Current and potential utility of transcranial magnetic stimulation in the diagnostics before brain tumor surgery

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Practice points

- Navigated transcranial magnetic stimulation (nTMS) is the only noninvasive technology to electrically stimulate or inhibit circumscribed areas of the cortex analogous to the gold standard of direct cortical stimulation.
- nTMS motor mapping is of equal accuracy and validity like direct cortical stimulation.
- nTMS improves presurgical decision-making and outcome in patients with motor-related brain tumors.
- Repetitive nTMS allows to probe cortical areas with respect to their involvement in language processing.

SUMMARY This article describes the evolution and state-of-the-art of navigated transcranial magnetic stimulation for evaluation of patients with brain tumors in presumed eloquent location. Alternative noninvasive technologies for functional brain mapping are described and assessed in the context of their usability and clinical needs. In addition to the description of the current validation level and clinical application of navigated transcranial magnetic stimulation for motor and language mapping, the manuscript highlights ongoing research efforts and provides an outlook on upcoming developments in the field of noninvasive brain mapping. Finally, the clinical rationale for presurgical noninvasive brain mapping is discussed in the light of current developments in neurosurgery.

KEYWORDS

• brain tumor • functional diagnostics • language mapping • motor mapping • noninvasive mapping • surgery • TMS • transcranial magnetic stimulation

Noninvasive functional mapping prior to brain tumor surgery: pros & cons

Despite all research efforts and billions of dollars invested into neuroscience with efforts predominating to decipher the functioning of the brain, neurosurgery in general has remained the same since introduction of intraoperative electrostimulation in the first half of the 20th century and the introduction of microsurgical technique in the second half. Yet, currently, we are in the midst of another fundamental paradigm shift. The concept of a modular, largely static system of functional topography has been questioned by longitudinal mapping studies and refined imaging studies. The neurosurgical community is gradually adopting a new concept in which function is represented in parallel networks of dynamic large-scale cortico–subcortical systems, commonly referred to as the ‘hodotopical’ understanding of brain function [1,2]. This has significant implications especially for the treatment of intrinsic brain tumors. The traditional view that certain locations of brain lesions render them *a priori* as inoperable has to be questioned. Certainly, preservation of crucial neurological function is of utmost importance in neurosurgical treatment, but the potential for functional reorganization when a brain tumor threatens to compromise functioning by activation of alternative

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or latent pathways cannot be overestimated [3–6]. Recent studies applying noninvasive functional studies have demonstrated the significant short- and long-term impact of brain lesions on the functional topography in tumor, as well as epilepsy patients [7,8]. The functional relevance of cortex surrounding a tumor is almost impossible to predict from anatomical imaging studies. The concept of the minimal common brain describes this phenomenon by demonstrating that outside a few ‘common’ locations all cortical areas can be potentially resected without neurological sequel [9]. This paradigm shift implicates the need for functional imaging studies to delineate the tumor’s spatial relations within the functional network and to follow-up functional reorganization in patients with lesions in critical location. It is mandatory to have a noninvasive method for this, since repeat surgery to detect potential plastic changes is not feasible. For patients with brain tumors in critical location, the paradigm shift is only beneficiary if noninvasive functional imaging is broadly available. Certainly, this noninvasive technique would need to be as reliable as the gold standard of intraoperative electrical mapping (IOM), easy available and preferably quick and cheap.

On the other hand, the majority of ‘routine’ brain tumor surgeries can be performed safely without time consuming and costly imaging or intraoperative studies. The question whether widespread availability of functional imaging studies and the implementation of these results into the clinical routine can lead to a neglect of important basic neurosurgical skills, namely fundamental anatomical knowledge and the capability of intraoperative orientation has been raised.

The conclusion of this opening paragraph is that the basic principle of improving quality in healthcare has to be honored keep the established capabilities and workflows and add new technical possibilities in a careful and goal-orientated way.

The evolution of transcranial magnetic stimulation in neurosurgery

Although transcranial magnetic stimulation (TMS) has been used in clinical practice since 1985 [10], it has been largely neglected in neurosurgery for over two decades. A couple of manuscripts hinted at the potential of TMS as a mapping tool in neurosurgery as early as 1996, but these sporadic studies did not go beyond proof-of-concept analyses [11–13].

Three almost parallel developments triggered the introduction of TMS mapping into neurosurgery. First, the realization that task-dependent functional imaging does not routinely fulfill requirements for accuracy or availability mandatory for neurosurgical planning especially for language mapping [14], but also for motor mapping [15]. Second, the technical improvement of combining TMS and neuronavigation, which led to the development of E-field navigated TMS [16]. Third, the recent paradigm shift from the concept of rigid anatomico-functional systems depicting certain functions to specific brain regions to the concept of dynamic functional networks in which function is represented and maintained by a highly individual connectivity pattern [1].

Interestingly, TMS was scrutinized with respect to its accuracy in comparison to direct cortical stimulation from the beginning. This can be seen as a major difference to the introduction of functional MRI (fMRI) into neurosurgical practice in the early 1990s, when the technology was used for neurosurgical planning and only after a couple of years, studies dedicated to its accuracy in comparison to the gold-standard were undertaken [17,18].

Single-pulse mapping

• Motor mapping

Neurons are electrically excited at lower thresholds when applied voltages induce currents oriented longitudinally along the axon rather than transversely across the axon [19–21]. Therefore, single-pulse TMS motor responses are sensitive to the orientation of the coil (i.e., the parallel orientation of the E-field and the trajectories of pyramidal tract axons) [22,23]. The columnar organization of the cortex explains why single-pulse motor mapping should be carried out with the coil orientated perpendicular to the nearest sulcus. Optimal coil orientation and tilting allow for evoking motor responses at very low stimulation intensities, a key element to enable focal mapping. Low stimulation intensities result in rapid decay of the induced E-field with increasing distance from the coil and activation of the corticospinal tract results from a combined activation of trans-synaptic pathways and direct stimulation of the axons deeper in the gray matter [24].

The introduction of E-field navigated TMS into neurosurgery has enabled clinicians to adhere to the above-mentioned guidelines in

clinical routine. Several studies have been conducted to examine the accuracy of navigated TMS in comparison to the result of direct cortical stimulation. The results consistently reported a high validity of navigated TMS for identification of the primary motor cortex. In 11 studies, 125 attempts to identify the primary motor cortex in 124 patients with brain tumors in presumed motor eloquent location were described. In total, 124 attempts (99.7%) were successful [25–35]. In addition, the congruency between IOM and navigated TMS for outlining the cortical representation of specific muscle was analyzed. Again, a good to excellent correlation was reported [36].

For routine clinical use, the consistency of the resulting functional map over time and between different examiners is equally as important as the accuracy. For navigated TMS, the consistency of the motor map over time and between different examiners has been proven [37–40]. It has been demonstrated that implementation of navigated TMS motor mapping into the routine preoperative work-up can lead to modification of the treatment strategy in up to 55% of the cases [28,30]. Recently, a study comparing the outcome of patients with brain tumors in the vicinity of motor areas treated with preoperative TMS mapping and before the introduction of TMS reported improved oncological and functional outcome for the TMS group [41].

• TMS-based diffusion tensor imaging tracking (motor)

The hodotopical view of cerebral function (i.e., its organization in dynamic networks) stresses the importance of long association fibers for functional integrity. Evidence is increasing that compromise to the connectivity between two cortical functional hubs is even more detrimental (i.e., more unlikely to allow for recovery, than cortical damage) [9,42].

Although the rapid decay of the magnetic field with distance to the coil restricts the effect of TMS in preoperative mapping with stimulation intensities just above the resting motor threshold predominantly to the cortex, direct effect on superficial parts of the white matter or confounding network effects cannot be ruled out. However, TMS has been validated to reliably allow for delineation between functional important and ‘resectable’ cortical tissue. Consequently, it can be deferred that tracts originating from ‘TMS-positive’ cortical motor spots

are also functionally indispensable. In addition, this approach has the advantage over conventional knowledge-based seed point determination that it allows for standardization of the procedure, making comparison between diffusion tensor imaging (DTI) trackings of different examiners possible [43,44]. Whether this approach does represent the functionally relevant tracts or under- or over-calls their spatial extension still needs to be clarified. It should be stressed that preservation of subcortical connectivity is crucial to avoid postoperative permanent deficits. The current level of evidence does not justify the use of DTI tracking for definition of subcortical resection margins. Consequently, intraoperative subcortical stimulation mapping has still to be considered mandatory for surgery of invasive brain tumours in critical subcortical location.

• Neurophysiological evaluation of motor system integrity

The time it takes neural impulses elicited over the motor cortex to reach the target muscle is routinely measured to estimate the severity of neurological disorders affecting the motor system. The impact of brain tumors on the conduction time and other neurophysiological measures has recently been addressed. Whereas the resting motor threshold (as a measure of cortical excitability), the motor evoked potential (MEP) latency (motor conduction time) and the MEP amplitude (quantifying the peripheral response) do not vary between TMS excitation of the left or right motor cortex in healthy volunteers [45]; these measures demonstrate significant variation in patients with brain tumors. Interestingly, these variations are seen also in patients without neurological symptoms, which theoretically qualify the neurophysiological variables to serve as predictors for imminent neurological deterioration – or high risk for surgically inflicted motor deficits [46]. In addition, regular MEPs evoked over the motor cortex in a paretic patient can be predictive of postoperative functional recovery [47].

Inhibition mapping

• Principles

The electric field induced by TMS stimulates neurons, particularly in superficial regions of the brain. This mechanism serves for excitation mapping such as that outlined above for the motor cortex. But depending on the stimulation intensity of the single impulse or the cumulative

stimulation dose in repetitive stimulation, TMS can also interfere with cognitive function. Higher intensities can disrupt processing by causing an artificial synchronization of neuronal populations followed by a transient GABAergic inhibition [48]. This phenomenon is generally termed ‘virtual lesion’. Smaller TMS intensities or doses may not stop cognitive operations but add enough noise to effectively suppress the intended outcome of the respective operation. Increasing noise and true inhibition probably occur both together in clinical practice as a function of stimulation intensity and dose.

Inhibition mapping by disturbing or disrupting neuronal processing does not provide the same anatomico–functional causal relationship like single-pulse motor mapping. Whereas it is likely that an area, the stimulation of which suppresses a certain function, is critically involved in the respective task, it is also possible that the effect is provoked by projections to the critical area but that the stimulated area itself has no or at least no essential part in this task [49]. In addition to the possibility of disrupting processing in brain regions far away from the stimulation site via white matter projections, the ‘state of mind’ also influences inhibitory mapping more than excitatory mapping. The exact pattern of the cognitive performance (reflecting the task design), the attention level of the subject (invariably subject to fluctuation) and the existence of confounding actions (it is virtually impossible to perform exclusively one task without any co-activation) significantly influence the susceptibility of the network to TMS disruption. Stimulation at the same site can lead to different results depending on the current attention level of the subject and the specific task performance. The underlying processes have been termed ‘state-dependency’ of TMS-induced effects [50]. According to this concept, the effect of TMS on a certain brain region also reflects the activation state of that area and of functionally connected brain regions. A strong disruptive TMS effect in an activated neuronal population presumably is also transmitted stronger to the connected brain regions; yet, interpretation of state-dependent effects is always speculative [49]. The activation dependency within the complexity of cortico–subcortical networks certainly also confounds the interpretation of efforts to map cognition.

Reliable presurgical mapping of cognitive function depends on stable examination protocols and settings. It is more demanding and

prone to misinterpretation than single-pulse motor mapping.

• Language mapping

TMS has been used to investigate language function since the early 1990s [51]. Clinically efforts were initially targeted at establishing TMS as an alternative tool to WADA testing for identifying the dominant hemisphere [52,53]. Interestingly, with respect to examination of language processing, TMS has been shown from early on to suppress but also to enhance functioning [54,55]. The potential of TMS to also map language function with high spatial accuracy was, for example, demonstrated by studies that observed distinct locations within the left inferior frontal gyrus for semantic and phonological processing [55].

Language mapping in brain tumor patients faces the same obstacle like the early attempts to identify the dominant hemisphere (i.e., the tendency to overcall involvement of atypical left or right hemispheric involvement) [56]. This is exemplified by studies that have demonstrated an overall increased susceptibility to repetitive TMS and in particular a ‘shift’ of language function towards the right hemisphere in patients with left-sided brain pathologies [57,58]. This observation adds to the growing body of evidence that the language network is based on an almost parallel connectivity map of both hemispheres as demonstrated in noninvasive imaging [59,60] and IOM studies [61,62]. It has been proposed that basic language processing, for example, repeating a syllable, is processed bilaterally. But when the basic sound mosaics are put together to create meaning and language (i.e., when more complex computation and integration of subfunctions is necessary), the role of the left hemisphere is clearly dominating [2]. The challenge for presurgical language mapping is to identify those areas that are essential for language processing against the background noise of the whole language network, which spreads over large parts of both hemispheres.

In analogy to the well-established procedure of intraoperative confrontational object naming during awake craniotomy, attempts have been made to use repetitive TMS to disrupt object naming in healthy volunteers and also in patients. Interestingly, even with very similar set-ups in terms of stimulation parameters and language task presentation, the success rates reported in the literature differed markedly in early studies [51,54,55,63]. Nevertheless, these

studies already presented convincing evidence that disruption of object naming with repetitive TMS of frequencies between 4 and 10 Hz is feasible.

More recently, three studies have compared navigated repetitive TMS language mapping to the gold standard of intraoperative language mapping during awake surgery [64–66]. The studies applied similar stimulation parameters and used a standard object naming task. The major methodological differences in comparison to the earlier studies were the implementation of neuronavigation and the analysis of the stimulation result based on a detailed review of video recordings [67]. The current studies report significant differences with respect to the observed sensitivity and specificity of the TMS results in comparison to the IOM results. The first study reported a significant overcalling of language-positive sites in comparison to IOM resulting in a low specificity (0.24) [64]. The more recent study demonstrated the same sensitivity (0.98) like the former study, but significant improvement in specificity (0.90) [65]. This variation between the study results cannot be attributed to the stimulation pattern or task design, but can only be explained by the subjective definition of a ‘language-positive’ cortical site. The best correlation between TMS and IOM results was observed when rigorous standards for error definition were applied and a cortical site was only deemed language positive when at least two out of three stimulations at the same site induced a clear language error [65].

The efforts to establish a TMS protocol, which allows performing cortical language mapping at comparable accuracy to the gold standard of intraoperative mapping, have so far produced promising results, but the specificity for identification of essential language sites is not yet satisfactory. Whereas several studies with similar protocols have proven the general capability of repetitive TMS to disturb language in a location-specific manner, the consistency of the mapping results is not yet fulfilling clinical needs. Further validation of protocols and testing of new stimulation patterns and task designs is needed.

Future directions

• Mapping of cognitive function

For almost a century, the focus of neurosurgeons with respect to preservation of function was almost exclusively targeted at motor and

language. Accordingly, the testing during awake surgery was composed of a motor task (e.g., fist clenching) and a standardized language task (object naming). In fact, this is still the standard set-up in many centers.

Only in recent years more comprehensive pre- and post-operative neuropsychological assessment has pointed out that regularly ‘other’ functions are deficient or are surgically compromised with a resulting decrease of quality of life. These other functions, often referred to as higher-order neurocognitive functions, typically include memory, attention, planning, learning, behavioral, motivational and visuo-spatial function. It has been pointed out in this context that an individualized intraoperative mapping regimen should not only correspond to the tumor location, but also to the socio-professional profile of the individual patient and also to his ‘tolerance’ for a potential neurological deficit [68]. Certainly, these considerations have to be balanced against the background of the intraoperative setting in which additional surgical time consumed by extensive testing automatically increases the surgical risk (infection, noncompliance, and so on).

It has been stated that the classical localizationist view of brain functioning (i.e., function is organized in modular, segregated areas) has to be replaced by a hodotopical view with brain function being represented in dynamic large-scale cortico–subcortical networks, which often work in parallel [69]. The huge plastic potential of the brain on the basis of these redundant networks has been demonstrated [3,70]. Here, the functional reorganization occurs almost exclusively on the cortical level rendering landmark-based localization of cortical function extremely unreliable in the presence of a brain tumor. Subcortically, the potential for functional reorganization appears to be much less pronounced [9] and damage to the long association fibers is frequently not compensable [42]. Two conclusions can be drawn from these observations. One, whenever subcortical involvement of long association fibers by an invasive tumor is suspected, subcortical IOM is mandatory. Two, the emerging awareness that quality of life is not only determined by the ability to move and to speak and the dilemma that extensive testing of various higher-order cognitive functions can be too time consuming for an awake surgery necessitates reliable preoperative mapping of different aspects of cognition.

In addition to the standard intraoperative motor and language mapping, the following

properties have been successfully mapped during brain surgery (i.e., the respective functions have been disturbed with trains of bipolar 50 or 60 Hz stimulation) [68], vision (induction of phosphenes or visual field deficits over the temporo-occipital junction), spatial awareness (disturbing of line-bisection task over the right parietooccipital junction), calculation (inhibition over the left parietal lobe), writing (inhibition over the medial prefrontal cortex), counting/naming/reading (inhibition over left posterior temporal lobe/perisylvian cortex), memory (inhibition dominant premotor cortex, temporal lobe), attention (inhibition over the frontal eye field), cross-modal judgement (inhibition over dominant dorsolateral prefrontal cortex, posterior temporal cortex) and emotion (disturbance over the posterior perisylvian cortex).

Navigated TMS with its capability to excite and inhibit cortical neuronal populations in a targeted fashion has the potential to transfer these intraoperative findings to the noninvasive setting [50]. Comparative studies between TMS and IOM findings for mapping of higher-order cognitive functions need to be conducted to better understand the potential of navigated TMS for presurgical cognitive mapping.

• Data interpretation & integration

Medical institutions of today are more and more driven by economic considerations and the average hospitalization time of the patient is continuously reduced. Physicians have to make more treatment decisions in shorter time, which implies that the decision-making process also has to become faster. Decisions for treatment of intracranial lesions are typically based on the patient's history and his current clinical status, but predominantly they are based on the imaging results. When uncertainty exists about presumed involvement of critical (i.e., potentially functionally essential) areas, noninvasive mapping results will be gratefully accepted as decision-makers [71]. The power of images in this setting cannot be overestimated. Consequently, the personnel creating these images have to apply strict rules in regard to the quality of the mapping results. The type of data and the way the data are implemented into the further clinical process has to be regulated carefully. It is mandatory to stick to the rule 'less is more' and use only data that are robust, with a similar decision-making power like IOM results.

Conclusion

• 'The best information you can get': the personalized approach

Major changes in medical practice are seldom. In neurosurgery the introduction of awake mapping and the microsurgical technique were cornerstones in the 20th century. The change from a localizationistic perspective of brain function towards the understanding of dynamic, interconnected and redundant networks is another historic change. For the individual patient, this means that phrases like 'A tumor in this location is inoperable' are or will become mostly outdated. We are obliged to make treatment decisions based on the best available evidence and major decisions are already done preoperatively, such as the decision about surgical indication. This implies that we have to use all necessary resources to understand the relationship between the disease (tumor) and the host (brain) as comprehensive as possible before counseling the patient preoperatively. Due to the interindividual variability of functional topography and the enormous potential for functional reorganization of the human brain, all lesions in 'presumed eloquent location' should be mapped routinely preoperatively before the patient is advised about the treatment alternatives. Questioning the usefulness of presurgical brain mapping is typically guided by two misconceptions. One, noninvasive mapping is threatening to take away IOM or at least delude surgeons to forgo IOM and be satisfied with the presurgical map. Two, there is no reliable noninvasive mapping tool.

The advantage of having detailed information about the functional topography available for patient counseling is as evident as having the anatomical resolution of MRI available in comparison to rely on CAT scan data only (and no study has ever proven the clinical benefit of using MRI). Routine integration of valid functional data into the presurgical imaging work-up is a logical consequence of scientific findings (i.e., the highly individual organization of functional networks) and technical improvements (i.e., TMS as a validated tool for noninvasive mapping).

• 'A plethora of opportunities': keeping a clear overview

Although various methods for noninvasive functional mapping have been introduced over the last decades (electroencephalogram, PET, magnetoencephalography [MEG] and fMRI)

Figure 1. Case example: 'Clarifying the location of an extra-axial tumor in relation to the precentral gyrus and the pyramidal tract'. (A) Centrally located metastasis in a 64-year-old male with a mild right-sided hemiparesis (T1 gadolinium-enhanced MRI); tumor location in regard to central sulcus unclear. (B) Overlay of the virtual 3D head model derived from MRI imaging and the actual patient head by means of surface registration to enable real-time neuronavigation. (C) nTMS stimulation mapping. Navigation of the stimulation coil in relation to the patient head is enabled by reflective spheres attached to the nTMS coil and to the custom-made glasses. (D) Postcentral location demonstrated by nTMS. (E) Left: neuronavigational planning: tumor (red), cortical nTMS-positive spots and nTMS-based DTI tracts (yellow); right: injection of nTMS motor-positive spots into the microscopic view (dotted yellow circles) to depict the precentral gyrus; note the mandatory congruency between the virtual outline of the precentral gyrus and the real anatomy. Surgery was performed without intraoperative electrical mapping with full functional recovery postoperatively. DTI: Diffusion tensor imaging; MR: Magnetic resonance; nTMS: Navigated transcranial magnetic stimulation.

For color images please see www.futuremedicine.com/doi/full/10.2217/cns.14.25.

Figure 2. Case example: ‘Clarifying the resectability of an invasive tumor located within the precentral gyrus’. (A) Gadolinium-enhanced T1 MRI of a low-grade glioma within the precentral gyrus (hand knob) in a 23-year-old male with no neurological deficit; well-defined brain–tumor interface (same tumor volume in T1 and fluid attenuation inversion recovery weighted images); difficult risk–benefit balancing. (B) Overlay of the virtual 3D head model derived from MRI imaging and the actual patient head by means of surface registration to enable real-time neuronavigation. (C) nTMS stimulation mapping. Navigation of the stimulation coil in relation to the patient head is enabled by reflective spheres attached to the nTMS coil and to the custom-made glasses. (D) nTMS demonstrates no motor function within the cortical aspect of the tumor; mutual agreement in favor of tumor resection is reached. (E) Left: tumor (red), cortical nTMS-positive spots (yellow) and nTMS-based DTI tracts (blue); right: microscopic view of resection cavity with injected DTI tracts. Note: DTI tracts are only used for guidance of the subcortical stimulation probe. Surgery was performed with continuous intraoperative electrical mapping. No permanent postoperative motor deficit occurred. DTI: Diffusion tensor imaging; MR: Magnetic resonance; nTMS: Navigated transcranial magnetic stimulation.

For color images please see www.futuremedicine.com/doi/full/10.2217/cns.14.25.

their clinical use for surgical planning has been limited to specialized centers. The reason is that none of the available methods so far has fulfilled all three demands for a clinical imaging tool: accuracy, reliability and availability. All methods have their specific advantages (e.g., the temporal resolution of MEG) and their specific disadvantages (e.g., the investment/maintenance costs and time-consuming data analysis of MEG). The most widely available methodology, fMRI, is routinely used to visualize motor and language representations preoperatively and can currently be regarded as the methodology of choice to investigate whole brain patterns of functional connectivity. Although all functional imaging methods can deliver reliable results in expert hands, their task dependency and complex statistical analysis of raw data prevents their implementation as a routine tool for preoperative decision-making.

Certainly, adhering to the motto ‘stay with what you know’, individual set-ups for functional imaging can work well with all mentioned technologies if the imaging team and the surgical team work closely together and have profound knowledge of and experience in interpretation of the functional imaging results. The only method so far that can be considered as a useful routine clinical tool (i.e., fulfilling the above-mentioned three criteria) is navigated TMS for mapping of the primary motor cortex. The scientific evidence that the mapping result satisfies demands for accuracy and reliability is sound and the procedure is fast and cost effective. The interpretation of the result is intuitive and the functional information can be readily integrated into neuronavigation systems (Figures 1 & 2). Still, TMS also has its disadvantages in its restriction to the cortical analysis, the dependency of the size of the motor area on the stimulation intensity [72] and its comparable limited capacity to visualize functional networks.

Navigated TMS motor mapping has made the transition from the research setting to the clinical routine for presurgical mapping – all other

available methodologies have to be currently regarded as research tools with limited clinical value.

Future perspective

The positive impact of navigated TMS motor mapping on the treatment outcome has been demonstrated recently, but the incidence of cases with unclear cortical motor anatomy might be rather low outside of large institutions. Yet, the usability of navigated TMS in the work-up of motor area-related brain tumors will, in the near future, further increase by a better understanding of the functional relevance of navigated TMS-based DTI fiber tracking. In addition, the predictive potential of the neurophysiological measurements (especially the bihemispheric motor threshold and MEP latency values) will be further explored and positively impact the presurgical risk–benefit balancing.

Repetitive navigated TMS is currently under intense investigation with respect to its potential to explore cortical language function – not only in the neurosurgical context, but by neuroscientists from all fields. Basic paradigms such as the unquestionableness that certain cortical areas carry essential language function will be scrutinized and the already outdated concept of serial processing of language by distinct brain areas will be further revised. Navigated TMS will play an important role in this research and the neurosurgical community and, ultimately, our patients will profit from these developments in the not too far future.

Financial & competing interests disclosure

The author has served as an advisor and consultant for a manufacturer of a nTMS system (Nexstim Oy, Helsinki, Finland). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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