8 Preoperative Assessment by Navigated Transcranial Magnetic Stimulation

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This chapter includes an accompanying lecture presentation that has been prepared by the authors: Video 8.1.

KEY CONCEPTS

- Navigated transcranial magnetic stimulation (nTMS) is able to identify cortical function, such as motor and language function, but also other higher functions such as arithmetic processing or facial recognition.
- nTMS is able to assign function to tractography techniques, which allows adding specific information to this otherwise nonspecific modality.
- nTMS in combination with nTMS-based tractography allows for preoperative risk stratification regarding motor and language function.
- Intraoperative monitoring (IOM) starts but does not end with nTMS mapping; both are complementary methods which are stronger if used in combination.
- nTMS facilitates an objective definition of eloquence for Spetzler-Martin grading of brain arteriovenous malformations (AVMs).

BASIC PRINCIPLES OF NTMS, NTMS MOTOR AND LANGUAGE MAPPING, AND SAFETY CONSIDERATIONS

General

After the introduction of transcranial magnetic stimulation (TMS) into clinical neurology in 1985, several studies quickly demonstrated the potential of the modality to assign individual muscles to their cortical representation.[1] TMS is based on the law of induction, which states that a time-varying magnetic field induces an electrical current in an electrically conductive medium.[2] In TMS, the magnetic field is induced by a strong, rapidly rising current in a coil. The resulting magnetic field decreases exponentially with increasing distance from the coil.[3] The current intensity induced in the body depends directly on the conductivity of the medium. As a result, the primary magnetic field reaches the cortex almost completely undamped, because skin, hair, and bones have a high specific resistance—that is, poor electrical conductivity. This also explains the painlessness of the method, as the TMS pulse has only a very small effect on the tissue between coil and cortex.[4]

Two technical innovations were necessary for useful application within neurosurgery. First, the development of so-called double-ring or figure-eight coils was a prerequisite to enable meaningful mapping. With this type of magnetic coil, a conically configured magnetic field is created at the intersection of two round coils, enabling focused stimulation.[5] Focused stimulation is especially possible when working with low stimulation intensities, so that only the tip of the conical magnetic field stimulates the cortex at suprathreshold intensity. The spatial resolution is in the millimeter range.[6]

Furthermore, the combination of the TMS stimulation and the spatial image information was necessary in order to make the mapping of the cortical representation of the limb muscles visible—that is, to assign it to the respective anatomic localization. This could be guaranteed for the first time at the end of the 1990s.[7] The first study, which focused on the accuracy of navigated transcranial magnetic stimulation (nTMS) compared with the "gold standard" of direct intraoperative electrical cortex stimulation in a larger patient population, was published in 2009.[8] Further improvement of the localization systems and the modeling of the TMS effect on the cortex level ("e-field navigated TMS"; Fig. 8.1) enabled a continuous optimization of the accuracy of frameless nTMS.[9,10] Modern systems enable software-controlled optimization of the coil tilting in order to optimally align the induced electric field with respect to the local cortical anatomy and provide online feedback on the strength (V/m) of the induced electric field at cortex level. By this means, individual differences in the local anatomy and varying distance between coil and cortex can be taken into account.[11]

Motor Function

Mapping of cortical motor representations with an nTMS system achieves highest focality when applying just suprathreshold stimulation intensities. To implement this concept in practice, it is necessary to determine the individual resting motor threshold (RMT) before each measurement, because the RMT varies interindividually and also intraindividually, depending on various internal (e.g., level of alertness) and external (e.g., electrode montage) factors.[12] The subsequent mapping of the relevant peritumoral cortex area is then performed usually at 105% to 110% of the RMT. Owing to the somatotopy of the gyrus, 10% to 20% higher stimulation intensities are required for mapping muscles of the lower extremity than for the small hand muscles. During the mapping, it must also be ensured that the induced current flow is always perpendicular to the nearest sulcus. This is due to the fact that the axons of the pyramidal cells are arranged perpendicular to the gyral surface, and axons are depolarized most easily with a parallel current flow.[13,14] Another factor that significantly influences the reliability of the investigation is the quality of the electromyography (EMG) signal, and it is important to ensure a sufficiently good EMG quality during the examination, wherein the resting activity is always below the threshold for positive motor evoked potential (MEP) responses (usually 50 mV).[15]

With high stimulation intensities, an electrical current can be induced at a depth of several centimeters, but the focus is lost, so targeted stimulation in the sense of mapping subcortical structures is not possible. The presurgical TMS examination is therefore limited to the cortex. The hodotopic concept of brain function—that is, its organization in dynamic networks—emphasizes the role of the long association fibers in maintaining functional integrity.[16,17] There is increasing evidence that a loss of connectivity between two cortical nodes has even more serious consequences (i.e., worse prospects for functional recovery)

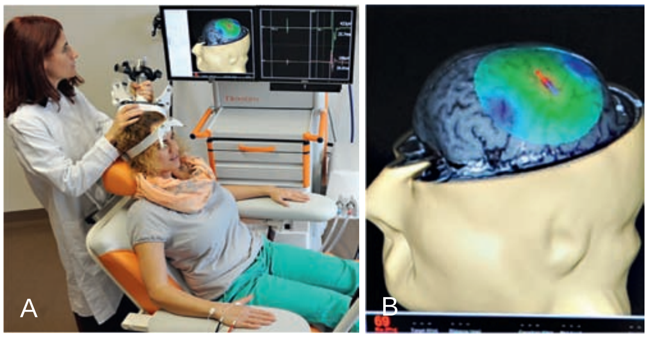

Figure 8.1. E-field navigated transcranial magnetic stimulation (nTMS) motor. (A) nTMS examination. The position of the patient's head and the transcranial magnetic stimulation (TMS) coil in space is continuously determined by a camera (not shown) using the reflectors fixed to the coil and head. The TMS coil is guided freehand during the examination. The position of the coil in relation to the patient's head (MRI three-dimensional reconstruction) is visualized on the left screen in real time. Stimulation pulses are triggered by the examiner using a foot pedal (not shown). If the stimulation hits a motor area, the stimulation effect is recorded by electromyographic electrodes (surface electrodes; here, patient's left hand), and the resulting muscle action potential is displayed and recorded on the right screen. (B) Detail enlargement of the left screen. The *red and blue arrow* shows the direction of the biphasic electric field induced by the magnetic pulse. A bright arrow indicates optimal coil tilting with maximal e-field induction in the underlying cortex. The central *red area* corresponds to the cortex area, which is stimulated with suprathreshold intensity. In the *green* and *blue areas,* the exponentially decreasing electric field no longer has an excitatory effect.

than cortical damage.[18] Accordingly, maintaining subcortical connectivity is at least as important as maintaining cortical integrity to preserve neurological function. Diffusion tensor imaging (DTI) fiber tracking (FT) has found rapid acceptance in recent years in the neurosciences and is increasingly being used in presurgical diagnostics.[19] However, the result of DTI imaging depends largely on the experience of the examiner and the software used.[20] In particular, the selected analysis threshold and the selection of starting points for the DTI algorithm influence the configuration of the resulting fiber networks. By identifying those motor areas at cortical level that are essential for motor functioning with high spatial accuracy, nTMS provides starting points for the DTI algorithm, which will display only functionally irreplaceable and therefore surgically relevant tracts.[21-23] However, when evaluating DTI images, one needs to keep in mind that DTI is anatomic imaging and not functional imaging. Its interpretation must be based on the knowledge that it has not yet been fully clinically validated and that diffusion is susceptible to confounding tumor effects.[24]

Language

Starting with the first language model in the late 19th century, it has become evident that the capacity for language is maintained in complex connections between language-related areas, encompassing highly specialized and less specific areas for language processing in both hemispheres.[25] Knowledge about patients' individual language networks predominantly stems from intraoperative stimulation mapping. These studies during awake surgery have revealed strong interindividual differences in the cortical sites producing language disturbances.[26,27] The present models include a frontoparietal "dorsal stream" involved in mapping sound onto articulation-based representations and a "ventral stream" in the temporal lobes, which maps sound onto meaning. In light of the recent paradigm shift from the traditional localizationist view of language function located in specific cortical regions toward a view of parallel, highly dynamic, cortico-cortical and cortico-subcortical networks supporting speech and language function,[27] TMS, as the only noninvasive methodology allowing for electrical stimulation mapping analogous to direct cortical stimulation (DCS), has received increasing interest as a tool for presurgical language mapping.

From the very first reports on TMS language mapping to recent studies, stimulation frequencies between 4 and 10 Hz have been found most effective.[28,29] The induced disturbance of language processing can result in a variety of behavioral changes ranging from discrete prolongation of response delays to clear anomias. The clinical experience from awake surgery suggests that object naming is the most effective experimental setup to map the language-related cortical areas, because it is robust, explores different language submodalities, and can be easily introduced into a short task design.[30]

rTMS trains usually have 4-10 Hz, start immediately with the object presentation or delayed for up to 300 ms. The whole pulse train is then applied for 1 to 2 seconds.[31] In modern TMS devices, the electric field is calculated at the stimulation site. This allows avoiding too low stimulation intensity, which should be above 50 V/m. Depending on the patient's abilities and the region of interest, around 200-300 different stimulation sites are chosen per hemisphere. The baseline session in which the patients needs to name all presented objects properly leads to discarding of all misnamed objects. During stimulation, these recordings of properly named objects can then be directly compared with the patients' answers during stimulation which clearly reveals the stimulation effects.[32,33] Because of the distributed and highly individual composition of the language network, the indication for preoperative TMS language mapping has a wide range, going beyond tumors in classical left-hemispheric language areas.[34,35] Preservation of language function also depends on preventing disconnection of the cortical nodes identified by TMS mapping. Therefore combination of the cortical TMS language mapping with white matter tractography is essential for presurgical planning. Here, different approaches implementing either anatomic and/or functional seed areas for DTI tractography have been proposed.[36-38] The TMS and tractography data enable one to counsel the patient with respect to the difficult risk-benefit balancing of surgery based on these objective measurements.[39-42] Because of the easy-to-grasp methodology and transparent nature of TMS mapping, the patient will be able to take part in the shared decision-making process well informed and confident. In addition to providing a map of individual language function, the TMS experiment also prepares the patient for potential awake surgery, because the procedure of stimulus presentation, stimulation, and experience of language impairment is analogous to the events during intraoperative language mapping. Despite all efforts, the occurrence of new language deficits after preparatory TMS and DTI and intraoperative awake language mapping cannot be completely prevented when the goal is also to maximize resection for longer survival.

Safety

TMS mapping of presumed eloquent brain areas has been shown over the years to be extremely safe with minimal side effects.[43,44] The guideline recommendations for upper limits for number, frequency, intensity, and duration of stimulation refer primarily to the risk of inducing an epileptic seizure.[45] The incidence of TMS-induced clinical seizures for all types of TMS patterns is low with, with rates of 0.01% to 0.1% being reported in the literature. For single-pulse TMS, only anecdotal reports are available for induced epileptic seizures in patients with intracranial disease.[46] Other possible side effects are syncope or pain, the incidences of which are also very low in the literature.[47]

While nTMS was introduced in some departments over 10 years ago, it is still new for many. Since it is not affected by oxygenation changes and proofed a high navigation accuracy as well, it was repeatedly shown that the correlation of nTMS to DCS is superior to other noninvasive techniques, such as FMRI and MEG.[48] nTMS therefore offers the possibility of a standard workflow for the preoperative workup before surgery for eloquent lesions. Despite its active stimulation, no severy adverse events were reported for nTMS in the past 10 years.[49] This mentioned study showed in 733 patients of which half suffered from symptomatic seizures and were operated on in 3 large neuro-oncological centers, that no patients showed any severe side effect except pain during or after stimulation. The very recent 2021 guidelines on brain stimulation analyzed the literature of recent years comprehensively and came to the same conclusion.[49a] TMS is therefore widely applicable, including in the pediatric population and in preparation for epilepsy surgery.[50,51] These have also been put in context of newer data in the most recent guidelines.[49a] With respect to the importance and benefit of such data, the potentially minor risks of nTM should be put in context.

NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION MOTOR MAPPING

nTMS Mapping and nTMS-Based DTI Fiber Tracking of Motor Pathways and Their Clinical Use

Several studies have demonstrated that when using a focusing double-ring coil in combination with the navigation of the electric field, the cortical areas whose stimulation leads to a muscle response can be regarded as eloquent with the same reliability as in the invasive examination with the gold standard of direct electrical stimulation of the cortex.[8,9,52-54] It has also been shown that nTMS leads to congruent results independent of the examiner—an important prerequisite for a routine clinical instrument.[55] The limitation of TMS that only cortical areas are accessible for direct stimulation, but not deep white matter structures, has been compensated for in various studies demonstrating the usefulness of TMS-derived starting points for clinical tractography (i.e., by using software certified for clinical use). In order to address the functionally important subcortical connectivity in surgical planning, it has been shown that the standardized reconstruction of DTI fiber tracts using the cortical TMS positive points as starting points for the algorithm significantly increases the clinical value of the DTI tractography.[21,23] In addition, it has been shown that the use of nTMS data increases the accuracy and specificity of cortical spinal tractography in a user-independent manner compared with those achieved with conventional FT based on anatomic landmarks.[22,24] Although predominantly used for presurgical counseling and planning, the TMS and TMS-based DTI results are also used during surgery by importing the data into the neuronavigation.

In terms of comparing treatment outcomes of patients with tumors in presumably motor-eloquent locations who received a preoperative TMS examination with the outcomes of patients before the introduction of nTMS, studies have shown that significantly more complete resections were achieved in the TMS group with a reduced incidence of new long-term postoperative motor deficits.[56-58] In the subpopulation of low-grade gliomas, prolonged progression-free survival and reduction in the rate of permanent deficits has been claimed as a result of the improved resection extent.[59] Also, shorter operation times due to more efficient intraoperative orientation and guidance of intraoperative monitoring (IOM), as well as shorter hospital stay and an overall beneficial impact on treatment efficiency and cost-effectiveness, have been reported.[60,61] The TMS work-up might also be beneficial for patients with metastatic brain disease.[62]

From a practical point of view, preoperative nTMS work-up including the mapping procedure itself and nTMS-based functional tractography requires 1 hour per patient. Dedicated staff is not necessary but was frequently shown to ease the whole workflow for the clinical team if present.

Because of the overall improved workflow, the implementation of nTMS in the clinical setting seems to be cost-effective on the one hand, but also potentially cost neutral owing to quicker surgery and more targeted approaches.[60,62]

Risk Stratification by Means of nTMS via Corticospinal Excitability in Motor and Language Area–Related Surgery

In surgery of intrinsic brain tumors, any residual tumor volume negatively affects progression-free survival.[63-65] The surgical goal is therefore to achieve as extensive a resection of the tumor as possible, without compromising function. However, following this principle in eloquent brain tumor surgery poses a special challenge to the preoperative pact between patient and surgeon and always includes the risk of inducing a new functional deficit, which usually decreases the patient's quality of life and correlates with shorter survival.[66] In the context of patient counseling, the possible gain in survival time through surgery must therefore always be estimated as accurately as possible against the morbidity risk. In brain tumor surgery and especially in the case of gliomas located in presumably eloquent areas, counseling the patient exclusively based on anatomic data is not sufficient. First, anatomic landmarks can be misleading for identification of functional areas even in healthy people, and even more so in patients with lesioned brains.[67] Second, the anatomic imaging and also the clinical status of the patient do not allow one to infer any reliable assessment about the "functionality" of the functional—here, the motor—system. The functionality and functional reserve can differ in seemingly similar cases significantly, making one motor system much more vulnerable and therefore prone to surgically inflicted motor deficits than another.[68] The aim of any preoperative functional analysis must therefore be to identify those areas that carry essential function—that is, functional areas that are not redundant and in which damage would cause a permanent neurological deficit—and to specify the vulnerability of these areas to potential surgically inflicted injury.

With nTMS, clinicians have a procedure at their disposal that allows them to localize the motor areas preoperatively with sufficient accuracy and reliability to routinely use this information for risk-benefit considerations in the case of supposedly eloquently located tumors. In combination with TMS-based DTI tractography, it enables patients to be divided into high-risk and low-risk cases depending on the spatial relationship between the tumor and motor-eloquent brain tissue and the excitability profile of the motor system between both hemispheres. The combination of anatomicofunctional and neurophysiologic measurements derived from presurgical nTMS analysis allows one to assess the risk of functional deterioration and the potential for functional recovery in eloquent brain tumor surgery by using objective data. This kind of risk stratification analysis can facilitate preoperative risk-benefit balancing and patient counseling as well as the consequent decision making before, during, and after surgery.[68,69]

The current risk stratification model is based on three items. First, on the cortical level, tumorous invasion of the primary motor cortex—that is, nTMS-proven function within the border zone of the cortical aspect of the glioma—is a significant risk factor for postoperative functional deficit. Second, subcortically, studies on large clinical samples have identified 8 to 11 mm of minimal distance between the TMS-based depiction of the corticospinal tract (CST) and the tumor—that is, the targeted resection volume as depicted in the surgical planning software—as a safe distance

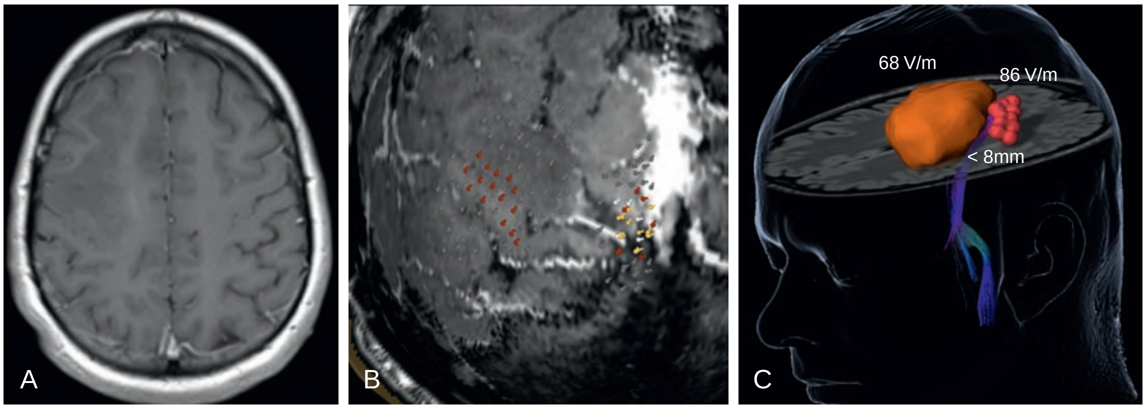

Figure 8.2. Transcranial magnetic stimulation (TMS) risk stratification for lesions presumably affecting the motor system. (A) Axial T1 contrast enhanced MRI scan demonstrating a hypointense lesion of the posterior frontal lobe in a 37-year-old man with a discrete coordination impairment of his left hand. (B) TMS mapping result. *Colored pins* = TMS-induced motor evoked potentials outlining the primary motor cortex for hand and lower limb muscles (*red* = motor evoked potential [MEP] 50–500 μV; *yellow* = MEP 500–1000 μV; *white* = MEP > 1 MV; *gray* = no primary motor function). (C) Three-tier risk stratification. (1) Targeted resection volume *(orange)* does not involve the primary motor cortex *(red).* (2) Minimal distance between targeted resection volume and TMS-derived corticospinal tract <8 mm (increased risk). (3) Resting motor threshold (RMT): *left,* 86 V/m; *right,* 68 V/m = pathologic excitability profile (increased risk). The results indicate a high-risk case in terms of probability of a new motor deficit after surgery; statistically the risk for a new motor deficit after 3 months is 47% in this case.

without increased risk for a new postoperative motor deficit (Fig. 8.2). Third, with respect to cortical excitability, equally excitable hemispheres as seen in healthy subjects are associated with a better outcome and can therefore be handled as low-risk cases. Although increased as well as decreased excitability of the tumorous hemisphere has been demonstrated to be predictive of postoperative motor deterioration, impaired excitability of the tumor hemisphere is especially associated with an increased morbidity risk, confirming observations from stroke studies.[70] The reliable differentiation of eloquent from resectable areas is crucial to ensure the best possible surgical treatment success for the individual patient. By creating an individual risk profile, the nTMS enables an optimized risk-benefit assessment, and patients can be better informed about individual chances and risks of their treatment options.

Concerning nTMS-based risk stratification for motor-eloquent lesions, one study proved that patients with a distance between the lesion and the nTMS-based DTI FT of at least 11 mm do not have an increased risk of sustaining permanent worsening of language function due to resection. As for motor function, such data allow not only for patient consultation but also for altering the surgical approach.

In addition to measuring the distance between the lesion and tracts, another approach has been proved to correlate with the risk of a new postoperative aphasia. Error rates (ERs) provide data on the number of induced naming errors during language mapping divided by the number of nTMS stimulations in this area. If both hemispheres are mapped, ERs can be computed for each individual hemisphere, and thus the calculation of a so-called hemispheric dominance ratio (HDR) can be done by dividing the left-hemispheric ER by the right-hemispheric ER.[71-73] This HDR can then be used to quantify hemispheric language dominance (following the terms of nTMS): HDR >1 reflects left-hemispheric language dominance, whereas HDR <1 indicates right-hemispheric language dominance.[71-73] For this HDR, two studies have shown (1) that patients with left-sided perisylvian lesion have more language function on the right hemisphere compared with healthy volunteers,[71] and (2) that HDR indicating left-sided language dominance leads to a higher risk of sustaining a surgery-related transient aphasia in left-hemispheric tumor surgery compared with patients with a lower HDR, thus indicating more right-sided language function.[72]

nTMS LANGUAGE MAPPING

nTMS Data and Tractography of Language Networks

General Aspects

In contrast to motor mapping via single-pulse TMS, the examination of language function uses rTMS, which induces language errors by disturbing cortical function momentarily by means of a "virtual brain lesion."[74,75] This causes depolarization of the underlying neurons, firing a series of pulses followed by a longer phase of GABAergic inhibition.[76] This concept of inducing a "virtual brain lesion" is also used via DCS during awake surgery and mapping. In general, language mapping with rTMS has been extensively studied in the past 20 years, and studies have shown that it was safe, tolerable, and reproducible.[28,77,78] However, only the introduction of neuronavigated rTMS established this technique for preoperative mapping. It enables brain maps of language-positive and language-negative regions for preoperative planning, consulting, and intraoperative guidance. Studies comparing preoperative mapping results of rTMS with intraoperative language mapping by DCS during awake surgery have shown that specificity and positive predictive values are too low but sensitivity and negative predictive values are considerably high. rTMS seems to identify not only language-eloquent but also language-involved cortical areas, thus allowing one to identify language-negative cortical areas reliably with a negative predictive value of 98% to 100%.[33] Moreover, for both motor and language function, nTMS has been shown to be less susceptible to artifacts than fMRI because it is not affected by oxygenation changes.[54,79]

Diffusion Tensor Imaging

DTI demonstrates white matter tracts by using the anisotropic nature of the white matter substance through measurement of the translational displacement of water molecules.[80-82] Because water diffuses most easily along subcortical fibers rather than perpendicular to them, the direction of fastest water diffusion shows the orientation of white matter fibers.[83] This technique is routinely used in neuroscience for various approaches, but also to calculate white matter tracts by using DTI FT in neurosurgical patients for preoperative work-up, such as the CST and language-eloquent

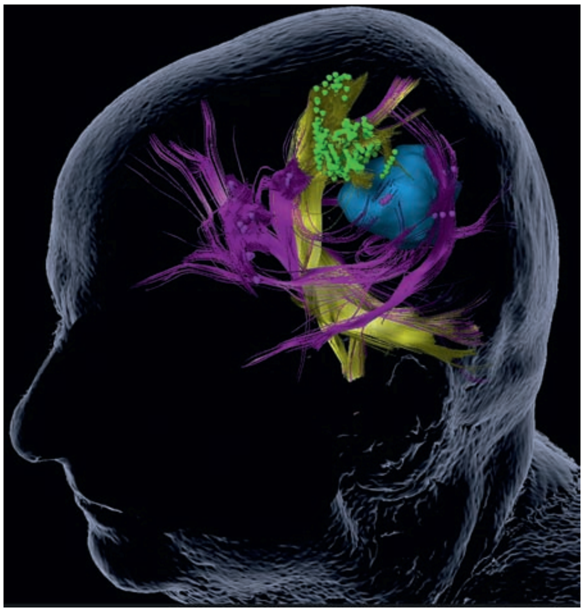

Figure 8.3. Visualizing function anatomy. This screenshot shows preoperative planning for a patient with a left angular glioblastoma. *Blue:* Tumor; *purple dots:* language-involved cortical areas; *purple fibers:* language-involved fiber tracts; *green:* motor evoked potential (MEP)–positive motor areas; *yellow:* corticospinal tract.

fiber bundles. However, although many studies have investigated the usefulness and different approaches for this technique, its major weakness is its limitation to structural connectivity. DTI FT does not give any information about the type of function of the visualized fibers. In order to assign particular functions to the visualized fibers, so-called regions of interest (ROIs) need to be defined either by using anatomic data or based on functional data.

nTMS offers us a unique possibility to assign functional specifics to the visualized tracts, as has already been shown for use of nTMS data for ROI seeding of the CST.[21-23] Single-pulse nTMS is performed to identify the motor-eloquent cortex, and nTMS spots, eliciting a muscle stimulation, were defined as part of the motor cortex, thus allowing specific tractography of fibers originating only from cortical spots with a motor response (the CST). Cortical language areas vary from patient to patient. In addition, anatomy-based ROI seeding strongly depends on the individual examiner.[84,85] Function-based DTI FT is based on functional data for ROI seeding gained from fMRI, MEG, or nTMS. Therefore function-based ROI seeding and DTI FT appear more suitable. nTMS-based DTI FT is done by increasing the volume of the identified cortical language-involved areas first, and then providing a considerable minimum fiber length of 80 to 100 mm and a functional anisotropy threshold of 0.1.[86] These enlarged cortical spots are than used as seed regions for reconstruction of language-associated white matter, which has even been shown to correlate with the clinical status over time.[39,40,87]

Language processing is a complex and especially subcortical mechanism,[27] yet it is crucial to take all known language-associated subcortical white matter tracts into account when planning surgical approaches. nTMS-based DTI FT allows for standardized visualization of subcortical anatomy and therefore superior surgical planning (Fig. 8.3).

nTMS Language Mapping and Its Clinical Use

In the last 4 years there have been an increasing number of studies investigating the feasibility but also the clinical value of nTMS-based DTI FT for the reconstruction of language-related subcortical white matter tracts for preoperative planning and intraoperative application for patients with left-hemispheric perisylvian space-occupying lesions.

Because classical language models, including the Broca and Wernicke areas as expressive and receptive language regions, have been mostly discarded in favor of a hodotopic model of language function, the definition of language-eloquently located brain tumors is no longer an anatomic one, but requires individual mapping.[27,88] In particular, studies have been able to show that tumors commonly defined as language eloquent by anatomy are frequently located in areas not involved in language processing at all.[89-92] Moreover, several studies have also shown the same phenomenon: language-eloquent areas, in particular, reveal function reorganization enabling further resection over time.[35,41,93-95] Thus language-eloquent cortical regions widely vary from patient to patient but also over time, and likewise subcortical functional anatomy.[96] Therefore there is a strong need for preoperative functional mapping for cortical and subcortical visualization of language-eloquent anatomy in modern glioma surgery. nTMS has been shown to reveal such reorganization and therefore is the only noninvasive method that is actually able to include functional reorganization in surgical neuro-oncology on a cortical[41,95] but also a subcortical level.[39]

For the clinical application of nTMS language data, it is crucial to consider that compared with DCS, nTMS has only a high negative predictive value.[31] Clinically, this means that we cannot reliably predict DCS-positive sites, but we are able to define and predict DCS-negative sites, thus allowing definition of which areas are safe to resect.

Currently nTMS has three different applications when it comes to language mapping:

1. Identifying cortical areas involved in language production for indication planning awake surgery versus wait and scan versus asleep surgery
2. Providing seed regions for nTMS-based DTI FT
3. Providing data for intraoperative use to guide awake DCS mapping (Fig. 8.4)[97]

For small noninfiltrative lesions such as cavernomas or metastases in supposedly language-eloquent locations, nTMS data can help in deciding whether resection and corticotomy can be performed during asleep surgery or whether resection might be safer with the patient awake. For glioma patients, nTMS data can be used to identify function reorganization, enabling further tumor resection.[41]

However, nTMS is not meant to replace awake DCS mapping, but rather to guide it. By having the data available during awake DCS mapping, the surgeon is able to perform faster and more focused DCS mapping if integrated in the neuronavigational system (see Figs. 8.4 and 8.5). This can enable tailoring of not only the mapping procedure but also the surgical approach with use of smaller craniotomies, as implied by published data.[98]

An increasing number of studies are reporting the sole use of nTMS and nTMS-based DTI FT for the resection of language-eloquent lesions. In addition to strict indication planning, these investigators report excellent functional and oncologic outcomes.[99,100]

SPECIAL ASPECTS

Integration of Functional Data in the Clinical Workflow

The success and adoption of any new technique requires suitable and smooth integration into the departments' procedural and electronic workflows, including easy availability of these data. These aspects are decisive for acceptance but also the active use of the exceptional information nTMS can deliver. Consequently, any implementation of nTMS data into a neurosurgical department

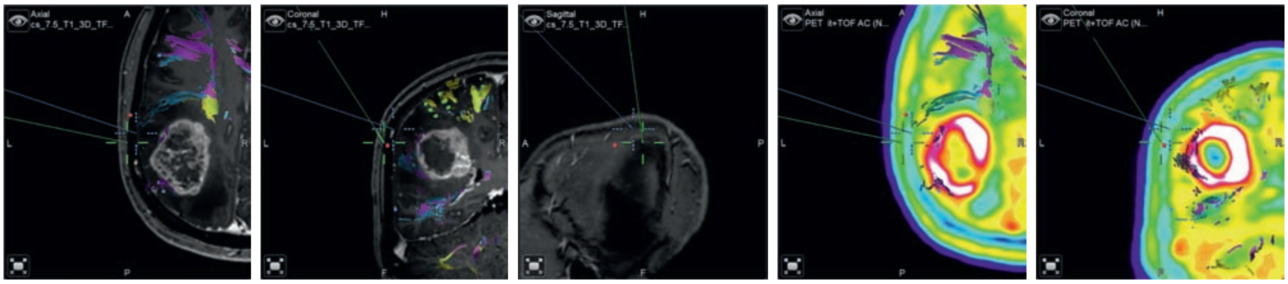

Figure 8.4. Intraoperative navigated transcranial magnetic stimulation (nTMS)–guided direct cortical stimulation (DCS) mapping. Intraoperative screenshots during awake mapping in another patient with a left angular glioblastoma. *Purple dots:* Language-involved cortical areas; *purple fibers:* language-involved fiber tracts; *green:* motor evoked potential (MEP)–positive motor areas; *yellow:* corticospinal tract; *blue dots:* cortical areas involved in arithmetic processing; *blue fibers:* white matter tracts involved in arithmetic processing. Preoperatively acquired functional guide intraoperative DCS mapping.

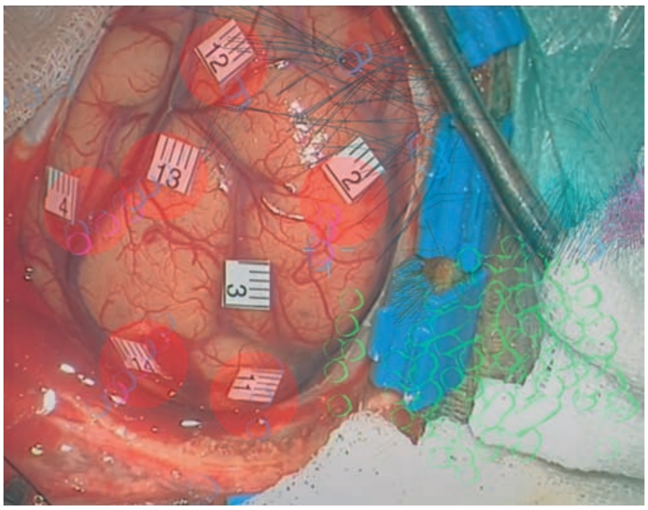

Figure 8.5. Functional overlay. This intraoperative photograph shows the data overlay during awake mapping. The one-digit paper tags show cortical areas involved in language processing; two-digit paper tags indicate cortical areas involved in arithmetic processing.

involves not only the mapping process and workflow itself, but also other aspects, such as:

- Full integration into the respective cancer center's clinical workflow, and likewise for the neurovascular center
- Smooth integration into the hospital's electronic infrastructure—that is, the picture archiving and communication system (PACS), hospital information system (HIS), and neuronavigational infrastructure (Brainlab iPlan Net, Medtronic StealthStation, and others)
- Staff education regarding the potential and limitations of nTMS

To begin with, indication for nTMS mapping is usually based on anatomic tumor location according to MRI. Therefore nTMS mapping needs to be performed prior to the discussion of the case by the interdisciplinary tumor or neurovascular board. As outlined earlier, nTMS mapping is indicated if language- or motor-related brain areas are affected via compression or infiltration of the anatomically suspected functional cortex with or without proximity to the respective subcortical pathways. Likewise, even transient impairment of function can be a potential sign of tumor proximity to eloquent cortical or subcortical structures despite anatomic considerations that might not suggest an eloquent location.

Concerning electronic infrastructure, nTMS data can be easily integrated into the HIS via a tailored software mask, which can be programmed individually by the manufacturer of the HIS or the hospital's information technology department within days. By doing so, relevant patient details, timing of the examination, availability of relevant imaging data, neurological status, medication, and potential contraindications, and also the specific question regarding the nTMS investigation, can be integrated into the electronic documentation. The same is true for the mapping results. Standardized reporting not only helps in obtaining easily understandable data but also eases reimbursement. Thoese details can be stimulation details, RMT, infiltration of cortical and subcortical structures, and distances between lesion and functionally relevant brain areas. Moreover, mapping data need to be stored within the PACS for long-term storage. Thus the data can be exported and transferred in Digital Imaging and Communications in Medicine (DICOM) format. The DICOM format allows nTMS data to be imported to the PACS of any hospital, like any other imaging data from external institutions.

Yet, as with any other technique, it is crucial for success that the staff be provided sufficient time to learn how to use nTMS data effectively. Surgeons need to gain trust in the data and also to learn for themselves how they can use the provided data for their own practice appropriately. For more information on this topic, we put together our own experiences of 7 years with nearly daily clinical use of nTMS data in our neurosurgical department in a recent article.[101] This experience resulted in a stepwise integration into our electronic infrastructure and our clinical workflow including standardized reports of each nTMS examination and availability during tumor board meetings, but also for other departments such as the department of radiation oncology.

Arteriovenous Malformations

nTMS data have also been reported to be useful for a more objective grading of arteriovenous malformations (AVMs).[102-105] Although nidus size and drainage are fully objective parameters, eloquence is, in light of current findings on neuroplasticity, a definition requiring a more objective approach. nTMS was shown to change Spetzler-Martin grading in 9 of 34 cases, and in 6 cases nTMS data changed the indication toward a nonsurgical approach.

RADIOTHERAPY

Several studies in recent years have analyzed the usefulness of nTMS for radiosurgery and radiation therapy planning.[106-110] Especially for radiation therapy of brain metastases and gliomas, it could be shown that the dose to eloquent cortex could be reduced without affecting the treatment dose to the target area. In these studies, treatment plans were optimized by defining nTMS motor areas as organs at risk, which were therefore spared during contouring of the treatment plan. Although randomized data are not yet available, the available cohort data from four different centers seems rather convincing, as the treatment dose to the target volume was not at all affected. Whether this fact will enable more aggressive radiation treatment has yet to be investigated, but it nevertheless provides interesting new options.

POTENTIALS AND LIMITATIONS

Independently of the person who is actually performing the mappings, accurate and standardized mapping algorithms need to be ensured in order to generate beneficial data for surgery and patient consultation. However, despite the fact that nTMS data can guide and shorten intraoperative DCS mapping, it should not replace DCS mapping or IOM. It is a valuable adjunct for every experienced IOM program but not a competing technique. IOM starts rather than ends with nTMS; nTMS facilitates appropriate patient selection and approach planning.

A further limitation is the range of the magnetic field, which makes it impossible to reach temporomesial and frontobasal gyri, as well as brain areas covered by large meningiomas or arachnoid cysts. Because we cannot rule out eloquent cortex underneath such lesions owing to stimulation intensity that is too low to reach the cortex, the use of nTMS in meningiomas can even be harmful. Thus, despite the fact that stimulation does not elicit any motor responses or language impairment, the low stimulation intensity may not reveal eloquent cortex.

Besides such limitations, another potential use of nTMS might lie in the objective evaluation of visual pathway pathology. Although many other functional systems are well investigated, only a small number of studies on eliciting phosphenes by visual cortex stimulation have been performed.[111]

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