Abstracts from the 4th International Symposium on Navigated Brain Stimulation in Neurosurgery

November 16-17, 2012

The 2012 Symposium Faculty

Department of Neurosurgery
Charité - Universitätsmedizin Berlin, Germany
and
Department of Neurosurgery
Klinikum rechts der Isar
Technische Universität München, Germany
**Introduction**

This 4th International Symposium on Navigated Brain Stimulation (NBS) was held to allow experts in functional mapping and imaging to continue to share their experiences with NBS. To further that goal, the presenters agreed to make abstracts and images from their presentations available to colleagues unable to attend in person. Many of the Symposium presentations contained previously unpublished data and we are grateful to the authors for their permission to publish their abstracts. The content of several of the presentations were under review for publishing in a peer-reviewed journals.

Navigated Brain Stimulation (NBS) has proven to be a reliable and accurate non-invasive tool for the assessment of the functional significance of cortical structures adjacent to a lesion prior to surgery, or indeed, any treatment decision. NBS may also prove to have a role as a prognostic marker of motor status after resection.

NBS mapping results have been shown to be easily integrated into dose planning systems for radiosurgery – and first results show that the information is useful for assessing risks and minimizing doses to critical structures. Further evidence of the value of using NBS data as seeding points in subcortical fiber tracking using diffusion tensor imaging has been presented, including the elucidation of language-related fiber tracts.

Overall, language mapping again played a large role in the Symposium, with half of the presentations concerned with or touching on experiences with NBS for language mapping. This year’s award for best poster went to Rogić, Fernandez-Conejero and Jerončić for their work describing a novel methodology for differentiating between M1 for laryngeal muscles and opercular part of Broca’s area by simultaneous measurement of SLR and LLR during induced speech disorders, the method might be applicable in preoperative mapping to facilitate surgical planning and intraoperative speech mapping.

This was the first NBS Symposium to run by a joint faculty from Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, (TUM) and the Department of Neurosurgery, Charité Universitätsmedizin Berlin. The faculty is pleased to note the continued desire or clinicians and researchers to ensure that the potential benefits of using NBS are being built on a firm scientific foundation of peer-reviewed publications. We hope this publication will serve as an introduction to the 5th International Symposium on Navigated Brain Stimulation in Neurosurgery, to be jointly arranged by TUM and the Charité later in 2013, here in Berlin.

**The Faculty**

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Identification of somatomotor and motor speech-related cortical areas using nTMS

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Various cortical areas in the frontal cortices have been found to be involved in inducing speech arrest by electrical or magnetic stimulation, including the opercular part of Broca’s area and the primary motor cortex (M1) for laryngeal muscles. It has been shown that M1 for laryngeal muscles is responsible for controlling the muscles for vocalization, whereas the opercular part of Broca’s area is involved in motor planning and control of speech. Functional connections have been shown between the M1 for the laryngeal muscles and the opercular part of Broca’s area by cortico-cortical evoked potential recordings (1).

The M1 for laryngeal muscles can clearly be differentiated from the opercular part of Broca’s area, due to significantly different latencies of evoked potentials recorded from laryngeal muscles (cricothyroid and vocal muscles). Stimulation of the M1 for laryngeal muscles generates a short latency response (SLR) while the stimulation of the opercular part of Broca’s area generates a long latency response (LLR) (2,3,4,5). It has been proposed that transient speech disruptions elicited by stimulation of these cortical spots produces evoked potentials in laryngeal muscles and can be regarded as a marker to depict motor speech-related areas (5). Stimulation of the cortical spot which generates LLR produces speech arrest, while stimulation of the cortical spot which generates SLR produces dysarthric speech.

In anesthetized patients, without using muscle relaxants, mapping of the M1 for the laryngeal muscles and the opercular part of Broca’s area, has earlier been achieved by endotracheally inserting a hook wire electrode in the vocal muscle. In awake patients, the hook wire electrode can be placed in the cricothyroid muscle percutaneously. Short trains of electrical stimuli over the opercular part of Broca’s area and M1 for laryngeal muscles activate the corticobulbar tract for the vagal nucleus (directly when stimulating M1 and indirectly, via M1, when stimulating Broca’s area) generating a LLR and a SLR in the laryngeal muscles, respectively.

Figure 1: Centre: The anatomical localization of somatomotor and motor speech related cortical areas elicited by nTMS, CS = central sulcus, PCS = precentral sulcus, IFS = inferior frontal sulcus, SF = Sylvian fissure, ASR = ascending sylvian ramus. Left: enlarged anatomy of centre image (grid square represents 5 mm²). Right: APB = motor evoked potential recorded from abductor pollicis muscle, SLR = neurophysiologic marker for cricothyroid muscle, LLR = neurophysiologic marker for part of Broca’s area.
Recently, it has been shown that non-invasive navigated transcranial magnetic stimulation (nTMS) can locate the representation area of the cricothyroid muscle in the M1 and the opercular part of Broca’s area using a modified, patterned rTMS protocol (NBS System, Nexstim Oy, Finland) (6). The SLRs (corticobulbar motor evoked potentials) and LLRs are recorded by 76 μm hook wire electrodes inserted in the cricothyroid muscle, indicating that, in healthy subjects, the M1 for cricothyroid muscle is located approximately 25 mm more lateral with regard to M1 for the hand muscle (abductor pollicis brevis muscle) (7).

There has been progress in the techniques available for non-invasive localization of motor speech-related cortical areas. Having reliable neurophysiologic markers for these areas would significantly contribute to the selection of surgical candidates and planning of safer access to lesions. Additionally, such information would help to preserve motor speech-related cortical areas in anesthetized patients. Mapping of M1 for cricothyroid muscle might represent an important neurophysiologic marker for motor speech-related cortical areas due to the proximity of motor cortical representation of the laryngeal muscles and the opercular part of Broca’s area. The nTMS is a powerful diagnostic tool which will probably in the future have the potential to finely map cortical regions for which we do not yet have a methodology.

References


6. Rogić M, Deletis V, Fernandez Conejero I. Inducing transient language disruptions by mapping of Broca’s area with modified patterned rTMS protocol. Journal of Neurosurgery, accepted for publication.

The role of NBS in a state-of-the-art neurosurgery workflow

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The evidence supporting the accuracy of nTMS (NBS System, Helsinki, Finland) for pre-surgical investigation of the motor cortex is overwhelming. To date, eight studies have compared nTMS to DCS with the primary goal of establishing accuracy relative to the “gold standard” direct cortical stimulation (DCS). All the studies have concluded that nTMS is a reliable tool for identification of individual cortical muscle representations with a level of accuracy similar to DCS. Additionally, three studies have shown superior accuracy of nTMS mapping compared to non-invasive imaging-based methods. When nTMS results are used for seeding, fiber tracking by DTI has been shown to be a more reliable tool for non-invasive, subcortical investigation. Recently, it has also been demonstrated that the NBS System is a useful tool for speech mapping of the perisylvian area. The safety of nTMS has also been established, with no seizures induced during clinical use, and a very low level of adverse events. The issue before us today is therefore to what extent nTMS can help us in practice in the neurosurgical workflow in the clinic.

The contribution of nTMS to presurgical planning has been documented at the Department of Neurosurgery of the Charité. We have established that in 55% of cases where tumors are in, or near, the primary motor cortex (M1), having nTMS data available presurgically has benefited the surgical plan. In our experience, the visualization of functional data in addition to anatomical data has also had a positive motivational effect on patients who face the difficult decision of whether or not to agree to surgery.

Unsurprisingly, a patient’s greatest concern regarding surgical treatment is his or her outcome. It has been known for some time that tumor-induced paresis can be reversed by surgery, with one prerequisite being the preservation of the motor tracts in the peritumoral region. By measuring amplitudes and latencies of MEPs, nTMS is a convenient tool for establishing the integrity of the affected motor tracts in the presence of paresis. Information that movement might be restored by surgery is very reassuring for the affected patient.

Quantifying the functional motor status of the brain in patients with rolandic tumors may hold unexpected benefits. We have observed that a deviation from the normally observed balance of hemispheric excitability has been a predictive marker for postoperative reversal of sustained (>6 weeks) paresis. From our database of resected patients with rolandic tumors mapped by nTMS (n = 175), we have calculated that in patients with a preoperative motor deficit of all histologies (n = 83), an interhemispheric resting motor threshold (rMT) ratio of < 1.03 has a predictive value of 82% (p = 0.05) for a paresis resolving postsurgically. Additionally, we have calculated that in rolandic tumor patients with no apparent motor deficit (n = 92) a marked interhemispheric difference in excitability, rMT ratio > 1.12, is a marker, predictive value 78%, for a post-operatively worsened motor status (p = 0.05).

It is well-known that the proximity of a tumor to presumed eloquent areas impacts post-surgical outcome. From a patient database (n = 210), morbidity was 12.8% in the group of patients (n = 117) where the lesion was involved in M1. For risk stratification, these patients can therefore be considered to be high-risk. When the tumor does not involve M1, morbidity was lower (6.5%), as expected, but this still represents a level of risk which can benefit from further risk stratification.

In the group of patients where the tumor does not involve M1 (n = 93), we did not observe any cases of post-operative deficits (morbidity 0%) when the tumor margin was >12 mm from the motor tracts (by DTI-imaging). Conversely, morbidity was 11.2% in this same group when the tumor margin was found to be <12 mm from the motor tracts – a similar incidence of morbidity as in patients where their tumor did involve the M1. These data suggest that for risk stratification, patients with tumors not involved with M1 but nevertheless close to motor tracts should also be classified as high-risk cases. Following this two-stage risk...
classification of patients in our database \( n = 210 \), morbidity was 0% in the low-risk group \( n = 67 \) which represented 32% of patients. The morbidity in the high-risk group \( n = 143 \) was 11.4%.

We have found that the functional maps generated by nTMS can positively affect workflow during surgery. Visualization of pre-surgically confirmed motor areas and fiber tracts in the microscope field can be advantageous when guiding subcortical stimulation probe placement, saving valuable time. When tumors are presumed to be in non-eloquent areas, confirming agreement between the exposed anatomical landmarks and the functional data in the microscope gives the neurosurgeon confidence to proceed with the resection without intra-operative monitoring (IOM).

Figure 1. Left: The index ratio of interhemispheric resting motor threshold (rMT) measured bilaterally at the first dorsal interosseous (FDI) muscle hot spot (red square) in conjunction with clinical data helps to objectify prognostication of functional outcomes before and after surgery. Right: Distribution of bilateral rMT ratios in 175 consecutively mapped patients undergoing surgical resection for rolandic tumor.

**Conclusion**

nTMS is a safe and accurate technique for localizing motor cortices. The surgical plan has been shown to benefit form presurgical investigation in more than half of cases when nTMS results are made available. Quantitatively assessing the patient’s functional motor status has the potential for predicting recovery from paresis and estimating the likelihood of new post-surgical deficit. More reliable fiber tracking, making use of nTMS data with diffusion tensor imaging techniques, may enable more comprehensive risk-stratification and help better allocate hospital resources for intraoperative monitoring. In cases of post-surgical motor deficits, functional assessment by nTMS may be an early predictive marker for deficit recovery or the need for early rehabilitation. Using nTMS for mapping plastic relocation of cortical function may permit safe reoperations in cases of incomplete resection and residual tumor – and opens up the potential for multiple, staged surgeries for treatment of low-grade gliomas and other challenging brain diseases.
The role of NBS in cortical motor mapping and sub-cortical fiber tracking

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Recently, navigated transcranial magnetic stimulation (nTMS) has become available for use in the clinic, potentially offering electrophysiological mapping of the motor cortex already in the presurgical workup phase. At the Technische Universität München (TUM), the accuracy of the nTMS technique has been compared to direct cortical stimulation (DCS) and functional MRI (fMRI). The benefits of nTMS mapping have been assessed and the usefulness of the technique has been evaluated in resection of gliomas. We have also tested the hypothesis that fiber tracking by diffusion tensor imaging (DTI) can be improved by using nTMS-confirmed functional motor areas as seeding regions.

Since April, 2010 an nTMS device (NBS System, Nexstim Oy, Finland) has been available in the Department of Neurosurgery, TUM. Cortical motor mapping by nTMS has been performed in 65 patients with brain lesions: 61 patients had tumors of various histologies and 4 patients had AVMs. Mapping of the representation areas of upper extremity muscles was successful in all patients, despite significant edema and previous surgery for tumor in 13 of the patients. nTMS mapping of the representation areas for lower extremity muscles was successful in 48% of patients.

In a study of 33 patients with brain tumors, we assessed the clinical accuracy of nTMS in motor mapping, by comparing the mapping results with intraoperative DCS as well as the results of preoperative fMRI. The mean distances between the corresponding centers of activation for all techniques were calculated in a neuronavigation system (Brainlab AG, Feldkirchen, Germany). The results showed good spatial correlation between muscle representation areas determined by nTMS and DCS, with a mean distance of 4.5 mm ± 3.5 mm for both hand and foot extremities. However, the spatial correlation between muscle representation areas determined by nTMS and fMRI was weaker. For the hand muscles, the mean distance was 9.6 mm ± 7.9 mm and for the foot muscles the mean distance was 15.0 mm ± 12.8 mm. The nTMS mapping procedure was well tolerated. Although 58% of the patients had had a history of seizures, there were no seizures associated with stimulation. None of the patients experienced nTMS mapping as painful, although 3% of patients (n = 1) felt that TMS stimulation was unpleasant.

In order to assess the workflow benefit of nTMS mapping we performed a survey of neurosurgeon experience with the nTMS data. In 62% of the cases the neurosurgeon said that having nTMS data available made intraoperative identification of the central region easier. In 35% of cases, presurgical data increased the neurosurgeon’s confidence level. In 28% of the cases the nTMS data had a positive influence on the result of the surgery and 10% of the cases the nTMS data changed the surgical strategy (defined as the neurosurgeon changing the trajectory of approach to the tumor, or the extent of the resection).

It is important to be aware of the reliability of available investigation methods also in challenging cases. We therefore investigated nTMS, fMRI and DCS in recurrent glioma patients where scar tissue and cortical reorganization has the potential to confound measurement techniques. In a group of 31 patients with supratentorial tumors (WHO grade I-IV), 23 patients had newly diagnosed tumors and 8 patients had recurrent gliomas. In 8 patients we found that there was no deviation in the accuracy of nTMS mapping compared to DCS between the two groups. When comparing fMRI to nTMS, we found a large deviation in motor area location for the hand region by fMRI, and even larger deviation when comparing localization of the leg region muscle representation areas by fMRI.

Using DTI to visualize subcortical fiber tracts, the neurosurgeon selects a ROI in the precentral gyrus as a “seed” and performs fiber tracking to the brain stem. This standard method requires subjective
interpretation of brain anatomy. Since the result of fiber tracking is critically dependent on the location of the seed ROI, we investigated whether using the data from nTMS motor mapping could improve reliability and reproducibility. Reliability was assessed by calculating the ratio of aberrant tracts to the number of tracts meeting the corticospinal tract. Reproducibility was tested by measuring inter-observer variability in estimation of the number of fibers generated, the fiber-tumor distance and the tract volume. Compared to anatomically-defined ROI, defining the seed ROI based on nTMS mapping resulted in significantly better circumscribed tracts, as well as fewer aberrant tracts. A comparison of inter-observer interpretation of the fiber tracking results showed that nTMS mapping-based fiber tracking was less subjective and more reproducible, when compared to standard fiber tracking method.

Conclusions

We have found good correlation between nTMS mapping results and intraoperative DCS results and delineation of functional motor areas seems superior to fMRI. nTMS mapping appears to be unaffected by edema and the nTMS technique maintains its reliability when mapping glioma patients, even in recurrent glioma tumors where scar tissue and vascular changes appear to confound fMRI. Adding the nTMS service to the department’s workflow has supported neurosurgeons in planning, assessing expected resectability and identifying the central region in brain tumor patients. The nTMS motor mapping data appear to be more useful as seed regions for DTI-based fiber tracking than standard interpretation of anatomy.

References


Fiber-tracking based on navigated TMS: a standardized approach for pre-operative brain modeling

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Diffusion tensor imaging (DTI) reflects water diffusion, which in the brain is restricted by axons, cell bodies, and myelin. With DTI, direction of white matter structures can be determined and, furthermore, specific fiber tracts can be identified. The role of DTI-based tractography has become increasingly important in the preoperative mapping of brain white matter.

Fiber tracking relies crucially on selection of seed points by the investigator. In conventional fiber tracking, the investigator uses his or her previous knowledge and experience to determine seed point based on the individual patient’s anatomical landmarks, i.e. brainstem and/or internal capsule and cortical topography. When tumors distort the anatomy, however, interpretation of the anatomical landmarks can be challenging. The conventional tracking method is performed by individual assessment and independent of functional data. Additionally, selection of the fractional anisotropy (FA) threshold is also based on individual assessment. The limitations of a subjective approach lead to a low test-retest reliability for the conventional method. Functional mapping based on navigated transcranial magnetic stimulation (nTMS) and EMG-measurement of elicited responses offers a potentially useful contribution to fiber tractography, since nTMS establishes a causal relationship between a motor area of the cortex and motor function. Seed points can therefore now be objectively selected, based on function.

A study to test whether a more rigorous, standardized technique for tractography using nTMS mapping results could improve the clinical value of tractography was designed. The first aim of the study was to determine the feasibility of fiber tracking using a functional seed point provided by nTMS. A second aim of the study was to establish a standard FA threshold. Finally, we assessed the impact of standardized nTMS-based fiber tracking on surgical strategy, compared to conventional experience-based tractography.

Methods

50 patients with tumors compromising primary motor cortex and/or the corticospinal tract participated in the study. DTI scanning was performed by 3T-MRI and nTMS was performed using an NBS System (Nexstim Oy, Finland). Functional motor areas determined by nTMS were imported into the surgical navigation software (Brainlab AG, Germany).

The parameters of fiber tracking can be summarized as fiber length, vector step length, angular threshold, seed point and the FA-threshold. The first three parameters were fixed at the standard values of: vector step length = 1.6 mm, fiber length > 110 mm and angular threshold = 30°. The seed points were determined by nTMS mapping. A common FA-threshold for all patients is a prerequisite for objective inter-patients and intra-individual comparisons. For this study, a common FA-threshold setting was determined by neurosurgeon-assessed usability of various threshold values. After increasing the FA-threshold until no fibers were detected, and subsequently reducing the FA-threshold in 0.01 steps up to 100%, an FA-threshold of 75% was determined to be the optimal level.

Results

The results of nTMS-based fiber tracking changed or modified surgical strategy in 23 out of 50 patients (46%). In comparison, the results of knowledge-based fiber tracking would have changed surgical strategy in only 11 patients (22%). Additionally, the availability of reliable fiber tracking results facilitated intraoperative orientation and electrical stimulation. In 28 patients (56%) the neurosurgeon felt that the
nTMS mapping results made it unnecessary to identify the central sulcus through phase-reversal. In this series of 50 patients, no new neurological deficit was seen when the measured tumor-tract distance exceeded a threshold of 12mm.

Figure 1. A: Peritumoral nTMS motor map of one patient in the study. B-E: fiber tracking at 100% FA-threshold. C-F: fiber tracking at 50% FA-threshold. D-G: fiber tracking at 75% FA-threshold. H: result from conventional fiber tracking approach. I: result from nTMS-based fiber tracking method at the standardized 75% FA-threshold.

Conclusions

DTI-based fiber tracking based on functionally-determined seeding points and a standardized algorithm represents an objective method for visualizing subcortical tracts. Adding objective fiber tracking to the presurgical workup changed the surgical strategy in approximately one half of cases, approximately double the impact of conventional, experience-based fiber-tracking. During surgery, the availability of reliable information facilitated intraoperative orientation and monitoring. A standardized technique enables objective comparison both of inter-patient results as well as intra-individual results. The ability to objectively compare intra-patient data allows for longitudinal studies of sub-cortical fiber tract integrity. As a surrogate parameter for tract integrity nTMS-based, objective tractography may be a useful prognostic indicator of potential recovery in neurosurgical patients with post-operative motor deficits.
NBS and MEG mapping of children undergoing epilepsy or tumor surgery

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By Faraday’s law, the electrical activity in neuronal networks required to initiate voluntary movement generates magnetic fields. Although weak, these fields can be detected non-invasively outside the scalp using magnetoencephalography (MEG). Inversely, electric fields induced in the motor cortex by transcranial magnetic stimulation (TMS) can activate the neuronal networks for movement. Motor evoked potentials (MEP) can be registered from electrodes placed over appropriate muscles when the induced electric field exceeds the motor threshold. Based principally on the interaction of magnetic fields, neither TMS nor MEG are affected by the tissue and bone overlying the cortex. Unlike surface EEG methods, both TMS and MEG have good spatial, as well as temporal, resolution. When co-registered with the anatomical MRI, the TMS-generated electric field can be accurately guided and orientated within intracranial structures.

For several years we have used commercial MEG and navigated TMS (nTMS) devices for investigating the brain in patients as well as healthy subjects. The 306-sensor MEG has proven useful for, e.g., identifying ictal foci in epilepsy surgery workup. nTMS, using the NBS System (Nexstim Oy, Helsinki, Finland) adds information from another modality in localizing motor function, as well as in identifying speech-sensitive sites in preoperative planning. Initially, we used TMS-EEG techniques to monitor for epileptiform activity during the nTMS mapping. However after not observing any such activity, either during or after stimulation, we no longer use EEG monitoring routinely.

Correlation of nTMS and ECoG in epilepsy

We have found a generally good match between nTMS and invasive grid recordings. Motor representations localized by nTMS correlate with activity elicited by invasive subdural grid electrocorticography (ECoG), in children and young adults with epilepsy. In a series of 13 patients with intractable epilepsy, we compared the concordance of nTMS mapping with ECoG grid electrode mapping. In 12 of the patients maximum responses were elicited in the same gyrus by both techniques, with a spatial correspondence of 11 mm ± 4 mm in three-dimensions between the centers of gravity of the sites activating hand muscles, calculated for both methods separately (Vitikainen et al., Acta Neurochirurgica 155, 507-518, 2013). This concordance between nTMS and direct stimulation in pediatric and young adult epilepsy patients compares well with results from other published studies comparing nTMS to direct stimulation in adult patients with tumors in the rolandic or central cortical areas. When comparing spatial concordance between applications, the effect of the fixed 10 mm inter-electrode distances in the subdural electrode grid needs to be considered.

nTMS in speech mapping

We have also used nTMS for investigating speech-related cortical networks. Using the NBS System with off-line review of video-recorded behavioral responses to stimuli, we have developed useful methods for mapping speech-related cortical areas. The arrangement has been similar to the object-naming paradigm used in awake surgery, with the addition of having the off-line video recording analyzed by an experienced neuropsychologist able to classify the evoked speech errors. Speech errors are primarily evoked by stimulation over the left fronto-parieto-temporal cortical regions. Analyzing a mapping session off-line also allows for an unbiased approach: complete anomias, semantic, phonological and performance errors have been observed also in real-time, but several speech-related errors have only been discriminated properly, or even detected, by off-line analysis. Showing the video recording to the patient adds further precision to the analysis by providing subjective information about what occurred during the stimulation. (Lioumis et al.
Journal of Neuroscience Methods, 204, 349-354, 2012). Additionally, the preoperative nTMS naming experiment also prepares the patient for the experience of speech mapping during awake surgery.

Our initial, limited experience suggest that speech arrest areas detected by nTMS overlap well with those obtained by direct cortical stimulation. However, nTMS mapping may show larger areas of speech responses than the electrocortical stimulation (ECS) methods. Although the methodology uses rTMS bursts, we have not had any adverse reactions in our patients with epilepsy. Interestingly, the 4-8 Hz rTMS frequencies typically used to induce speech disturbance are similar to the frequency of syllabic rhythm during speech. It is possible that rTMS modifies such rhythmic activities in the speech-related cortical networks and further research with TMS-EEG may well be warranted here.

Figure: Image A) nTMS to the participant’s left frontotemporal region blocks naming of the presented object. Image B) nTMS sites disturbing naming displayed on patient’s 3-D MRI. Red tags: sites producing anomia. Image C) Stimulation of depth electrodes surrounded by red circles elicited anomia in the patient. The arrows indicate corresponding anomia sites in images B and C.

Conclusions

The good spatial agreement between nTMS and ECoG methods for the localization of motor areas enables nTMS results to be reliably used for planning the placement of subdural grid electrodes. When MEG is able to reliably localize the ictal onset zones, the generally good match between nTMS and ECoG results opens the possibility that nTMS mapping could make invasive grid placement unnecessary in some cases. However, in patients with focal cortical dysplasia near to motor areas, the results of nTMS motor mapping may be confounded by epileptiform activity.

Off-line video analysis appears to be a useful technique in nTMS mapping of speech-related areas of the brain. However, there is a need to better understand the mechanisms behind our observations of the speech effects induced by nTMS. A simple inhibition-excitation explanation is not supported by the different types of speech errors obtained by nTMS in separate sessions of practically the same stimulus site and orientation, for example. Further research is also needed to determine optimal stimulation paradigms for various patient populations. Much of the published work regarding nTMS speech mapping has been in patients with tumors and, so far, little is known about possible lateralization or modification of language in epilepsy patients: nTMS may, for example, entrain speech- or epilepsy-related neuronal networks. Finally, the clinical usefulness of nTMS speech investigations needs to be verified by ECS intraoperatively.
NBS in language mapping: experiences in patients undergoing awake craniotomies

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For motor mapping, there is an ample body of evidence showing that Navigated Brain stimulation (NBS) has advantages in neurosurgery. Good correlation of NBS mapping results to intraoperative DCS mapping allows for reliable and accurate motor maps prior to surgery. Delineation of the functional motor area by NBS seems to be superior to the fMRI method, and NBS has been shown to be reliable even in recurrent tumors. When used as seed region for DTI fiber tracking, the NBS hotspots have been shown to reveal tracts of higher quality. Usability results suggest that NBS presurgical mapping supports the surgeon in identifying the central region and estimating expected tumor resectability.

By utilizing the ability of rTMS to cause “virtual lesions”, NBS can also be used for language mapping. The first experiences with NBS for preoperative language mapping have been positive and encouraging. However, appropriate frequency and timing – relative to the task – are crucial. Additionally, the human language and language networks are complex and, so far, less well understood than the connectivity of the motor system. Without the benefit of a direct marker like muscle-specific EMG, investigational paradigms need to be developed in order to gain the optimal benefit from the technique.

Initial experiences with language mapping

Using NBS, (eXimia NBS Systems 3.2 and 4.3, Nexstim Oy, Helsinki, Finland), 20 patients (17 right-handed, 3 left-handed) with a variety of left-hemisphere lesions were studied preoperatively by NBS and by DCS during awake surgery. Two departments of neurosurgery participated in the study: Technische Universität München and Charité - Universitätsmedizin Berlin.

Mapping by NBS was reasonably well-tolerated and could be performed in 19 (20) patients. The patient’s experience of pain was related to stimulation intensity. Using a 10-point visual analogue scale to measure the experience of pain, pain was much more pronounced when stimulating over the temporal area (4.1 ± 1.9) rather than the convexity (1.6 ± 1.3). Out of the 20 patients, 1 patient could not be mapped due to the patient’s inability to tolerate even a low level of stimulation intensity.

Language mapping was performed by object naming, with stimulation over the left frontal, temporal and angular regions. The median stimulation was 452 trains (range: 166 - 683), with trains of 5-10 pulses at 5-10 Hz. Language mapping generated a median of 61.5 naming error-points (mean 61.5) with each point validated by generating 2 or more errors from 3 stimulations.

The results of presurgical language mapping showed partial correlation with DCS in awake language mapping. We found a high reliability of NBS negative responses when correlated with DCS in awake language mapping. For the anterior area – the classical Broca’s area – the negative predictive value is close to 100%. Correlation of NBS with DCS for the posterior area was not as good. The NBS method generated a high number of language-related positive points which were not confirmed by DCS in awake language mapping – these could be classified as “false positive”- responses.
Figure: Comparison of language mapping results by nTMS vs. awake cortical mapping. The markers are color-coded according to the induced language error: Red = Speech arrest, White = Performance and Green = Hesitation – all highlighted by green spheres. Other induced language errors are color-coded as: Dark red = Semantic, Orange = Phonological, Yellow = Neologism.

Conclusion

Navigated Brain Stimulation (NBS) is a useful technique for language mapping and for language lateralization. NBS has shown itself to be superior to fMRI in language mapping, especially when the Broca’s area is pathologically impaired. However, optimizing the mapping parameters is a time-consuming process. Understandably, severe language impairment hampers language mapping. Additionally, if the patient is in bad health, discriminating between language errors like hesitation or an inability to focus is difficult. In general, the investigator needs to consider which potential language errors are “real” or even relevant. Compared to motor mapping, language mapping is less well tolerated. In particular, stimulation of the temporal muscle can cause pain and in some cases the pain can prevent NBS mapping.
Perioperative multi-modal motor mapping: nTMS, MEG and DCS

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The NBS System (Nexstim Oy, Helsinki, Finland) is a recent and welcome addition to the tools available for mapping motor-related cortical areas in patients with lesions in the central areas. However, since each of the modalities for functional investigation: Magnetic Source Imaging (MSI), Navigated Transcranial Magnetic Stimulation (nTMS), and Direct Cortical Stimulation (DCS) all have their inherent strengths and weaknesses, the use of all these techniques in combination can offer vital additional data in certain cases. Intraoperative navigation techniques have an intrinsic level of inaccuracy, and for that reason we normally use a photograph image of the exposed cortex with visible vasculature together with physically-labeled DCS sites when correlating multiple sets of data. Using this method, we have observed a close concordance of TMS mapping results with DCS (average spatial distance between localizations of 2.1 mm) and MSI using magnetoencephalography (average spatial distance between localizations of 4.7 mm). Regarding the clinical interpretation of DCS findings, the paradigm for resection has changed with neurosurgeons today trusting more and more the role of negative results to guide decision-making. The practical advantage of not requiring positive DCS response points is a smaller craniotomy and, consequently, less trauma for the patient. nTMS motor mapping fits nicely into this paradigm when a resection needs to be performed in or near the primary motor cortex – generating reliable negative maps which permit the planning of small craniotomies.

Figure 1. Left frontal lesion mapped by Navigated Brain Stimulation.
Language mapping

In order to assess the relative concordance of the three functional techniques for language area identification, nTMS and MSI were performed on 12 patients with lesions around cortical language areas prior to surgery. The nTMS maps were generated using a NBS System (Nexstim Oy, Helsinki, Finland) with an rTMS protocol designed to deliver time-locked trains of stimulations during an object-naming task. During surgery, language mapping was performed by DCS.

Preoperative nTMS mapping resulted in 21 positive language disruption sites (11 speech arrest, 5 anomia, and 5 other). With language tasks, MSI isolated 32 sites of peak activation. During subsequent awake surgery, DCS yielded 10 positive sites (2 speech arrest, 5 anomia, and 3 other). 9 of the 10 positive DCS sites corresponded to a positive nTMS site, while in 1 case the positive DCS site did not. In 4 instances, positive nTMS sites did not correspond to negative DCS sites. In total, 169 instances of negative nTMS and negative DCS were recorded.

In this study, we found the sensitivity of nTMS to be 90% with specificity 98%. The positive predictive value for nTMS mapping was 69% and the negative predictive value was 99% when compared with intraoperative DCS. MSI-determined sites for verb generation and object-naming correlated with nTMS-mapped sites in 5 patients, and with DCS sites in 2 patients. By anatomic location, the predominant site of positivity for language by DCS was the superior temporal gyrus, whereas for nTMS mapping and MSI, the predominant site of positivity for language was the pars opercularis.

Conclusion

Language mapping using nTMS is safe and with careful application is well-tolerated. Maps of language function generated with nTMS correlate well with those generated by DCS. Negative nTMS mapping correlates very well with negative DCS mapping. MSI was found to have a lower level of correlation with intraoperative mapping, but nevertheless the method can provide useful additional information in certain cases. nTMS is a valuable additional method for noninvasively interrogating language pathways, however the results of nTMS technique need to be interpreted with care and supplemented by data from other available mapping and imaging techniques when planning resections. nTMS provides a map of potentially positive language sites, allowing for more rapid DCS during surgery. Further development of nTMS language mapping technique using other paradigms than object naming, for example use of verbs, or recognition of famous faces, may improve the positive predictive value of the nTMS technique.

Reference

In a grade II glioma, nTMS mapping was able to provide reliable planning information (case)

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A 44-year-old female patient who had experienced slowly progressing hemiparesis on her left side for a period of 18 months was evaluated for surgery. MRI showed a large non-enhancing tumor in the motor area. fMRI results initially suggested that the motor areas for the hand and leg were outside the lesioned area and the tumor could be removed without risk. However, the patient’s symptoms suggested a cautious interpretation of the fMRI activation map. The patient was therefore additionally mapped with nTMS using the NBS System (Nexstim Oy, Helsinki, Finland). NBS mapping for the hand and leg representations revealed that motor relevant areas were almost anterior to the tumor – a significant discrepancy compared to the fMRI results.

With surgery now presenting a clear potential risk to postoperative status, a biopsy was performed. The biopsy revealed that the tumor was a grade II malignant glioma with a consequent poor prognosis for the patient. Our experience with the reliability of the NBS technique and accuracy gave us the confidence to now recommend a complete resection of the glioma. The glioma was clearly delineated and, by visual inspection, could be completely removed. At one day post-surgery, the left arm of the patient was plegic. However, this deficit quickly resolved and after one week motor function in the limb had returned to its pre-operative status.

Figure: fMRI study of hand (upper left), fMRI of leg (upper middle) and NBS map of stimulation sites eliciting responses in the hand and leg muscles (right). Preoperative and postoperative MR-image (lower left and center).
Mapping speech-related areas in patients with brain tumors, where to stimulate?

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The preservation of speech is a major concern when a resection in the dominant perisylvian areas is proposed. Localization of speech-related functional areas during awake surgery using direct cortical stimulation (DCS) is an established method, but localization techniques for neurosurgical planning would be valuable.

Navigated transcranial magnetic stimulation (nTMS) uses a direct stimulation concept analogous to the gold standard (DCS); single-pulse nTMS has been successfully used for presurgical localization of motor function in patients with brain tumors. When delivered at higher frequencies, repetitive TMS (rTMS) can selectively interfere with cortical function. If the neurons in the focus of the electric field are crucial for the language task, speech can exhibit alterations, such as speech arrest, paraphasia or anomia during rTMS. The intensity of the rTMS required to elicit interference can be ascertained from a patient’s motor threshold.

Mapping for speech with navigated repetitive TMS (nrTMS) is far more time-consuming than TMS mapping for motor areas, and the time required can be a problem for patients with brain tumors. Unlike in motor mapping, there are no anatomical or readily elicitable functional landmarks to guide speech mapping. Additionally, the need to map the cortex twice for bilingual patients can make for very long investigations.

It is a challenge to estimate beforehand which areas of a cortex are speech-relevant. We have demonstrated this by superimposing the speech locations identified in neurosurgical patients mapped by both nTMS (NBS) and intraoperative DCS: speech-positive points are scattered over virtually the whole side of the hemisphere (figure 1).

Figure 1: The extent of speech-positive locations identified in neurosurgical patients mapped by both nrTMS using the NBS System and intraoperative DCS. Responses: matched nrTMS spot (blue circle), matching DCS spot (red square), unmatched nrTMS spot (red triangle), nrTMS unexplored DCS spot (red diamond) – data from all 6 patients superimposed.
Duffau et al. have earlier shown that there is good correspondence between positive stimulation sites and fiber tracts. This finding suggests that the fiber tracking by DT imaging may be able to identify the cortical areas where functional language sites are most likely to be located for the individual patient.

Based on the techniques pioneered by Deletis et al., which allow measurement of motor responses elicited by nTMS in the cricothyroid muscle, we have tested the value of using the cricothyroid representation as the seed ROI (region of interest) for speech-related fiber tracking.

11 subjects underwent DTI followed by nrTMS mapping using an eXimia NBS System (Nexstim Oy, Helsinki, Finland). Out of 8 subjects available for analysis, the tract to the cortico-bulbar tract could be visualized in 7 (8) subjects, the tract to the Broca’s region in 8 (8), the tract to the Wernicke’s area in 8 (8), the tract to the pre-motor area in 4 (8) patients and the tracts to the supplementary motor area in 4 (8). In this investigation, the subjects were all healthy and the ability of the DTI method to visualize tracts is presumably limited by angulations of the fibers.

Figure 2: Empirical template for guiding nrTMS speech mapping derived from DTI-tractography of speech-related fiber tracts in 11 subjects, white rectangles indicate the locations likely to elicit speech-positive responses to nrTMS.

Conclusion
Motor mapping by Navigated Brain Stimulation can be used to accurately locate the cricothyroid muscle representation area, providing a reliable region of interest (ROI) for seeding. From the DTI dataset it is then possible to visualize the speech-related fiber tracts to the Broca’s region, the pre-motor area, the supplementary motor area, the opercular area, the gyrus angularis and the supramarginalis (Wernicke’s area). With this knowledge, the locations of cortical sites presumably most likely to be related to speech can be projected onto the cortex, potentially reducing the total time needed for speech mapping by NBS.
Individually-tailored treatment of eloquently-localized intracerebral tumors adjacent to the primary motor cortex representation and the pyramidal tract

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Presurgical functional brain mapping is essential for optimized treatment planning for eloquently-located brain tumors, i.e. tumors adjacent to the primary motor cortex (M1) or the associated fiber tracks. The main goal of a multimodal imaging approach is to preserve motor function and thus quality of life, whilst optimizing the extent of cytoreduction by surgical resection or other means.

Although functional magnetic resonance imaging (fMRI) may still be the most established method for presurgical motor mapping, navigated transcranial magnetic stimulation (nTMS) has gained widespread attention and is regularly used for clinical decision making and planning of the surgical approach, especially when combined with DTI fiber tracking. However, which of the two methods may be more eligible for mapping the M1 is still controversial.

Moreover, functional plasticity may impact treatment strategy and timing, since multiple methods – such as multiplanar irradiation, stereotactic brachytherapy, chemotherapy and surgery – are available for treatment. The following three case reports illustrate a function-preserving approach for optimized cytoreduction combining metabolic, functional and anatomical imaging including DTI fiber tracking.
Case 1

A 48-year-old male patient presented with seizures and transient (Todd’s), left-sided hemiparesis. Anatomical MR imaging revealed a non-contrast-enhancing, T2-hyperintense lesion within the area thought to correspond to the M1 representation of the hand. A FET-PET investigation suggested a benign lesion and after a thorough discussion of the therapeutic options, a strategy of “wait and see” was pursued. Three years later, a generalized seizure led to a repeat of the FET-PET investigation (Figure 1), this time showing an increase in the mean and maximum brain-to-lesion index. In order to clarify the resulting suspicion of malignant transformation, the patient was previewed for stereotactic biopsy or surgery, depending on the functional imaging results. fMRI was performed and nTMS mapping was made using an NBS System (Nexstim Oy, Helsinki, Finland). Both methods revealed a clearly precentral tumor location, with a certain functional or anatomical posterior shift more pronounced on fMRI (Figure 2) than on the nTMS maps (Figure 3). Based on surgeon confidence in these results, the patient was scheduled for resection.

Figure for Case 1.
Left: at three years, a repeated FET-PET investigation revealed an increased tracer uptake (mean and maximum brain-to-lesion index) at the tumor site.
Center: fMRI using a thumb abduction paradigm revealed a clearly precentral tumor location. Comparing the ipsilesional and contralesional locations, a certain functional or anatomical posterior shift may be hypothesized.
Right: nTMS mapping results with entire motor response maps labeled in orange/yellow and hot spots highlighted in red/green. The contralateral (left) hemisphere was also mapped and corresponding hotspots are also shown in red/green. The tumor is labeled in blue (dark blue: contrast-enhancing tumor volume investigated by MRI; light blue: FET-PET-“hotspot”, i.e. the volume with highly increased tracer uptake). The nTMS mapping results are colored: orange/red for the thumb (APB) representation areas and yellow/green for the foot representation area (Plantaris). nTMS mapping indicated only a slight functional or anatomical posterior shift of the M1 representation.

Case 2

A 65-year-old male patient presented with seizures since childhood, the frequency and severity of the seizures having increased in the preceding months. A cranial MRI showed a non-contrast-enhancing, T2-hyperintense lesion directly adjacent to the hand knob. Stereotactic biopsy revealed a low grade glioma (WHO II°). Presurgical mapping and follow-up mappings by nTMS, using an NBS System (Nexstim Oy, Helsinki, Finland), revealed a central tumor location, between the M1 representations of the foot and the hand. Compared to the contralateral nTMS results, no significant functional shift was observed on the lesioned side, however. The patient underwent stereotactic brachytherapy using an Iodine$^{125}$, 50 Gy permanent implant. nTMS mappings post-implantation revealed no functional shift; on the contrary, the
results show high test-retest repeatability (3.3 mm +/- 1.1 mm SED, referring to the hotspots). The tumor responded to the brachytherapy with no recurrence to date. To date, no worsening of motor function has been observed clinically. Due to an increase in the frequency of the focal seizures, the anticonvulsant dosage needed to be increased, however.

**Case 3**

A 67-year-old male patient presented with an 8-week history of moderate facial palsy, swallowing impairment and dysarthria. An MRI revealed a bulky, frontal lesion strongly contrast-enhancing in the margins, suggestive of glioblastoma (confirmed by histology later on). The tumor potentially involved the M1 representation of the face/tongue and the upper limbs. fMRI and nTMS, using the NBS System (Nexstim Oy, Helsinki, Finland), as well as function-associated DTI fiber tracking were performed. The nTMS mapping results confirmed the presumed precentral tumor location: the tongue representation being mapped in the lateral part of the precentral gyrus, adjacent to the opercular part. However, the fMRI hotspot for the hand M1 representation was plotted slightly anterior to the corresponding nTMS hotspot and the fMRI hotspot for the tongue was located within the nTMS map of hand representation.

The discrepancy in the location of tongue representation by fMRI compared to the nTMS mapping result may be explained by this dysphasic patient’s problems with alertness and problems performing the tongue movement task for fMRI as well as other difficulties. Intraoperatively, the nTMS-determined tongue representation was confirmed by monopolar direct cortical stimulation. Interestingly, the course of the function-associated (pyramidal tract) fibers differed significantly when using either the fMRI or the nTMS-located hotspots as seed points: the nTMS mapping-based tracts passing posteriorly to the tumor; the fMRI-based tracts passing medially, anteriorly to the tumor. The patient underwent surgery without significant postoperative clinical deterioration and the dysarthria improved slowly after surgery.

**Conclusions**

Multimodal functional and metabolic imaging and function-associated fiber tracking can be considered to be beneficial, and in some cases even crucial, for individually-tailored, function-preserving treatment of intracerebral tumors eloquently located adjacent to the M1 region and associated fiber tracts. In most cases, both the fMRI and nTMS methods reveal similar representations for M1 which increases the confidence of the surgeon when making decisions. However, the cases presented show the controversy within some patients regarding the results of fMRI versus nTMS mapping as well as their function-based fiber tractography. Further investigations may help better interpret these kinds of discrepancies. Additionally, stereotactic brachytherapy may be a safe (function-preserving) and effective treatment option for highly eloquently-located low grade gliomas.
Navigated TMS of the brain: improved Cyberknife radiosurgery planning

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With new devices like the Cyberknife® (Accuray Inc., Sunnyvale, CA, USA) enabling patient-friendly treatment, stereotactic radiosurgery is now a mainstream neurosurgical procedure. As in other interventions, the risk of post-procedural deficits near to cortical areas has been shown to be elevated also in radiosurgery, especially when treating cerebral arteriovenous malformations (AVMs) and metastases. Presurgical localization of eloquent cortical areas may provide a valuable contribution to radiosurgical safety by guiding prescription of the radiation dose and conformity of dose gradients in order to spare vital structures. The use of navigated TMS (nTMS) for functional mapping has recently been shown to contribute positively to the planning of conventional resection surgery. We have recently investigated the ease and potential clinical value of integrating nTMS data into the radiosurgical planning process.

The workflow required for integrating the nTMS data is relatively straightforward when using the NBS System (Nexstim Oy, Helsinki, Finland). After the DICOM structure is exported from the NBS System to the Multiplan Cyberknife treatment planning system, data integration is achieved by fusing the 3D MRI MP-RAGE sequence, containing the nTMS-mapped data points, with the CT-image set for planning.

Our department is taking a prospective approach to quantify the added value that nTMS mapping brings to clinical workflow in patients referred for radiosurgery with lesions close to the M1. The lesions include AVMs, metastases, acoustic neuromas and meningiomas – gliomas are generally not indicated for radiosurgery. Using a standardized questionnaire, we are assessing the usefulness of the nTMS mapping data for:

- Influence on isodose contouring,
- Modifying the dose of radiation prescribed,
- Impact on planning process,
- Any change in therapy indication,
- Contribution to the patient’s understanding of the procedure and its risks and
- The patient’s willingness to give informed consent to radiosurgery.

Additionally, we will be assessing the technical ease of integrating the nTMS data into the surgical plan, A preliminary review of the data shows that nTMS mapping has already been useful in modifying the dose prescribed to better preserve critical structures.
Figure: Screenshots from the CyberKnife® planning workstation showing the nTMS mapping data overlaid on the planning CT-scans. The positive responses to TMS are indicated by the white rectangular (when shown in 2D) markers. The innermost line surrounding the defined target volume corresponds to the 70% prescription isodose (in green and bold). The surrounding isodose lines each show a 10 percent drop-off in dose, with the 60%, 50% and 40% isodose lines drawn in yellow; the 30% and 20% isodose lines are drawn in white. Note the steep dose drop-off (tight isodose lines) ventrally of the target towards the motor cortex in the lower sagittal view (lower left quadrant of figure).

Conclusion

Radiosurgery uses radiation for ablation without any possibility for traditional direct electrophysiological mapping or monitoring of the brain. Mapping by Navigated Brain Stimulation (NBS), or preoperative imaging, are therefore the only means of integrating functional information into stereotactic radiosurgery. NBS data import and integration are neither difficult nor time-consuming. Preliminary analysis suggests that NBS data are useful both for planning as well as for risk-estimation. Additionally, the NBS mapping procedure offers valuable information for the patient and can help in obtaining informed consent. For lesions in deep-seated locations, the integration of fiber tracking information into the plan is a logical next step. Further, NBS mapping may have a role as a prognostic indicator of post-procedural course if the method can help differentiate between patient symptoms due to edema, self-resolving reactions to radiation or possible radionecrosis.
Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain

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In the treatment of chronic neuropathic pain by rTMS, the precentral motor region is the target normally chosen for stimulation. In order to achieve an analgesic effect, rTMS needs to stimulate the horizontal fibers in the superficial layers of the brain. Through multiple circuits, these fibers activate various neural structures distant from the site of stimulation. Pain relief requires rapid rTMS, typically in a frequency range of 10 - 20 Hz; low frequency rTMS has not shown an analgesic effect. The onset of the therapeutic effect of rapid rTMS is delayed, and the maximum treatment efficacy is not experienced until 2 to 3 days after a stimulation session.

The results of recent research studies have suggested that the functional motor “hotspot” itself is generally not the optimal target for rTMS stimulation and a more effective target has been adjacent to the hotspot. We have found that the optimal target is more often the anatomical location of the motor cortex (M1). However, since this location varies from patient to patient, accurate targeting of rTMS requires the anatomical information provided by MRI. Navigated TMS (nTMS), which uses the patient's MRI data for guidance, is a method which has been shown to allow for accurate targeting of stimulation. However, the efficacy of nTMS-guided stimulation relative to hotspot-targeted stimulation has not previously been studied.

We compared the efficacy of stimulating the anatomical M1 location, by MRI-guided rTMS, with stimulation of the classical motor hotspot by rTMS, and compared both of these active methods to the effect of sham stimulation.

Methods: 66 adult patients with peripheral or central, unilateral or asymmetrical neuropathic pain of various origin located in the face, the hemi-body, lower limb or upper limb were recruited for the study. Each of the patients received three treatment sessions: one session of each of the active therapies together with a session of sham stimulation. There was an inter-session “wash-out” interval of more than 3 weeks. Therapeutic rTMS was delivered at a high frequency of 10 Hz and at 90% of resting motor threshold (rMT). In total, each session comprised 3,000 pulses over a period of 15 min. In both active and sham sessions the TMS coil was positioned such that the current was induced in the anterior-posterior direction, parallel to the interhemispheric midline. For anatomical targeting of stimulation by MRI navigation, an eXimia NBS System (Nexstim Oy, Helsinki, Finland) was used.

For each patient, in the first session, sham rTMS was targeted to the motor hot spot for the hand muscle on the painful side (the same target for all locations of pain). In the second session, active rTMS was targeted to the motor hot spot for the hand on the painful side (the same target for all locations of pain). In the third session, active navigated rTMS was targeted to the anatomical representation of the painful zone on the anterior lip of the central sulcus: for lower limb pain the target was F1, for hemibody or upper limb pain the target was F2 and for facial pain the target was F3. Assessment of therapy efficacy was made using a Visual Analog Scale (VAS) with pain intensity daily scored for one week before and after each session. A special attention was paid on days 2 and 3 of each week of assessment, the period of optimal therapy effect.

Results: Both anatomically-navigated therapy and motor hot spot-targeted therapy showed efficacy, sham stimulation had no effect during the week of assessment. At 2-3 days post-stimulation, anatomically-navigated therapy resulted in 17.4% reduction in pain on VAS, while motor hot spot-targeted therapy resulted in 12.2% reduction in pain in the whole series of patients.
According to pain location, we observed a placebo effect from sham stimulation in facial pain; no analgesic effect from any method in hemibody pain; significant analgesic effect for both active stimulation conditions on lower limb pain, if marginally better effect from anatomically-navigated therapy than from motor hot spot-targeted therapy (29.8% vs. 26.0% pain reduction); significant analgesic effect for both active stimulation conditions on upper limb pain, with anatomically-navigated therapy being more effective than motor hot spot-targeted therapy (23.3% vs. 17.4%).

Figure 1: Using an NBS System (Nexstim Oy, Helsinki, Finland), nTMS of the motor area of the lower limb in a patient with peripheral neuropathic pain originating in the lower limb. The image shows a target with direction of current and magnetic field over the anatomical location of the lower limb (F1 on the anterior lip of the central sulcus). The target marker without the magnetic field is located over the motor hotspot of the hand (hand knob). nTMS allows for correct localization of the target in the sulcal anatomy before administering stimulation therapy.

Conclusion

Compared to sham stimulation, high-frequency rTMS over a single point of the precentral cortex results in analgesic effects in focal pain but does not ameliorate pain of diffuse origin (hemibody pain). Using MRI-guidance to target stimulation over the anatomical location of the motor cortex shows higher efficacy in pain control than classical, motor hot spot-targeted stimulation. The advantage of MRI-guided stimulation was more pronounced in pain of facial, and especially, upper limb origin. In order to validate the MRI-navigated stimulation method, the results of this first study need to be replicated, and the number of sessions in the study needs to be increased. A comparison of the efficacy of the anatomically-navigated and motor hot spot-targeted methods with stimulation targeted by fMRI activation areas is also warranted.