Abstracts from the 3rd International Symposium on Navigated Brain Stimulation in Neurosurgery
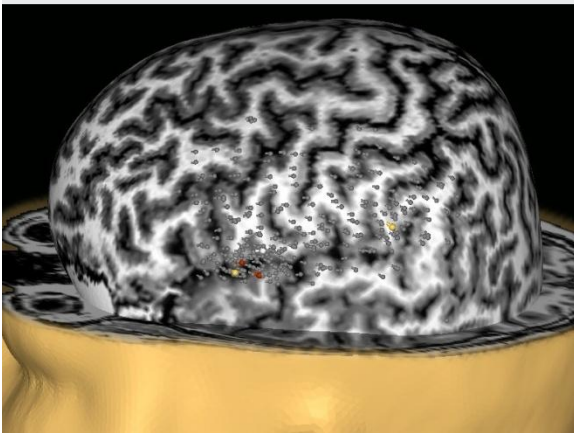
Introduction to the 3rd International Symposium on Navigated Brain Stimulation in Neurosurgery

This 3rd International Symposium on Navigated Brain Stimulation (NBS) was held to allow experts in NBS, TMS, DCS and MEG to continue to share their results and experiences with the new techniques. 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 Many of the Symposium presentations contained previously unpublished data and we are grateful to the authors for their permission to publish their abstracts.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 are also under review for publishing in a peer-reviewed journal, including the presentation by Forster and Szelényi on the use of NBS to measure neurosurgically induced plasticity, which could therefore not be included in this publication.

Navigated Brain Stimulation (NBS) has proven to be a reliable and accurate tool for the assessment of the functional motoric significance of cortical structures adjacent to, or in close proximity to a lesion. By virtue of being noninvasive, the NBS technique offers us a new tool for neurosurgical workup prior to any treatment decision. By mode of action, NBS also complements the well-established electrophysiological techniques of direct cortical and sub-cortical stimulation for the examination of cortical functions during surgery. Indeed, like DCS, the NBS method can be performed also in in children and in patients with paresis – unlike imaging-based methods. Professor Lindquist has also shown how NBS mapping can be used for improved therapy planning and risk management in neurological radiosurgery – where invasive mapping is naturally not available. As demonstrated by Krieg et al. and others presenting at the Symposium, NBS results can be applied to further the diagnostic value of subcortical fiber tracking using diffusion tensor imaging based on MRI.

Although the topic was already of interest last year, it was gratifying to note the advancement in techniques for speech mapping using navigated repetitive TMS (rTMS) delivered by the NBS System. Indeed, in this 3rd Symposium, over half of the presentations concerned or touched on experiences of speech mapping by NBS. The audience was also treated to a live demonstration of a commercial application of the NBS System for speech mapping, which is due to be made available in 2012. The experimental use of the NBS System to help treat chronic neurological disease states, such as stroke and pain, has also shown significant advancement. The NBS System can not only be used for reliable implant diagnostics but also for accurate delivery of rTMS therapy in pain management, as, for example, demonstrated by Professor Nurmikko from Liverpool University. This year's award for best poster went to Professor Gharabaghi's team at Tübingen University for their poster on using NBS as a diagnostic aid in the neurosurgical implantation of motor cortex stimulation electrodes for the treatment of chronic stroke.

The Symposium organizers wish to remind the audience that enthusiasm for NBS needs to be tempered by the obligation to place applications of the technique onto a firm scientific foundation by the peer-reviewed publication of carefully planned clinical studies. We also hope this publication will serve as an introduction to the 4th International Symposium on Navigated Brain Stimulation in Neurosurgery, to be held later in 2012, here in Berlin.

The organizers,

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Basics of TMS and NBS

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Although widespread experimental use of TMS has led to an enormous body of data suggesting that TMS may play a role in brain therapy for many diseases, invariably the results achieved have not been repeatable. However, that does not mean that TMS is not having an effect. Progress in the understanding of TMS cannot happen if the brain is treated as a "black box" to which a shock is simply given and we are satisfied only to measure increased or decreased excitability. The key to unlocking the door to increased clinical application of TMS lies in understanding of how the human brain works, that is to say how it is functionally organized.

Complex output from a simple stimulus

To the casual observer, a single pulse of transcranial magnetic stimulation (TMS) over the human head evokes a simple muscle response. However, the actual output of the motor cortex produced by even a single pulse of TMS is far more complex than this casual observation might suggest. In fact, a TMS pulse evokes not just a single descending wave, but a multiple wave discharge at around 700 Hz. This high frequency, multi-wave phenomenon was first discovered by studying evoked descending waves both before and after removal of the cerebral cortex in the monkey primate (Patton and Amassian, 1954). The early researchers observed that following removal of the cerebral cortex, the early descending wave activity was still recordable but the later activity was absent. They therefore proposed that the stimulated motor output comprises both D-waves and late-activity I-waves, where the D-waves are directly evoked in the corticospinal axons without involvement of the cerebral cortex, and the I-waves are produced in the cerebral cortex due to the indirect activation of corticospinal cells.

Also in humans, it has been shown that I-waves are produced within the cerebral cortex (Di Lazzaro, 1998). By recording output directly from the spinal cord, in conscious subjects with an electrode implanted in the cervical epidural space for the control of pain, it has been verified that single pulse TMS to the motor cortex evokes the same kind of high frequency repetitive discharge of the cortical spinal axons as seen earlier in primates.

Modeling neural circuits

Being the most excitable cells, it is reasonable to assume that the superficial pyramidal neurons, or their axons, are the initial target of a TMS pulse, but the question as to why a single TMS pulse results in a repetitive discharge still remains. The likely origin of the I-waves is the main excitatory circuit of the motor cortex, a circuit composed of two or three superficial layers of pyramidal cells connected with the large pyramidal neurons, the corticospinal cells. A simple and effective model that can be used to explain the properties of the cerebral cortex is the "canonical circuit", in which superficial pyramidal neurons in the upper 2 or 3 layers of the cortex have reciprocal connections to lower large pyramidal neurons in layer V, all of which are connected with GABA cells.

Using low intensity TMS, we can activate axons of layer II and III pyramidal cells which, in turn, activate corticospinal cells, resulting in single indirect descending wave (I1-wave) – an excitatory monosynaptic potential. However, when increasing the intensity of the TMS pulse, late I-waves appear and, the stronger

the stimulus pulse, the more the I-wave discharge is prolonged. Not all individual neurons would need to participate in each discharge, since neurons are organized in clusters: it would be sufficient for TMS to be able to excite clusters of excitatory and inhibitory neurons and hence evoke a peak discharge to the corticospinal cells.

The canonical circuit model suggests that these late I-waves are recurrent activity due to the reciprocal connections between the superficial and deep pyramidal neurons and to connections with the GABA cells. In other words, a higher intensity pulse results in excitatory synaptic potentials which are foiled by inhibitory synaptic potentials. Studies of cortical network organization predict that, with a synaptic delay of 1.5 ms, there is a peak of activity at approximately 676 Hz (the periodicity of I-waves) due to the activation of synchronized clusters of excitatory and inhibitory neurons (Brunel, 2000). In fact, this is the pattern of corticospinal discharge that we have been able to directly record in humans. The existence of phases of excitation and inhibition following a single TMS pulse has also been experimentally confirmed using repetitive TMS (rTMS). When rTMS pulses are delivered at very short inter-stimulus intervals (close to 1.5 ms) following a single TMS pulse, the rTMS can be observed to interrupt the phases of excitation and inhibition caused by the initial TMS pulse.

TMS and neurotransmission

Since glutamate is the main excitatory neurotransmitter of the human brain, it would be natural to expect glutamate to be involved in the duration of the I-wave volleys. Indeed, the role of glutamate can be confirmed by applying doses of CNS-active drugs with well-understood neuromodulatory modes of action. There are two main receptors to glutamate: NMDA and AMPA receptors. By blocking the NMDA receptors with ketamine and therefore selectively modulating glutamatergic transmission, it can be shown that the excitatory effect of TMS is dependent on non-NMDA glutamatergic neurotransmission.

A direct demonstration of the role of GABA circuits in the generation of I-waves can be performed by the administration of lorazepam, which enhances inhibitory GABA activity. Direct measurements from human subjects show clear suppression of later I-waves but no effect on the I1-wave. The sensitivity of later I-waves to decreased cortical excitability suggests that the I-waves are presynaptic in origin and, therefore, GABA circuits are involved in I-wave generation.

Impact of direction of induced current

In the above discussion, we have applied single-pulse TMS from a focal coil, with a posterior-anterior (PA) direction of the induced current across the central sulcus. However, changing the direction of the induced current in the brain significantly changes the output. For example, changing the orientation of the coil from lateral to medial can be directly observed to result in a larger D-wave in response to a single TMS pulse.

Reversing the orientation of the coil to anterior-posterior (AP) also changes the output. In fact, direct measurement shows a more complex pattern of activation with the coil in the AP compared to the PA orientation: stimulation resulting in different peak latency and more prolonged duration of I-waves. It appears that by reversing the orientation of the coil we can also access cortical-cortical axons in the premotor cortex, which, in turn, activate local motor circuits, evoking I-waves.

These findings suggest that by modifying the orientation of the TMS coil, we can target different populations of cortical neurons. This is quite logical since the anatomical folds in the cortex suggest that there are many populations of neurons with a common orientation: some populations will be more easily stimulated by one particular direction of current and other populations by another direction.

Navigated TMS

Presurgical mapping with fMRI is useful, but has limitations. There are numerous reports of cases where fMRI results have been shown to be erroneous and the lack of a direct relation between fMRI signals and underlying neuronal activity is an increasing source of concern. There may well be good correspondence between fMRI data and physiology in healthy subjects, but not necessarily when there is a lesion in the brain. For presurgical investigation, it would therefore be valuable to be able to integrate electrophysiology and imaging. The recent development of navigated TMS (nTMS), using stereotactic techniques to define and control the location and direction of TMS-induced current in the brain using MR-images, has resulted in the availability of the first commercial device for clinical use: the Navigated Brain Stimulation (NBS) System.

Figure: The NBS System (Nexstim Oy, Helsinki, Finland) is a commercially available device with an integrated TMS stimulator, EMG recorder and infrared tracking system *(top).* Using dual screens, the directly evoked EMG signals can be displayed alongside the location, strength and direction of the electric field induced in the cortex by TMS *(bottom).*

Compared to direct electrical stimulation, a clear advantage of nTMS is that it is non-invasive. Moreover, since nTMS targets cortico-cortical connections, in addition to corticospinal projections, it is likely to offer additional information compared to electrical stimulation which targets only corticospinal axons. Finally, it must be considered that during surgery the pharmacokinetic activity of the anesthetics may interfere with the possibility to evoke cortico-cortical activity.

Conclusions

The human motor cortex can be activated by transcranial magnetic stimulation (TMS) evoking a high-frequency repetitive discharge of corticospinal neurons. The physiological mechanisms producing the corticospinal activity are due to complex interactions between the currents induced in the brain and the circuits of cerebral cortex, composed of multiple excitatory and inhibitory neurons and axons of different size, location, orientation and function. The main characteristics of the activity evoked by TMS can be accounted for by the interaction of the induced currents in the brain. A simple cortical circuit can be used to model the most essential cortical input-output operations and to explain the nature of the repetitive discharge evoked by TMS, its dose-dependency and pharmacologic modulation. This circuit provides a good framework for the interpretation of changes in cortical output produced by paired and repetitive TMS, as well as single-pulse TMS.

Direct measurements provide convincing evidence that TMS is a powerful tool for modulating the output of the human cortex. By using different intensities of stimulation and different orientations of current induced in the brain it is possible to non-invasively target different populations of neurons in the cortex. Precisely because effect of TMS on the brain is critically dependent on the strength and direction of the induced current, the ability to control the orientation of the TMS coil will be the key to making clinical observations in individual cases repeatable in other patients. Here, navigated TMS is likely to play a major role in the future.

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The rationale for using NBS in neurosurgery

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The Department of Neurosurgery of the Charité - Universitätsmedizin Berlin (CUB) has investigated the utility of a navigated TMS (nTMS) device, the NBS System (Nexstim Oy, Helsinki, Finland), in preoperative planning since late 2007. The NBS System uses infrared-based stereotactic tracking to determine the location and orientation of the TMS coil relative to the head, enabling accurate targeting and repeatable stimulation of the cortex. Co-registration of the patient's MR-image with the patient's head and the system's components enables 3D-visualization of the coil-induced electric field in the intracranial structures. The nTMS system automatically takes into account stimulation intensity, coil parameters and the individual patient's brain anatomy. Based on the spherical model, the intracranial electric field calculation is accurately visualized in a 3D rendering of the individual patient's MRI. EMG responses to stimuli are shown as a color-coded map in the 3D rendering, enabling the user to systematically, and rapidly, map a lesioned area.

NBS mapping as part of a neurosurgical clinical workflow

In our Department, all patients admitted for brain tumor presumed to be in, or near eloquent motor cortex are mapped using the NBS System. Immediately following the cortical motor mapping sessions, the 3D anatomical-functional images can be used as an aid to explain the therapy options available to the patient and their associated risks and benefits. Once the therapy decision has been made, further planning can be made. When surgical resection is chosen, the NBS functional maps are exported to a surgical planning station (Brainlab AG, Feldkirchen, Germany). If NBS mapping confirms that the tumor is in, or near, the motor cortex, fiber tracking from the motor areas is performed in the surgical planning station; for seeding points, we now use the NBS-derived functional definition of the motor areas. Once the plan is complete, all the functional and anatomical data are co-registered in the surgical planning station for intraoperative guidance and reference. Intraoperatively, cortical and subcortical stimulation is guided by the presurgically localized motor areas. In addition, the ability to overlay motor area and motor fiber tracks in the surgical microscope's field-of-view improves intraoperative workflow.

Our Department integrated the NBS System into clinical workflow three years ago. With an annual case volume of over 50 patients admitted for tumors in the central regions, we have been able to make a preliminary, evidence-based assessment of the value that this new mapping technology has brought to patient care, treatment strategies and clinical outcomes. In all patients investigated so far (n=160), the NBS-determined presurgical localization of the precentral gyrus has been found to be in 100% agreement with the phase-reversal method using an epidural electrode strip. Routine use of the phase-reversal technique in surgery has consequently been abandoned.

Assessment of the impact of NBS mapping on treatment planning

In order to more objectively assess the impact of adopting presurgical NBS mapping on surgical planning, the CUB performed a survey. The survey was conducted as a self-assessment questionnaire by the neurosurgeons in 100 consecutive patients admitted for brain tumor during 2009-2010.
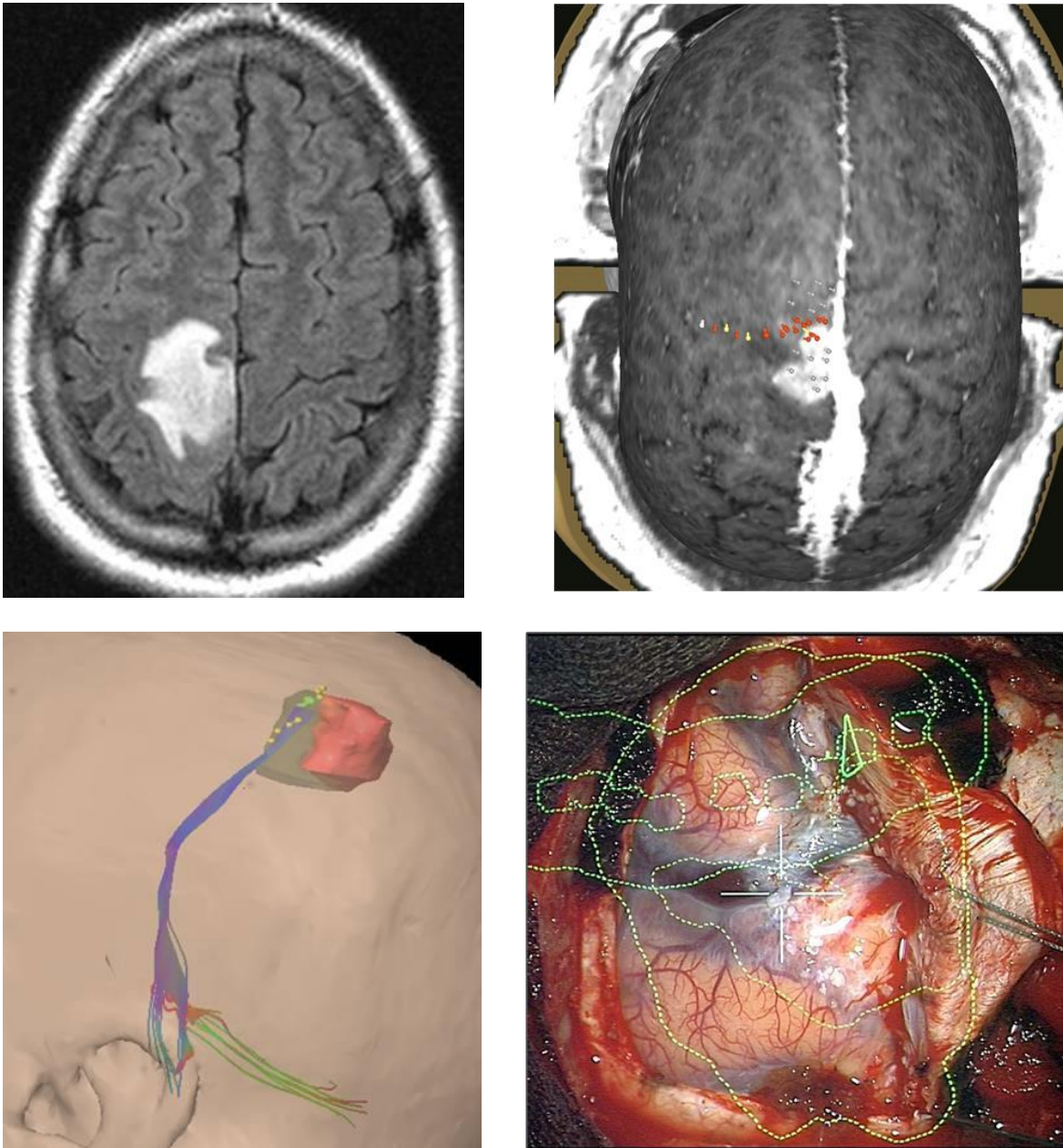
Figure 1. Case example of NBS mapping results altering the surgical indication: a 27-year-old male patient admitted with high-grade paresis of the right foot.

Upper left: MR-imaging revealed a contrast-enhancing lesion located left centrally, with a surrounding area of altered FLAIR signal. Since the imaging and clinical findings suggested that the tumor involved the primary motor areas, the initial treatment decision was to perform a burr hole biopsy for inoperable tumor.

Top right, bottom left: Motor responses from NBS mapping showed that although the motor area was in, or near, the presumed infiltration zone by altered FLAIR signal, the motor strip was clearly anterior to the contrast-enhanced presumed malignant tumor border. As a result of the information provided by the NBS motor map, the treatment indication was changed to open surgery with removal of the malignant part of the suspected glioma.

Bottom right: Intraoperative field-of-view in surgical microscope, with tumor ROIs and motor responses delineated by green dashed borders.

The neurosurgeon was requested to initially determine the surgical indication and surgical approach for each patient based on anatomical MR-images and clinical assessment. Subsequently, the NBS mapping results were made available to the neurosurgeon for review and the neurosurgeon was requested to rank the impact of the additional NBS mapping data on the final treatment plan. The questionnaire employed a 7-scale descriptive ranking scale. The survey showed that, overall, NBS mapping had a positive benefit on the surgical plan in 55% of the cases (ranking 3-6), as illustrated in Figure 2.
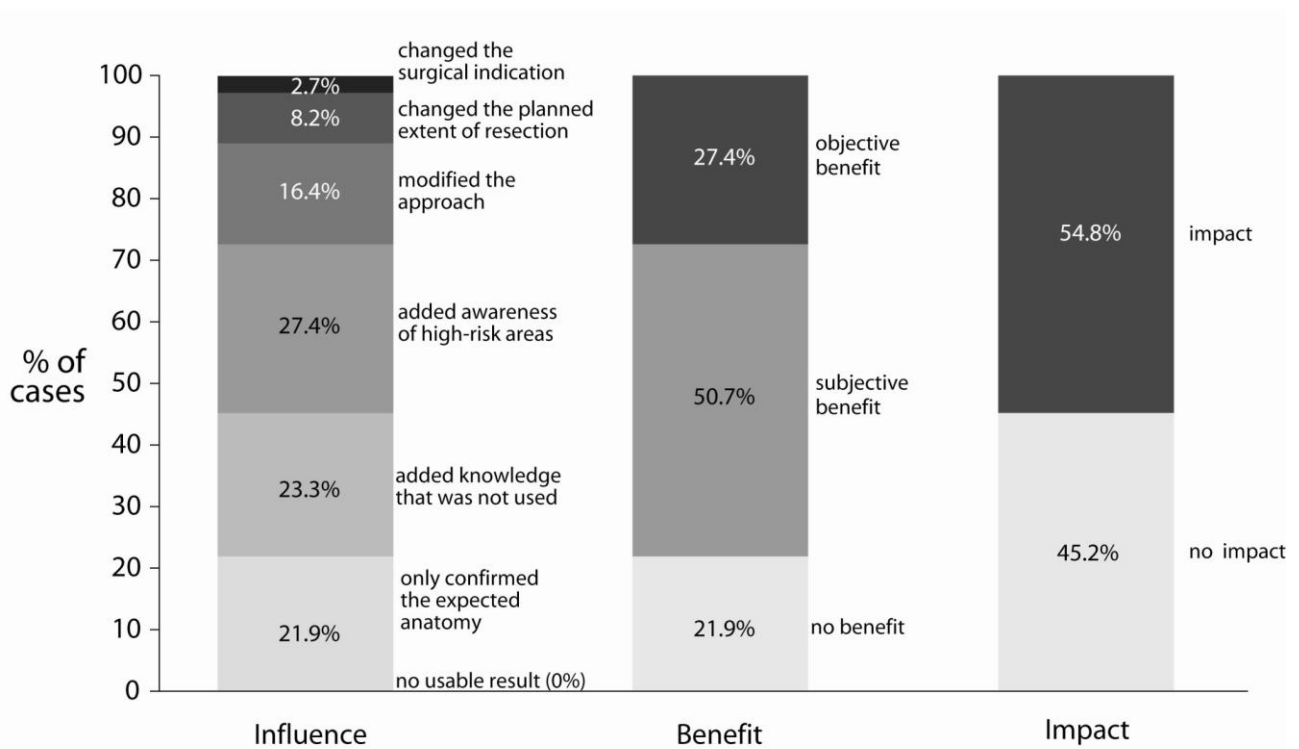
Figure 2. Impact of presurgical NBS mapping on the final surgical indication and treatment plan for tumors presumed to be in, or near, the motor cortex (series of 100 patients), by self-assessment questionnaire.

NBS mapping is helping to change the approach to LGG

Adult low-grade gliomas (LGG) grow slowly, but eventually most undergo malignant transformation with consequent morbidity and the need for treatment. We retrospectively compared our Department's approach to treatment of LGG with suspected involvement of the primary motor cortex both before, and after, we adopted the NBS System for motor mapping in November, 2007. Treatment of LGG patients in the period 2004 - November 2007 (the 2004 cohort) was therefore compared to LGG treatment from the period November, 2007 - 2011 (the 2011 cohort). Both cohorts were well-matched by age and tumor volume. In both cohorts, all patients had an intact motor status and there were no discernible anatomical differences visible between the MRIs in the two cohorts. For the 2004 cohort the average age was 43 (range 31-71) and the average tumor volume 25 ml (range 5 - 57 ml); for the 2011 cohort: the average age was 38 (range 2-59) and the average tumor volume was 24 ml (range 4 - 105 ml).

In terms of treatment, however, there was a marked difference between the two cohorts. In the 2004 cohort, 27% of LGG patients (n = 3) were offered surgery, with total resection achieved in one patient. In the 2011 cohort, 91% of LGG patients (n=10) had surgical treatment, with total resection achieved in 9 out of 10 cases. Additionally, in the 2011 cohort, total resection of infiltrated tissue, by altered FLAIR signal on

MRI, was successful in 5 patients. The surgical outcome in both the 2004 and 2011 cohorts was good, with no permanent motor deficits observed in either cohort.

Although there has been a gradual paradigm shift in the neurosurgical approach to LGGs, from "watchful waiting" towards more aggressive, early-stage treatment of a glioma, the only objective change in the treatment decision-making process has been the introduction of NBS mapping into the presurgical workup. In particular, the ability of the neurosurgeon to be confident that an LGG-related hypodensity on T1-weighted MRI does not contain eloquent motor cortex, as shown by NBS mapping, appears to have been a crucial factor in changing our neurosurgeons' attitudes to early surgical intervention. For relatively young patients with gliomas in the precentral gyrus, reliable information helps to motivate them for early surgical treatment before they experience paresis.

Pre- and postsurgical NBS mapping for prognostic neurophysiological information

As well as providing localization information, NBS also provides neurophysiological data which may have prognostic value in clinical neurosurgery. As part of the standard mapping procedure in our Department we measure the motor excitability of the healthy hemisphere as well as the lesioned hemisphere, thereby obtaining intra-subject control values for the resting motor threshold (MT) and the evoked MEP latencies and amplitudes. We have observed significant intra-subject hemispherical differences in patients admitted for brain tumor, with frequently much higher MTs in the lesioned side compared to the healthy hemisphere. It appears that patients with an MT imbalance have a higher risk of motor deficits, although this needs to be confirmed by further research.

We have also studied the prognostic value of NBS mapping post-operatively at Day 1 after resection of supplementary motor area (SMA) tumors in patients with initial plegia. We have found a strong agreement between the pre- and postoperatively measured MTs of the affected hemisphere to be a prognostic indicator of development following Day 1 paresis: a large increase in affected hemisphere MT predicting permanent postoperative deficit.

Conclusion

At the CUB Department of Neurosurgery, the NBS System has been used in more than 160 patients admitted for brain tumor, to date. In all cases, the presurgical, NBS-defined localization of the precentral gyrus has been found to be in 100% agreement with phase-reversal localization using an epidural electrode strip. Since adopting the NBS System in presurgical workup, treatment decision-making, surgical approach, knowledge-level and confidence have all improved (overall, NBS has had an impact on 55% of cases). The ability to show the results of the presurgical workup in a clear format has also benefitted our presurgical consultation with patients. By current departmental protocol, all patients with brain tumors presumed to be near eloquent cortical areas are now mapped using the NBS System. The success rate for NBS mapping has been 100% and in approximately two out of three cases, NBS has confirmed that the tumor is in, or in close proximity to, the motor cortex. The NBS mapping information can be used to improve fiber tracking for presurgical planning and the information is also valuable for guidance of cortical and subcortical intraoperative mapping when the tumor is confirmed by NBS to be in, or near, the eloquent areas. At the same time as being able to offer earlier and more aggressive treatment of tumors, we have not observed any deterioration in surgical outcomes. Of the NBS-mapped patients receiving surgical therapy, 46% have had new post-operative deficits, with permanent deficits in 9%. Our experiences with the NBS System in motor cortex localization are also encouraging us to examine whether the method can be adapted for localization of eloquent language cortex in patients with tumor in the perisylvian area.

Perioperative multi-modal motor mapping: nTMS, MEG and DCS

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Magnetoencephalography (MEG) has been used less frequently than functional MRI (fMRI) for preoperative mapping, partly due to limited access, and partly due to the complexity of post-processing and analysis of the data. However, non-invasive MEG has been extensively validated for cortical motor and somatosensory mapping. The gold standard for motor mapping, direct cortical stimulation (DCS), is invasive and can only be performed intraoperatively. Noninvasive navigated TMS (nTMS) has only recently been introduced for presurgical motor mapping. By measuring the magnetic field directly produced by electrical neuronal activity, MEG is fundamentally different from fMRI, which measures blood oxygenation changes on a much slower time-scale. Using MEG, motor and somatosensory areas can be mapped by asking the patient to perform tasks, such as button-pressing by the index finger, or touching the lip with air puffs. In patients with brain tumor, techniques have recently been developed to identify and localize hand and mouth motor cortex centers with sensitivity approaching 99% and specificity at an adequate, greater than 94%, level[1].

We compared the accuracy of cortical motor maps generated by nTMS to motor maps generated by MEG and DCS. Additionally, we explored the relevance of a negative nTMS motor map (the inability to elicit MEPs) – given the trend towards smaller and more tailored craniotomy in brain tumor, it would be helpful if negative preoperative mapping could rule out the need for intraoperative DCS.

The nTMS device (NBS System, Nexstim Oy, Finland) relies on stereotactic-guided TMS and measurement of motor evoked potentials to register muscle representation sites in an MRI dataset. The MEG device (CTF Systems Inc., British Columbia, Canada) uses an array of 264 superconducting quantum interference devices (SQUID) to perform magnetic source imaging from the entire cortex.

Over a five month period, 24 out of 31 patients presenting with brain tumors were included in a comparative study. 7 patients were excluded: 5 patients refused to participate in the study, one patient had a history of frequent seizures and one patient had metastatic lacrimal cell tumor.

Results and analysis

Using the nTMS device, the cortical motor areas were mapped in all 24 patients. A total of 49 motor sites were delineated, primarily the abductor digiti minimi (ADM), the abductor pollicis brevis (APB) muscle and the orbicularis oris (OO) muscle. Using MEG, either the right or left index finger (IF) could be localized in all 24 patients. 18 of the 24 patients were mapped using DCS (6 out of the 24 patients were not mapped due to the location of the tumor), however positive cortical motor maps could be generated in only 5 patients, yielding 8 motor sites in total. When the motor site was not exposed intraoperatively, the MEG result was used as a positive control for the nTMS-determined location. Perioperatively, 13 patients of the 18 patients mapped by DCS were also mapped by subcortical stimulation.

21 out of the 24 patients (88%) had intact motor strength postoperatively. In two cases, postoperative motor weakness had significantly resolved at three month follow-up. At three months, one patient had significant apraxia and 4/5 strength in proximal arm muscles. For this patient it had not been possible to elicit MEPs either by nTMS or DCS (a negative nTMS map and a negative DCS motor map).

Due to basic electromagnetic laws dictating the direction of magnetic field dipoles from flow of electric current, MEG is sensitive to current sources which originate from inside sulci, rather than the current sources at the tops of gyri. Consequently, MEG-detected motor sites are not localized on the surface of the

brain as is the case for DCS and nTMS. For comparative analysis of spatial agreement, MEG-located sites therefore need to be projected up to the surface of the cortex.

There was fairly good spatial correspondence between the motor sites determined by nTMS, MEG and DCS, all within the levels of tolerance for the systems involved. The median distance between the nTMS-located sites and the DCS-located sites was 2.1 mm, while the median distance between the nTMS-located sites and the MEG-located sites was 8.2 mm.

In comparing MEG mapping results to the results from other modalities, there is an inherent discrepancy due to activation of different muscles. In MEG mapping, the best response was achieved from the index finger-task. In nTMS mapping however, the best responses were elicited in the APB and abductor digiti quinti (ADQ) muscles, with a poor response from the index finger muscle. To overcome the spatial discrepancy in the muscle representation regions being compared, an interpolated distance between the nTMS-located APB and ADQ muscle representation sites was used for an additional comparison of nTMS and MEG mapping results. Using interpolation, the median distance between the TMS-located sites and the MEG-determined sites was then calculated to be 4.8 mm, while the median distance between the nTMS-located sites and DCS-located sites was 2.1 mm.

There was 100% concordance between the ability of nTMS and DCS to elicit motor sites: if it was possible to localize a motor site by DCS, it was also possible to localize that same site by nTMS. The negative predictive value of an nTMS map in a given cortical region was therefore found to be very high.
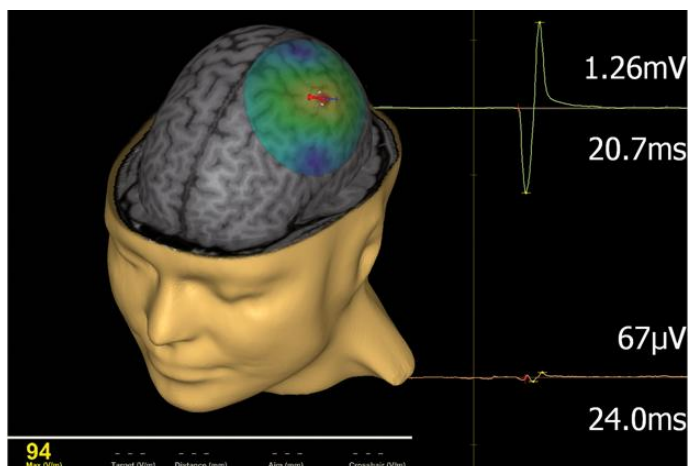
Figure 1: Electric field-targeted navigated TMS: motor evoked potential responses to a single TMS pulse using a focal "figure-of-eight" coil. EMG recordings from the APB muscle (top, 1.26mV) and the ADM muscle (bottom, 67µV).

Conclusions

nTMS-generated cortical motor maps show good agreement with DCS-generated motor maps, the gold standard. The measured median spatial difference of 2.1 mm is similar to the inherent tolerance of the nTMS device used. The nTMS-generated motor maps also agreed well with the motor maps derived by MEG, a well-validated method of localizing cortical M1 strips. Results of nTMS motor mapping correlated better with the results of DCS mapping than the results obtained by MEG. Additionally, a negative result from preoperative nTMS motor mapping is a reliable indicator of negative results by intraoperative DCS mapping.

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Navigated transcranial magnetic stimulation of the brain: increasing safety of radiosurgery

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Radiosurgery requires an understanding of, and conformance to, the same physiological principles that apply in surgical resection. However, radiosurgery differs in one major respect compared to surgical intervention since radiosurgery is noninvasive. Although noninvasiveness is a major advantage, it also means that the neurosurgeon can neither see the vital structures of the brain before treatment, nor receives any immediate visual feedback on the effects of treatment, including complications. In the absence of direct visual aids, the neurosurgeon needs to recognize all pertinent factors from imaging workup and carefully preplan every step of the treatment. There is no possibility to perform physiologically tests on the tissues in the neighborhood of the target. Navigated transcranial magnetic stimulation (nTMS) is an accurate, non-invasive method of physiological testing which has been recently introduced into planning surgery. We have explored the use of the nTMS technique to improve the safety of radiosurgery.
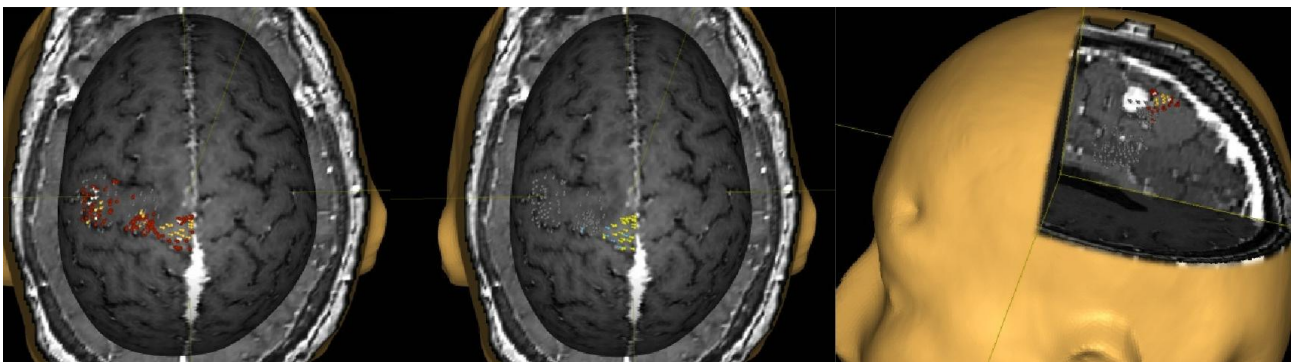
Figure: Presurgical mapping of motor areas around tumor in the left hemisphere prior to radiosurgery.

Safety in radiosurgery for arteriovenous malformations

The clinical management of intracerebral arteriovenous malformations (AVM) of the brain can be achieved by radiosurgery, microsurgery or endovascular microembolization, in addition to watchful waiting. The therapeutic choice is often not obvious, and the choice is influenced not only by the hemodynamic features of the AVM, but also by considerations of the extent of intervention-related complications. Since AVMs are congenital developmental vascular lesions, it is not surprising that the presence of an AVM in close proximity to the primary motor cortex can lead to reorganization of the normal somatotopy, and even displacement of function into non-primary motor areas. Careful planning of treatment to avoid vital functional areas and structures is paramount, since treatment of an AVM by radiosurgery essentially involves obliterating the target with a high dose of radiation (typically, a single fraction dose of 20 - 25 Gy). Epidemiological studies indicate that a significant percentage of discovered AVMs are near eloquent areas, with 12% of AVMs near the sensory motor area, and a further 11% in the occipital area[1]. As a noninvasive functional mapping technique, nTMS could be a very valuable tool for more informed management decisions when considering the use of radiosurgery for the treatment of AVMs.

Safety in radiosurgery for tumor

Radiosurgery is increasingly being used in the management of patients with brain metastases. Compared to surgical resection, radiosurgery offers a much lower local recurrence rate and can be used for multiple tumors even in eloquent areas, while being noninvasive and less expensive. The ideal goal is to deliver the therapeutic dose to the target volume, while sparing the surrounding tissue completely. In reality, however, dose limitation is required, and is achieved by modifying the treatment field. Multiple technological advancements have been made with the goal of shaping the radiation to the target tumor and conforming the therapeutic dose.

The physiological effects of single-fraction radiation are dependent on the pathology treated. For example, dosing up to 35 Gy can be used for the treatment of secreting pituitary adenoma without complications, whereas high doses of radiation in the treatment of astrocytoma is contraindicated. In radiosurgery, complications are related to the pathology itself, the edema surrounding the target, the location of the lesion in relation to surrounding white matter and even pressure from large tumor mass. Additionally, the tumor volume itself has an effect: perhaps counter-intuitively, the larger the tumor, the lower the treatment dose needed. Recently introduced radiosurgery devices, for example the Leksell Gamma-Knife Perfexion^{TM} (Elekta Instrument AB, Stockholm, Sweden), offer highly conformal isodose distribution as well as a very steep gradient of dose fall-off beyond the prescribed isodose line. However, we can never avoid some radiation to the tissues surrounding the tumor, and treatment planning would benefit from better knowledge of the functional importance of the tissues surrounding the target.

Case: A female 52-year-old patient, who had had a large, mainly left-sided parafalcine meningioma tumor surgically resected at 37 years, presented with recurrence of the tumor in the parasagittal area of the right hemisphere. Having suffered significant right-sided hemiparesis from resection, the patient's wish was for radiosurgery. MRI revealed that, although the tumor was centrally located along the falx, it could also be seen to be protruding into the right hemisphere. nTMS functional mapping (NBS System, Nexstim Oy, Finland) showed that the tumor was actually very close to the motor areas from which EMG responses were elicited in the tibialis anterior and extensor pollicis brevis muscles. With this new information, the neurosurgical team concluded that the best outcome would most likely be achieved by microsurgical resection since the tumor border was in close proximity to the motor cortices. The clear and unambiguous presentation of results of the functional motor mapping in a 3D MRI rendering significantly helped to convince the patient of the relative safety of microsurgery in her particular case. In terms of outcome, the tumor was successfully resected, with no new postoperative neurological deficit due to microsurgery.

Conclusions

Radiosurgery has an important and growing role in the treatment of an increasing number of brain pathologies. The noninvasive functional mapping information provided by nTMS complements the noninvasive nature of radiosurgery and partially compensates for the absence of visual aids and feedback, when compared to resection. nTMS has the potential to improve the safety of radiosurgery for patients with regard to treatment selection and treatment planning. As well as mapping the motor cortices, it appears that there is the potential for nTMS technique to be extended to allow mapping of the eloquent speech areas, as well as the visual cortex.

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Latest findings in functional NBS and MEG mapping of patients undergoing epilepsy or tumor surgery

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Single-pulse transcranial magnetic stimulation (TMS) applied to the motor cortex can activate the neuronal networks which code for movement. By measuring EMG over the corresponding muscles, motor evoked potentials (MEP) can be registered when the induced electric field exceeds the motor threshold. Inversely, the electrical activity in neuronal networks required to initiate voluntary movement induces magnetic fields in the cortex which, although weak, can be detected outside the skull using magnetoencephalography (MEG). Based on the interaction of magnetic fields, TMS and MEG are essentially unaffected by overlying tissue and bone and therefore, unlike surface EEG methods, both TMS and MEG have good spatial, as well as temporal, resolution. When co-registered with the anatomical MRI, navigated TMS (nTMS) can be accurately guided and orientated within intracranial structures. For several years we have used a commercial device, the NBS System (Nexstim Oy, Helsinki, Finland), for investigating the brain in both healthy controls and brain tumor patients and, together with MEG, for preoperative planning of epilepsy surgery.

Correlation of nTMS and ECoG in epilepsy

nTMS is a practical clinical tool for the localization of motor representation in brain tumour patients. However, it is not yet been shown to the same extent how well representations defined by nTMS correlate with activity elicited by invasive subdural grid electrocorticography (ECoG) in epilepsy, particularly in children. In our investigations with epilepsy patients, we have found a general good match between nTMS and invasive grid recordings in children and young adults. In a series of 12 patients with intractable epilepsy, we compared the concordance of nTMS mapping with EcoG grid electrode mapping. In 11 out of the 12 patients maximum responses were elicited in the same gyrus, with a spatial correspondence of 14 mm ± 6 mm between the centers of gravity calculated separately for both methods (Vitikainen et al., in preparation). When evaluating the spatial correspondence of the two methods, one needs to take into account the fixed 10-mm inter-electrode distances in the subdural electrode grid. Our results in pediatric and young adult epilepsy patients also compare well with results from other published studies comparing nTMS to direct cortical stimulation (DCS) in adult patients with tumors in the rolandic or central cortical areas. In tumor, published studies have shown a concordance between nTMS and DCS of, for example, 8 mm ± 1 mm (Picht et al., Neurosurgery 2011) and 11 mm ± 6 mm (Forster et al., Neurosurgery 2011).

A significant number of epilepsy surgery patients need preoperative localization of epileptogenic and eloquent cortical regions, which has been conventionally performed by ECoG grid mapping. Adding TMS and MEG to the workup can improve decision-making regarding the exact location of the subsequent grid installation, as well as the extent of the resection. nTMS and MEG can sometimes provide information not available from other methods, and prove decisive in cases where ECoG results are confounded by after-discharges or seizure induction. The monitoring and mapping via grid electrodes is a costly and invasive method, associated with serious complications in a small subset of patients. The availability of the noninvasive methods, nTMS and MEG, may reduce the need for invasive mapping and monitoring in the future.

Investigating the use of nTMS in speech mapping

With nTMS established as an accurate and useful modality for mapping the motor cortex, we are now exploring new paradigms to study the potential of extending the use of nTMS for mapping the speech-related cortical areas. We have based our investigations of speech-related networks on the off-line review of recorded behavioral responses to nTMS using the NBS System. The separate display screens for NBS System stimulus presentation and showing object are cloned and a commercial digital camera used to record both the cloned screens and the subject's performance. We have tested a paradigm where subjects name pictures of objects presented every 2.5 s and 5 Hz TMS is applied for 1 s, 300 ms after the presentation of a new object on the screen. The video recording of the session has been analyzed by an experienced neuropsychologist who classified the speech errors evoked by nTMS during the object naming. Complete anomias, semantic, phonological and performance errors have been observed during nTMS over the left fronto-parieto-temporal cortical regions. Several speech-related errors were detected only by off-line analysis of the video recordings (Lioumis et al. 2012).

Preliminary results in healthy controls have been encouraging. In a series of six healthy control subjects, our technique was able to produce speech blocking in four out of the six controls and dysnomias in five out of the six controls (nTMS was not able to interfere with speech in one case). We have also used nTMS study the paradigm in patients with brain tumors, a case example is shown in Figure 1.
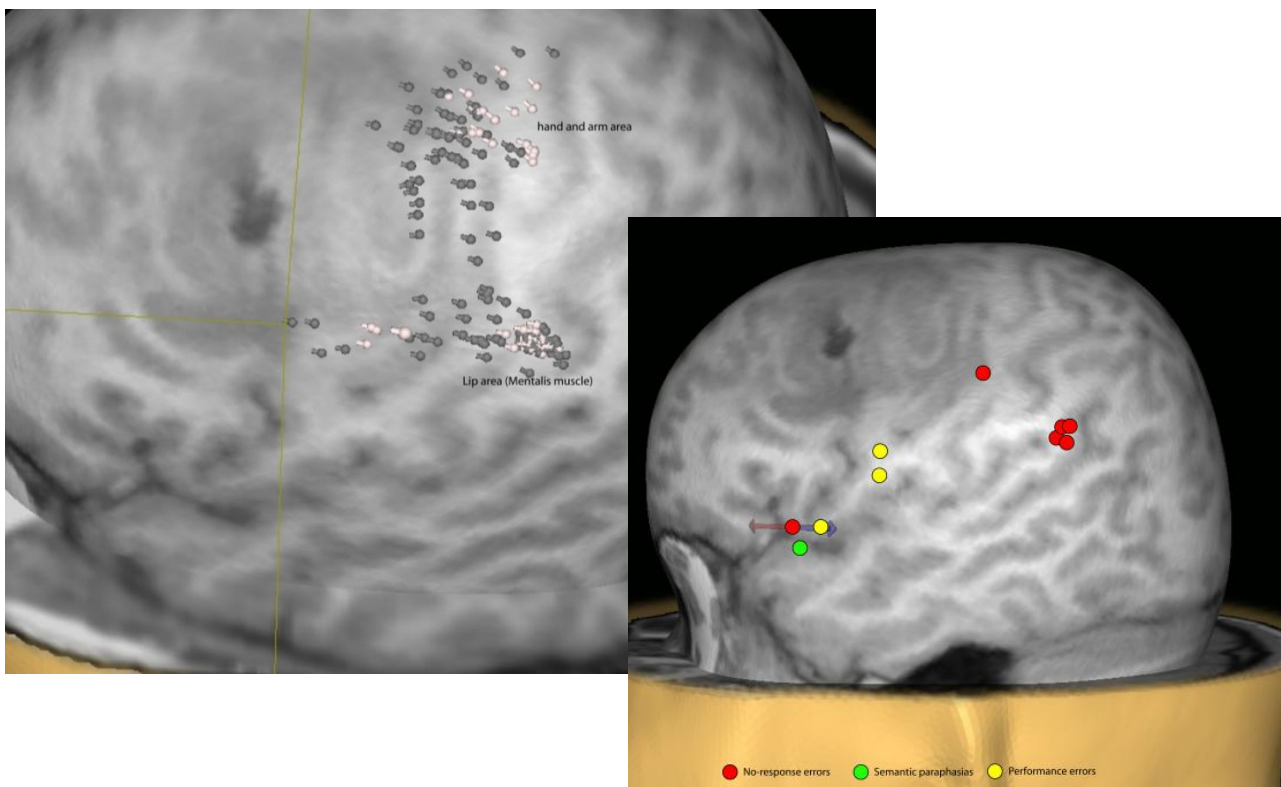
Figure 1: Patient with supplementary motor cortex tumor underwent resection following motor and speech mapping using the NBS System. *Left image:* motor map showing hand and arm representation areas and lip area representation from the mentalis muscle responses. Postoperatively the patient had right hemiparesis and dysphasia, which almost completely resolved after 1 month. *Right:* result of speech mapping with the NBS System: red = no-response errors, green = semantic paraphasias, yellow = performance errors induced by rTMS.

Figure 2: Overview of speech mapping with nTMS. *Upper:* a train of nTMS applied to the temporal lobe while the subject is naming the object. Lower: cloned screens of real-time location of nTMS electric field and the object used in the naming task. The entire session is video-recorded and analyzed off-line (modified from Lioumis et al., 2012).

Conclusions

The good concordance of the nTMS and ECoG methods for the localization of motor areas in epilepsy patients suggests that nTMS mapping results can be reliably used for planning the placement of subdural grid electrodes and further raises the possibility that nTMS could replace invasive grid electrode mapping in some cases, especially when MEG is able to reliably localize the ictal onset zones. Off-line expert analysis of video recordings from nTMS sessions appears to be a useful technique for mapping speech-related areas of the brain although further research to better understand the mechanisms of TMS in speech disturbance is warranted. The clinical relevance of nTMS techniques in speech mapping needs to be carefully verified by DCS mapping.

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NBS in tumor and epilepsy surgery in children, with a comparison to fMRI

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As part of a presurgical workup, identification of the cortical motor areas is as essential in children as it is in adults. However, use of the most common technique, functional magnetic resonance imaging (fMRI), is often difficult in children, especially in the very young. Cognitive impairment can also make fMRI studies impossible. Navigated transcranial magnetic stimulation (nTMS), utilizing the patient's MR-image for stimulation guidance, does not require that the patient cooperates in tasks and may therefore be more suitable for use in children. nTMS mapping has been shown to offer precise demarcation of primary motor areas in patients with brain lesions, although published studies have been limited to investigations in adults.

Comparing of intra-subject measurements by fMRI and TMS has revealed that the two techniques often give discordant results. Published studies comparing the spatial distances between independently measured centers of activity for nTMS and fMRI with intra-operative direct cortical stimulation (DCS) have shown that nTMS results more closely approximate DCS results - suggesting that fMRI may not, in fact, be mapping the same physiological phenomenon as both DCS and nTMS. We have observed a similar discordance between fMRI and nTMS localization of motor areas in children. Additionally, fMRI in young children is sometimes possible only by sensory activation. However, brain injury early in life has been shown to result in sensory and motor cortical reorganization, with the possibility of normal contralateral activation of the sensory pathways, but abnormal ipsilateral motoric projections of the affected limb. Figure 1 below illustrates one such case of ipsilateral motor reorganization in an 8-year-old child.

With nTMS mapping the child may sit in the lap of a parent for the duration of the investigation, and movement is not restricted. TMS-EMG studies in children are more challenging than in adults. In children the motor threshold to elicit motor evoked potentials (MEPs) is high and pre-activation of the muscles is often necessary in order to obtain measurable responses. Here, the presence of the parents and their ability to activate and play with the child during the mapping session can be crucial to obtaining a successful result. In children taking anti-epileptic drugs, the stimulator output typically needs to be at, or near, maximum in order to evoke MEP responses. However, for some children on anti-epileptic drugs no MEPs can be recognized from a lesioned hemisphere, even with preactivation and at maximum stimulator output. TMS mapping, and off-line analysis of the EMGs, is usually much more time-consuming for children than adults. In children, the "latency jump" - the difference between the latency of a TMS-evoked MEP with muscle pre-activation compared to MEPs evoked at rest - is greater than in adults, which can further complicate EMG interpretation.
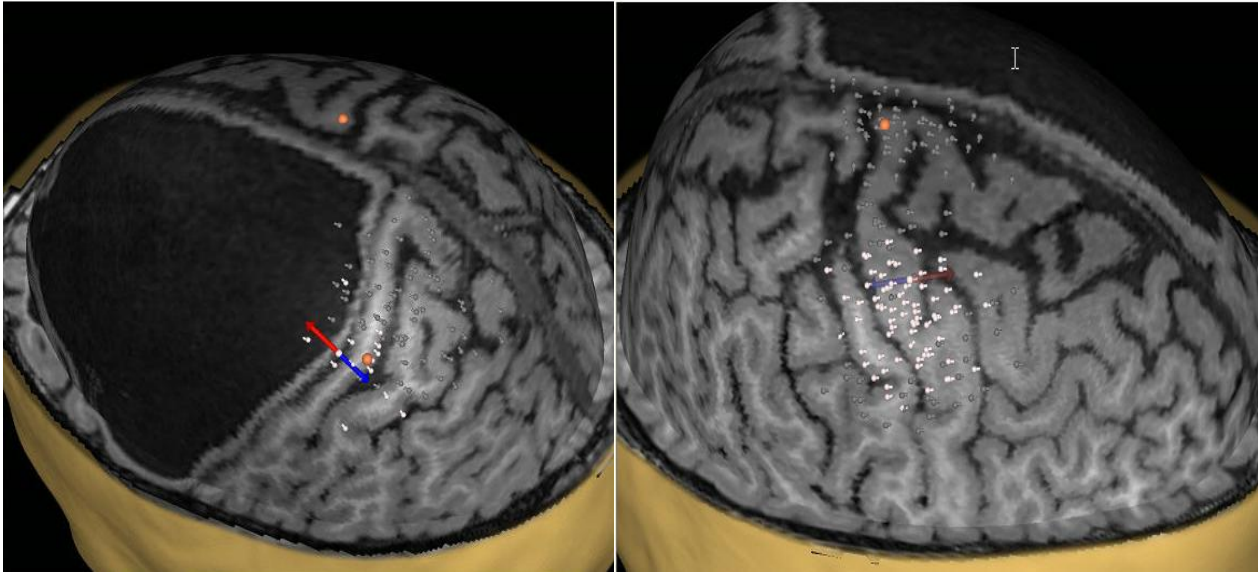
Figure 1: MRI revealed a large defect in the anterior part of the left hemisphere in an 8-year-old girl, born prematurely with left-sided, grade IV intraventricular hemorrhage, which resulted in right-side hemiplegia and seizures. fMRI showed sensory activation of right hand in left hemisphere, posterior to the lesion, (motor activation not possible). The presurgical workup for a possible hemispherotomy included an nTMS investigation. Left image: nTMS mapping of the left hemisphere elicited MEPs in the right-sided hand muscles. Right image: From the undamaged right hemisphere, MEPs were elicited for both the ipsilateral and contralateral hand and leg muscles (the hand muscle activations are illustrated here). Thus, nTMS showed that most motor activity had reorganized to the undamaged side (markers in the images: white = MEP elicited, grey = no response).

nTMS in child epilepsy, case study:

At 32 months of age, a young girl was first investigated due to symptoms including broad-based walking, falling and blinking. At that age the clinical workup did not reveal any abnormalities. However, at 42-months the girl experienced seizures, with other symptoms including jerking of the right shoulder, episodes of jerking during sleep, and atypical absences with bilateral blinking. Additionally the girl had difficulty with articulation, word-finding and gait. After an epilepsy diagnosis was confirmed, pharmaceutical therapy initially controlled the symptoms. After a further ten months the symptoms reappeared and her epilepsy proved to be resistant to all pharmaceutical therapies. Steroids provided seizure control with a normal EEG while awake, but symptoms of continuous spike wave syndrome (CSWS) manifested during sleep. The steroids caused severe side-effects, but tapering them resulted in seizures, speech problems and mild paresis in the right hand. The girl was therefore considered for surgical intervention and nTMS mapping was performed to evaluate the cortical motor areas.

Method: nTMS mapping was performed using an NBS System (Nexstim Oy, Helsinki, Finland). The child was positioned in the lap of one of the parents, who, in turn, sat in a comfortable chair. The tracker eyeframe with reflecting spheres was kept tightly in place by fixating it with a net "helmet" pulled over the child's head. The child's left hemisphere was extensively stimulated while one parent played with the child to preactivate the muscles. The muscles investigated were the abductor pollicis brevis (APB), the abductor digiti minimi (ADM), the extensor carpi radialis (ECR), the deltoideus (Delt) and the trapezius (Trap).

Result: nTMS mapping showed a normal somatotopy. An electroencephalographic examination pointed to an origin of ictal spike activity in the posterior part of the precentral gyrus. The results of the EEG examination were manually fused with the motor map from the NBS System for further presurgical evaluation (Figure 2). During subsequent surgery, the child was found to have a non-malignant gliotic area in the left precental gyrus which was successfully resected. Postoperatively the child was free from seizures and had a normal EEG; she also recovered use of the right hand and had a remarkable recovery of speech function. Steroid administration was slowly tapered, successfully.
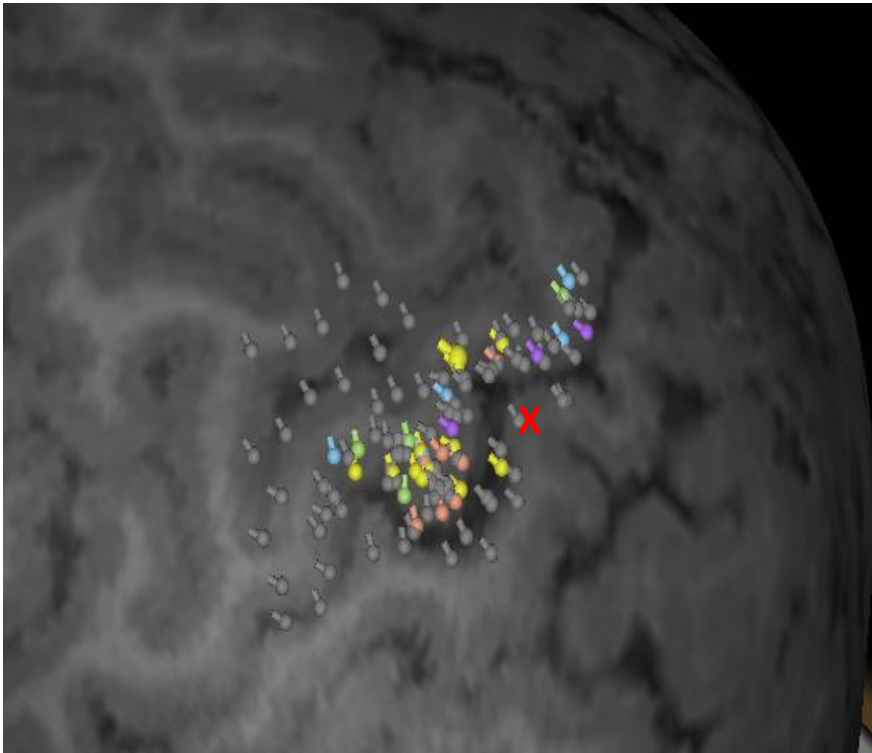
Figure 2. The NBS display of responses from nTMS mapping along the left precentral gyrus in a 3-year-old patient. The color-coded symbols indicate the locations from which motor responses were elicited in muscles: green - APB, orange - ADM, yellow - ECR, blue - Delt, purple -Trap (grey indicates locations from which no MEPs could be elicited). The red X marks the probable origin of the CSWS, as indicated by electroencephalography.

Conclusion

nTMS allows reliable, precision mapping of motor function in young children. High stimulator outputs may be required, together with muscle preactivation and for children on anti-epileptic drugs, even maximal stimulation may not succeed in eliciting motor responses. In children with perinatal brain injuries, nTMS can be used to demonstrate motor reorganization when fMRI indicates that sensory organization is normal. In children, CSWS should be treated as a clinical symptom and its underlying etiology needs to be carefully investigated, especially if there are focal signs.

nTMS in clinical practice for mapping patients with brain tumors

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The boundaries of a brain tumor or other lesion to be resected can be defined by MRI preoperatively, and differentiated intraoperatively by tissue consistency and visualizing adjuncts, e.g. 5-aminolevulinic acid in cases of high grade glioma. However, in order to avoid an absence or reduction in the patient's post-operative functions, of more concern to the neurosurgeon are the tissues which may not be resected.

Direct electro-cortical stimulation (DECS) is considered the gold standard for cortical mapping, preferably performed on the awake patient. Asleep-awake-asleep brain surgeries can be long procedures and tiring for the patient; and it is not uncommon for patients to request a return to sleep before the end of the awake period. However, this is typically the most critical time of the resection and for safety it would be important that the patient can still be awake. New applications of stereotactic navigation techniques for enhanced preoperative planning and re-engineering workflow in tumor neurosurgery are now becoming practical, and have the potential for shortening awake surgeries.

Navigated transcranial magnetic stimulation (nTMS) is a recently introduced method for localizing the motor areas of the cortex. Unlike with earlier mapping methods, nTMS has high temporal resolution and good spatial resolution which has been well established. The good spatial correlation between the results from nTMS and DECS allows the two methods to be used in a complementary way.

Improved workflow with navigated mapping methods

The availability of reliable preoperative functional mapping data allows new operative approaches. Instead of extensive craniotomy, a smaller, more tailored bone flap can be made centered, or off-centered, with respect to the region of interest (ROI) based on functional, as well as anatomical, data. It is recommended to include within the limits of bone flap a muscle representation point positively identified by nTMS mapping (typically the abductor pollicis brevis (*APB*) or the tibialis anterior (*TA*), depending on flap location) in order to facilitate DECS mapping.

When the sites of the ROI and the functional areas are projected up onto the scalp, the markings can be used as an aid to optimally position the patient before skull fixation. It is important that the patient's skull is fixed such that the tumor is located as much as possible at the zenith of the head; in this manner, brain shift is limited by being directed in the vertical direction and guidance by intraoperative ultrasound is better.

Where possible, awake surgery is the preferred technique, since it is also important to preserve other eloquent functions - not only motor function. Once the patient is awake, DECS can be performed, but without reliable and accurate functional mapping data, the cortex needs to be explored as "terra incognita" which can be time-consuming. Displaying locations of the nTMS-mapped points as an overlay in the microscope field can significantly shorten the time normally needed for DECS mapping. The nTMS-positive points can be systematically and sequentially confirmed by DECS, with nTMS-negative points stimulated at least twice by DECS to confirm that they are true negatives.

Given the critical role awake mapping can play in the asleep-awake-asleep approach, the resection should be performed as fast and as efficiently as possible in the awake phase. To permit resection during the awake phase, maximal mapping should be performed preoperatively or in the asleep phase. In order to shorten the awake mapping time, navigated methods allow for the stimulation locations and color-coded responses to be overlaid together with color-coded maps of all relevant gyri in the microscope field.

When the neurosurgeon employs navigated methods, it is important to minimize the multiple possible sources of errors. Already when MRIs are acquired, distortion due to patient movement needs to be avoided. Since most surgeries are also performed in the supine patient, it is reasonable to consider performing nTMS mapping also in the supine position. Fixation of the tracker and co-registration of systems are sources of error, which can be limited by using a skull clamp, for example.

Tumor surgery performed with the aid of nTMS mapping

Case: A 45-year-old right-handed male presented with headache and right sided hemiparesis; the patient also had difficulty in naming objects and counting. On MRI a left parieto-temporal intra-axial lesion with large mass and surrounded by extensive edema was seen. No anatomical definition of the central sulcus was possible on MRI.

Methods: Prior to surgery, the patient was administered steroids in order to permit awake resection. nTMS mapping using an NBS System (Nexstim Oy, Finland) located motor cortices eliciting clear responses in the APB and ADM muscles. Results of nTMS mapping were entered into the surgical navigation system. Navigated bipolar DECS confirmed the functional responses elicited by nTMS mapping.

Outcome: Total resection of the tumor was achieved. Post-operatively, there was total regression of paresis and a partial regression of errors in naming and counting.
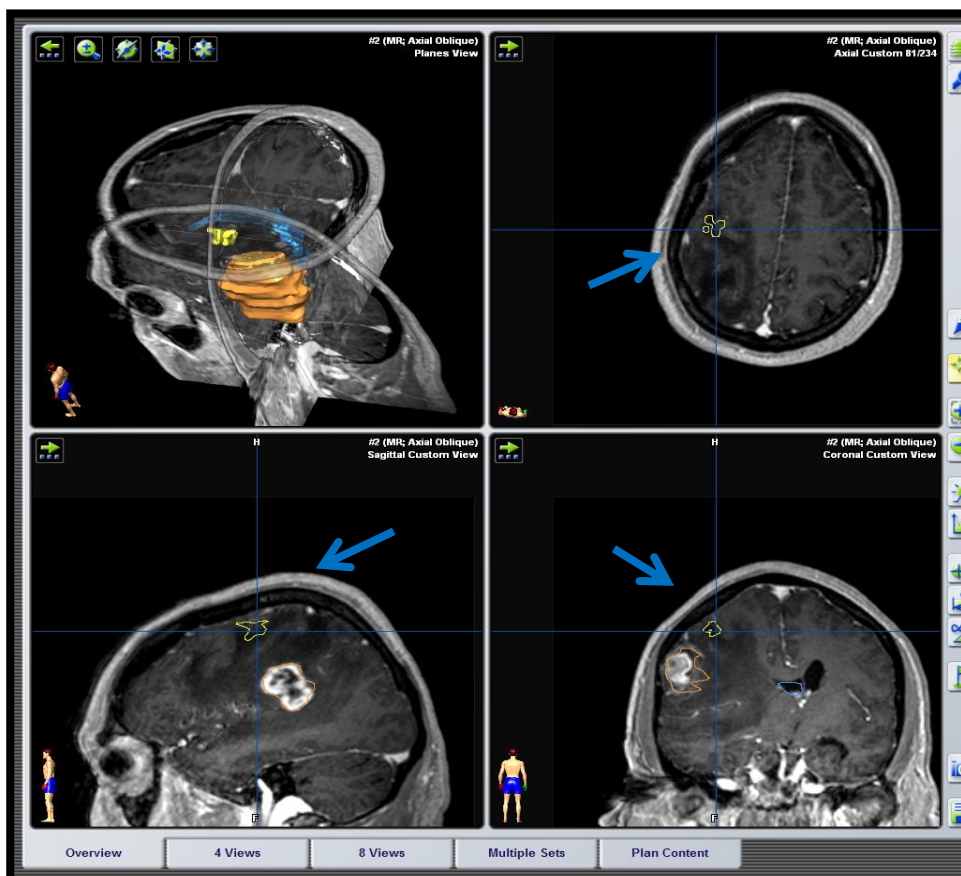

Figure 1: Preoperative planning view displayed in the neuronavigator. The motor area "hotspots" for abductor pollicis brevis (APB) muscle and the abductor digiti minimi (ADM) muscle elicited by nTMS mapping are drawn as objects and imported into the neuronavigator.
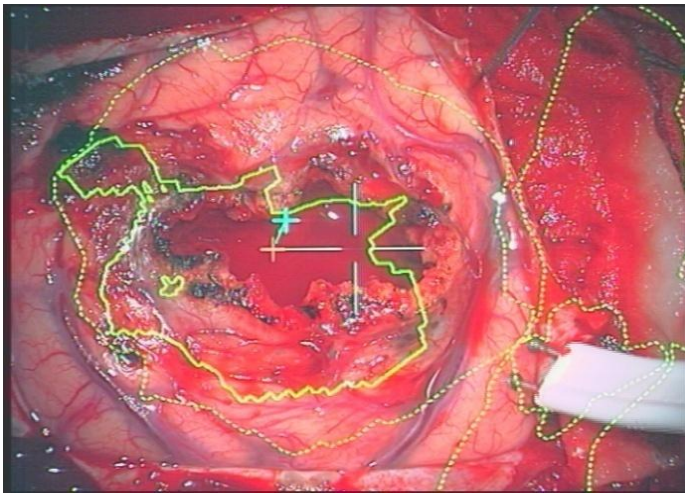
Figure 2: Viewing field of the surgical microscope including an overlay of the tumor ROI and the ADM muscle representation area, both drawn as objects. The Bipolar DECS probe is seen over the ADM muscle representation area (shown at bottom, right).
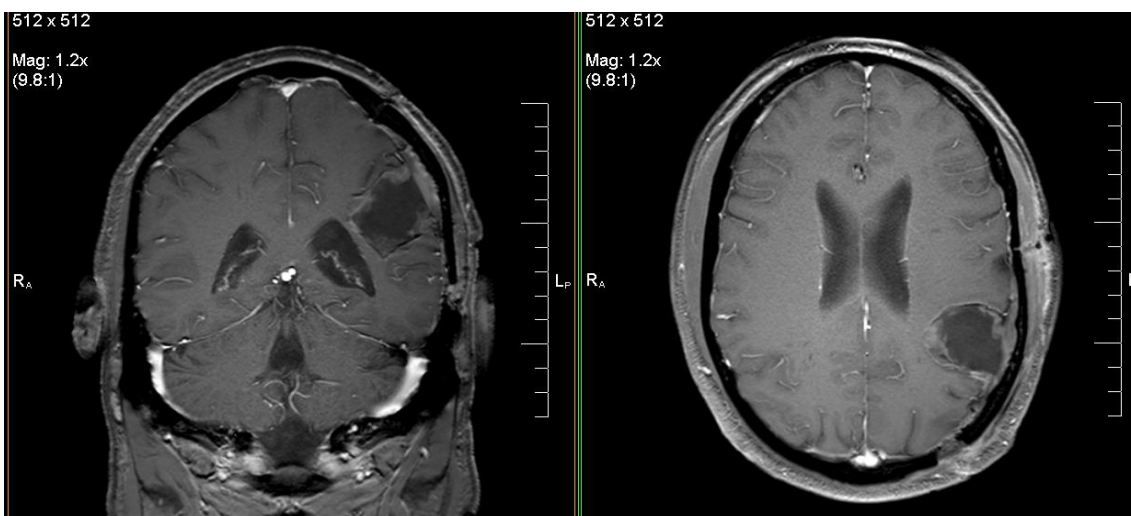

Figure 3: Post-operative outcome on MRI.

Conclusion

Although time-consuming and challenging for the patient, awake mapping is critical for the preservation of function when resecting central lesions. Functional mapping in the preoperative and asleep phases maximizes the time available in the awake phase for resection. When considering treatment of lesions near to eloquent areas, preoperative functional motor mapping is mandatory, if possible. Methods introduced earlier, including fMRI and MEG have insufficient spatial resolution for neurosurgery, and the voluntary movement may not be achievable for localization of functional hotspots. However, nTMS appears to be as accurate and reliable as DECS and the method can induce movement regardless of mental or neurological status of the patient - provided corticospinal tract remains functional. We have observed good correlation, spatially to within 10 mm, between the motor localization results for preoperative nTMS and intraoperative DECS, despite the non-point accuracy of bipolar stimulation. Although not as sensitive in revealing cortical motor function representation as DECS, nTMS remains reliable in cases of distorted anatomy due to presence of tumor or edema, or a decrease in motor function. In both nTMS and navigated DECS, rigorous co-registration, with appropriate fixation to the skull or similar positioning is mandatory for high accuracy and correlation. In language mapping, nTMS appears show promise, although the issues of low sensitivity and a lack of a standardized protocol need to be overcome.

NBS mapping in chronic pain

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Perceived in the brain, pain is a sensation related to potential, or actual, damage to tissue with numerous and diverse mechanisms of transmission and perception. Pain normally results in the activation of areas of the brain not only associated with somatosensation but also emotions, such as anxiety and fear. Although acute pain plays a warning role and is vital for survival, the causes of pain perception in chronic pain are not always clear. In chronic pain, the survival or warning action of pain has an unclear function and the mechanisms behind pain are still not fully resolved. Lesions due to trauma or pathological changes in the central or peripheral nervous systems should, by classical prediction, only lead to numbness, but patients frequently have severe, enduring pain. This chronic neuropathic pain is probably due to the human neural system's ability to enhance, amplify and prolong pain as a further warning mechanism, or to facilitate restoration of function, but in these patients this protective processing has become maladaptive, outlasting its short-term usefulness.

Despite recent therapeutic advances, more than one-half of patients with neuropathic pain experience unsatisfactory pain control. The main strategies for pain control include interruption of pain signals at various levels of the neuraxis, or strengthening the body's own pain control systems. Converging, albeit limited, evidence so far suggests that the motor system becomes integrated with the complex processing of nociceptive signals. In patients with amputated limbs, part of the primary motor cortex essentially becomes redundant for its prior motor tasks while being deprived of the sensory feedback confirming that movement has taken place. We have hypothesized that in this situation a critical role of the motor cortex, that of suppressing excessive sensory input into the thalamus and inducing descending pain modulation, is compromised, resulting in spontaneous pain. If so, it may be possible to modulate pain perception in chronic pain simply by modulating the activity of the motor cortex.

Cortical reorganization in phantom limb pain

An experiment with mental imagery was performed in order to test the hypothesis that, were redundant motor cortex to be re-engaged in "worthwhile" tasks, brain activation would normalize with a consequent reduction in pain perception[1]. Thirteen adult patients with chronic phantom limb pain were recruited for the experiment. An initial baseline functional MRI (fMRI) investigation revealed that the purse lips test activated the deafferented site (i.e. the hand area of the primary motor cortex contralateral to the amputated arm) and that reported pain correlated with this abnormal activation. In order to test the possibility of modulating the pain by reactivation of dormant motor cortex, the patients underwent a therapy intervention comprising a course of mental imagery. Over a period of 6 weeks, the patients were instructed to follow a protocol which included imagining the performance of daily exercises with their phantom limbs. All participants successfully completed the 6-week therapy intervention. Follow-up fMRI at 6 weeks showed that the abnormal activity in the contralateral motor area had disappeared after the intervention. Patients also experienced a reduction in pain score levels, particularly in the intensity and frequency of exacerbations which are the most debilitating symptoms of phantom pain. Furthermore, the reduction in ongoing pain correlated with normalization of cortical activity.

This experiment shows that a small intervention in the function of the motor cortex was able to reduce pain exacerbations, as well as modestly relieve underlying pain, to a greater extent than typically seen in response to pharmacological intervention. So far, experimental evidence suggests that pain relief is correlated with motor cortex reorganization, at least in a subset of chronic pain patients, which raises the possibility that cortical stimulation may be able to induce beneficial neuroplasticity, and this in turn will be beneficial by leading to greater modulation of pain signals via the descending pain pathways.

nTMS for mapping cortical organization in chronic pain

We used navigated TMS (nTMS) to more accurately study cortical reorganization in complex regional pain syndrome and central post stroke pain. All patients had lateralized pain, allowing us to use the unaffected hemisphere as the control for the affected hemisphere. A Navigated Brain Stimulation (NBS) device (NBS System, Nexstim Oy, Helsinki, Finland), was used to delineate the representation areas for both the affected and unaffected limbs. When comparing the affected to the unaffected side, preliminary findings in 8 patients show differences in the shape and size of the cortical probability maps, with an increase in the representation area on the affected side ranging between 4% - 43%. In addition to an enlarged motor area, from past experience with fMRI we also expected to find a medial-lateral shift in representation area, however such a shift of > 10% was rarely found using nTMS.

Navigated rTMS in chronic pain therapy

Repetitive TMS (rTMS) has earlier been shown to induce temporary alterations in the excitability of the cortex. Our research work using the NBS System to target rTMS into the motor cortex in patients with dispersed, over-active limb representation suggests that it is possible to at least temporarily ameliorate pain for up to 2 weeks. Comparing follow-up NBS cortical maps at 2 weeks to pre-intervention maps also revealed a modest, but measurable, reduction in the representation area of the affected limb, suggesting that beneficial neuroplastic changes had taken place.
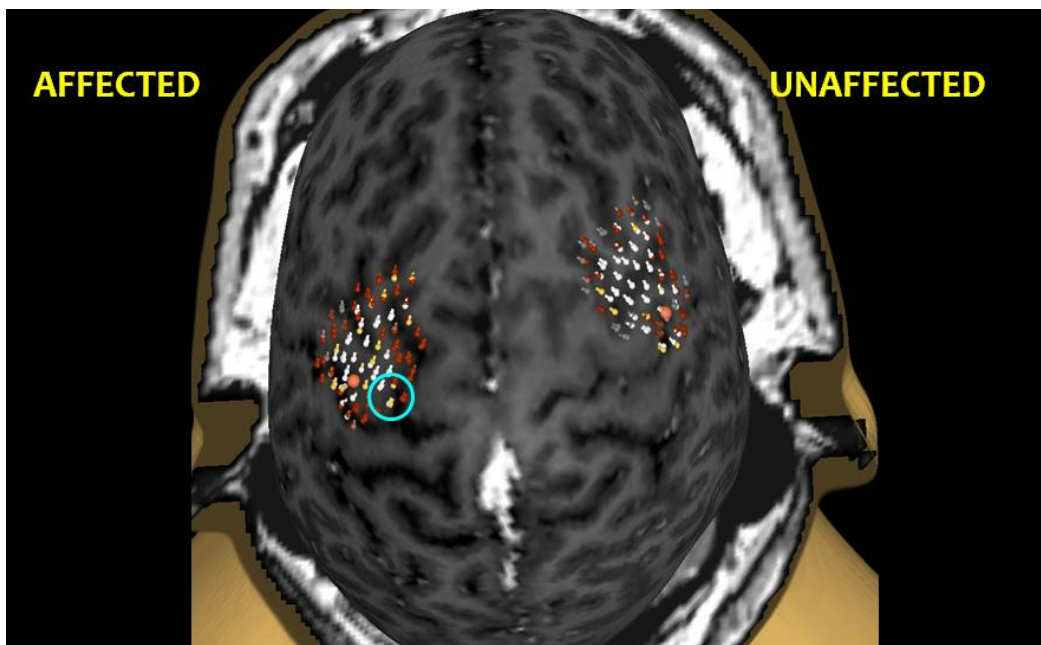

Figure: Single-pulse nTMS shows expansion of the M1 hand representation area posteriorly and medially in a 37-year-old female patient with central post stroke pain (white = maximum response, grey = no response).

Conclusions

In chronic pain there is significant cortical reorganization within the primary motor cortex. The dispersion of cortico-motor projections is a common feature in these patients and has potential clinical significance when designing new treatment interventions. Preliminary findings suggest that probability maps of differential cortical representation may have clinical value as biomarkers in complex regional pain syndrome and central post-stroke pain.

Normalizing motor cortex representation is a promising therapeutic goal in treating patients with chronic pain. Possible therapies include mental imagery, non-invasive rTMS, or permanent implantation of an epidural stimulator. Initial results suggest that, in certain cases, navigated rTMS sessions can normalize the representation area of the primary motor cortex and have a therapeutic effect. Additionally, results also show that patients who experience no reduction in pain in response to rTMS therapy also do not show any normalization in the motor cortex. Taken together, these findings suggest that Navigated Brain Stimulation may have the potential to be used for the planning and administration of non-invasive therapies in chronic pain, as well as planning the accurate implantation of epidural motor cortex stimulators.

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NBS and implanted cortical stimulation in the treatment of refractory chronic pain

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Surgically implanted motor cortex stimulation (MCS) has been used to treat refractory chronic neuropathic pain since the earlier 1990s, achieved by epidural implantation of two quadripolar leads over the precentral gyrus (primary motor cortex). Correct placement of the stimulation leads can be confirmed intraoperatively by determining the cortical site providing the motor responses of the greatest amplitude following suprathreshold anodal stimulation. However, long-term pain control is achieved by low-intensity monopolar cathodal stimulation performed at the same site. The surgical technique has proven to be safe and effective in the treatment of refractory neuropathic pain, with more than half of implanted patients responding to MCS therapy (e.g. pain reduction of greater than 40%).

Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex can also produce neuropathic pain relief. The precision and repeatability of rTMS targeting is now provided by navigated TMS procedures (nTMS), using, for example, the NBS System (Nexstim Oy, Helsinki, Finland). This type of procedure makes rTMS particularly suitable as a preoperative screening tool to select good candidates for MCS and also to study the mechanisms involved in the modulation of pain perception by MCS.

The analgesic effect of rTMS depends on the frequency of stimulation: rTMS at 5 Hz or higher can relieve pain, whereas rTMS at 1Hz has no effect on chronic neuropathic pain when applied to the motor cortex contralateral to the painful side. High frequencies are thought to increase cortical excitability beyond the time of stimulation, whereas low frequencies could rather decrease cortical excitability, but these effects depend on the functional state of the cortical site of stimulation and the connected regions. The analgesic effects are related to the excitation of neural circuits lying in the superficial layers of the cortex, tangential to the surface of the precentral gyrus. Some rTMS results showed evidence of more pronounced rTMS effects when the region adjacent to the painful region is targeted. However, the effect of epidural MCS closely follows somatotopic organization and the difference between MCS and rTMS may be due to the different geometry of the induced current. In our experience, the analgesic effect of rTMS is dependent on anatomical rather than functional location. For hand motor area, for example, the target is located at the level of the median genu of the motor knob, which is easily identifiable on MRI in 90% of cases. However, since the target needs to be precisely determined in the sulcal anatomy, image-guided nTMS is recommended. rTMS efficacy also depends on the spatial orientation of the coil: analgesic effects are obtained when the current induced in the brain has a posterior-anterior orientation, corresponding to indirect corticospinal descending volleys (I-waves) generated by MCS, and more particularly to late I-waves. In contrast, when the stimulation coil has a lateromedial orientation, direct corticospinal volleys (D-waves) are generated, not I-waves, and the analgesic effects are lost. These observations reflect the preferential involvement of horizontal fibers in the precentral gyrus at the origin of motor cortex rTMS-induced analgesia. The same conclusion can be made for the analgesic effect of epidural MCS related to the preferential activation of horizontal fibers in the precentral gyrus by the stimulating implanted cathodes.

Both epidural MCS and motor cortex rTMS relieve pain by activating various neural structures distant from the site of stimulation through the recruitment of cortico-cortical, cortico-subcortical, or even corticospinal connections. By these pathways, MCS and rTMS modulate not only the sensory-discriminative, but also the affective-emotional aspects of pain. This impact on affective-emotional aspects of pain is mediated via the activation of limbic structures, such as the anterior cingulate cortex. This may explain why rTMS over the left dorsolateral prefrontal cortex (DLPFC), a structure largely involved in affective neural pathways, also appears to be able to modulate pain, in addition to having an antidepressant effect. The use of the DLPFC as a target for the neuromodulation of pain would be another argument for the use of image-guided nTMS, since it is doubtful whether the DLPFC can be accurately targeted without using a dedicated navigation system.

Cortical excitability studies using paired-pulse TMS paradigms, have shown that the analgesic effect of motor cortex rTMS correlates to the restoration of a gabaergic process of intracortical inhibition, which is known to be reduced at baseline in patients with chronic neuropathic pain. The maximal analgesic effect of one single session of rTMS occurs after 2 to 3 days and may extend for up to one week. rTMS has shown a better efficacy in patients with neuropathic pain of cortical or peripheral origin than in patients with lesions affecting the brainstem or the spinal cord. In fibromyalgia, it has been shown that pain control can be maintained for up to six months by monthly rTMS treatments, following an induction phase of daily 20-min rTMS sessions for 5 days.
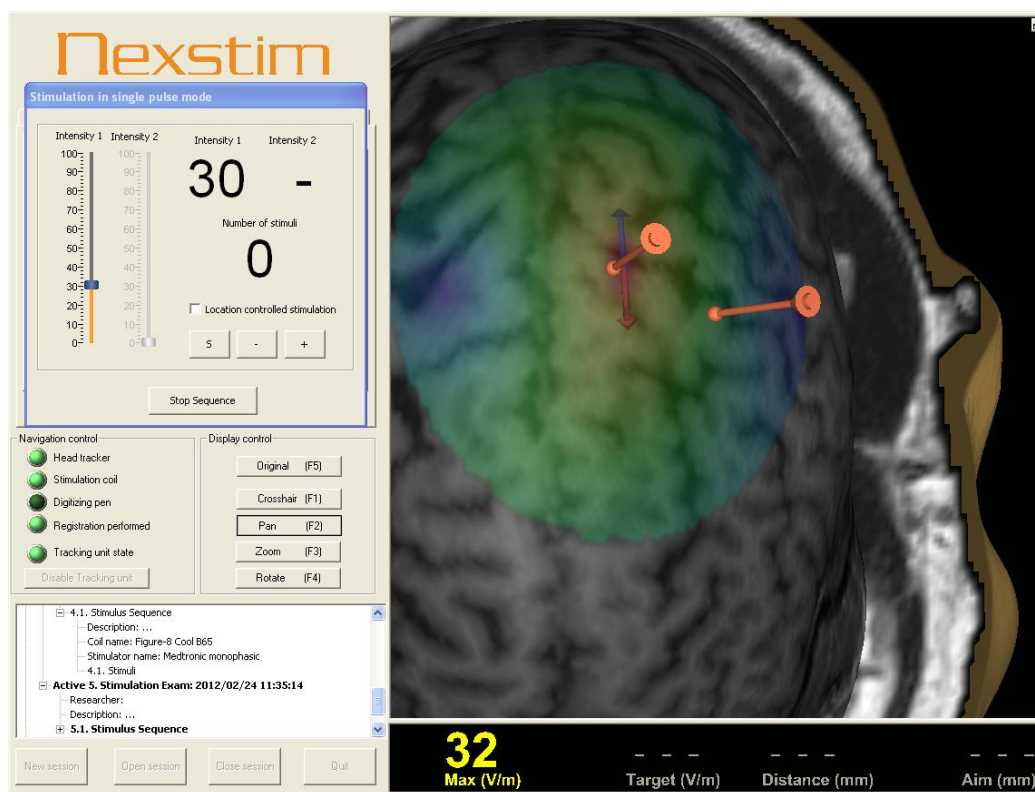
Figure 1: nTMS of the motor area of the lower limb in a female patient with peripheral neuropathic pain at the left ankle. The figure shows the target, the direction of the current and the magnetic field over the motor representation of the lower limb (situated above the frontal superior sulcus). The target without magnetic field is situated over the motor representation of the hand (hand knob). nTMS allows for correct localization of the target before epidural MCS implantation. nTMS data can be transferred to the stereotactic software when using the NBS System (Nexstim Oy, Helsinki, Finland).

Although epidural MCS can be an effective method to treat drug-resistant neuropathic pain syndromes, reliable preoperative criteria to predict patient outcome are lacking. Since rTMS is noninvasive, it can play a role in preoperatively identifying responders to MCS. Positive rTMS responders (to active stimulation compared to placebo response) will respond to MCS with an extremely high positive predictive value. In contrast, rTMS seems to have a low negative predictive value to discard patients from surgery. On the other hand, the experience of a positive response to rTMS therapy can help the patient to better accept the indication of MCS system implantation. Technically, the validation of a cortical target by preoperative nTMS testing can be useful to optimize electrode placement for subsequent MCS implantation.

Neurostimulation therapy for chronic pain has clearly benefited from the development of rTMS and the recent development of image-guided navigated techniques for rTMS. The use of rTMS therapy in the pain domain is promising, especially before MCS implantation for neuropathic pain syndromes and in the treatment of non-neuropathic pain conditions. Further research on the potential of other targets as well as the parameters of stimulation is warranted.

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Motor mapping and intraoperative monitoring

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Motor mapping

In the treatment of brain tumors, it has been shown that surgical resection status influences survival (Stummer et al., 2008), and various surgical techniques have been developed with the aim of achieving macroscopic complete resection of tumors. However, at the same time as maximizing the extent of resection, the neurosurgeon also needs to avoid new neurological deficits, which is a major challenge for tumors in, or adjacent to, eloquent areas of the cortex. In addition to selecting the optimum surgical technique, a successful outcome also requires appropriate use of neurosurgical tools. Today, the neurosurgeon's tool box includes anatomical imaging, pre-surgical planning, image guidance, functional mapping and real-time, intraoperative functional monitoring. In general, we can divide the tools into two sets: one set for the intraoperative period and the other for the preoperative domain.

Whereas the intraoperative tools are considered to be relatively robust, the tools needed for preoperative use are still under development. For example, when the goal is to resect tissue in eloquent areas, functional MRI (fMRI) cannot be relied on since the imaging-based modality often gives unreliable results. Diffusion tensor imaging (DTI) for subcortical fiber tracking is potentially a powerful planning tool, but DTI requires careful application and the results are open to subjective interpretation. Recently, navigated transcranial brain stimulation (nTMS) has become available for use in the clinic, bringing electrophysiological mapping of the motor cortex into the presurgical workup phase. Interestingly, in addition to being a robust mapping tool, nTMS has the potential to improve the application and interpretation of fiber tracking by DTI.

nTMS for presurgical mapping of the motor cortex

Between May, 2010 and October 2011, an nTMS device (NBS System, Nexstim Oy, Finland) was used for cortical motor mapping in 50 patients with brain tumor. Mapping of the representation areas of upper extremity muscles was successful in all 50 patients, despite significant edema and previous surgery for tumor in 6 of the 50 patients. nTMS mapping of the representation areas for lower extremity muscles was successful in 48.5% of patients.

In order to assess the clinical accuracy of nTMS in motor mapping, we compared the accuracy of nTMS with the results of preoperative fMRI mapping and intraoperative direct cortical stimulation (DCS). Comparative data was available for 33 of the 50 patients. Of the 33 patients, 17 had tumors in, or close to, the precentral gyrus and 16 patients had tumors close to the subcortical white matter tracts. The results of nTMS and fMRI mapping were compared by transferring all co-ordinates to a neuronavigation system (Brainlab AG, Feldkirchen, Germany) and calculating the mean distance between the corresponding centers of activation. During surgery, areas eliciting positive responses by DCS were documented intraoperatively in the neuronavigation system. Postoperatively, the DCS results were compared to the results from the fMRI and the nTMS mapping sessions.

Results: There was 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. For the foot muscle representation areas, the spatial correlation was weaker, with a mean distance of 15.0 mm ± 12.8 mm. The nTMS mapping procedure was well tolerated. Although 19 of the patients had had a history of seizures, there were no seizures associated with the nTMS mapping procedure. None of the patients experienced nTMS mapping as painful, although one patient felt that TMS stimulation was unpleasant.

Clinical value of nTMS mapping

We reviewed whether nTMS mapping results actually help the neurosurgeon to confirm or improve clinical decision making in the presurgical planning phase. In 17 cases, the neurosurgeon was asked to self-assess the clinical impact the availability of nTMS mapping data had had on decision-making.

Results: In 16 cases (94%) the neurosurgeon agreed that the nTMS results had made the intraoperative identification of the central region easier. In 10 cases (59%), the neurosurgeon agreed that the availability of the nTMS data increased their confidence level. In 6 cases (35%), the neurosurgeon agreed that the additional nTMS data had had a positive influence on the operative result. In 2 cases (12%), the additional nTMS data changed the surgical strategy (defined as the neurosurgeon changing the trajectory of approach to the tumor).

In one case where the patient had a large lesion, fMRI and nTMS mapping gave conflicting results. The fMRI map showed the hand representation area to be behind the lesion, whereas the nTMS map clearly showed the hand area to be in front of the lesion. The neurosurgeon planned the resection based on the nTMS data, with a successful outcome for the patient.

Use of nTMS mapping results in fiber tractography

Visualizing of subcortical fiber tracts in the white matter can be performed preoperatively by diffusion tensor imaging (DTI). In order to visualize the tracts, the neurosurgeon typically selects a point in the precentral gyrus as a "seed" ROI and performs fiber tracking to the corticospinal tract. However, this technique is based solely on individual expertise and subjective interpretation of brain anatomy. Since the results of fiber tracking are critically dependent on the location of the seed ROI selected in the cortex, we investigated whether using the data from nTMS motor mapping to functionally define a seed ROI could improve the reliability and reproducibility of fiber tracking in patients with subcortical lesions. 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.

Results: Compared to anatomically-defined seeding, 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 fiber tracking based on anatomically selected seed ROIs. When functionally-defined seed ROIs were used, inter-observer variability was lower when assessing the number of fibers, lower when estimating distances from the tumor to the fibers, and lower when estimating tract volumes.

Figure: Result of fiber tracking based on diffusion tensor imaging, using NBS motor mapping data to determine functionally-relevant regions of interest (ROI) for seeding.

Conclusion

The results of motor mapping using the NBS System show good correlation to the results from intraoperative direct cortical stimulation, despite the many factors which are supposed to contribute to inaccuracy of TMS, with good delineation of functional areas. Compared to fMRI, nTMS mapping is clearly superior in terms of accuracy and appears to be less susceptible to edema. nTMS motor mapping is safe, well-tolerated and supports the neurosurgeon in resection planning and in decision-making. nTMS mapping results can help determine, already preoperatively, whether a tumor is completely resectable. The use of nTMS results to functionally define seeding ROIs improves the use and interpretation of subcortical fiber tracking by DTI. Furthermore, during resection it is useful to be able to mutually confirm the preoperative fiber tracking data with the results of intraoperative navigated subcortical mapping.

Intraoperative monitoring

Despite the fact that the resection of gliomas in, or adjacent to, the corticospinal tract (CST) or the rolandic region is widely performed using intraoperative monitoring (IOM), the significance and predictive value of IOM is still under discussion. Since the possibility of false-negative IOM results, defined as an outcome with postoperative deficit despite stable intraoperative motor evoked potentials (MEPs), can affect the neurosurgeon's confidence in IOM, we investigated the etiology of perceived false-negative IOM results.

The etiology of perceived false-negative IOM results

Methods: Between 2007 and 2010, 117 consecutive supratentorial gliomas in, or close to, the eloquent motor areas were resected. Monitoring of MEPs from the border of the resection cavity was by direct cathodal stimulation, with a greater than 50% decline in MEP amplitude used as the warning criterion. After surgery, IOM data were reviewed and related to changes seen on MR-imaging and clinical presentation of new postoperative motor deficits. Patient clinical outcomes were continually assessed during the follow-up period.

Results: MEP monitoring was successful in 113 of the 117 cases (96.6%). Follow-up time for the patient cohort was 9.7 months (range: 0.5 - 40.6 months). Postoperatively, 30.3% of all patients had a new motor deficit, which remained permanent in 12.5% of the cases. IOM elicited stable MEPs throughout the operation in 65.2% of all cases. Postoperatively, 5 of these patients (4.5%) presented with permanently deteriorated motor function and 10 patients (8.9%) had a new temporary motor deficit. However, in all of these cases, the deficits were caused either by secondary hemorrhage, ischemia or caused by resection of the supplementary motor area and no case was the deficit due to a false-negative IOM result.

MEP-threshold sensitivity of CST to distance of stimulating IOM probe

By basic electrophysiological principles, the threshold current required to elicit MEPs in the CST by monopolar stimulation is dependent on the distance of the stimulation probe from the CST. We tested the assumption that a 1mA stimulation intensity threshold approximates a probe-CST distance of 1 mm. In 12 patients clips were placed in the resection cavity border at the probe stimulation points and IOM data were recorded. Probe distance to the CST was measured postoperatively on MRI using fiber tracking, with the clips acting as markers for the points intraoperatively stimulated.

Results: In the 12 patients there were no new, permanent deficits. 2 patients (17%) had new temporary deficits which all resolved during follow-up. We found a linear relationship between the probe -CST distance and the MEP-threshold stimulation current, with a probe-CST distance of 1.5 mm ~ 1 mA.

Conclusion

Continuous monitoring of MEPs by IOM provides reliable intraoperative monitoring of the motor system and is not associated with false negative results. Subcortical IOM sensitivity was shown to be 1 mA per 1.5 mm. IOM may influence the course of resection in some patients and should be regarded as the standard for intraoperative monitoring of the motor system.

NBS in speech mapping: experiences in patients undergoing awake craniotomies

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Macroscopically complete resection improves survival in patients with either high- or low-grade gliomas, However, many gliomas, are located in eloquent areas of the brain, including the areas important for speech. Because these patients benefit significantly from surgical treatment, these lesions should be resected by functional monitoring in order to avoid damage to critical eloquent areas. It would, therefore, help the surgeon significantly if reliable functional information were already available preoperatively for planning the approach.

Most centers performing resections in language eloquent tumors perform language mapping during awake surgery using direct cortical stimulation (DCS). Current strategies for language mapping include diffusion tensor imaging (DTI) for fiber tracking of the arcuate fasciculus, as well as fMRI. Experience with fMRI has, however, shown that the technique does not produce results reliable enough for planning surgery in language-eloquent areas. Consequently, the use of navigated TMS (nTMS) for presurgical language mapping has been explored. Using the patient's MR-image for guidance, an nTMS device (NBS System, Nexstim Oy, Finland) was used to accurately target repetitive TMS (rTMS) to the language circuits in the cortex. A focal, biphasic figure-of-8 coil, the same coil as used for motor mapping with the NBS System, was also used for rTMS.

Methods

Over a six-month period up to October 2011, an NBS System was used to perform noninvasive language mapping in nine patients with lesions in the language-eloquent areas of the left hemisphere. Six patients were right-handed and three left-handed. Six of the patients had glioblastomas, two patients had anaplastic astrocytomas and one patient had a cavernoma.

Initially, the resting motor threshold (MT) of the APB muscle representation area in the right hemisphere was determined for setting the stimulator output for language mapping, based on the patient's cortical excitability. Speech function was tested by each patient's ability to name everyday objects from a series of pictures, under normal conditions without stimulation. This subset of familiar objects then formed an initial baseline set, unique for each patient. During mapping, the object pictures familiar to the patient were re-shown with time-locked delivery of rTMS from the NBS System. Initially, a kind of baseline "language threshold" was established for each patient by defining the optimal number of pulses and the frequency of the rTMS pulse train needed to elicit language errors. Using the patient-specific thresholds, the presumed language areas of the left hemisphere were then mapped three times, in a similar manner as in awake surgery. As in intraoperative mapping, valid, or language-positive points, were defined as those locations where a language disturbance occurred in at least two out of three consecutive stimulations.

Subsequent to presurgical cortical mapping, all 9 patients underwent surgery for tumor resection with a standard asleep-awake-asleep regime. Anesthesia was by remifentanil/propofol and electrocorticography was performed to rule out focal seizures during mapping. For awake speech mapping by bipolar direct cortical stimulation, number counting and object naming paradigms were followed.

Intra-operative awake speech mapping was performed blinded to the preoperative mapping data. Confirmation of a language-positive site was by two or more disturbances elicited out of three consecutive stimuli at the same site. Data from the DCS mapping were exported to the surgical navigator, Brainlab Vector Vision Sky or Brainlab Curve (Brainlab, Feldkirchen, Germany), for later correlation with the nTMS data.

Analysis and results

The evoked language errors were categorized according to previously published criteria (Corina et al, 2010): speech arrest, performance, hesitation, semantic (coordinate, superordinate, associate, subordinate, part-whole, visual), phonological, neologism, or other errors (language pain circumlocution). It appears that speech arrest, performance and hesitation have the same anatomical basis since locations where rTMS caused these types of errors were always close to one another, and always in the same area.

In all 9 patients it was possible to map and positively identify language areas, both by presurgical nTMS mapping and by intraoperative DCS. We found that mapping results with non-invasive nTMS correlated, at least partially, with the results from intraoperative awake language mapping by DCS.
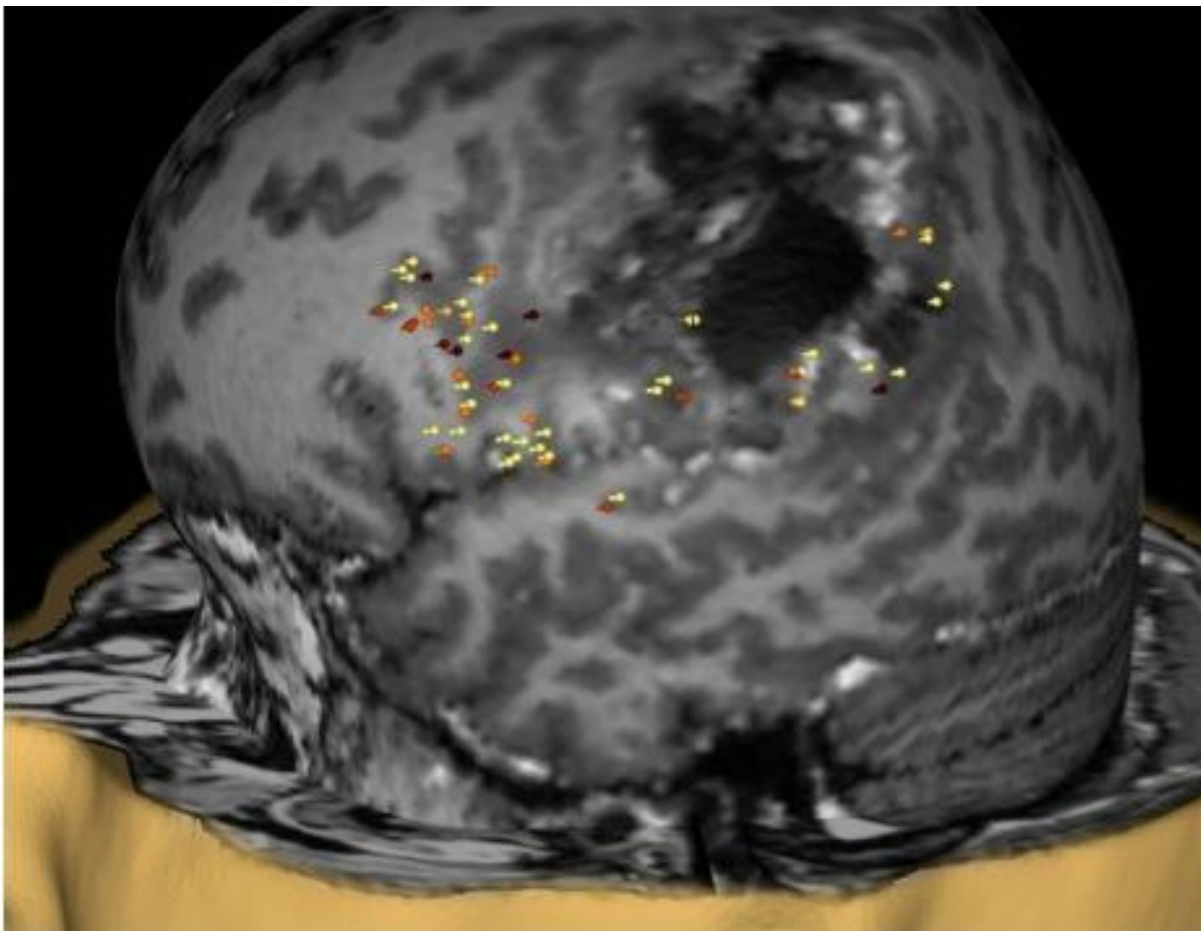

Figure: Results of language area mapping shown on the NBS System screen. Colored markers at stimulation locations indicate: red = speech arrest, white = performance error, green = hesitation, dark orange = semantic error, orange = phonological error, yellow = neologism.

Tolerability of nTMS language mapping

Compared to motor mapping, patients can experience significantly more discomfort, and even pain, during language mapping. Using a visual analogue scale of 0 - 10 (0 = no pain, 10 = maximum pain), patients reported a pain level of 1.4 ± 0.5 when rTMS was applied over the convexity, a pain level which can be characterized as low to mild. However, when rTMS was performed over the temporal muscle area, patients reported a much higher pain level of 4.4 ± 2.3, on the same scale. One patient expressed a score of 8 on the scale of 0 – 10. Although language mapping can be experienced as quite painful by an individual, the pain level is dependent on the stimulation intensity, which can be reduced in some cases. Patient-experienced pain was also found to be dependent on the number of pulses and their frequency. For patients who experienced pain from rTMS over the temporal muscle, the pain can also interfere with the quality of the language mapping.

Conclusion

nTMS language mapping by object-naming tasks appears to be a feasible clinical concept. Results with non-invasive nTMS correlate, at least partially, with results from intraoperative awake language mapping by DCS. Compared to experiences of mapping by fMRI, nTMS mapping has already shown superior performance, since nTMS has been successful even when the Broca area has been pathologically impaired, or the lesion has infiltrated the angular gyrus. Additionally, the nTMS technique can be modified to enable mapping of severely aphasic patients.

Language mapping is significantly more time-consuming than motor mapping, and requires more skill and patience from the nTMS device operator. The procedure is also more demanding on the patients, who are generally also weaker and less able to concentrate and participate than those patients previously undergoing motor mapping only. However, the presurgical mapping experience also has a positive aspect in that it helps patients better prepare for the awake surgery mapping procedure.

Unlike mapping of the motor cortex, mapping of the language areas causes general discomfort to patients and can be experienced as painful when performed over the temporal muscle area. If pain is induced, it is likely to also impact the quality of the mapping results. Further experience with nTMS is needed to discriminate between the relevant and spurious evoked language errors.

Neurophysiologic markers generated by stimulation of cortical areas of motor speech

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The final common organ for speech is the larynx and its associate muscles. Over the past decade, a number of studies in humans have confirmed the motor cortical representation of the larynx and have provided some information about its interactions with other cortical regions involved in vocal motor control of speech production. As a structure, the larynx is phylogenetically much older than its present role as a vocal organ, and it is therefore believed that the laryngeal muscles have evolved relatively recently to specialize in speech production. Furthermore, it has been proposed that areas of the motor cortex required for controlling vocalization are closely, and uniquely, associated with the laryngeal muscles.

By electrically stimulating the cortical areas of motor speech, we believe that the larynx can be used as a target organ from which a neurophysiological marker for speech can be generated. As with accepted biochemical markers, such a neurophysiological marker for the individual patient would share the following clinical attributes: central nervous system specificity, predictability of serious injury and reproducibility, as well as being relatively inexpensive.

Three different cortical areas in the frontal cortices have been found to be involved in speech arrest, all with similar clinical appearance. Speech arrest has been achieved after stimulation of the primary negative motor areas, the supplementary negative motor areas, the opercular part of the posterior inferior frontal gyrus (Broca's area) and the representation area for the laryngeal muscle in the primary motor cortex (M1).

The responses evoked by transcranial electric stimulation (TES) in the laryngeal muscles (cricothyroid and vocal muscles) can be clearly recognized due to their significantly different latencies: stimulation of the M1 produces a short latency response (SLR), whereas stimulation of the opercular part of Broca's area produces a long latency response (LLR)[1]. Identical positioning of stimulating points over the opercular part of Broca's area also generates an LLR, and when stimulated at 50 Hz has been shown to result in speech arrest. Studies indicate that the laryngeal muscle representation areas of the M1 are responsible for controlling the muscle movements needed for vocalization, whereas the opercular part of Broca's area is responsible for phonological processing. Evidence of functional connections between M1 for laryngeal muscles and the opercular part of Broca's area using cortical-cortical evoked potential recording has been found[2]. These findings have been recently confirmed by fiber tractography showing functional connectivity between the supplementary motor area and Broca's areas and connectivity between Broca's area and M1.

In anesthetized patients without muscle relaxants, mapping of the M1 for the laryngeal muscles and the opercular part of Broca's area can be performed by inserting a small hook wire electrode in the vocal muscle[3]. Short trains of stimuli, applied either by transcranial electric stimulation (TES) or direct stimulation of exposed motor cortex, activate the corticobulbar tract for the vagal nucleus. This technique can be easily mastered and can be used to monitor the functional integrity of the upper motoneuron as well as the lower motoneuron, including the vagal nucleus, laryngeal nerves and laryngeal muscles. Stimulating M1 generates an SLR, while stimulating the opercular part of Broca's area generates a LLR.

In awake patients, the hook wire electrode can be placed in the cricothyroid (CTHY) muscle[4]. Although the procedure entails some minor discomfort for the patient, it is not painful. In place of TES, navigated transcranial magnetic stimulation (nTMS) is used, which has the advantage of being focal as well as painless. Using an nTMS device (NBS System, Nexstim Oy, Finland), it has been shown that it is possible to accurately locate the representation area of the cricothyroid muscle in the M1 by eliciting an SLR and to locate the speech-related opercular part of Broca's area by eliciting an LLR in the laryngeal muscles (Figure 1).
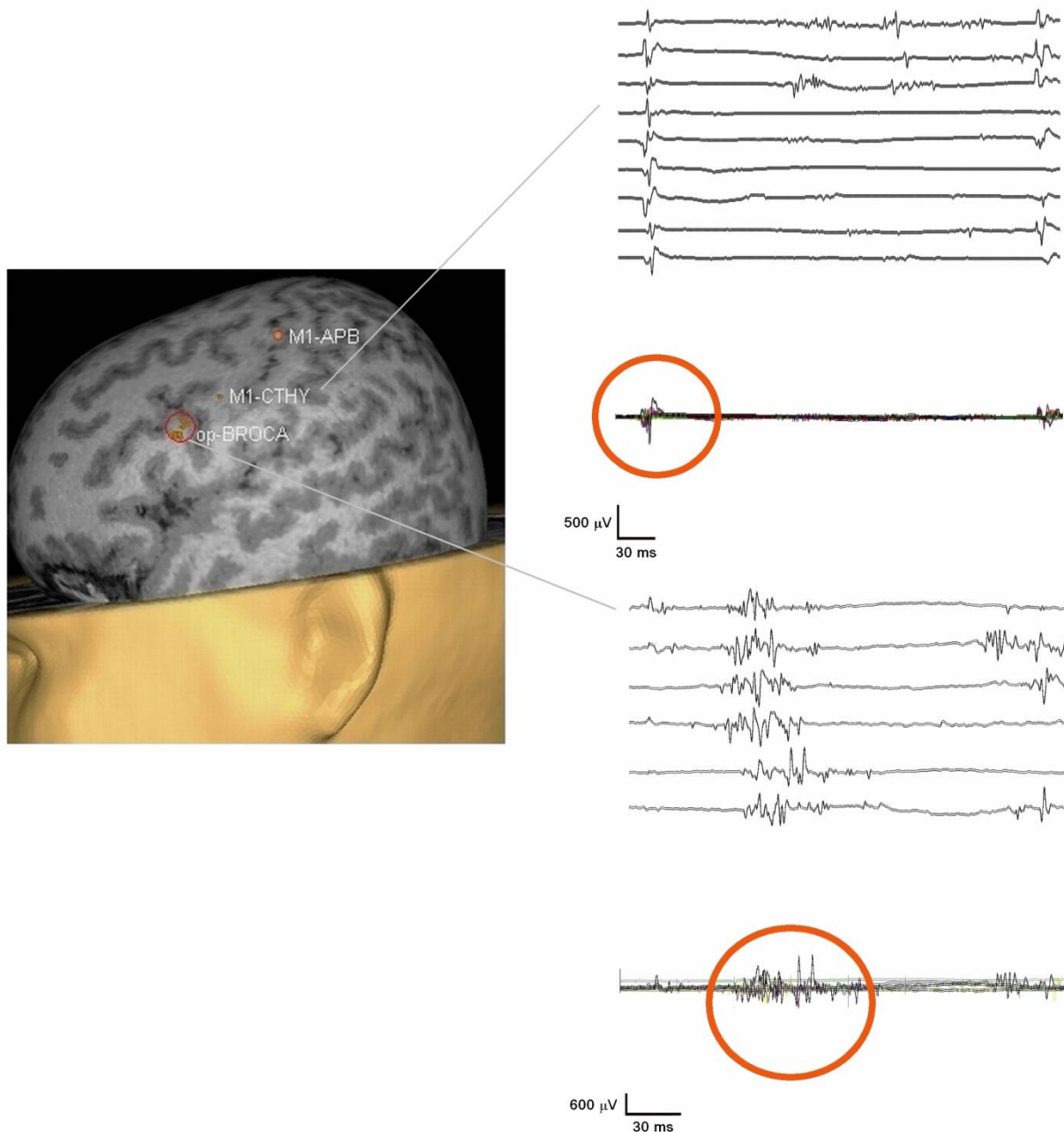

Figure 1. The motor speech related cortical areas for a single subject, elicited by nTMS. The primary motor representations for the abductor pollicis brevis (APB) muscle, the cricothyroid (CTHY) muscle and the opercular part of Broca's are highlighted. The repeatability of the SLR responses recorded from the CTHY muscle and the LLR responses from the opercular part of Broca' region are presented in cascade mode. Below each cascade, the superimposed responses are presented (red circles).

Conclusion

Defining reliable neurophysiologic markers of the motor speech-related cortical areas would significantly contribute to surgical care of lesions in the frontal lobe. Such markers could not only help in the selection of patients for surgery and planning of safe access to lesions, but also in preserving motor speech-related cortical areas in patients undergoing surgery with general anesthesia. Eliciting MEPs from the vocalis muscles is a promising target for a robust neurophysiological marker for expressive speech detection, once the localization/mapping methods have been validated. There has also been progress in the techniques available for non-invasive speech localization. The recent introduction of nTMS, which uses MRI-based stereotactic navigation, avoids the shortcomings of TES for awake patients and opens the possibility of incorporating speech mapping into presurgical planning.

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Presurgical speech mapping with NBS

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The preservation of language function is of major concern when tumor resection in the dominant perisylvian areas is proposed. Direct cortical stimulation (DCS) is still considered the gold standard both for cortical and subcortical speech mapping. However, since DCS is an intraoperative "awake" technique, no information on the language areas is available for planning prior to surgery. Although noninvasive functional MRI (fMRI) has been used for presurgical planning in language area resection, the fMRI method only defines areas that participate in a given language task, but does not determine which of them or, indeed, if any of them are essential and therefore need to be preserved. Transcranial magnetic stimulation (TMS) uses a concept analogous to DCS and the single-pulse TMS method has been successfully used for localization of the motor function in the cortex. Using repetitive TMS (rTMS), the method can noninvasively interfere with brain function. For example, the alternating electrical current induced in the cortex by a pulsating magnetic field can interfere with a language task by temporarily inhibiting neuronal function. If the neurons in the focus of the electric field are crucial for the language task, the patient's speech can exhibit alterations, such as speech arrest, paraphasia or anomia. With navigated rTMS (nrTMS), the use of a stereotactic navigation system allows precise localization of the electric field induced by the TMS coil in relation to the intracortical structures. We examined whether nrTMS has the potential to be an alternative noninvasive method for presurgical speech mapping.

Methodology

Eleven patients with tumors in the perisylvian area scheduled for awake resection underwent nrTMS mapping using an eXimia Navigated Brain Stimulation (NBS) System (Nexstim Oy, Helsinki, Finland). The biphasic stimulator output was adjusted to deliver an output equivalent to 120% of the motor threshold (MT) found for the patient's abductor pollicis brevis (APB) muscle. The tasks given to the patients were reading, counting and naming of objects. During task performance, 10 Hz rTMS was delivered from the coil for a duration of 2s (20 pulses in total), and any interference with the language task was recorded. During surgery, DCS was performed during awake resection using biphasic 50 Hz trains of 2s duration, with current intensity rising from 1mA in 1mA steps. The task performances performed during awake resection were spontaneous speech, use of verbs and naming of objects.

Results

Comparative data was available from 9 patients, the condition of two of the 11 patients mapped deteriorated prior to surgery and their tumors were resected under general anesthesia without speech mapping. Using nrTMS we found a total of 25 points eliciting speech arrest points (2 points eliciting dysarthrias and 3 points eliciting paraphasias). Using DCS, we found 38 points eliciting speech arrest (7 points eliciting dysarthrias and 1 point eliciting a paraphasia).

A simple comparison of responses from the two mapping methods is of little value, as it would entail comparing one large "cloud" of positive and negative points with another. Since the language system in humans is distributed in the cortex in a mosaic fashion, a method able to compare each piece of the language mosaic separately would be of interest. It has been suggested that a speech area can be located

up to 20 mm^2 from a stimulated point[1]. Since the area of the cortex stimulated by TMS is approximately 10 mm^2 and the distance between the anode and cathode electrodes in a bipolar DCS stimulation probe is approximately 8mm, we propose that if DCS- and nrTMS-elicited language points are closer than 20 mm^2 apart, they relate to the same speech area and can be compared directly. Correspondingly, if language points elicted by nrTMS and DCS are further apart than 20 mm, we propose that the points correspond to different language areas and are therefore not compared. Using this proposed boundary distance of 20 mm, subsets of 17 DCS points corresponding to 17 TMS points were compared. The average distance between nrTMS- and DCS-mapped language-positive points was 5 mm (range 0 - 15 mm), with the nrTMS- and DCS-mapped surface areas on the cortex overlapping by 50%. By this method we found the sensitivity of DCS compared to nrTMS to be 88.4% in this group of patients. Specificity was 95.5%, implying that there was a 95.5% probability that DCS would locate a language area at the same location as found by nrTMS.
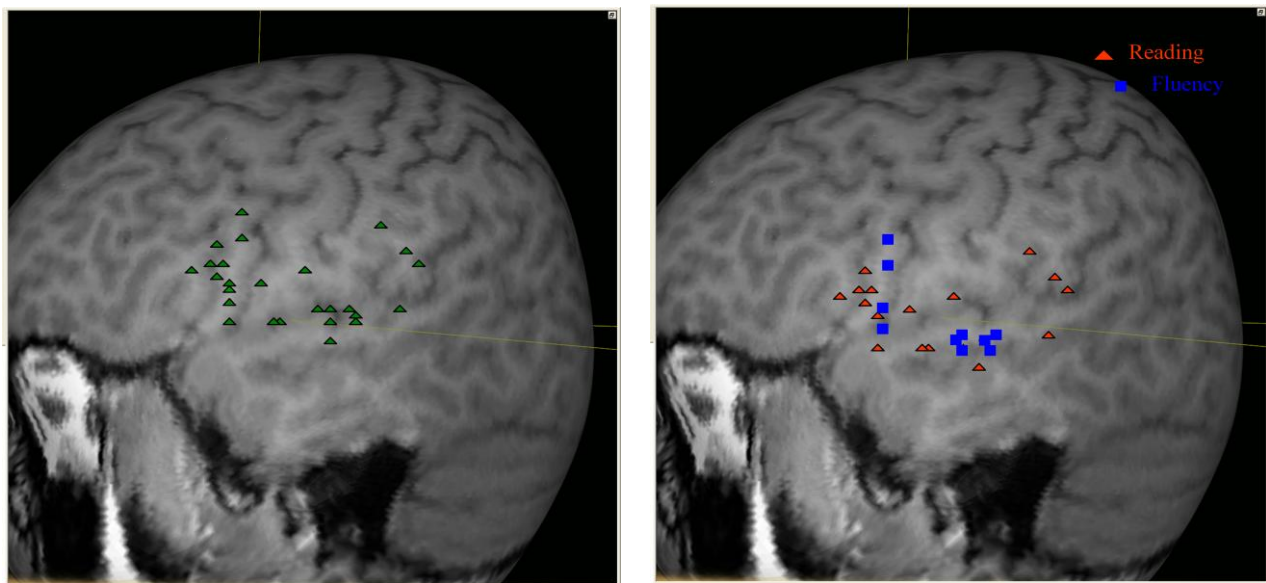

Figure 1: Comparison of the results from DCS and nTMS methods based on reconstructed maps from all patients. *Left:* nomination by DCS mapping. *Right:* reading task (red markers) and fluency task (blue markers) by nrTMS.

Discussion

Compared to motor mapping, speech mapping presents far more challenges. In motor mapping, the EMG response amplitudes and muscle hotspots themselves guide the mapping sequence. This feedback is not available in speech mapping and makes stimulation more time-consuming.The lower sensitivity of nrTMS can be explained by a number of factors. In particular, anatomical constraints affected our ability to differentiate true events from artefact. Activation of the fronto-temporal areas caused pain from tetanisation and, when stimulating near the lower temporal areas, activation and involvement of facial nerves disturbed pronunciation. Additionally, the eye-frame worn by the patient made it difficult to orientate the coil and it was not an optimal tracking solution in our setup. In order to differentiate between speech arrest and dysarthria due to muscle activation, the method should incorporate EMG monitoring of the orbicularis oris and cricothyroid muscles.

In our TMS-mapping paradigm it was not possible to achieve speech arrest by the naming task, since we did not use time-locked synchronization of stimulation. However, most of the language points located by DCS were from naming tasks, as this was the quickest task for patients to perform. Nevertheless, there was

good agreement between nrTMS and DCS language points, suggesting that there is physiological agreement between the DCS and the nrTMS methods, independent of the task. A possible explanation for task-independence is that both methods primarily interfere with the final steps of speech production. In counting tasks, for example, we have observed that although stimulation interferes with actual speech production, the patient nevertheless continues the counting sequence correctly, despite the interference. The reason TMS preferentially activates the motor cortex may well lie in the anatomical structure of the gyri: when the coil is over the motor cortex, the motor neurons are generally orientated perpendicular to the coil's magnetic field, whereas neurons of the speech cortex are orientated in many directions since they need to connect with the widely distributed language cortices.

Our findings with nrTMS in patients bilingual since early childhood support the concept that bilingual patients can have distinct cortical representations for each language, although it is likely that many of the other speech areas in the cortex are common for both languages.
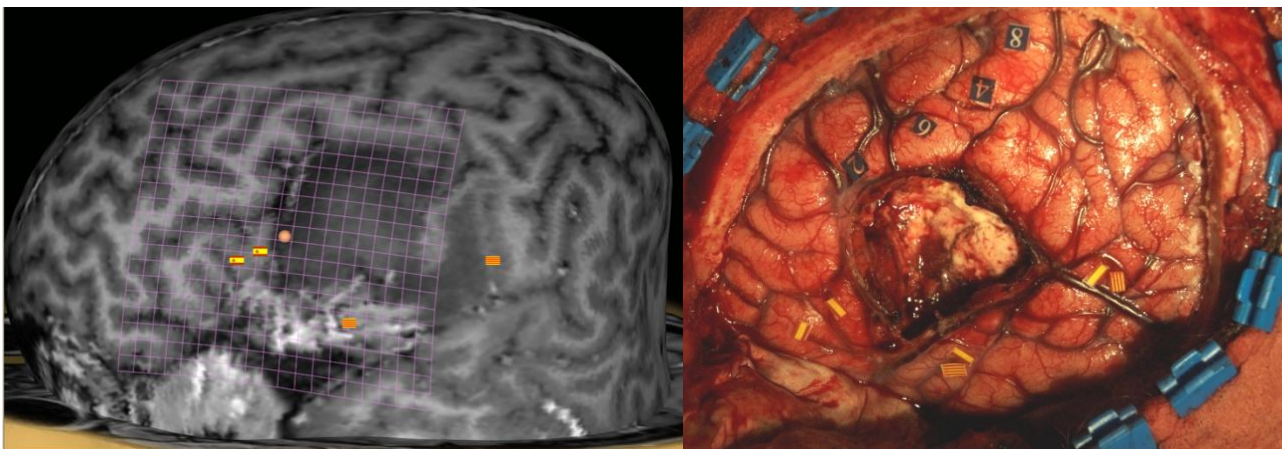

Figure 2: Example of the patient "CI", showing not only anatomic accuracy, but also language specificity. *Left:* presurgical nTMS language map; *right:* intraoperative DCS map, the flags indicate localization of Spanish and Catalan language areas.

Using nrTMS-detected functional mosaics to guide fiber tractography (using nrTMS results as the seeding volume ROIs) is also a unique paradigm for better understanding the functional meaning of the anatomical fiber tracts. These pathways can be further investigated when assigning specific language functions to the nrTMS ROIs, since nrTMS can discriminate between "sub-functions", such as reading and naming.

Conclusions

Using nrTMS, Navigated Brain Stimulation appears to be an accurate and specific method for preoperative language mapping, with good agreement with intraoperative DCS language mapping (even in bilingual patients). Nonetheless, language tasks paradigms need to be improved for more comprehensive speech mapping. The nrTMS method has certain limitations, especially in relation to stimulation over the temporal areas, and these need to be overcome to fulfill the potential of this novel technique.

Reference

Ojemann G, Ojemann J, Lettich E, Berger M. **Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients**. J Neurosurg. 1989 Sep;71(3):316-26