

nexTalk EUROPE

Leading the Way in Non-Invasive, Navigated Brain Stimulation



Second landmark study confirms NBS improves patient outcomes

An important new paper on the impact of NBS published in the Oxford journal *Neuro-Oncology* was published in June. The 365-patient study *Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations* by Dr. Dietmar Frey and Professor Peter Vajkoczy's team from the Department of Neurosurgery, Charité University Hospital, Berlin confirms the clinical benefits of navigated TMS (nTMS) found by a separate team of clinicians at the Technical University Munich in another study earlier this year.

The Charité neurosurgeons consider NBS as a landmark advancement in the treatment of brain tumor patients and likely to change general clinical practice. Key findings from the new study were, for NBS prior to DCS, vs. DCS alone:

- **Expanded the surgical indication**
- **Significantly higher ratio of gross total resections (+ 40%), 59% vs. 42%**
- **Significantly longer progression-free survival in LGG, (+ 45%), 22.4 vs. 15.4 months**

Dr. Thomas Picht, one of the paper's authors commented: "This cumulating evidence suggests patients suffering from tumors in critical motor-related locations should be screened by NBS mapping at the first opportunity. It will take time to overcome the traditional view that these tumors cannot be radically resected – or are even "inoperable" – since the risks of surgery are too high. A key mission for all of us in both the neurological and neurosurgical communities is to enable patient counseling to be based on objective, reliable information as early as possible in the process". See also our Clinical Spotlight article.

2014 DGNC dedicates entire session to nTMS

"Preoperative NBS mapping resulted in shorter length-of-stay" – Dr. Krieg, Munich



Prof. Dr. Cordula Matthes, Head of Functional Neurosurgery and Vice Clinical Director, Dept. of Neurosurgery, University Clinic Würzburg introduced the Motor System-session.

The 65th Annual Meeting of the German Society of Neurosurgery (DGNC), held this year in early May had an entire session (MI.19) dedicated to nTMS mapping, moderated by Dr. Thomas Picht and Dr. Sandro Krieg. Remarkably, 8 out of the 9 presentations were based on experiences with the NBS System. The usefulness of NBS was also noted in the

Motor System-session the previous day moderated by Dr. Andrea Szelényi from Düsseldorf.

In Dr. Krieg's own presentation "Preoperative motor mapping by navigated transcranial magnetic brain stimulation improves surgical outcome for motor eloquent lesions," he stated that their large comparative study offers convincing proof of the value of preoperative motor mapping by nTMS in rolandic lesions. The study significantly increases the level of evidence for nTMS and clinicians at Munich strongly advocate nTMS to become increasingly used for these lesions.

Importantly, Dr. Krieg noted in his presentation that the patients who underwent preoperative nTMS mapping in addition to intraoperative DCS, had a two-day shorter Length-of-Stay (LOS) compared to

patients who had DCS alone – despite the fact that the nTMS-mapped patients had more extensive removal of tumorous tissue.

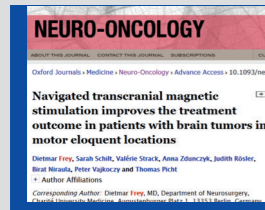
In a presentation on perilesional edema of the inner capsule, Dr. Carolin Weiss from Cologne noted that when localizing facial muscle representations, the Centres of Gravity (CoG) of NBS maps are up to 10 mm closer to the DCS data, compared to CoGs by fMRI. With the difference corresponding to approximately one gyrus, relying on NBS data means the neurosurgeon can more safely and accurately plan to achieve extensive, but function-preserving resection in these cases.

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Clinical Spotlight

Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations



Clinicians at the Charité conducted a retrospective study comparing the functional and oncological outcomes of 250 consecutive patients evaluated for surgery for tumor in a motor eloquent location of the brain (the nTMS group) with a matched control group of

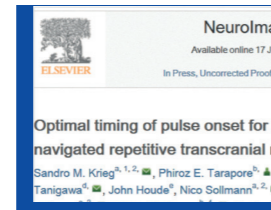
115 patients similarly evaluated immediately prior to the NBS System becoming available. The nTMS group and the historical control group were well-matched and the surgical teams and their available expertise in intraoperative direct cortical stimulation mapping were similar for all patients. In the enrolled 250 patients, 215 were initially suspected of having tumor in the eloquent motor areas. Subsequent nTMS mapping showed that 25% did not – and an additional 37 patients (69 %) had surgery. There was a 28% reduction in post-operative deficits after nTMS mapping, although this change did not reach significance. Additionally, the availability of nTMS results enabled the use of smaller craniotomies.

Adding nTMS mapping was crucial in achieving more tumorous tissue removal. Gross total resections were achieved in 60% of the nTMS patient group, compared to 42% achieved in the control group, with no increase in the morbidity rate. The addition of nTMS mapping improved progression-free-survival to 15.5 months in glioma patients, a significantly longer period than in the control group, which was 12.4 months. The 3.1 additional months represents an additional 25% longer time to disease progression. For patients with low grade gliomas, progression-free survival after nTMS mapping was also significantly longer at 22.4 months compared to 15.4 months in the control group. The additional 7 months for the nTMS group represents a 45% longer time to disease progression.

The authors conclude that nTMS mapping improves pre-operative planning, counseling and the surgical procedure; and, by expanding the indications and extent of resection, leads to longer progression-free survival rates and better neurological outcomes. Additionally, the neurosurgeons believe this study opens the door to resections for many patients who are currently denied surgical treatment. Finally, the authors strongly advocate nTMS becoming more widely available, “The results of this study should be applied to the neurological and neurosurgical community as a whole. Thus, the introduction of nTMS could soon be regarded as landmark advancement in the treatment of brain tumor patients and will likely change general clinical practice.”

Frey D et al., *Neuro Oncol.* 2014 Jun 12.

Optimal Timing of Pulse Onset for Language Mapping with Navigated Repetitive Transcranial Magnetic Stimulation



This study compared language mapping with two different timings of rTMS onset relative to object picture presentation, 300 ms and 0 ms; correlating the resulting maps with maps generated by DCS language mapping during awake surgery. Out of 32 patients with left-sided perisylvian tumors, 20 underwent mapping with

rTMS starting at 300 ms after picture presentation and 12 patients with rTMS starting at the picture presentation onset.

Within and around Broca's area, an immediate rTMS onset of 0 ms did not affect sensitivity, negative predictive value (NPV) or positive predictive value (PPV), although specificity improved significantly, compared to the onset timing delay of 300 ms. In contrast, for posterior language regions, such as supramarginal gyrus, angular gyrus, and posterior superior temporal gyrus, immediate rTMS onset with picture presentation showed greater specificity, NPV and PPV with comparable sensitivity. The results from both rTMS timing protocols correlated well with DCS results, especially in Broca's region, and particularly with regard to NPV. The authors concluded that rTMS stimulation onset coincident with picture presentation onset improves the accuracy of preoperative language maps, particularly within posterior language areas. Moreover, immediate and delayed pulse train onsets may have complementary disruption patterns that could differentially capture cortical regions causally necessary for semantic and pre-vo-calization phonological networks.

Krieg SM, Tarapore PE, Picht T et al. *Neuroimage.* 2014 Jun 16

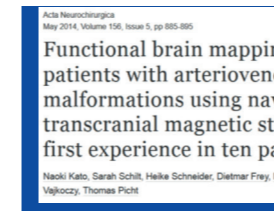
Bamberg, Germany joins the Nexstim family

After a brief training session, Director of Neurosurgery Dr. Christoph Wedekind and Senior Consultant Dr. Günther C. Feigl at the Klinikum Bamberg, Germany will shortly be offering their patients cortical mapping with the Nexstim NBS System. Welcome!

Vice President for Pre-Surgical Mapping appointed

Nexstim has appointed John Hardin, a seasoned commercial executive in the medical device field, as Vice President, Pre-Surgical Mapping. Based in the USA, John brings more than 30 years of experience spanning the neurosurgical and cardiovascular markets to Nexstim.

Functional brain mapping of patients with arteriovenous malformations using navigated transcranial magnetic stimulation: first experience in ten patients



nTMS motor mapping was conducted for six patients with AVMs near the rolandic region; speech mapping was performed for four patients with left perisylvian AVMs. In all patients with rolandic AVMs, delineation of the primary motor cortex was successful, even when the anatomy was severely obscured by

the AVM. No plastic relocation of the primary motor cortex was observed. rTMS of the left ventral precentral gyrus led to speech impairments in all four cases that underwent speech mapping. Right hemispheric involvement was observed in one of the patients, potentially indicated plastic changes. The authors concluded that nTMS allowed for detailed delineation of eloquent areas even within hypervascularized cortical areas, indicating that nTMS mapping is feasible in AVMs. Kato N et al. 2014 Mar 18.

Neurophysiologic markers in laryngeal muscles indicate functional anatomy of laryngeal primary motor cortex and premotor cortex in the caudal opercular part of inferior frontal gyrus



Ten right-handed healthy subjects underwent nTMS and 18 patients underwent DCS over the left hemisphere, while recording the neurophysiologic markers –short latency response (SLR) and long latency response (LLR) – from the cricothyroid muscle. Both healthy subjects and patients were engaged in the visual object-naming task. For the healthy subjects, stimulation was time-locked at 10-300 ms after picture presentation while in the patients stimulation was at 0 ms. The latency of SLR in healthy subjects was 12.66±1.09ms and in patients 12.67±1.23ms. The latency of LLR in healthy subjects was 58.5±5.9ms, while in patients 54.25±3.69ms. SLR elicited by the

stimulation of M1 for laryngeal muscles corresponded to induced dysarthria, while LLR elicited by stimulation of the premotor cortex in the caudal opercular part of inferior frontal gyrus, recorded from laryngeal muscle, corresponded to speech arrest in patients and speech arrest and/or language disturbances in healthy subjects. In both groups, SLR indicated location of M1 for the laryngeal muscles, and LLR the location of the premotor cortex in the caudal opercular part of inferior frontal gyrus, recorded from laryngeal muscle; while stimulation of these areas in the dominant hemisphere induced transient speech disruptions. This method, combining stimulation with SLR and LLR markers, is applicable to preoperative planning and intraoperative mapping, thus helping preserve these motor speech areas.

Deletis V, Rogić M et al. *Clin Neurophysiol.* 2014 Feb 11.

Nexstim initiates NICHE – multicenter trial on nrTMS in stroke rehabilitation



The “Navigated Inhibitory rTMS in Contralesional Hemisphere Evaluation”- trial, NICHE for short, is a multicenter double-blinded, randomized, and sham-controlled trial to determine the therapeutic effects of combining nrTMS (navigated repetitive TMS) with occupational therapy for stroke rehabilitation. Anticipated to be a two-year study, NICHE will enroll up to 200 patients at twelve leading stroke rehabilitation sites in the United States. NICHE will look to replicate the initial findings of the CONTRASTIM stroke study* where a team at the Rehabilitation Institute of Chicago (RIC), led by Dr. Richard L. Harvey, demonstrated that a combination of navigated repetitive transcranial stimulation (nrTMS) using the NBS System along with occupational therapy (OT) produced

significantly greater gains in patients' motor function than OT alone. Patients in the active NBS group improved function by 13+ points on the UEFM score, compared to the controls. The study also showed that more than 80% of the patients in the active NBS group gained a clinically meaningful response, compared to 50% of the patients in the control arm. The protocol used by Dr. Harvey's team used low frequency, 1Hz nrTMS to downregulate the activity of the unaffected healthy hemisphere of the stroke patient's brain. The RIC researchers concluded that since notable improvements from the stimulation therapy can still be seen six months after the therapy, nrTMS could offer stroke patients long-lasting functional benefit when added to standard occupational therapy. Catherine Lapp, vCNIM who has over a decade of neuroscience-related experience has joined Nexstim as the US Clinical Trials Manager.

*Harvey RL et al. *The Contrastim Stroke Study: Improving Hand and Arm Function After Stroke With Combined Non-Invasive Brain Stimulation and Task-Oriented Therapy - A Pilot Study ISC 2014; Abstract 152*

Experiences with NBS at UCSF, California

Dr. Phiroz E. Tarapore, M.D., now an Assistant Professor at the Department of Neurological Surgery at the University of California, San Francisco School of Medicine, is one of the pioneering users of the NBS System for surgical planning in the USA.



Q: How long have you been using the NBS System at UCSF and what have been the results?

A: I first started using an NBS System during my residency four years ago. The two main efforts thus far have been to validate the preoperative motor and language maps generated using NBS. First, we found excellent correlation between the motor maps generated with NBS and those generated with DCS during surgery. Our findings have agreed with the earlier findings from other groups, and showed that NBS produces reliable and reproducible motor maps. Second, we examined the correlation between NBS-generated speech maps and those generated with intraoperative stimulation. Again, the maps correlated; however, these speech maps had some discrepancies which are inherent to the greater complexity of language systems as compared with motor systems.

Q: Can you share some of your experiences using NBS with patients?

A: One of my favorite experiences with NBS was mapping a young, 5-year-old boy who had intractable epilepsy and was to undergo a lobectomy for treatment. He was one of the happiest kids I've met, and when he found out that he got to watch "Cars" - his favorite

movie - during the mapping session, he was so excited I could barely keep him in the chair. Eventually he settled down, and we were able to get an excellent map of his entire motor system. In fact, his motor map was one of the best I've ever seen: clean signals, clear peaks and excellent demarcation between muscle groups. The only problem was that, when we were finished, the movie was only half-over. I ended up letting him finish watching the movie in the chair as a reward for being so cooperative.

Q: What has been the biggest impact NBS has made in your practice?

A: The ability to map patients preoperatively has enormous value in the preoperative conversation. Because the navigated TMS method gives such accurate information, I can now tell a patient with fairly good certainty whether a tumor involves the motor system or not; I can also give a much better analysis of the surgical risks and the risks of postoperative deficits. Finally, the practice of going through the language tasks is valuable for patients undergoing awake surgery. Moreover, experiencing speech arrest for the first time in the OR can be disconcerting. Because our NBS patients have undergone these experiences in the preoperative setting, they are more comfortable with them and better able to perform the needed tasks in surgery.



Join us in Berlin!

The 6th International Symposium on NBS in Neuro-surgery will be held in Berlin, October 10th-11th 2014. Register now at nbssymposium@gmail.com.

New Area Sales Director

Mathias Jähnichen joins Nexstim as Area Sales Director for Germany, Austria and Switzerland. Based in Berlin, Mathias is a 35-year-old professional who joins us after a 6-year career at Intuitive Surgical, previously he was with Philips Medical Systems.



Nexstim across the globe



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