First preoperative functional mapping via navigated transcranial magnetic stimulation in a 3-year-old boy

Case report

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Preoperative functional mapping in children younger than 5 years old remains a challenge. Awake functional MRI (fMRI) is usually not an option for these patients. Except for a description of passive fMRI in sedated patients and magnetoencephalography, no other noninvasive mapping method has been reported as a preoperative diagnostic tool in children. Therefore, invasive intraoperative direct cortical stimulation remains the method of choice. To the authors’ knowledge, this is the first case of a young child undergoing preoperative functional motor cortex mapping with the aid of navigated transcranial magnetic stimulation (nTMS).

In this 3-year-old boy with a rolandic ganglioglioma, awake preoperative mapping was performed using nTMS. A precise location of Broca area 4 could be established. The surgical approach was planned according to the preoperative findings. Intraoperative direct cortical stimulation verified the location of the nTMS hotspots, and complete resection of the precentral tumor was achieved.

Navigated TMS is a precise tool for preoperative motor cortex mapping and is feasible even in very young pediatric patients. In children for whom performing the fMRI motor paradigm is challenging, nTMS is the only available option for functional mapping.

Key Words • navigated transcranial magnetic stimulation • oncology • tumor • pediatric neurosurgery • functional mapping • functional magnetic resonance imaging

Preoperative functional mapping is a standard procedure for mapping central region tumors in adults. Modern, individually “tailored” craniotomies require precise preoperative planning. Functional information about the anatomical target area should be integrated in the navigation software to determine the least harmful trajectory to preserve function of eloquent areas and to achieve complete removal of tumors. Achieving these goals in the pediatric patient group poses unique challenges.9

The most commonly used functional mapping technique in adults is fMRI. However, in the pediatric patient group, use of fMRI is limited. Performing the activation paradigm for fMRI is challenging, especially in very young patients. An alternative method, MEG, is only available in a few centers. In a study focusing on presurgical mapping with the aid of fMRI in “very young” pediatric patients, the youngest patient in whom clinically valuable results were obtained was 5 years old.17 Passive range of motion testing in sedated children undergoing fMRI has allowed imaging to be performed in a 3-year-old child.10 However, no activation was seen in the paretic extremities. Another promising noninvasive MRI-based method is resting state correlation mapping. In 2009, Zhang et al.18 reported on preoperative visualization of the sensorimotor cortex using the spontaneous fluctuation of blood oxygen level–dependent data in 4 patients with rolandic lesions that correlated with the intraoperative DCS findings. No data exist using this method in sedated pediatric patients. However, some publications have suggested a significant influence of sedation on the default mode network.2,18

An additional limitation of fMRI in a clinical situa-
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tion is the indirect measurement of functional tissue, displaying elevated blood flow and thus metabolic activity. Local edema, pathological vessel architecture, and space-consuming effects of the neighboring lesions can compromise the interpretation of fMRI data. Furthermore, adjacent arteriovenous malformations can lead to misinterpretation of the localization of the eloquent area.6,7

Transcranial magnetic stimulation is the only preoperative technique directly comparable to intraoperative DCS. Transcranial magnetic stimulation is a safe and well-established diagnostic method for the pediatric patient group and has been used mostly for examining maturation and neuronal plasticity or in epilepsy diagnosis.15 However, because of the immaturity of axon myelination in children, a higher stimulation intensity is needed in pediatric patients than in adult patients. In children younger than 3 years, the stimulation intensity is usually at a level of 100% of stimulator output. Thus, a resting motor threshold as can be used in the adult population often cannot be established. As a consequence, in these cases the “active” motor threshold has to be used. Electromyography potentials can be elicited by previous activation of the required muscles at a much lower level of stimulation. Thus, eliciting TMS evoked potentials is possible even in newborns when the targeted muscle is active.3,5

For clinical mapping purposes, TMS alone is only a coarse measurement for locating the central sulcus and primary motor cortex. Combining this method with a neuronavigation system theoretically enables direct localization of eloquent tissue comparable to intraoperative mapping with the advantage of using it both for preoperative planning and for the integration to an intraoperative neuronavigation system. Most modern nTMS instruments use online calculation and targeting of the stimulus-evoked electric field.16

The first studies of nTMS in the adult population suggested a high congruence between DCS and preoperative fMRI data.4,12 Additionally, it was feasible to localize the central motor cortex even in noncompliant or hemiparetic patients.1,10,13 Hence, theoretically, nTMS seems to be a very promising option for pediatric patients with a Rolandic lesion who have no other option of preoperative functional mapping.

To our knowledge, we present the first case of preoperative motor cortex localization with nTMS in a 3-year-old boy with a central mass.

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History. When this boy was 1 year of age, a central region mass was incidentally diagnosed. We advocated a biopsy of the lesion; however, the patient’s parents decided against surgery and opted instead for additional MRI. A slow progression and further cystic formation of the lesion was seen (Fig. 1). Because of the eloquent site of the lesion, a stereotactic biopsy procedure was performed. The final histopathological diagnosis showed a WHO Grade I ganglioglioma. With the diagnosis of a low-grade glioma confirmed, a total resection of the tumor was thought to be highly beneficial for the child. The posterior border of the cystic mass seemed to be located in the precentral gyrus. Preoperative mapping of the functional motor cortex was therefore of great interest to assess the patient’s operative risk and to determine the least harmful trajectory for surgery.

Preoperative Functional Mapping. After induction of general anesthesia with propofol and remifentanil without muscle relaxants, MRI with a 3D MPRAGE (magnetization-prepared rapid acquisition with gradient echo) sequence and diffusion tensor imaging were performed. The 3D image set was used as the basis for nTMS.

Navigated TMS was first attempted while the patient was still under general anesthesia after the MRI procedure. The nTMS procedure started with linking the structural MRI (preferably high-resolution images) to the actual head of the patient by aligning easily recognizable external landmarks. Next, the stimulation coil was guided above the desired anatomical structures by using optical tracking. Finally, physiological responses, normally EMG studies, were recorded and temporally linked to each stimulus pulse to map the functional relevance of stimulated cortical area. Individual anatomical structures and the lesion were easily visualized during nTMS, but no reliable muscle responses could be evoked despite the use of maximal TMS output.

Anesthesia was discontinued, and the patient woke up rapidly with no ill effects. Since the patient and family were compliant and highly motivated, we decided to continue the nTMS mapping while the patient was awake. The nTMS system that we used (NBS System 4, Nexstim

Fig. 1. Preoperative T1-weighted MRI study with contrast showing a cystic Rolandic lesion.
Ltd.) utilizes optical trackers that are fixed to goggles; thus, the patient was able to move freely in his bed and play with a handheld video game during the entire mapping procedure. One researcher followed the patient’s moving head using the optical tracking unit while the other researcher targeted and stimulated the lesion and surrounding areas. Electromyography was performed on the tibialis anterior, quadriceps femoris, abductor pollicis brevis, biceps brachii, first dorsal interosseous, and extensor digitorum muscles (Fig. 2).

In the awake state, motor evoked potentials were detected from all recorded muscles with average stimulus intensities of 60% of the stimulator output (approximately 130 V/m) for the upper extremities and 80% for the lower extremities (approximately 220 V/m). The functional cortical muscle representations pinpointed by nTMS showed that the cystic lesion was anterior to the precentral gyrus. Fiber tracking was performed according to the obtained diffusion tensor imaging studies using neuronavigation software (version 2.0, iPlan, Brainlab). The posteriorly dislocated corticospinal tract in the fiber tracking corresponded to the findings of the nTMS.

Operation. The boy underwent surgery via a minimally invasive precentral craniotomy with the aid of neuronavigation, navigated ultrasound, and DCS, as well as phase reversal of somatosensory evoked potentials for cortical mapping and continuous motor evoked potential recording. General anesthesia was maintained using propofol and remifentanil. After craniotomy and dural opening, a strip electrode with 4 contacts was placed posteriorly. The precentral and postcentral gyri could be localized posterior to the tumor by using phase reversal. We conducted anodal cortical and cathodal subcortical stimulation by using a 2-mm DCS probe that was referenced in the neuronavigation system. Electromyography was performed using paired subdermal needle electrodes placed routinely in the tibialis anterior, quadratus femoris, first dorsal interosseous, biceps brachii, extensor digitorum, and abductor pollicis brevis muscles. Short trains of 5 stimuli with a pulse width of 0.5 msec and an interstimulus interval of 4 msec at a repetition rate of 0.5 Hz were applied. The stimulation intensity was increased in increments of 1 mA with an upper-intensity limit of 25 mA, until an electromyographic response was recorded. Intraoperative electrophysiology was performed using a Nicolet Endeavor neuromonitoring system (Cardinal Health). The gyrus posteriorly adjacent to the cyst was confirmed as the motor cortex. The maximum intensity of upper-extremity response to EMG was seen at the point marked with “2” in Fig. 3. Because of the extent of the craniotomy, the lower-extremity motor cortex could not be stimulated using the DCS probe. Good responses from the lower limbs were seen only after tumor removal via subcortical stimulation of the corticospinal tract. The gyral localization of preoperative nTMS corresponded to the intraoperative findings with DCS. The motor strip was precisely identified preoperatively.

Postoperative Course. Complete tumor removal was achieved as confirmed by postoperative MRI (Fig. 4). The boy exhibited slight postoperative weakness of the left arm, which recovered completely after physical therapy.

Discussion

Navigated TMS has entered the clinical realm for preoperative functional mapping of the central region in the adult population. It correlates with fMRI in detecting the central motor cortex.4 A recent publication demonstrated mapping of the speech-related cortical network in an experimental setting.8 Several clinical studies have shown a congruency of preoperative nTMS hotspots with intraoperative DCS.4,11,12 Navigated TMS is a helpful tool...

**Fig. 2.** Screenshot of the nTMS system displaying biceps and extensor digitorum muscle responses (right; upper two recordings, respectively) at the stimulation site shown on the head model (left). The gray marks covering the cortical surface show the location of previous stimulation.
in preoperative functional mapping and influences surgical decision making in adults.\textsuperscript{14} Contrary to fMRI, nTMS can be used in patients with impaired cooperation without changing the routine setting.\textsuperscript{1} Therefore, the evaluation of this method, especially in very young pediatric patients, is warranted. Navigated TMS requires only a minimum level of compliance, while cooperation with the fMRI motor paradigm is often demanding. Hence, in children younger than 5 years, nTMS might be the only option that is easily available. However, due to the immaturity of myelination in children younger than 3 years, high stimulation intensities are needed. Activation of the muscles addressed prior to stimulation must be considered in these cases. In the present case, it was shown that undirected spontaneous active movements, as performed by the boy playing a video game, are sufficient to elicit reliable EMG responses. The local cortical resolution of nTMS was very precise. No “overstimulation” was seen, even though stimulation intensities of more than twice those used in adults (around 60–80 V/m) were needed. The preoperative functional mapping was thoroughly confirmed using the intraoperative DCS. Further evaluation of nTMS is needed to assess the accuracy of the method in more detail.

Disclosure

Jari Karhu, M.D., is working part time as Chief Medical Officer of and is a consultant for Nexstim Ltd., the company that developed the specific nTMS system used in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Coburger, Karhu, Hopf. Acquisition of data: Coburger, Karhu, Bittl. Analysis and interpretation of data: Coburger, Karhu. Drafting the article: Coburger, Karhu. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Coburger. Statistical analysis: Coburger. Administrative/technical/material support: Hopf. Study supervision: Coburger, Hopf.

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