Case Report

Limitations of functional magnetic resonance imaging in mapping function near a vascular lesion: A case study

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Abstract We present a case of functional reorganization of the somatosensory system in a 15 year-old female with a history of perinatal stroke of the middle cerebral artery. The patient presented with hemiparesis and epilepsy and underwent comprehensive pre-surgical evaluation for epilepsy surgery, including mapping of somatosensory function with functional magnetic resonance imaging (fMRI). The fMRI results indicated inter-hemispheric reorganization of somatosensory function from the left to the right hemisphere, and showed no residual somatosensory function in the peri-lesional area of the affected left hemisphere. However, following implantation of subdural electroencephalography (EEG) electrodes, recordings from left hemisphere lesion and peri-lesional areas showed evoked electrophysiological responses to tactile stimulation. Bedside and intra-operative stimulation mapping confirmed multiple somatosensory responsive sites in the left hemisphere in or near the lesion, in contradiction of the fMRI results. Since the BOLD signal is a measure of the local ratio of oxygenated to deoxygenated blood, fMRI represents only an indirect measure of neuronal activity. Modeling of fMRI activation depends on intact neurovascular coupling and adequate signal to noise ratios, which may be altered in the presence of a vascular lesion. Our results suggest that pre-surgical mapping of cortical function with fMRI can be unreliable in the presence of a vascular lesion and can lead to false-negative results. In such cases, direct measures of electrophysiological activity, such as electrocorticography, scalp EEG and MEG should be preferred.

Keywords: Functional imaging, stroke, electrical stimulation, epilepsy surgery, evoked potentials

1. Introduction

In patients who are candidates for resective epilepsy surgery it is important to localize eloquent cortex in relation to epileptogenic tissue to preserve cognitive and sensorimotor function. Functional magnetic resonance imaging (fMRI) is an invaluable tool for mapping brain function due to its high spatial resolution of the whole brain and non-invasive qualities. While electrophysiological recordings such as electroencephalography (EEG) and MEG have superior temporal resolution, they are spatially under-sampled compared to fMRI and have low sensitivity to subcortical sources. For these reasons, fMRI has become the most widely used functional neuroimaging method. It has been employed in pre-surgical mapping of visual,
somatosensory and motor function [1–3]. In many comprehensive epilepsy centers, it has replaced the Wada test for determination of cerebral dominance for language and memory [4, 5]. fMRI is used pre-operatively to assess the risks and benefits of surgery, and intra-operatively to inform cortical stimulation and determination of resection margins.

Blood oxygen level dependent (BOLD) fMRI signals measure the ratio of non-paramagnetic oxygenated hemoglobin to paramagnetic deoxygenated hemoglobin [6, 7]. Changes in fMRI signal arise from changes in hemodynamic variables associated with neuronal activity, including: cerebral blood flow, cerebral blood volume, and cerebral rate of oxygen consumption [8]. Thus, fMRI is an indirect measure of neuronal activity and depends on the close coupling between neural activity and hemodynamic changes.

In healthy controls, fMRI activation is correlated with the amplitude of electromagnetic responses [9] and reflects the local neurophysiology [10]. However, in the lesional hemisphere of stroke patients, fMRI has a reduced signal compared to MEG responses to electrical stimulation of the median nerve. Similarly, BOLD fMRI and cerebral blood volume-weighted fMRI have low covariance in the lesional hemisphere of stroke rat models while the unaffected hemisphere remains correlated. It is unclear how well normal neurovascular coupling is preserved in patients with vascular lesions and whether neuronal processing occurs in the absence of positive fMRI evidence.

In the present study, we used fMRI to localize somatosensory function pre-surgically in a patient with a large perinatal vascular lesion. To assess the validity of the hemodynamic response, we used invasive electrocorticography (ECoG) measurements and electrical cortical stimulation (ECS) measurements to confirm the presence or absence of somatosensory areas in the lesional hemisphere. Results show electrophysiologically active functional sites where fMRI did not show functional activity.

2. Case report

A 15 year-old left handed girl completed functional mapping procedures as part of epilepsy surgery planning. She presented with a history of perinatal stroke, mild cerebral palsy, and refractory partial epilepsy since 8 yr of age. The patient underwent left frontal resection at 12 yr of age resulting in seizure cessation until 14 yr of age. Seizures increased in intensity and duration from 14 to 15 yr of age, and she experienced 1 cluster of 2–3 seizures every 2–6 weeks at 15 yr of age. Video-electrocorticography monitoring localized seizure onset to the left centro-temporal region, and the patient was referred for additional ECoG monitoring.

The patient had moderate impairment of strength and fine motor skills on the right side. Sensory exam was normal for light touch and cold but proprioception was slightly impaired on the right. A structural magnetic resonance imaging (MRI) was consistent with a left MCA infarct and left cerebral hemiatrophy and leuko-encephalomalacia involving insular, posterior frontal and parietal regions. The Wada procedure demonstrated right hemisphere dominance for language and memory function. As part of surgical planning, the patient underwent four methods of functional mapping: a) fMRI, b) evoked potential mapping (SSEP) using ECoG recordings, c) bedside ECS, and d) intra-operative ECS. See Table 1 for a comparison of peri-lesional functional mapping results.

2.1. BOLD fMRI mapping

Functional MRI data were acquired three months prior to epilepsy surgery as part of pre-surgical testing. fMRI data were acquired on a Siemens Allegra 3T head-only scanner. Functional BOLD signals were measured using a T2*-sensitive echo-planar imaging sequence (TR = 3000 ms, TE = 25 ms, flip angle 90 degrees, 3 × 3 × 3 mm voxel dimensions, FoV (field of view) = 256 mm). After the functional image acquisition, a sagittal 3D T1-weighted volume (MPRAGE) was acquired (TR = 2530 ms, TE = 3.25 ms, flip angle: 7 degrees, slice thickness = 1.3 mm, FoV = 250 mm). The patient had moderate impairment of strength and fine motor skills on the right side. Sensory exam was normal for light touch and cold but proprioception was slightly impaired on the right. A structural magnetic resonance imaging (MRI) was consistent with a left MCA infarct and left cerebral hemiatrophy and leuko-encephalomalacia involving insular, posterior frontal and parietal regions. The Wada procedure demonstrated right hemisphere dominance for language and memory function. As part of surgical planning, the patient underwent four methods of functional mapping: a) fMRI, b) evoked potential mapping (SSEP) using ECoG recordings, c) bedside ECS, and d) intra-operative ECS. See Table 1 for a comparison of peri-lesional functional mapping results.

<table>
<thead>
<tr>
<th>Method</th>
<th>Response</th>
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<tbody>
<tr>
<td>BOLD fMRI</td>
<td>No BOLD fMRI response in peri-lesional area.</td>
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<tr>
<td>ECoG SSEP</td>
<td>Positive evoked responses in two electrode pairs (e1, e2) located in peri-lesional area</td>
</tr>
<tr>
<td>Bedside ECS</td>
<td>Positive responses in two electrode pairs (e6-7, e8-9) located in peri-lesional area</td>
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<tr>
<td>Intra-op ECS</td>
<td>Positive sensory sites identified in peri-lesional frontal lobe</td>
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Table 1 Peri-lesional responses to right somatosensory stimulation

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During the active period, the back of the patient’s hand was stroked with a foam pad paced at 1 Hz. During rest periods, the patient’s hand remained rested and supported by a pillow.

Functional MRI data were preprocessed using FSL (www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: motion correction using FLIRT [11], non-brain removal, spatial smoothing using a 5-mm full width half-maximum Gaussian kernel, grand-mean intensity normalized, and high-pass filtering at sigma = 50 sm, and pre-whitening using FILM [12]. MATLAB (The Mathworks, Natick, MA) was used for time-series statistical analysis using local autocorrelation correction. Z (Gaussianised T/F) statistic images were thresholded for sensory > rest using GRF-theory-based maximum height thresholding with a corrected significance threshold of $p < 0.05$.

Region of interest (ROI) analysis was carried out using FEATQuery (FMRI Expert Analysis Tool), part of FSL. ROIs were placed in the somatosensory cortex of each hemisphere. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$ [13].

Functional MRI results (Fig. 1a) show normal organization of somatosensory function for the unaffected left hand. However, somatosensory function for the affected right hand showed intra- and inter-hemispheric reorganization to the ipsilateral secondary sensory area and contralateral middle temporal lobe (Fig. 1b). Block-averaged time courses of BOLD signal change are presented for each ROI in the affected and unaffected hemispheres (Fig. 2). The unaffected hemisphere shows a change in BOLD signal to stimulation of the contralateral hand, while there is no change in BOLD signal for the affected hemisphere.

2.2. Intracranial evoked response mapping

The patient underwent ECoG monitoring with coverage in the left hemisphere. Subdural arrays of platinum electrodes embedded in silastic sheeting, 2.3 mm exposed diameter, spaced 10 mm center-to-center, were placed according to clinical criteria. Four depth electrodes were used with 8 contacts spaced 5 mm center-to-center. Nicolet amplifiers recorded 128 electrodes at 512 Hz sampling rate. Screws in the skull served as reference and ground.

SSEPs were measured from ECoG recordings. An automated tap was delivered to the patient’s left and right thumb and index fingers at 1 Hz frequencies for 800 trials. Data were analyzed using MATLAB and EEGLAB toolbox (sccn.ucsd.edu/eegeb). Raw voltage signals were downsampled to 400 Hz. Epochs were measured at intervals of ~200 ms and 700 ms following stimulus, averaged, bandpass filtered from 0.1 – 50 Hz, and baseline corrected. SSEP analysis showed that stimulation of the right thumb and index finger resulted in amplitude changes for 5 out of 128 electrodes (Fig. 1c), including two peri-lesional electrodes (e1 and e2), and three depth electrodes more remote from the lesion area. There was no spatial correspondence between SSEPs and fMRI (Fig. 1c).

2.3. Cortical stimulation mapping

Bedside ECS mapping used a constant current output, pulse width of 500 μs, pulse frequency of 50 Hz, and maximum pulse train duration of 5 s. The stimulus current was manually controlled from 5 to 15 mA. Electrical stimulation was applied to adjoining electrode pairs, and the patient reported sensory changes. Two positive sensory sites were identified as a result. The patient described a sensation in the right head/torso and right leg in response to stimulation of e6-7 and e8-9, respectively (Fig. 1d). These positive sites were spatially adjacent to those showing evoked responses to tapping of the right hand (e1 and e2). In addition, intra-operative ECS was conducted using a Grass S-12 Isolated Biphasic Stimulator with a constant current output, pulse width of 500 μs, pulse frequency of 50 Hz, and maximum pulse train duration of 5 seconds. The stimulus current was manually controlled from 2.5 to 8.5 mA. Motor and sensory changes in response to stimulation were monitored throughout the left frontal lobe resection, with the mesial and lateral margins defined by functional boundaries. This resulted in preservation of function, although sparing of residual epileptogenic cortex may have contributed to only modest gains in seizure control postsurgically.

2.4. Visualization of mapping methods

Electrodes were localized on the cortical surface using in-house software [14] and manual identification using T1 images acquired after implantation of electrodes. The patient’s pre-operative T1 images, electrode coordinates, and fMRI maps were nonlinearly registered to a MNI template using the DARTEL.
Fig. 1. Comparing somatosensory mapping results for fMRI, ECoG SSEP, and ECS. (a) Somatosensory fMRI results for unaffected left hand and (b) affected right hand. Functional MRI of right hand shows intra- and inter-hemisphere reorganization. (c) ECoG SSEP hits for right sensory stimulation at implanted electrodes, with overlay of right hand sensory fMRI results. No fMRI activation is visible near electrodes showing SSEP responses. (d) Cortical stimulation hits for right sensory stimulation at implanted electrodes, with overlay of right hand sensory fMRI. No fMRI activation is visible near electrodes showing ECS hits. (e) ECoG SSEP averaged waveforms for right thumb and right index finger at electrode locations depicted in C.
Fig. 2. Representative block-averaged time courses for (a) unaffected and (b) affected hemispheres. ROIs were placed over somatosensory cortex. Contra-lateral somatosensory stimulation, depicted in gray, was applied for 18 seconds. (a) The unaffected hemisphere shows a positive BOLD response ($p < 0.05$). (b) The affected hemisphere shows no BOLD response to somatosensory stimulation.

algorithm via SPM [15]. Somatosensory mapping results from fMRI, ECoG SSEP, and bedside ECS were overlaid on T1 images acquired pre-operatively (Figs. 1c and 1d).

3. Discussion

Four methods of the left hemisphere functional brain mapping were compared in a patient with a perinatal left MCA stroke. All electrophysiological and cortical stimulation methods localized somatosensory function in the lesional area of the left hemisphere, however, fMRI failed to detect sensory function in the affected hemisphere. These findings caution against the sole use of fMRI for functional mapping in the vicinity of prior vascular insults.

The discrepancy between hemodynamic and electromagnetic mapping results may be attributed to vascular changes altering the neurovascular coupling that contributes to the fMRI signal. Normal age-related vascular changes, such as atherosclerosis, can result in a breakdown in neurovascular coupling [16]. Older adults compared to younger adults have a decreased BOLD fMRI signal amplitude [17, 18] and spatial extent of activation [17, 19], despite no apparent age-related difference in neuronal activity. Thus, the differences in fMRI signals can be partly attributed to vascular changes rather than underlying neuronal activity.

Alternatively, a perinatal stroke and previous resection may lead to noisier and/or more unstable signals due to open space in peri-lesional fMRI voxels. A decreased signal to noise ratio in fMRI would result in less voxels with significant activation and explain the absence of fMRI activation in peri-lesional areas. This is supported by findings that older adults with age-related vascular differences compared to younger adults have increased levels of noise in the presence of similar signal amplitudes [19, 20].

It’s possible that the fMRI task design or analysis methods led to the absent fMRI response in the peri-lesional area. We used a relatively shorter epoch (18 seconds) for fMRI mapping as reflected in current clinical practice. Since fMRI responses are slow to change, too short of a task epoch can result in overlap between fMRI responses and lead to false negative results. However, we do not believe the findings are due to task design or analysis methods, since the methods used show normal activation in the contra-lesional hemisphere, which serves as a control comparison. False negative responses can also occur from fMRI activation maps not accounting for negative BOLD responses. Although not as common, a negative BOLD response can sometimes reflect increased neuronal activity [21]. However, this cannot account for our current finding, since the BOLD signal in the peri-lesional region is neither positive nor negative.

It is important to note that our case presented sensory impairment that could have limited her ability to participate in the task and thus a lack of fMRI activation. However, the corresponding author was present during mapping procedures and the patient reported feeling somatosensory stimuli and completed tasks successfully. As a result, we show clear evoked potential responses to somatosensory stimuli using ECoG recordings, and only the BOLD fMRI response was absent in the peri-lesional area.

The results of this study show that fMRI can result in false negative findings in patients with stroke, even in the presence of verified local functional activity. Thus, standard fMRI may be an undesirable technique to localize function near a vascular lesion. In such instances, electrophysiological and stimulation methods are more reliable for assessing the location and extent of functional tissue.
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References


