Same Day Tri-Modality Functional Brain Mapping Prior to Resection of a Lesion Involving Eloquent Cortex: Technical Feasibility

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SUMMARY – *Non-invasive functional evaluation of the brain complements structural MRI imaging and has largely supplanted invasive techniques such as awake craniotomy. Techniques used for functional mapping of the brain include BOLD-functional MRI (fMRI), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). We describe the case of a right-handed patient with a lesion centered in the left inferior perirolandic cortex who underwent fMRI, MEG, and TMS on a single day to facilitate maximal lesion resection while preserving eloquent cortex and eloquent white matter tracts.*

Introduction

Non-invasive functional evaluation of the brain complements structural MRI imaging and has largely supplanted invasive techniques such as awake craniotomy¹. Techniques used for functional mapping of the brain include BOLD-functional MRI (fMRI)^{1–3}, magnetoencephalography (MEG)^{4–7}, and transcranial magnetic stimulation (TMS)⁸. These techniques provide complementary information, and concordance of multiple modalities increases confidence in the results. However, even at centers with more than one of these technologies, a multimodality workup is sometimes deferred due to concerns about the difficulty performing and coordinating the acquisition and processing of data.

We describe the case of a right-handed patient with a lesion centered in the left inferior perirolandic cortex who underwent fMRI,

MEG, and TMS on a single day to facilitate maximal lesion resection while preserving eloquent cortex and eloquent white matter tracts.

Case Report

A 52-year-old right-handed woman presented to the emergency department with a several week history of right-sided facial numbness, and new onset secondary generalized tonic clonic seizures with post-ictal aphasia. Computed tomography showed a hypodense mass lesion in the left anterior/inferior parietal lobe, confirmed on MRI to be in the inferior aspect of the post-central gyrus (Figure 1). A screening CT scan of the chest, abdomen, and pelvis showed no findings suspicious for a primary neoplasm outside the central nervous system.

An open biopsy/subtotal resection was planned, with a desire to obtain the maximum

resection possible without functional deficit. Given the location and clinical presentation, it was expected that the lesion would either involve or abut the facial motor and sensory cortex, as well as the arcuate fasciculus. fMRI was requested to map the facial motor cortex, to lateralize and localize language, and to use diffusion tensor imaging (DTI) and diffusion tensor fiber tracking (DT-FT) to map the arcuate fasciculus, for use in surgical planning⁹. As fMRI is a positive activation study showing areas of the cortex activated by a given task, but not specifically identifying the cortex essential to performing that task, TMS was requested. Due to the critical functions carried out by the adjacent parenchyma, confirmatory MEG mapping was also requested.

The patient was admitted to a separate hospital in our system, but needed the diagnostic studies for language mapping performed in our institution (but did not need admission). Therefore, all mapping had to occur in one afternoon. The sequence of this multi-modality mapping had several constraints. TMS requires structural MR images to guide functional mapping⁸. MEG overlays dipole activations to MRI^{4,5}, although the MRI does not have to be present at the time of acquisition. MEG is limited when performed within 24 hours of an MRI due to artifact caused by residual magnetization of ions, in particular iron within hemoglobin and neurons. Thus, to perform same-day tri-modality mapping, MEG was performed first, followed by fMRI and then TMS. While the MEG was performed first, analysis took place after fusion with structural MRI images, so fMRI will be discussed first.

Structural and Functional MRI

Structural and functional MR images were obtained on a 3 Tesla scanner (Siemens Verio, Siemens AG, Munich, Germany) with a 32 channel head coil. Functional MRI paradigms were delivered through an MRI compatible monitor which the patient could see using mirrors attached to the head coil. Five minute block designs with 15 second alternations between rest and activation were used for facial motor (tongue movement and lip puckering) and language (silent word generation, object naming, and sentence completion tasks) paradigms. BOLD-fMRI acquisition used a TR of three seconds, with five volumes acquired for each 15 second paradigm iteration. Paradigm

delivery was controlled using the Esys-fMRI system (InVivo Corp, Pewaukee, WI, USA). fMRI data was processed using an FDA-approved software package (Dynasuite Neuro 3.0, InVivo Corp, Pewaukee, WI, USA).

Magnetoencephalography

The patient was tested using a whole-head neuromagnetometer (4D Neuroimaging, Magnes WH3600) equipped with 248 magnetometer sensors and housed in a magnetically shielded room designed to reduce environmental magnetic noise that might interfere with biological signals. The magnetic flux measurements were digitized at 508 Hz, filtered off-line with a bandpass filter between 0.1 and 20 Hz and subjected to a noise reduction algorithm that is part of the 4D-Neuroimaging software. Hemispheric dominance for receptive language was assessed in the context of an auditory, continuous word recognition task⁷. Subsequently, mapping of the primary somatosensory cortex was conducted following tactile stimulation of the right index finger⁷.

Transcranial Magnetic Stimulation

Motor mapping was performed using single pulse neuronavigated TMS (Nexstim Inc, GA, USA) applied to the primary hand motor cortices bilaterally. Motor evoked potentials (MEP) were recorded using surface electrodes (Neuroline 720, Ambu Inc., MD, USA) from the contralateral adductor pollicis brevis, and brachioradialis muscles during TMS stimulation. EMG was sampled at 3 kHz and band-pass filtered from 10 Hz to 500 Hz. Peak-to-peak amplitude of the MEP and latency (time from TMS to MEP onset) were calculated. TMS was applied along the inferior extent of the central sulcus, along the anterior margin of the tumor to map the mouth motor cortex. Motor threshold (MT) was determined by standard methods⁸.

The left hemisphere engagement during expressive language was assessed in the context of disruption of speech during neuronavigated 5Hz TMS applied as the patient performed a picture-naming task. The pictures were presented for 500 ms and five pulses of TMS (one second of 5 Hz TMS) were applied beginning at 200 ms following stimulus presentation. TMS was applied to the inferior and middle frontal gyri and along the tumor margins.

Figure 1 Axial FLAIR (A), T1 post-contrast (B), diffusion-weighted (C), susceptibility-weighted (D) images of the brain through the left inferior perirolandic lesion, as well as single voxel MR spectroscopy with a TE of 270 ms (E). The lesion causes cortical thickening and infiltration of the juxtacortical white matter (A). There are areas of post-gadolinium enhancement (B), and areas of reduced water diffusion (C) with punctate areas of susceptibility hypointensity (D). MR Spectroscopy shows elevated choline (Cho) and reduced n-acetyl-aspartate (NAA) peaks, with a resulting Cho:NAA ratio greater than 2. There is also an elevated lactate doublet peak at 1.33 ppm indicative of anaerobic metabolism.

Figure 2 Axial FLAIR image with fMRI and DT-FT overlay shows the facial motor cortex abutting the anterior margin of the lesion (thin arrow). Expressive language (thick arrow) is depicted in the left pars opercularis and pars triangularis. The arcuate fasciculus (arrowhead), as determined using receptive and expressive language centers as DT-FT seed and target locations, respectively, runs subjacent to the lesion.

Figure 3 Functional mapping using MEG. The solid blue square on the left-hand side of the figure represents the peak early latency response associated with tactile stimulation of the right index finger, localized to the contralateral postcentral gyrus. In the right-hand side of the figure, the confluent red circles localized to Wernicke's area correspond to cortical activation sources associated with receptive language processing in the dominant left hemisphere.

Figure 4 Motor and expressive language mapping with TMS. Panel A: The location of the primary hand motor cortex of the left hemisphere (corresponding to right hand movement) is shown as orange pegs projected onto the patient’s MRI. The cortical locations of the left primary mouth-specific motor cortex are shown as white pegs projected onto the patient’s MRI. Gray pegs indicate no detectable muscle activity. The scalp is peeled to a depth of 24.5 mm to demonstrate the motor areas. Panel B: The cortical areas where TMS resulted in complete speech arrest are shown as white pegs projected onto the patient’s MRI. The cortical areas where TMS resulted in slowing/slurring of speech are shown as yellow pegs. The scalp is peeled to a depth of 20 mm to demonstrate the expressive language areas.

Figure 5 Multimodality overlay: sagittal T1 weighted image with overlay of motor mapping with MRI and TMS, and language mapping with functional MRI, MEG and TMS. Panel A: fMRI facial motor activation in green and TMS mouth motor mapping (red). Panel B: sagittal T1 weighted image with overlay of an fMRI (green) covert object-naming task, showing left inferior frontal gyrus expressive language, MEG (blue) during passive listening, and TMS induced speech disruption (red) during overt object-naming. Note the overlap between fMRI and TMS (yellow) in the inferior frontal gyrus (Broca’s area).

Results

The total time for the tri-modality non-invasive mapping was four hours. The time for MEG was 60 minutes, fMRI took approximately one hour (15 minutes patient education, 25 minutes structural imaging, 25 minutes functional imaging), and TMS took approximately 60 minutes. There was an approximately 20 minute gap between MEG and fMRI, and an approximately 45 minute gap between fMRI and TMS.

Anatomical MRI

MRI showed an intraaxial mass in the left inferior perirolandic cortex (Figure 1A) with a nodular area of enhancement (Figure 1B). There were areas of reduced water diffusion (Figure 1C), likely indicative of areas of increased cellularity and a high grade component; these areas did not directly correspond to the areas of enhancement. Punctate areas of susceptibility were seen in the lesion (Figure 1D), either indicative of micromineralization or hemosiderin from prior hemorrhage. Single-voxel MR spectroscopy of the lesion showed aggressive characteristics, including a choline to NAA ratio greater than 2 and a lactate doublet peak at 1.33ppm indicative of anaerobic metabolism (Figure 1E).

Functional MRI and DTI

fMRI showed that the facial motor cortex was at the anterior margin of the lesion, including some overlap (Figure 2). The patient had a left hemispheric language lateralization. The arcuate fasciculus, as determined using the receptive language cortex as a seed and the expressive language cortex as a target for DT-FT, coursed subjacent to the lesion.

Magnetoencephalography

The concentration of evoked activity sources during receptive language testing showed engagement of both hemispheres but with preponderance of the left, suggestive of left dominance for receptive language (Figure 3B, Figure 5B) thus cross-validating the fMRI and TMS findings. Mapping of the primary somatosensory cortex conducted using tactile stimulation of the right index finger resulted in the generation of a robust early somatosensory response localized to the contralateral post-central gyrus (Figure 3A) thus, in con-

junction with TMS, verifying the location of the central sulcus.

Transcranial Magnetic Stimulation

Both primary hand motor cortices were normally located in the precentral gyrus in the hand knob area. The MT for the left primary hand motor cortex was 37% of the machine output equivalent to an E-field of 64 V/m, and MT for the right primary hand motor cortex was 42% of the machine output equivalent to an E-field of 102 V/m. The corticomotor response latency was normal at 21 ms bilaterally. TMS applied along the left lateral/inferior aspect of the central sulcus resulted in visible jaw and lip movements. These cortical areas were identified as left primary mouth motor cortex (Figure 4A). The mouth motor cortex identified by TMS was compared with the fMRI motor map (see Figure 5A). The two foci were adjacent along the anterior margin of the tumor, with the mouth area identified by fMRI being more dorsal. This is most probably due to the fact that motor mapping by fMRI was done using tongue movements, while during TMS, jaw and lip movements were monitored. Therefore, while there was no exact overlap, the regions were adjacent confirming the motor somatotopy.

Disruption of speech was noted when TMS was applied to the left inferior frontal and premotor areas of the cortex. The speech disruptions included complete speech arrest, and slurring and slowing of speech. The cortical areas where TMS resulted in speech disruption are shown in Figure 4B. Brain areas where TMS resulted in speech arrest were contained within Brodmann area 44 (Broca's area) as assessed by fMRI during a covert object-naming task (see Figure 5B – yellow areas showing overlap of language areas identified by TMS and fMRI). These findings are consistent with a recent report of overlap between TMS and direct cortical stimulation¹⁰. However, some differences were noted between the expressive language mapping by TMS and fMRI. Since the fMRI was acquired during silent naming, activations were noted in Brodmann areas 44 and 47, and not in the premotor and motor cortices.

However, TMS mapping was different in that it examined the engagement of not only the language areas, but also the premotor and motor areas during speech production. In this particular case, the patient presented with

post-ictal aphasia indicating that motor and premotor cortices may play a role in expressive language. TMS indeed confirmed this. Speech arrest, characterized by no speech output, and the patient described the effect as knowing what the object is, but unable to initiate speech, was only elicited when Broca's area was stimulated (white pegs in Figure 4B). Stimulation of premotor and mouth areas resulted in slow and slurred speech that was more like apraxia (premotor) and dysarthria (M1 mouth, yellow pegs in Figure 4B). The fMRI activation extended into Brodmann area 47 (pars triangularis). Unfortunately, TMS to these more anterior areas was painful and was not tolerated by the patient.

Image-guided open biopsy and subtotal resection was performed, with a diagnosis of glioblastoma. The patient showed no new post-operative motor, sensory, or language deficits. Due to the adjacent eloquent cortex, further resection was not pursued and the patient was treated with radiation and temozolomide therapy.

Discussion

Tri-modality functional brain mapping allows non-invasive localization of motor, sensory, and language centers for surgical planning, as well as associated white matter pathways, and can be performed in a single afternoon with appropriate coordination. Each method of non-invasive brain mapping has strengths and weaknesses, and the potential for false positive and false negative results^{2,3}. Complementary and concordant data from different modalities increases the confidence in the accuracy of the mapping, which is required when attempting to perform surgery within or adjacent to highly eloquent parenchyma.

At our center, we have since performed a single session tri-modality workup on ten additional patients, without study compromise due to patient fatigue. Multidisciplinary preoperative consultation can be performed rapidly and aid in pre-surgical planning without excessively delaying surgical management of patients with lesions surrounded by eloquent cortex.

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