Direct intracranial stimulation and simultaneous fMRI using implanted electrodes

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**Target audience:** Foundations of fMRI, epilepsy, stimulated electrode connectivity, intracranial electrodes

**Purpose:** Cortico-cortical evoked potentials (CCEPs) use intracranial electrical stimulation and recording to study electrophysiological (EP) connectivity within the brain¹. CCEPs may help identify epileptogenic zone and networks, and guide resective surgery. In contrast, the BOLD response of fMRI can also reveal networks, either through task-related activation or in the resting-state. This study combines these methods to investigate the BOLD response to direct electrical stimulation of human cortex, and compare to direct electrical recordings from intracranial electrodes (SEEG). Although similar work has occurred in animals, to our knowledge, this is the first study in humans. Earlier stimulated fMRI of deep nuclei of Parkinson’s patients did not compare electrical activity². Our contribution is to electrically stimulate human cortex and directly compare the spatial activation patterns and strengths of BOLD response to recordings from electrodes placed throughout the brain. The context of these patients and investigation is intractable epilepsy.

**Methods:** Following routine clinical practice for intractable epilepsy requiring invasive evaluation, patients were implanted with up to 15 SEEG electrodes. Prior to explantation CCEPs were recorded while stimulating the putative lesion and control areas (1 Hz for 45 s, alternating unipolar 0.3 msec square wave pulses, currents up to 8 mA). EP connectivity was derived from the RMS of the mean waveform from 4 to 300 ms. During explantation in an intraoperative MRI suite and while under general anesthesia (sevoflurane and ketamine), with only one electrode remaining an EPI sequence was performed using a block design for stimulation (TR 2s, 32 sec blocks with 32 sec rest, four cycles, 4x4x9 mm voxels). Typically four acquisitions included stimulation of the putative lesion at low (4 mA) and high (8 or 15 mA) current, with similar control stimulation of distal contacts on electrode. FMRI analysis used AFNI. Extensive safety testing for heating using phantoms preceded this investigation.

**Results:**

Figure 1

Shown are results for one patient. Fig. 1 (best viewed in color) shows a t-statistic map thresholded at |t| > 3 ($p < .0032$). Stimulated contacts (15 mA) were in the medial left orbitofrontal lobe (arrow), deemed to be in the EZ. There is strong network activation in the limbic system, extending to hippocampus and lateral orbitofrontal lobe. There is also strong negative activation, for example bilateral motor strips. Fig. 2 correlates the CCEP activation strength at each contact-voxel against the fMRI t-value. Different colors/symbols represent different electrodes. There is a significant correlation ($p = 8.6e-6$, $r = .45$) between CCEP activity and fMRI response strength. The other two patients also show networks of positive and negative activation, with modest correlations to CCEP activity ($p = .10$ and $p = 7.2e-3$, at 8 mA.). In all subjects, fMRI activation patterns and strengths (as well as correlation with CCEP activity) were similar for 4 and 8 mA runs, but stimulating at 8 mA activated larger areas.

**Conclusion:** To our knowledge, we present the first stimulated fMRI experiment in a human, with comparison of fMRI maps to electrophysiological response. Early data shows stimulated fMRI patterns are consistent with those provided by CCEPs. Given the clinical utility of CCEPs, and the much larger spatial coverage afforded by fMRI, this technique has great potential in aiding the planning of epilepsy surgery. Furthermore, studying the results of CCEPs and fMRI in tandem can improve our understanding of both technologies.

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