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Navigated transcranial magnetic stimulation in clinical practice and research

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Abstract. Navigated transcranial magnetic stimulation (nTMS) enables precise targeting of the induced electric field to selected cortical targets found by alignment of the head with a 3-D model of the subject's brain. This is particularly important in studies of patients as some diseases, such as brain tumors, may modify the brain anatomy and function so that the external skull landmarks are not any more aligned with the brain structures. Comparison with the preoperative nTMS and intraoperative direct electrical cortical stimulation (DECS) localization of hand muscle cortical representations has given distances of 3-12 mm between the two methods. Preoperative nTMS mapping is associated with smaller craniotomies and more extensive resections of tumors. Mapping of speech areas with nTMS during videoed object naming is less specific but more sensitive than DECS and produces reliable "negative" maps: if speech nTMS does not find an active area from the area to be resected, DECS findings are highly improbable as well. The first study of clinical impact infers that speech nTMS is associated with smaller craniotomies and less postoperative speech dysfunctions. Good understanding of the relation of nTMS activation sites with those obtained by DECS adds attractivity of the use of nTMS also in the basic research of brain functions.

Keywords: nTMS, functional maps, preoperative planning, brain tumors, epilepsy surgery.

1. Introduction

Non-invasive transcranial magnetic stimulation (TMS) utilizes strong (about 1-2 T), rapidly changing (rise time about 100 μs) magnetic fields to induce electrical currents in the cortex. Navigated TMS (nTMS) displays a dynamic estimate of the TMS-induced electric field on the individual 3-D magnetic resonance imaging (MRI) reconstruction of the subject's brain. The effects of TMS can be induced on any selected cortical target within the limits of the penetration of the magnetic field into the brain [Ruohonen and Karhu 2010].

Navigated TMS induces currents into the cortex. In neurosurgery, the need of functional mapping of the cortex to avoid injury of eloquent areas has led to use of direct electrical cortical stimulation (DECS) during or before the operation [(for references, see, e.g. Ojemann et al. 1989]. The physiological changes induced by DECS are qualitatively similar to those induced by nTMS, whereas other preoperative non-invasive methods for functional cortical mapping (such as magnetoencephalo-graphy (MEG) or functional MRI (fMRI) rely on different physiological changes induced by sensory stimuli or motor activations (such as measurements of magnetic field in MEG or blood oxygenation changes in fMRI). Consequently, the preoperative non-invasive nTMS could be potentially well matched with the DECS, the current gold standard of neurosurgical functional localization. Indeed, non-invasive nTMS has been found to be useful in preoperative functional localization of motor cortex in patients having tumors close to the sensorimotor areas [Picht et al. 2009; 2012]. Protocols for preoperative localization of speech-related cortical areas by utilizing object naming and nTMS have also been developed [Lioumis et al., 2012]. This approach has been compared to DECS during awake craniotomy [Picht et al., 2013; Tarapore et al. 2013]. and the results appear promising although not as systematic as those obtained in nTMS mapping of the motor cortex.

2. Material and Methods

2.1. nTMS-EMG

In BioMag laboratory, the motor representations of the limb muscles are mapped with a figure-of-eight coil assisted by online MRI-based navigation and dynamic induced electric field estimation (eXimia NBS software, Nexstim Ltd., Helsinki, Finland, the only device approved for preoperative functional cortical mapping by FDA; [Eldaief et al. 2014]). The motor "hotspot" is determined as a stimulation point eliciting largest peak-to-peak motor evoked potential (MEP) response from the selected muscle. The resting motor threshold (rMT), the smallest TMS intensity to reliably induce MEPs of the muscles, is determined in a standardized manner [Rossini et al. 1994]. The relevant cortical regions are then mapped with point to point stimulation using a slightly higher TMS intensity, (about105-110% of rMT) to ensure the focality of the maps.

2.2. Video-nTMS

Sets of color pictures, normalized over visual and linguistic parameters, are displayed to the subjects who are asked to name them as quickly and precisely as possible. The experiment starts with baseline sessions without nTMS, followed by active nTMS sessions. Both are video-recorded for offline analysis. Unfamiliar or incorrectly named images in the baseline session are removed from the image set, and only fluently named images are used during nTMS. The pictures are displayed on a computer screen. The stimulation is done with 5-10 Hz, 1-2 s nTMS pulse trains delivered 300 ms after the picture onset. The stimulus intensity over different brain regions is calibrated by the strength of the electric field induced in the cortex. The coil is hand-held and moved freely between the pulse trains. Usually about 200-300 sites are stimulated within one hemisphere by moving the coil semi-randomly between the trains of pulses, following a grid-like pattern so that the tested target sites cover systematically a wide fronto-temporo-parietal cortical area (Figure 1). The baseline naming responses are compared with those recorded during nTMS. The types of nTMS-induced errors are classified, the corresponding nTMS locations are marked as speech-related, andare tagged by the observed error type. A commercial setup for the procedure (NexSpeech^{TM}, Nexstim Ltd., Helsinki Finland) is in use in more than 40 neurosurgical centers around the world.

Figure 1. The prototype of a videoed nTMS speech experiment in BioMag laboratory. For details, see [Lioumis et al. 2012].

The resulting activation points and maps are transferred into the hospital picture archive and communication system (PACS) for data storage and flexible use from different hospital departments [Mäkelä et al. 2015]. The points can, for example, be transferred into the neuronavigation system of the neurosurgical operation room to add functionality to the anatomical visualization, or to be used as seeds for mapping the white matter tracts to be avoided during surgery (Figure 2; [Frey et al. 2012]).

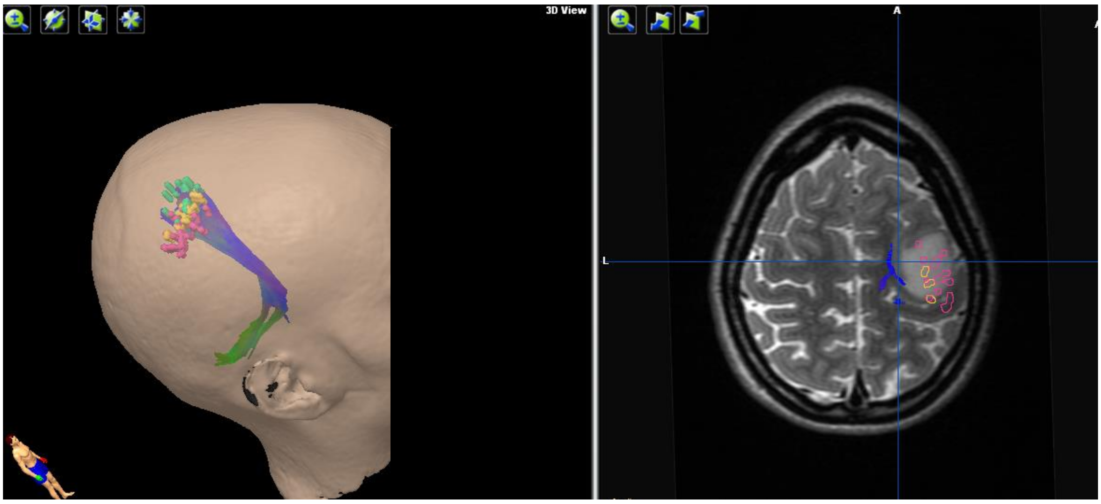

Figure 2: A figure capture from a neuronavigation station. Left: nTMS sites used as seeds to depict tractography. Right: nTMS sites for hand (red) and arm (orange) muscle activations drawn on the patient's MRI. Blue color indicates the tractography results Courtesy of dr. Aki Laakso.

3. Results

In several series of brain tumor patients, comparison of the preoperative nTMS and intraoperative DECS localization of hand muscle cortical representations has given differences of 3-12 mm [Picht et al. 2009; 2011; Forster et al. 2011; Krieg et al. 2012]. nTMS provides useful information also in preoperative planning of epilepsy surgery [Vitikainen et al. 2009]; here the difference between hand muscle representations of nTMS and DECS has been reported to be about 12 mm [Vitikainen et al. 2013]. nTMS appears to be able to track also motor cortical representations strongly modified by disease processes [Mäkelä et al. 2013]. No adverse effects, such as seizures, have occurred in our mapping studies although the patients in epilepsy surgery planning are particularly prone to seizures. When compared with DECS, results of preoperative mapping with nTMS in tumor patients appear to compare favorably with mappings by functional MRI [Forster et al. 2011] and by MEG [Tarapore et al. 2012]. Use of nTMS motor mapping in planning radiosurgery has also been advocated [Picht et al. 2014].

The clinical usefulness of preoperative motor nTMS mapping has been probed. Frey et al. [2014] studied 250 consecutive patients with motor cortex nTMS, matched with pre-nTMS era control group (n = 115). Suspected involvement of primary motor cortex was disproved by nTMS mapping in 25% of cases. nTMS expanded surgical indication in 15%, and aided in planning of more extensive resection in 35% of the patients. The rate of gross total resections increased significantly from 42% to 59%. Progression-free-survival for low grade glioma was significantly better in the nTMS group at 22 months than in the control group at 15 months [Frey et al. 2014]. Another study described a prospectively enrolled cohort of 70 patients with supratentorial lesions in motor eloquent areas, mapped with nTMS in years 2010-2014, and a matched control group of 70 patients operated on without nTMS in 2007-2010. Patients in the nTMS group had significantly smaller craniotomies, and had significantly lower rate of residual tumor on postoperative MRI. The 9-month survival was significantly better in the nTMS than non-nTMS group [Krieg et al. 2015].

The mapping of speech-related cortical areas by nTMS has also been compared to DECS during awake craniotomy [Picht et al., 2013; Tarapore et al. 2013]. nTMS is sensitive but relatively non-specific in detecting the sites producing speech disturbance in DECS. False negative findings in comparison with DECS are sparse and focus mainly on high parietal areas. Our experience indicates that mapping of speech-related cortex using the same parameters is approximately as accurate and safe also in patients undergoing planning for epilepsy surgery.

The first study probing clinical usefulness of preoperative speech nTMS has been published. Two groups of 25 patients were studied. Patients with an available rTMS speech mapping data had significantly smaller skull openings and less postoperative speech problems than those without the nTMS maps [Sollmann et al., 2015b]. The preoperative nTMS mappings of motor- and speech-related cortical areas are in routine clinical use in HUS.

4. Discussion

The preoperative functional mapping of the motor cortex by nTMS has proven to be useful and quite reliable, and has been adopted into a wide clinical use with a considerable speed. Preoperative mapping by nTMS can give important information to the neurosurgeons and has an impact on the surgery in more than half of the patients [Picht et al., 2012]. It may aid in objective preoperative risk-benefit balancing of the planned surgery, enable more targeted and smaller craniotomies, and faster and safer intraoperative DECS mappings. The first studies comparing the operational results of the patients with preoperative nTMS maps to historical controls without nTMS indicate a clear clinical benefit by preoperative nTMS motor cortex mapping [Frey et al. 2014; Krieg et al. 2015]. Double-blind studies are required to convincingly display this benefit. The mapping of speech-related cortical areas is still under development. Nevertheless, in addition to benefits described above for motor cortex mappings, preoperative speech mapping by nTMS has been suggested to be useful as speech-negative cortical areas need not to be tested by DECS, and to provide safer surgeries for patients that cannot undergo awake craniotomy [Picht et al., 2013]. The first results of clinical benefits in patients having preoperative speech mapping appear promising [Sollmann et al. 2015b]. Moreover, the speech nTMS results seem already to exceed those obtained by previously widely used fMRI speech mappings in brain tumor patients [Sollmann et al. 2013a; Ille et al. 2015].

Whereas the mapping of the motor cortex appears to be quite replicable across sessions [Forster et al. 2014] and successful in over 95% of the patients [Picht 2014], the efficacy of the nTMS to map the speech-related cortical areas varies considerably between individuals and experimental setups [Sollmann et al. 2013b]. The reported sensitivity and specificity values [Picht et al. 2013; Tarapore et al. 2013; Ille et al. 2015] are quite variable (between 15% - 98% for specificity) and suggest strong effects of slight variations in paradigms and interpretations of the results between the different laboratories using the methodology. Naming in some healthy subjects is quite resistant to nTMS. nTMS induces more errors in patients with speech disturbances than in those with fluent speech [Rösler et al. 2015]. Object naming is more sensitive to nTMS-induced disturbances than action naming [Hernandez-Pavon et al. 2014; Hauck et al. 2014]. Some anecdotal evidence suggests that the second language is more easily disrupted by nTMS than the mother tongue. The sites interfering with naming are not only limited to the left hemisphere, considered traditionally to be dominant in speech production; the functional significance of the right-hemisphere sites disturbing naming remains unclear [Rösler et al. 2015]. Thus, the methodology appears to provide ample opportunities for basic research as well. As the active sites display a considerable variability between subjects, adequate intra- and interindividual statistics are useful [Hernandez-Pavon et al. 2014].

The parameters of the nTMS speech mapping protocols are still not fully optimized for clinical use. False negative findings in parietal regions during nTMS speech disturbance are one of the unsolved issues. Use of action instead of object images probably does not diminish this problem [Hernandez-Pavon et al. 2014; Hauck et al. 2015], contrary to suggestions based on DECS [Lubrano et al. 2014]. The use of 0 ms lack between the picture and TMS train onset [Krieg et al. 2014] increases sensitivity in the parietal areas, but, unfortunately, may result in decreased specificity [Ille et al. 2015]. It has been convincingly demonstrated that small changes in stimulation site, coil orientation and its tilt with respect to the head surface influence the strength of induced MEPs [Schmidt et al. 2015]. At least similar sensitivity appears to affect the nTMS effects on picture naming [Sollmann et al. 2015b]. According to our experience, stimulation parameters may also need to be adjusted according to individual properties of the subjects. Probably a better understanding of the effects of nTMS on speech networks is required to iron out these issues. One possibility to advance the clinical usefulness of the results is to combine the nTMS mappings with MRI tractography, as suggested by a recent case report

[Sollmann et al. 2015c], preferably already during the stimulation sessions. Classification of various nTMS-elicited speech disturbances can probably be improved by recording associated modifications of vocalizations by sensitive accelerometers and automated analysis [Vitikainen et al. 2015].

5. Conclusions

Preoperative functional mapping of cortical regions by nTMS appears to be a useful, emerging approach for preoperative planning of neurosurgical operations. In addition, the precise match of the nTMS results with those obtained by DECS adds its attractiveness in non-invasive basic research of the brain functions.

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