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| Abstract | Navigated transcranial magnetic stimulation (nTMS) is increasingly used for noninvasive functional mapping of eloquent cortical areas in preoperative evaluation for brain surgery. Reliability of nTMS has been studied in healthy populations. Here we describe the methods and protocols for nTMS mapping of motor- and language-related cortical areas and describe results of nTMS in patients going through work-ups for epilepsy surgery. Clinical evidence indicates that nTMS mapping is a safe and useful tool in planning epilepsy surgery. | |
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# Navigated Transcranial Magnetic Stimulation in Planning Epilepsy Surgery

6

Pantelis Lioumis and Jyrki P. Mäkelä

Navigated transcranial magnetic stimulation (nTMS) is increasingly used for noninvasive functional mapping of eloquent cortical areas in preoperative evaluation for brain surgery. Reliability of nTMS has been studied in healthy populations. Here we describe the methods and protocols for nTMS mapping of motor- and language-related cortical areas and describe results of nTMS in patients going through work-ups for epilepsy surgery. Clinical evidence indicates that nTMS mapping is a safe and useful tool in planning epilepsy surgery.

Noninvasive transcranial magnetic stimulation (TMS) enables cortical neural excitation by means of brief and strong magnetic field pulses that induce weak intracortical currents in the tissue, resulting in membrane depolarization [1]. The initiation of cortical activation or its modulation depends on the characteristics of the TMS coil, its position and orientation with respect to the head [2], the waveform of the pulse generated by the coil, and the background activation of the neurons of the cortical region to be activated [3]. TMS is an important tool to investigate cortical functions in humans by evoking motor or behavioral responses or by interrupting task-related processing. Cortico-spinal excitability can be evaluated by recording electromyographic (EMG) responses elicited by single TMS pulses over the motor cortex, whereas intracortical excitability can be measured by means of paired pulse TMS. Repetitive TMS can be used as a therapeutic tool and to disturb various ongoing cognitive processes. Furthermore, TMS combined with simultaneous electroencephalography (EEG) enables the study of cortico-cortical excitability and connectivity. When TMS is assisted with neuronavigation (nTMS), precise test-retest paradigms can be executed, and the majority of the cortical mantle can be targeted and stimulated (including areas that do not produce measurable neurophysiologic or behavioral results; "silent" cortical regions). nTMS also enables a precise mapping of cortical functions. This is particularly important in designing epilepsy surgery. AU1

One of the goals in neurosurgery is to preserve the eloquent cortex and to optimize the extent of rejection of pathologic tissue [4]. Estimation of functional eloquence of brain areas based on anatomic landmarks is unpredictable as a result of anatomic, functional, and pathology-related variability [5]. Therefore, neuroimaging and intraoperative/extraoperative brain mapping are needed to limit postoperative functional deficits and to maximize the quality of postoperative life. Resection without intraoperative or extraoperative invasive mapping should not be considered in lesions estimated to be close to eloquent areas [5]. Invasive functional cortical mapping prior to resection is achieved by means of electrical direct electrical cortical stimulation (DCS) utilizing monopolar or bipolar electrode probes to stimulate the exposed cortex of tumor patients [6].

Patients with intractable epilepsy need accurate identification of the epileptogenic area. If the epileptic focus is suspected to be in the eloquent cortex, intracranial recordings and DCS are required. These procedures are done before the actual epilepsy surgery by surgical insertion of subdural grid electrodes (extraoperative direct cortical stimulation [ECS]). Recording and stimulations are then performed on the ward for about 1 week to obtain localization of epileptic foci and functional mapping [7]. This diagnostic surgery is associated with a non-trivial possibility of complications [8, 9], such as ECS-evoked after discharges and induced seizures that put patients at risk and make testing time consuming or even impossible [10]. Moreover, extraoperative procedures require good collaboration by the patient; this is not always easily obtained (e.g., in children or in patients with delayed development caused by the epilepsy). Nevertheless, invasive functional cortical mapping is the gold standard for functional mapping because it is able to localize the primary motor cortex accurately [11]. In addition, it has been well validated for

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localizing language-related cortical areas during awake craniotomy procedures [12, 13]. It also can be used for mapping of visuospatial and cognitive functions [14].

Lateralization of speech is necessary if the area to be resected is estimated to be near speech-related areas. The standard procedure for the identification of cerebral speech dominance is the WADA test [15], in which sodium amytal is injected into one of the carotid arteries to induce temporary loss of function of one hemisphere. The WADA test, although an efficient way to identify speech lateralization, has a number of constraints and risks [16]. Therefore, noninvasive preoperative neuroimaging methods are of high interest.

Utilization of neuroimaging has increased in work-ups for epilepsy surgery during the last decade. MRI, fMRI, diffusion tensor imaging (DTI), and magnetoencephalography (MEG) are used for preoperative mapping [17–19]. Anatomic MRI is crucial in localizing tumors and other epileptogenic lesions, but it does not necessarily reveal the location of epileptic foci. It can also be used in neuronavigation in the operation theater to guide the neurosurgeon to the cortical site of interest [20]. fMRI is used for localization of motor functions. It has also been widely used to identify speech-dominant hemispheres, although with variable results. Some studies have compared fMRI to DCS results for localization of speech-related areas (for a review, see Rutten and Ramsey [19]). fMRI produces false-positive activations when compared with DCS but may offer valuable information about the sensitivity of different tasks in the demonstration of eloquent cortical speech areas [21]. DTI can image the white-matter fiber tracts that connect different speech-related cortical regions (for review [22, 23]). It can illustrate the different connections in the speech network important for neurosurgical planning [19]. MEG is useful in detecting sources and spread of epileptiform activity [18]. Functional localization of sensorimotor cortex by MEG has been confirmed by DCS and appears to be more accurate than fMRI [24, 25].

Mapping of speech-related cortical areas can be useful for presurgical planning. Recent studies show that fMRI depicts the frontal speech-related activity better than MEG, whereas MEG is more useful in detecting temporoparietal speech-related cortices. MEG combined with fMRI may give valuable and accurate results for localizing speech functions [26].

MEG may turn out to be indispensable in designing surgical resection for epilepsy in accurately locating the epileptogenic zone [27]. MEG localization of epileptiform activity is valuable in predicting the findings of electrocorticography (EcoG), which is also often used in patients with intractable epilepsy. However, availability of MEG is limited, and it requires expertise for the data analysis and interpretation [18].

TMS has been used efficiently for preoperative mapping both in brain tumor [28, 29] and epilepsy patients [30–32]. Although promising results have been obtained in locating the motor cortex by non-navigated TMS [33], the development of nTMS has enabled its extensive use for preoperative mapping. In mapping of motor functions, nTMS is more accurate than fMRI [28, 34], and the results obtained by nTMS agree with DCS findings [29, 34]. Several studies suggest that nTMS mapping improves surgical planning [35] and increases the surgeon's confidence during resection [34]. In speech mapping, early studies [36] inspired several attempts producing variable results [37]. The use of nTMS has, however, opened new possibilities in mapping of speech-related cortex [38]. Comparisons of nTMS results with DCS during awake craniotomy in patients with brain tumors have been promising [39–41]. Mapping of cortical speech-related areas by nTMS is used in more than 40 neurosurgical centers around the world. Its clinical value is being improved by a unified effort from the clinical nTMS community to standardize methodology and compare the nTMS results with those of DCS in a homogeneous manner [42].

## 6.1 Methods

### 6.1.1 TMS

TMS induces focal electric fields that generate neuronal activation in the brain. The magnetic field used is approximately 1 tesla; the rise time of the field is usually less than 100 μs.

Conventional non-navigated TMS has a somewhat limited use in clinical applications and in basic research. It can be utilized to stimulate areas that can produce measurable neurophysiologic (e.g., motor-evoked potentials [MEPs]) or behavioral results. In addition, other cortical sites can be identified on the basis of external anatomic landmarks. But even in the motor cortex, where MEP can be easily generated, the precise cortical location of the targeted site is not known. Moreover, the distances of different cortical regions from the scalp may vary. Hence, the induced electric field is not the same in all cortical areas, although the stimulator output remains fixed. The individual variability of brain shape, size, location, and orientation of anatomic structures adds imprecision for the selection of the stimulation site. As a result, cortical functional mapping cannot be implemented reliably with the traditional TMS methodology [43].

### 6.1.2 Navigated TMS

In the state-of-the-art nTMS equipment, a figure-of-eight-shaped coil is moved manually with the help of optically guided navigation so that cortical sites selected from individual MRIs will be stimulated. In nTMS (Fig. 6.1a, b), individual MRIs are coregistered with the subject's head. For this purpose, an infra-red camera locates the trackers that are attached on the coil and on the subject's head. In aligning the 3-D MRI head model and the head, landmarks that have been set on the MRIs are chosen manually on the head with a digitizing pen. After this procedure, the coil can be visualized over the 3-D MRI head model. In this way, the stimulation site, the

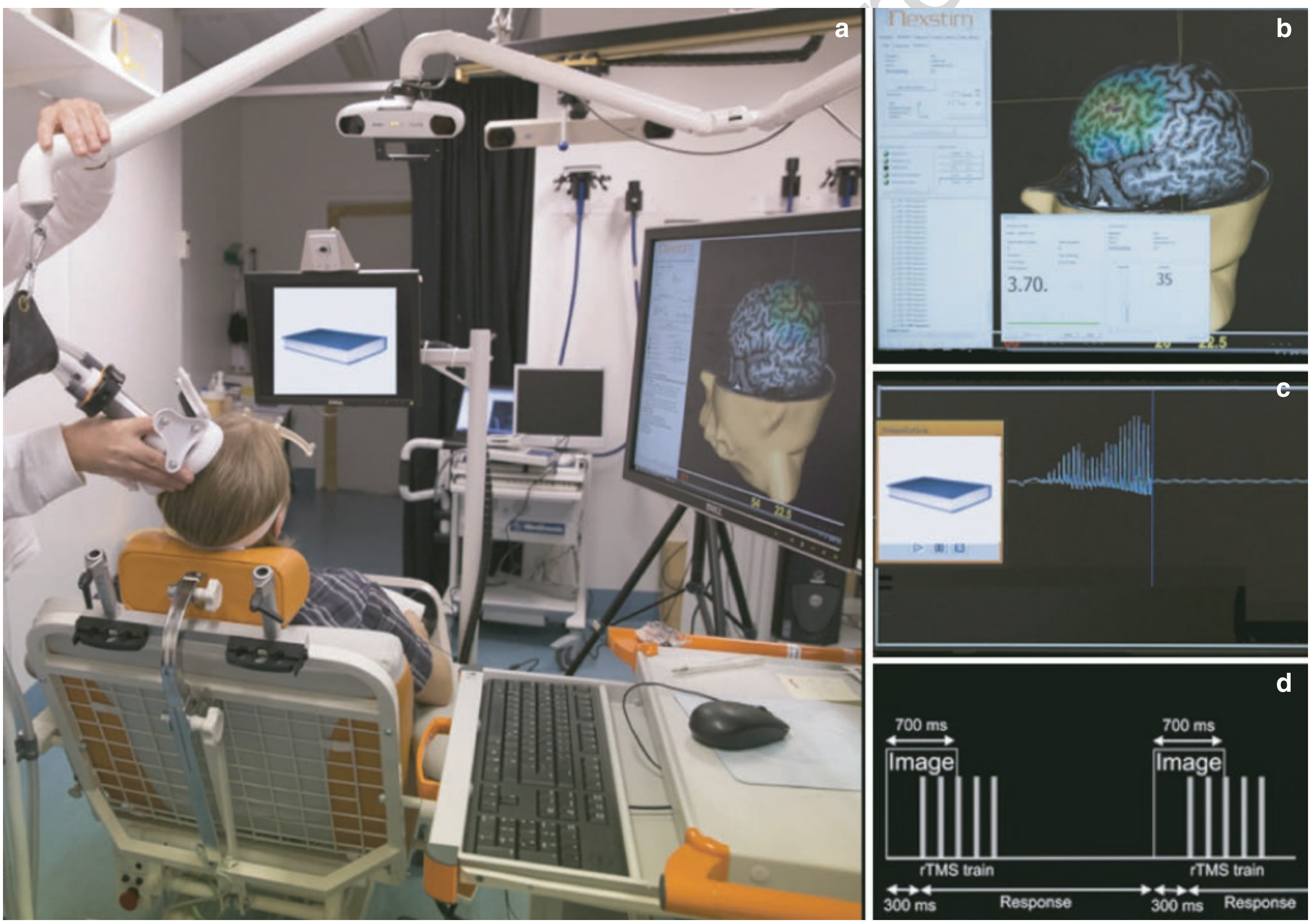




**Fig. 6.1** Navigated TMS for cortical motor and speech mapping. (**a**) The subject is seated in a chair wearing a band with head trackers. (**b**) Thereafter, both the coil projection on the individual's cortex and the induced field over the particular cortical site can be visualized in real time [43]. (**c**) For the speech mapping, the visual stimuli as well as the accelerometer signal recorded from the larynx [46] can be visualized simultaneously. (**d**) Schematic presentation of the picture presentation and nTMS trains for the object-naming paradigm. (Courtesy of Dr. Anne-Mari Vitikainen [47])

coil orientation, and the calculated estimate of the induced electric field can be visualized and reproduced in different measurements of the same subject as long as the registration error remains the same [43]. Navigated TMS enables the operator to plan, perform, monitor, and document the experiments in an accurate and reproducible manner [2].

### 6.1.3 Motor Cortical Mapping with nTMS

Cortical mapping with nTMS is used to determine locations of the eloquent motor and cortical areas. During motor cortical mapping, the TMS coil is moved around motor areas, over the lesion (tumor or suspected epileptogenic area), and in areas in close proximity to the lesion. If a TMS pulse over a cortical site elicits an MEP larger than 50 μV, this site is considered important for motor function. After the motor mapping, all motor-related cortical sites are colored and given to the neurosurgeon (in Helsinki University Hospital [HUH], this is done via radiological picture archiving system (PACS) [44]). This a priori information is used by the neurosurgeon to design the craniotomy and DCS. Motor mapping by nTMS has proved to be very accurate and important; it can potentially replace DCS in several conditions [28–30, 32].

#### 6.1.3.1 Mapping of Speech-Related Cortical Areas with nTMS

In mapping of speech-related cortical areas by nTMS, patients perform cognitive tasks such as object naming [38], and their performance is recorded by video (Fig. 6.1a–d). nTMS cannot elicit speech responses, but when it is used in its repetitive mode (rTMS), it can disturb the task performance if a task-related cortical site is stimulated at the time it participates in the task. The procedure requires a set of pictures that are normalized over linguistic and visual parameters [45]. A baseline naming study without any stimulation is performed first to discard all incorrectly named pictures from subsequent tests. Hence, a subject-validated image stack for the speech mapping is obtained. This aids the off-line analysis of the results, which is preferably done by a neuropsychologist; in HUH, the same person assists the neurosurgeon in speech tests during awake craniotomies. The aim is to identify errors caused by to the nTMS and to separate them from those owing to a lack of attention or disease-related speech impairment. Lately, an accelerometer attached in the larynx is used to record vibrations associated with vocalization to add information about speech response times in order to get more objective measurements about delays and hesitations during naming (Fig. 6.1c) [46].

After the baseline study, the TMS mapping starts. The investigator has to map large cortical areas, including the contralesional hemisphere, so as to map as many non–speech-related control areas as possible. The times of different protocols and parameters are used by different research groups [38–41]; detailed information about this can be found in Krieg et al. [42].

## 6.2 Results

### 6.2.1 Motor Mapping

The applicability of nTMS in mapping cortical motor representations in planning epilepsy surgery was demonstrated in two patients [30]. Localization of the epileptogenic area and somatosensory cortex by MEG was combined with nTMS data to design the insertion of the grid electrodes. For both patients, nTMS results matched with the motorotopy of the precentral gyrus and coincided accurately with the motor responses elicited by the ECS of grid electrodes. The preoperative somatosensory sources by MEG and the subdural cortical stimulation site that produced hand sensation were within 1 cm of distance from each other. The sources of ictal MEG activity for both patients were close or overlapped the cortical stimulation sites by ECS that triggered typical seizures. Histologic examinations of the removed area revealed focal microscopic cortical dysplasia type 2b (FCD; Taylor type) that was not detected preoperatively by 3-T MRI. No postoperative motor impairments occurred, and both patients have been seizure-free for at least 2 years after the surgery.

The feasibility and safety of nTMS as a clinical tool for the noninvasive preoperative localization of M1 in patients with intractable epilepsy have been demonstrated in subsequent studies. For example, 10 patients with different lesion pathologies were evaluated by nTMS before surgery. In 2 young patients nTMS did not elicit motor responses because of the safety limitation of nTMS intensity. In 6 out of 8 adult patients, nTMS localization of M1 was found essential or beneficial for subsequent surgery by changing the resection plan or confirming the safety of the planned resection. In addition, nTMS localized M1 accurately in all adult patients [31].

The nTMS motor cortical representation maps of hand and arm compare well with the results of ECS in patients with epilepsy surgery (Fig. 6.2). In 13 patients with both nTMS and DCS data from the same upper limb muscles, the distance between the average sites of the two maps was 11 ± 4 mm for hand and 16 ± 7 mm (mean ± standard deviation) for arm muscles [32]. These numbers match well with similar comparisons in patients with brain tumors [29, 48]; the reported match between nTMS and DCS (mean distance 7.8 ± 1.2 mm [29] and 3.4 ± 3.0 mm [48] for thenar muscles) corresponds to the match of nTMS and ECS. The slightly higher differences observed in epilepsy patients probably derive from the fact that in ECS the stimulating electrodes have fixed 10-mm distances, whereas in DCS the monophasic or biphasic probe can be moved freely.

nTMS may also reveal epilepsy-induced functional plasticity of cortical motor organization [49]. In one patient nTMS activated the premotor cortex rather than the expected precentral gyrus; the result was in line with the MEG and fMRI localizations of the motor cortex. During the operation, ECS localized finger motor functions into the precentral gyrus. The premotor area containing an FCD was removed,

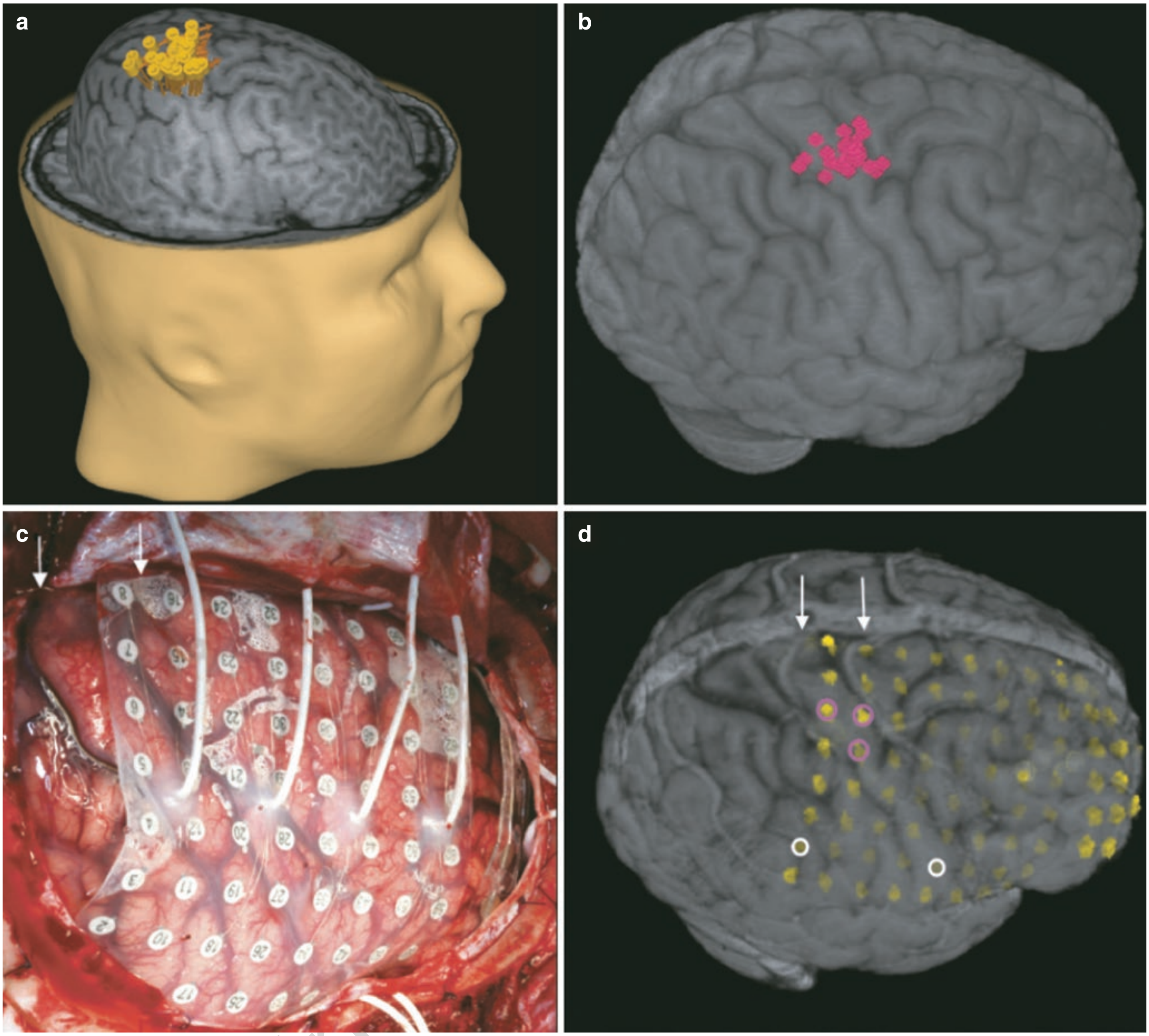


**Fig. 6.2** Example from one patient from Vitikainen et al. [32]. (**a**) The nTMS map of the upper arm muscle group from one patient. The estimated TMS-induced electric field maxima at each stimulation point are visualized as small spheres on the brain surface; the orientation and tilt of the stimulation coil are visualized as a stick, and the direction of the induced field is shown as a small arrow on top of each stick (eXimia NBS software, Nexstim Ltd., Helsinki, Finland). (**b**) The same result shown on a 3-D brain volume rendering. The individual response locations are projected to the MR brain surface segmentation. (**c**) A photograph of the intracranial electrode grid before skull closure. Note the cortical veins indicated with arrows. (**d**) The electrode grid (*yellow*) co-registered on the gadolinium-enhanced preoperative MRI brain segmentation; the cortical veins that correspond to those depicted in (**c**) are clearly visualized. The electrodes eliciting motor responses of the stimulations from the upper arm area are marked with *solid pink circles* and the reference electrodes with *solid white circles*. The error of a few millimeters in the placement of the electrodes between (**c, d**) can be noticed. (Adapted from Vitikainen et al. [32] with permission of Springer)

and the precentral gyrus was left intact. The patient had no new neurologic or cognitive postoperative impairments. Postoperatively, nTMS mapping was feasible with much lower intensity than preoperatively, and the motor representation was found posterior to the localization seen in the preoperative mapping. A similar change was observed in the postoperative motor mapping by fMRI and MEG. It was proposed that the preoperative absence of nTMS-elicited MEPs from the precentral gyrus resulted from the surrounding inhibition created by the frequently discharging epileptic focus. In another patient in epilepsy surgery work-up, nTMS indicated abnormal ipsilateral hand motor cortex localization and confirmed the functionality of aberrant motor cortical representations of the left foot in the heavily lesioned hemisphere; this was also indicated by fMRI and DTI. Similar findings were also presented in another study, suggesting that pathologic excitability caused by FCD can be located by nTMS with high spatial precision [50].

### 6.2.2 Speech Cortical Mapping

nTMS enables an extensive mapping of speech areas. Such a large area cannot be studied during awake craniotomy because of time constraints and the limited area of exposed cortex. nTMS speech mapping also helps in designing the craniotomy [51] and may speed up the speech mapping by DCS during surgery.

The methodology for nTMS mapping of speech-related cortical areas was developed in 2012 [38]. This nTMS methodology was validated in brain tumor patients when comparing the results between nTMS and DCS [39, 40] during awake craniotomy. The results have revealed a high sensitivity (90%) [39, 40] but occasionally a low specificity in one study [39]. nTMS may thus depict false-positive cortical sites in comparison to DCS [39, 40]. Nevertheless, nTMS did not produce false-negative activations. This aids in designing the DCS during awake craniotomy and speeds up the intraoperative procedure by limiting the number of sites to be tested by DCS. It is also advantageous that the neurosurgeon and the neuropsychologist have seen the speech performance of the patient before awake craniotomy. Moreover, patients are better prepared for speech tests during the awake craniotomy. Still, the method needs improvement for increasing its specificity.

Babajani-Feremi et al. [52] compared the localization of the language cortex using ECS with subdural grid electrodes, high gamma electrocorticography (hgEcoG), fMRI, and nTMS in patients with epilepsy. All these methods can identify language-related cortical areas. The average sensitivity/specificity of hgEcoG, fMRI, and TMS was 100%/85%, 50%/80%, and 67%/66%, respectively. In comparison to ECS, however, nTMS again indicated a very small amount of false-negative sites; the negative predictive value was 95%. The nTMS results in this study have been somewhat different from the studies performed on brain tumors, mainly because of the differences between ECS and DCS and also the methods used to estimate the sensitivity/specificity [40]. We have studied 20 patients with speech nTMS mapping during epilepsy surgery planning, and our experience suggests similar sensitivity and a small percentage of false-negative sites (Lehtinen et al. submitted). All these studies are in concordance in showing the limitation of nTMS in producing false-positive activations but highlighting its clinical importance for the design of awake craniotomy in producing very few false-negative cortical speech sites.

## 6.3 Safety

The nTMS mapping protocols for motor and speech functions that have been used in patients with intractable epilepsy did not elicit serious side effects [30–32, 52]. Moreover, EEG recordings during nTMS in 70 patients with Unverricht-Lundborg epilepsy did not reveal nTMS-related epileptiform phenomena [53]. Two recent studies [54, 55] on a large amount of data from brain tumor patients and healthy volunteers are in line with the above-mentioned studies, supporting the notion [42] that as long as the parameters follow the established safety guidelines, nTMS for both motor and language mapping is a safe method without adverse effects. The stimulation parameters need to stay within the established guidelines for safe application of single pulse and repetitive nTMS [54, 55].

**Conclusions**

The usefulness of nTMS in localizing the cortical motor and language representations in presurgical planning for patients with intractable epilepsy is apparent because of its spatial resolution, accuracy, and reliability. nTMS motor mapping shows excellent accuracy in comparison with ECS, and it could be included in the neurosurgical routine for epilepsy surgery planning. Evidence of nTMS precision in comparison with DCS from tumor patients also supports this notion. However, efficient mapping for epilepsy patients by nTMS may be affected by the plasticity that is produced by the pathophysiology of the epileptogenic area [49, 50]. This plasticity should be taken into consideration in preoperative planning of epilepsy surgeries. Potentially, nTMS can replace ECS under special circumstances as shown by Vitikainen et al. [30], but it should generally be used in combination with extra- or intraoperative mapping.

nTMS language mapping is a new and highly promising clinical tool. It is the only noninvasive method that can simulate the ECS procedure. It can give complementary information, and when combined with other neuroimaging methods it can overcome the limitations of ECS [52]. However, its low specificity should always be taken into consideration. The development of the experimental protocol [42] toward increasing the specificity and maintaining the high negative prediction value of nTMS speech mapping is highly desirable.



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# Author Queries

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| Queries | Details Required | Author's Response |
|---|---|---|
| AU1 | Please confirm identified heading levels. | |
| AU2 | Please update volume number and page range for Ref. [42]. | |
| AU3 | We have redrawn Fig 6.1. This is for your information. | |