



Combined use of non-invasive techniques for improved functional localization for a selected group of epilepsy surgery candidates

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ABSTRACT

Invasive cortical mapping is conventionally required for preoperative identification of epileptogenic and eloquent cortical regions before epilepsy surgery. The decision on the extent and exact location of the resection is always demanding and multimodal approach is desired for added certainty. The present study describes two non-invasive preoperative protocols, used in addition to the normal preoperative work-up for localization of the epileptogenic and sensorimotor cortical regions, in two young patients with epilepsy. Magnetoencephalography (MEG) was used to determine the primary somatosensory cortex (S1) and the ictal onset zones. Navigated transcranial magnetic stimulation (nTMS) was used to determine the location and the extent of the primary motor representation areas. The localization results from these non-invasive methods were used for guiding the subdural grid deployment and later compared with the results from electrical cortical stimulation (ECS) via subdural grids, and validated by surgery outcome. The results from MEG and nTMS localizations were consistent with the ECS results and provided improved spatial precision. Consistent results of our study suggest that these non-invasive methods can be added to the standard preoperative work-up and may even hold a potential to replace the ECS in a subgroup of patients with epilepsy who have the suspected epileptogenic zone near the sensorimotor cortex and seizures frequent enough for ictal MEG.

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Introduction

Epilepsy surgery candidates whose epileptic focus is close to eloquent cortical areas need accurate identification of the epileptogenic zone and the irretrievable cortex. This is usually done with intracranial recordings and electrical cortical stimulation (ECS), presently the standard technique for preoperative localization. However,

Abbreviations: ADM, Abductor digiti minimi; AEM, Antiepileptic medication; AH, Abductor hallucis; APB, Abductor pollicis brevis; BB, Biceps brachii; CT, Computed tomography; ECD, Equivalent current dipole; ECS, Electrical cortical stimulation; EDC, Extensor digitorum communis; FCR, Flexor carpi radialis; FDI, First dorsal interosseus; MEG, Magnetoencephalography; MEP, Motor evoked potential; MRI, fMRI, Magnetic resonance imaging, Functional magnetic resonance imaging; MT, Motor threshold; nTMS, TMS, Navigated transcranial magnetic stimulation, Transcranial magnetic stimulation; PET, Positron emission tomography; RF, Rectus femoris; S1, Primary somatosensory cortex; SEF, Somatosensory evoked field; TA, Tibialis anterior.

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subdural investigations require diagnostic surgery, associated with significant risk of complications (Hamer et al., 2002). Therefore accurate non-invasive methods for localizations with added precision and reliability would be highly appreciated. In two patients who subsequently underwent a weeklong intracranial recording via subdural electrodes and resective surgery, we applied two non-invasive methods; magnetoencephalography (MEG) to identify the ictal onset zone and primary somatosensory cortex (S1) (Mäkelä et al., 2006) and navigated transcranial magnetic stimulation (nTMS) to determine the boundaries of the primary motor cortical representation areas of selected muscles (Hannula et al., 2005; Krings et al., 1997a; Wilson et al., 1993).

Methods and patients

Mapping of the primary motor cortex with nTMS

Single-pulse nTMS delivered by a figure-of-eight coil, with concurrent electroencephalography (EEG) (eXimia NBS and EEG,

Nexstim Ltd., Helsinki, Finland) was used to map the primary motor cortical representation areas of selected upper and lower extremity muscles. The EEG amplifier keeps the signal constant from 100 μ s before the pulse to 2 ms after the TMS pulse by a sample-and-hold-circuitry (Virtanen et al., 1999). The motor area of the abductor pollicis brevis (APB) was first selected in magnetic resonance images (MRI) on the basis of the “hand knob” (Yousry et al., 1997). The resting motor threshold (MT) was defined as the lowest stimulation intensity at which 5 out of 10 pulses evoked a motor potential (MEP) of 50 μ Vp-p (peak-to-peak amplitude) or greater (Rossini et al., 1994; Rossini et al., 1999) recorded with a Keypoint EMG device (Keypoint, Medtronic, Minneapolis, USA). The localized motor cortex was stimulated at an intensity of 105–110% MT (Macdonell et al., 1991) with the coil held tangentially to the scalp with handle pointing backward and laterally; this induced a posterior-to-anterior current flow in the cortex, perpendicular to the central sulcus (Brasil-Neto et al., 1992). The area where nTMS evoked MEPs of 50 μ Vp-p or larger, or a clear silent period (Tataroglu et al., 2004) within the pre-activated target muscle, was determined as the primary motor representation area of the target muscle. Possible enhancement of epileptiform activity was constantly monitored with a 60-channel EEG; no such increase or seizures were induced during nTMS.

Localization of the epileptogenic and somatosensory cortices with MEG

Spontaneous interictal and ictal brain activity and somatosensory evoked fields (SEFs) to median and tibial nerve stimulation were recorded with a 306-channel magnetoencephalograph (Elekta, Helsinki, Finland) in a magnetically shielded room (Euroshield, ETS-Lindgren, Eura, Finland). Head movements were continuously monitored by four coils on the scalp activated at 154–166 Hz, enabling correction of the head movements (Medvedovsky et al., 2007; Uutela et al., 2001) and accurate ictal recordings. Due to frequent seizures, MEG recordings didn't require withdrawal of medication, and one or more habitual seizures were recorded in both patients within 1 h. Recording frequency band was 0.03–172 Hz and sampling frequency 600 Hz. SEFs were elicited by 100 constant current pulses at 0.5 Hz to wrist, and 500 to ankle, using stimulus intensity above the motor threshold. Data was band-pass filtered at 0.3–90 Hz in off-line analysis. All individual MEG traces were screened visually for epileptiform signal morphology according to traditional EEG criteria, and for corresponding dipolar magnetic field patterns, both during and between clinical seizures.

Single equivalent current dipoles (ECDs) were fitted to the magnetic field pattern of interest by the least-square search. The center of this pattern was focused on the largest gradiometer signal of interest, and a sufficient number (range 36–40) of sensor locations were selected to cover both magnetic field extremes. Single ECDs were first computed for the separate dipolar fields at different time points during the signal. Subsequently, these dipoles were used as initial guesses for a single- or multi-dipole fit for all 306 channels. Finally, the analysis period was extended to cover the entire signal of interest, and the optimal dipole strengths were computed assuming fixed dipoles at the locations and orientations given by the initial least-squares search (Scherg, 1990). Such an ECD (or set of ECDs) typically explained over 80% of the selected field. When testing the dipole with the measured data, we also accepted lower goodness-of-fit values, but required a good visual congruity between the measured signal and the waveform predicted from the estimated dipole. The dipole had to explain the signal of interest (e.g. a spike), but not other MEG signals (e.g. posterior alpha activity).

The nTMS and MEG recordings were analyzed by different experimenters, blinded to the results obtained with the other method. However, the results were used in guiding the subdural electrode grid deployment and were later combined and compared with the results from the ECS. All available expertise was used in the decision making process before the resection.

Electrical cortical stimulation

A subdural grid (AD-TECH, Racine, Wisconsin, USA) of 8, 32, or 64 platinum plate electrodes with 4.0/2.3 mm (overall/exposed) diameter and 10 mm center-to-center distance was inserted over the affected cortex. Five days later, ECS was done with a Grass S-12 biphasic stimulator (Grass Instrument Co., Quincy, MA, USA) using 5-s trains of repetitive square pulses (duration 0.3 ms/phase, pulse interval 50 Hz) of alternating polarity. The intensity was gradually increased to the level of a functional response or after-discharges induction in EEG; predetermined maximum current level was 13.5 mA (Lesser et al., 1984, 1987). A distance reference technique (Lesser et al., 1987) was used first to find a reference electrode with a high after-discharge threshold, located preferably at the periphery of the grid, and subsequently to determine the relative topography of the eloquent areas. When the known or suspected epileptogenic area intervened the line between the target and the reference electrode or when a spatially more focused stimulation was required in the region of interest, a bipolar stimulation arrangement was used between adjacent electrodes (Lesser et al., 1987). This forces the peak current density into the region immediately beneath the electrodes (Nathan et al., 1993). In the results, the number of active and reference electrodes are notated as G20–G9, G9 being the reference.

Image registration, fusion and 3-D visualizations

For visualization of all results relative to the patient's cerebral anatomy, nTMS, MEG, brain computed tomography (CT) data showing subdural cortical stimulation electrodes, and head MRI data sets were transformed to a common coordinate system. CT of the subdural grid electrode positions was acquired on the first postoperative day after the grid implantation. The T1-weighted contrast-agent enhanced MRI visualizing the superficial cortical veins, T1-weighted MRI for the general anatomy, CT and T2-weighted 3-T MRI emphasizing the lesion area were rigidly co-registered by maximizing mutual information metrics (Maes et al., 1997) with a medical image processing software (Van Leemput and Hämäläinen, 2004) utilizing the open-source Insight Segmentation and Registration Toolkit (Ibáñez et al., 2005). For Patient 2, a neuroradiologist defined the lesion area from T2-weighted MRI; for Patient 1, no lesion was detected. Subsequently, nTMS and MEG localizations were co-registered with MRI on the basis of two pre-auricular points and nasion. The brain area (including superficial cortical veins in contrast-agent enhanced MRI) was extracted from the T1-weighted MRIs, and the locations of the cortical electrodes were determined by intensity thresholding the CT data. The cortical grids, the lesion, and localizations from the nTMS and MEG were fused with the T1-weighted MRIs. The nTMS and MEG localization results were presented as small spheres in the combined data. The volume renderings (3-D visualizations) of the combined data were created using the medical image processing software utilizing the open-source VTK toolkit (Schroeder et al., 2003). The 3-D MRI reconstructions were available during resection. For Patient 2, the lesion outlines were uploaded to the neuronavigator.

Patients

A 22-year old woman (Patient 1) had drug-resistant epilepsy from the age of twelve. Typical seizures started with paraesthesia in the left arm and progressed to motor seizures, which rarely generalized. An MEG recording at age 14 revealed rare spikes 1 cm posterior to the S1 localized by the sources of 20 and 35 ms responses to left median and ulnar nerve stimulation. 3-T MRI carried out at age 22 was normal. Long-term video EEG recording done preoperatively with 39 scalp electrodes showed localized ictal epileptiform activity in electrodes C4 and P4 (International 10–20 system). Because weeklong periods of almost continuous drug-resistant seizures hampered the use of the

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