of nTMS in neurosurgery, this print article represents a shorter version of the original article, which is available as supplemental material to this report.

The workshop meeting

The nTMS workshop group, consisting of 11 experts with neurosurgical and scientific experience in nTMS motor and language mapping of up to 14 years, met in Helsinki, Finland, on 21–22 January 2016 and discussed current evidence and individual experiences to forge a recommended protocol for preoperative nTMS motor and language mappings.

To provide the best available evidence for the protocol, data from published clinical nTMS studies were used as a basis of these recommendations. Therefore, we reviewed the current literature via MEDLINE search and identified and analyzed all articles relevant for the use of nTMS in the neurosurgical field. The relevant articles for each aspect of nTMS mapping are cited in the particular paragraph.

For questions not dealt with in published reports, expert opinions were distilled to a common final statement. These recommendations, which cannot be proved to date by any available literature and are therefore based on our group consensus, do not possess any reference in their paragraph.

Methodological background on nTMS

Motor mapping

Transcranial magnetic stimulation (TMS) is an electrophysiological technique for the investigation of the human motor cortex and motor tracts [1]. Development of TMS coils producing more focal cortical stimulation increased the spatial resolution of TMS. TMS delivers a short (rise time 100 μs), strong (1–2.7 T) magnetic field (pulse), which penetrates the skull and induces an electric field within the cortex. When appropriate stimulus intensity is used, this electric field activates cortical motoneurons of the corticospinal tract (CST). The descending corticospinal volley then excites α-motoneurons of the anterior horn of the spinal cord generating a motor-evoked potential (MEP) in the muscle. The amplitude of the obtained MEP depends on stimulation intensity, coil shape and the quantity of excited motoneurons [7]. The efficacy of TMS is evaluated by continuous electromyography (EMG) monitoring to detect an MEP induced by stimulation of each cortical site comparable to intraoperative direct cortical stimulation (DCS) [16, 34, 35].

Language mapping

In contrast to motor mapping, which uses single TMS pulses to elicit a MEP, language mapping protocols utilize repetitive TMS pulses (rTMS) [25]. As in DCS mapping during awake surgery, patients perform language tasks and rTMS is used to impair task performance by disrupting language-involved cortical regions [6, 8, 44]. The exact mechanisms by which rTMS interferes with language processing are not fully understood, but they likely involve a focal depolarization and temporary inhibition of neuronal networks involved in language processing [8].

Neuronavigation

When a TMS pulse is delivered, the affected cortical structure as well as the field strength within the structure depends on the individual brain anatomy (Fig. 1). By integrating a frameless stereotactic navigation system with the TMS coil and pulse generator, precise, real-time navigation and quantification of the magnetic field become possible. Current nTMS systems use a focal figure-of-eight TMS coil referenced to coordinates of the patient's head via an infrared tracking system. The induced electric field is visualized on the surface of the 3D head model that is reconstructed from the patient-specific MRI data. This technique, known as "navigated TMS" (nTMS), thereby enables exact delivery of a specific electric field to a given cortical structure [16, 34, 35] and is a requirement for any pre-surgical mapping application.

NTMS motor mapping

General information

For more general information concerning clinical evidence, limitations of the method, troubleshooting, and patient selection, please see the supplemental material.

Recommended protocol

Preparation

An anatomical MRI with 1-mm slices is needed to create an adequate 3D brain reconstruction and enable accurate navigated coil positioning during nTMS mapping. In addition, a DWI data set for white matter tracking should be acquired to enable visualization of the cortico-subcortical connectivity.

Selection of the monitored muscles

Please see the supplemental material for a detailed list of used muscles for electrode placement. Most importantly, the muscles are chosen according to the tumor location and surgical approach planning.
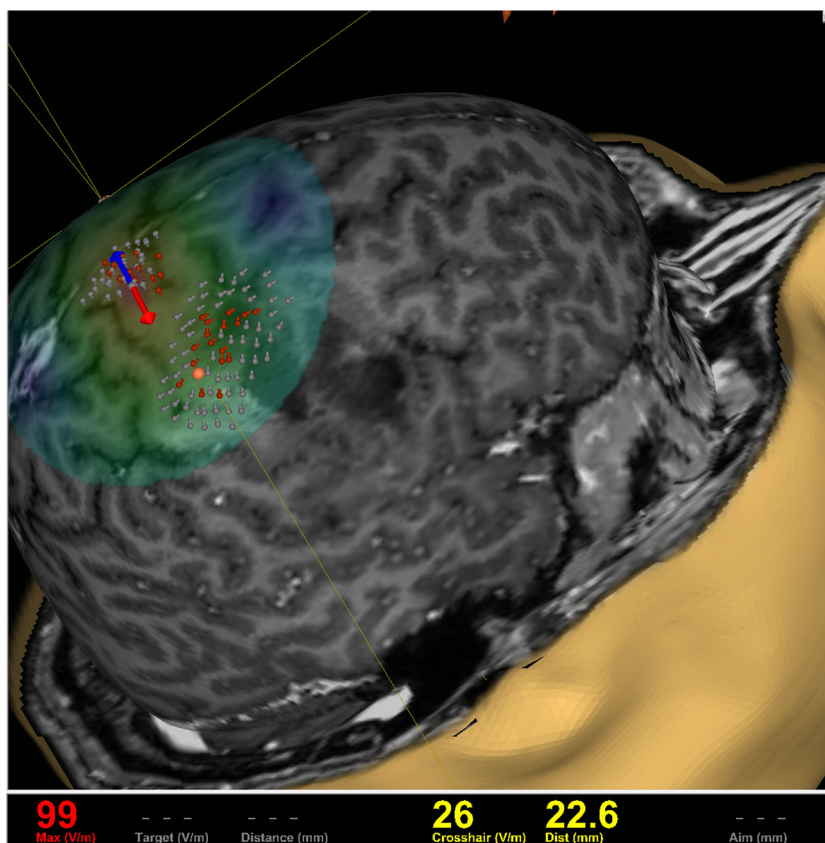
Mapping intensity

Intensities slightly above the resting motor threshold (RMT) limit the cortical volume of stimulation and produce the most precise functional maps. For practical reasons, the use of the RMT of one small hand muscle (e.g., first dorsal interosseus; FDI) is used for the mapping of all upper extremity muscle representations. For mapping of cortical representations of the lower extremity and facial muscles, the stimulation intensity usually needs to be adapted (see below).

FDI hot spot

The functional hand motor area can approximately be identified by the omega-shaped knob in the precentral gyrus [48]. The search for the hand (here: FDI) hotspot is started from the anatomically identified hand motor area within the precentral gyrus. The FDI and abductor digiti minimi muscle (ADM) are equally useful for calculation of the RMT [29] and as the first focus of mapping. The stimulator output is adjusted to induce an electrical field of 80–100 V/m on the cortex 20–25 mm below the coil (approximately 35–40% of the maximum stimulator output, MSO). A rough mapping is then performed with MEPs between 100 and 500 μV and extended along the central sulcus (CS) medially and laterally using the same intensity until the MEPs disappear while the orientation is kept perpendicular to the CS. The site eliciting maximum FDI MEPs defines the FDI hot spot.

Fig. 1 Electric field:
Visualization of the induced
electric field including
quantification of the induced
electric field strength in V/m

Resting motor threshold measurement

The RMT is defined as the lowest TMS intensity capable of
eliciting a 50-μV MEP amplitude (peak to peak) in a relaxed
small hand muscle (FDI or ADM) in five out of ten stimula-
tions [32].

Mapping of the hand motor area

To optimize accuracy, the mapping should be carried out at the
lowest possible intensity and done as described above for hot
spot identification (stimulation intensity: 105% RMT of FDI).
An investigation of motor mapping approaches was per-
formed by Raffin and colleagues; their paper describes in
greater detail the theoretical background of the recommenda-
tions provided here and in the supplementary material [29].

Mapping of lower extremity motor area

The cortical representations of most leg and foot mus-
cles are located deep within the interhemispheric fissure.
Consequently, higher nTMS intensities are needed to
elicit MEPs from the foot than from the hand muscles
(Fig. 2) [20, 28].

Mapping of the facial motor area

Mapping of the facial motor area is outlined in the supplemen-
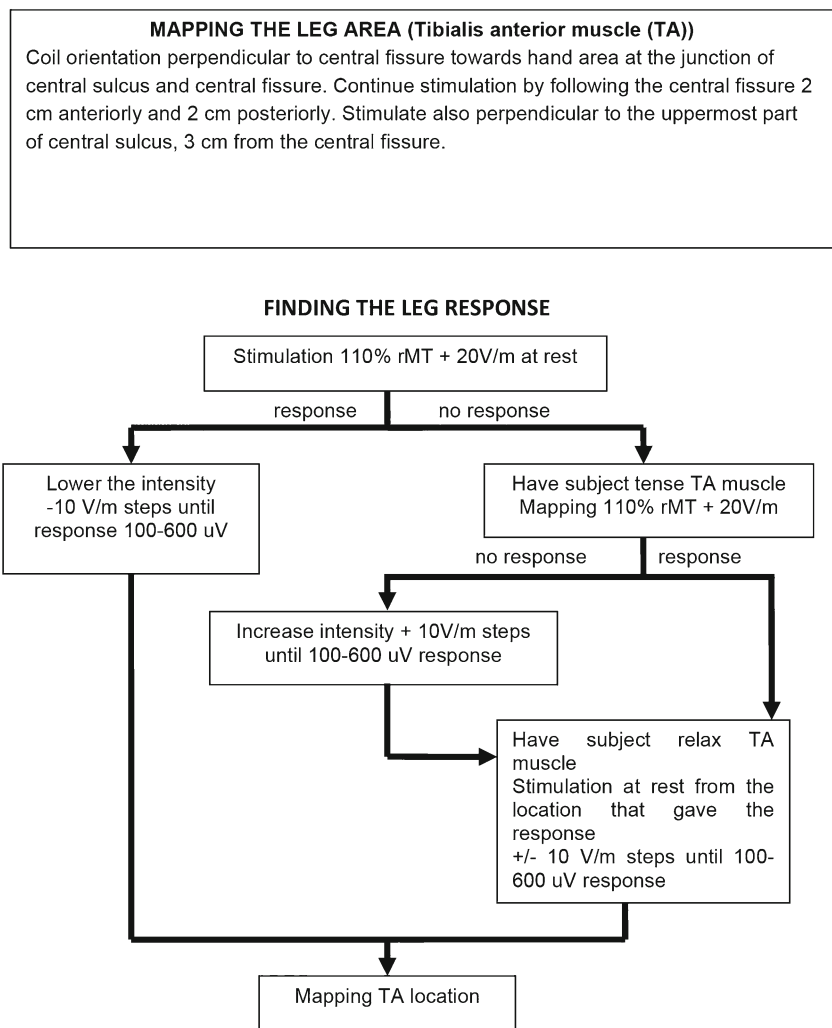tal material.

Utilization of mapping data for surgical planning

All nTMS-positive cortical sites should be exported to the
neuronavigation and can then be used as starting points for
(somatotopic) white matter tracking via nTMS-based fiber
tracking (FT) [4, 11, 17, 47]. In addition to the TMS-derived
topographical information, patient counseling and risk-benefit
balancing can be supported by the RMT ratio of the hemi-
sphere ipsilateral to the tumor divided by that of the contralat-
eral hemisphere. The ratios above 110% or below 90% indi-
cate an increased risk for postoperative motor deterioration
[31]. During surgery the TMS maps can then be used to iden-
tify the motor cortex and guide cortical and subcortical elec-
trical mapping [18].

NTMS language mapping

For more general information concerning clinical evidence,
limitations of the method, troubleshooting, and patient selec-
tion, please see the supplemental material.

Fig. 2 Motor mapping of the leg area: This graph shows a guide to obtaining optimal results for motor mapping of cortical leg areas

MAPPING THE LEG AREA (Tibialis anterior muscle (TA))
Coil orientation perpendicular to central fissure towards hand area at the junction of central sulcus and central fissure. Continue stimulation by following the central fissure 2 cm anteriorly and 2 cm posteriorly. Stimulate also perpendicular to the uppermost part of central sulcus, 3 cm from the central fissure.

FINDING THE LEG RESPONSE

Stimulation 110% rMT + 20V/m at rest

response / no response

Lower the intensity -10 V/m steps until response 100-600 uV

Have subject tense TA muscle Mapping 110% rMT + 20V/m

no response / response

Increase intensity + 10V/m steps until 100-600 uV response

Have subject relax TA muscle
Stimulation at rest from the location that gave the response
+/- 10 V/m steps until 100-600 uV response

Mapping TA location

Recommended protocol

Preparation

Preparation for rTMS language mapping is identical to that required for motor mapping with special emphasis of the necessity of focused attention throughout the procedure.

Language task

The content and complexity of the task during language mapping affect the incidence, location, and type of observed errors [9]. As for intraoperative language mapping during awake surgery, the most frequently used task is confrontational object-naming with or without a written lead-in phrase. This task is well tolerated, fits within the time and space requirements, and also interrogates multiple aspects of language and speech. No other task has been proven superior for general mapping of language-eloquent brain areas [13–15].

Baseline and rTMS object-naming

The image set should contain only objects without synonyms to prevent erroneous interpretation of subject performance. Moreover, it needs to be presented in full to the patient at least two times before actual rTMS mapping ("baseline naming") while all misnamed images are be discarded. During the actual naming task, the remaining images should be presented time-locked to trains of TMS pulses, and the stimulation coil should be moved randomly between the presentations of the images in roughly 10-mm steps over the perisylvian cortex. The induced current should be oriented perpendicular to the sulcus close to the stimulated point to induce a maximum effect. Table 1 shows an overview on the currently used rTMS setting of language mappings in the involved centers of the authors.

The following default parameters are recommended:

1. The baseline is repeated two to three times
2. Interpicture interval (IPI): 2500 ms
3. Picture presentation time (PPT): 700 ms
4. Stimulation intensity: ipsilateral RMT

Table 1 Language mapping parameters: This table shows the variability of stimulation parameters as recommended by the different groups

Group	Initial sentence	Stimulus onset delay (ms)	Frequency (Hz)	Pulses	Picture presentation time (ms)
1	Yes	0	n.r.	n.r.	500
2	No	0	5 or 7	5 or 7	700
3	No	0	7	7	700
4	No	150	5 or 7	5	700
5	No	0	5 or 7	5 or 7	700
6	Yes	0	5 or 7	5 or 7	700
7	No	150	5 or 7 or ….	5 or 7	700
8	Yes	300	7	7	700
9	No; but in pts. yes	0	7	7	700

n.r. = no recommendation

5. Duration and frequency of the stimulation: 5 Hz/5 pulses
6. Picture to rTMS trigger interval (PTI): 0 ms delay [21, 39]
7. The same cortical patch is repeated non-consecutively at least three times per mapping

During the examination, it is of utmost importance that the patient is comfortable and maintains a consistent level of attention. Video material demonstrating the language mapping procedure is available in the supplementary material of publications by the authors [14, 22].

Result analysis and interpretation

The enormous complexity of the cortico-subcortical network involved in the perception, processing, and production of language makes it a difficult target for single-trial mapping. The stimulation frequencies and the delivered electrical charge used in rTMS speech mapping differ significantly from DCS, and a single rTMS train does not give conclusive information about the language involvement of any particular cortical site. Successful rTMS language mapping is based on the application of several stimulation trains within the same cortical area and meticulous observation and documentation of the rTMS-induced behavioral changes. This analysis is only possible by video-based off-line review [22]. Clusters of sites inducing language disturbances within the same cortical area suggest that this area is relevant for speech processing. Interpretation of the rTMS language mapping results requires experience and careful consideration of each individual case.

Stepwise description of the procedure

This paragraph is only provided in the supplementary material.

Result analysis

Detection of subtle disturbances is achieved by comparing the baseline response to the response during rTMS stimulation [5, 27].

Result interpretation

It is crucial to realize that rTMS does not provide the same powerful blocking stimulus as DCS. Thus, ideally, a language specialist/neuropsychologist should be involved in the analysis of the language tasks.

Utilization of mapping data for surgical planning

The current experience and evidence suggest that cortical areas repeatedly targeted with no language disturbances induced by rTMS are most likely not carrying out essential language functions [21]. Clustering of rTMS-induced language disturbances within a distinct cortical area suggests relevant involvement in language processing, and DCS confirmation is recommended. Moreover, the combination of rTMS-positive cortical spots with tractography of subcortical language pathways via diffusion tensor imaging fiber tracking (DTI-FT) can aid in the interpretation of the results and add important information pertaining to the location of relevant cortical and subcortical structures. Protocols for rTMS-based DTI-FT have been described and compared to existing protocols [24, 40].

Use of nTMS data in the operating room

nTMS-positive sites for language and motor functions should be imported into the neuronavigation and hospital picture archiving system [23]. The DICOM standard supports this procedure. It is useful to export nTMS-positive stimulation points
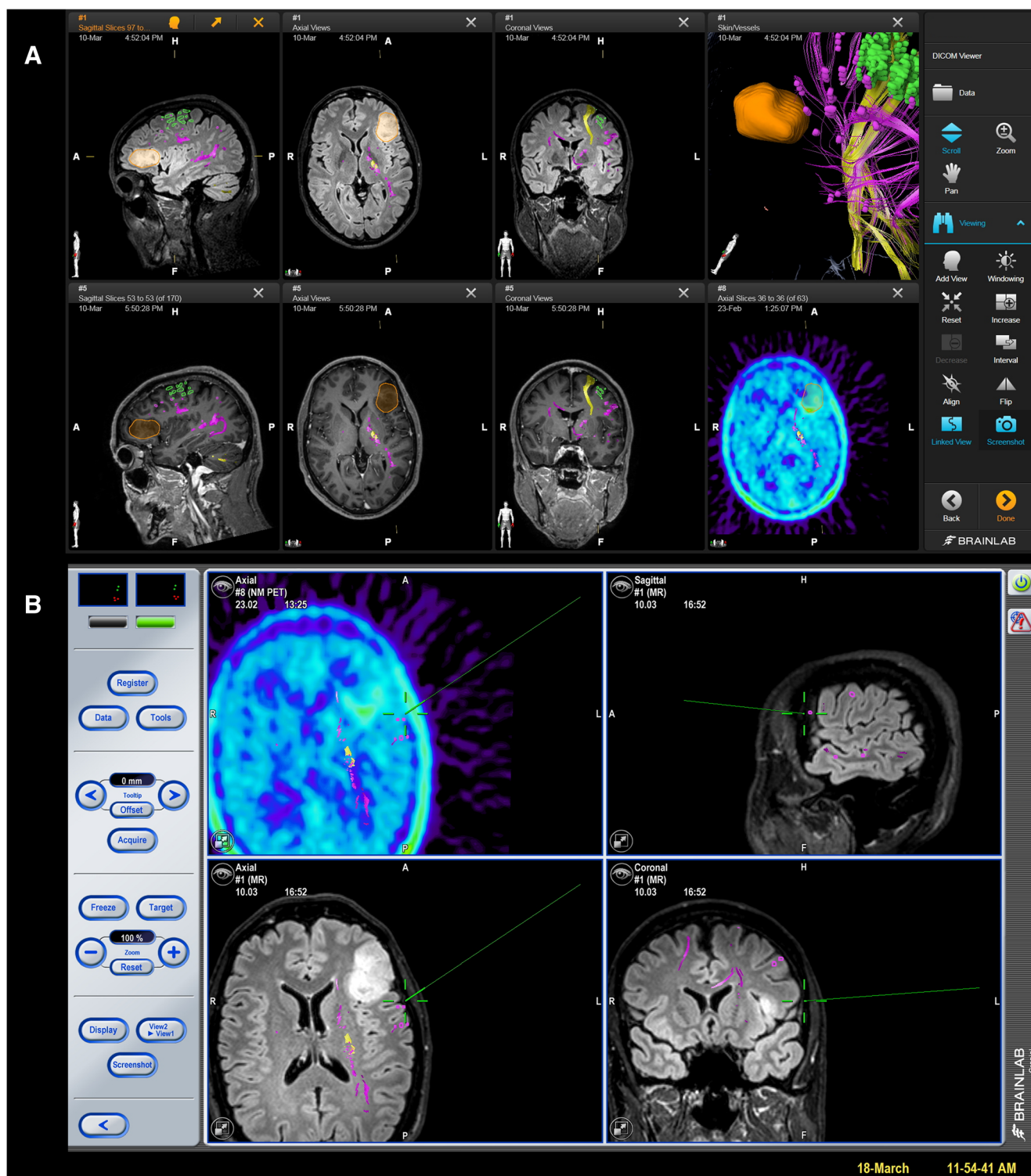
Fig. 3 Example of standardized color-coding: The screenshot shows a case of a left-sided oligodendroglioma WHO grade III located in the triangular part of the inferior frontal gyrus that was primarily judged by another neurosurgical department to be not resectable. This case gives an example of how nTMS can falsify presumed eloquence. Moreover, these screenshots show how to standardize different colors for the cortical motor areas (green), corticospinal tract (yellow), cortical language areas (purple), and subcortical language-related fiber tracts (purple). This allows an optimal preoperative preparation (A) and intraoperative clarification of the functional anatomy (B)

on various cortical and subcortical levels (i.e., peeling depths) to inform the surgeon. A standard color-coding of the implemented rTMS data should be established to aid interpretation of the depicted functional anatomy and intraoperative

use of the rTMS data (Fig. 3). The combination of rTMS results with rTMS-based FT to visualize language-related subcortical fibers and the CST is recommended. For language and motor eloquent lesions, however, final surgical decisions regarding the functional relevance of both cortical tissue and subcortical fiber tracts are made based on the intraoperative mapping and monitoring results [2, 3, 36, 37].

Safety issues

The protocols described here have been used for many years at the institutions of the authors. A safety analysis of these protocols revealed no major adverse events in 733 patients and 258 healthy subjects [42, 43].

Conclusion and outlook

nTMS motor mapping displays excellent accuracy in comparison with DCS, and the level of evidence is sufficient to recommend it for routine neurosurgical work-up. nTMS can be a valuable adjunct for established IOM workflows when planning and performing surgery in presumed motor eloquent areas.

The workshop group recommends nTMS language mapping in the frame of clinical studies but not to replace awake surgery for eloquent lesions. Moreover, development of experimental protocols should be a priority for clinicians interested in the management of lesions in eloquent brain regions. The group members involved in these recommendations will use the common protocols as they have been described and will compare the results in upcoming meetings.

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