Direct intracranial stimulation and simultaneous fMRI using implanted electrodes

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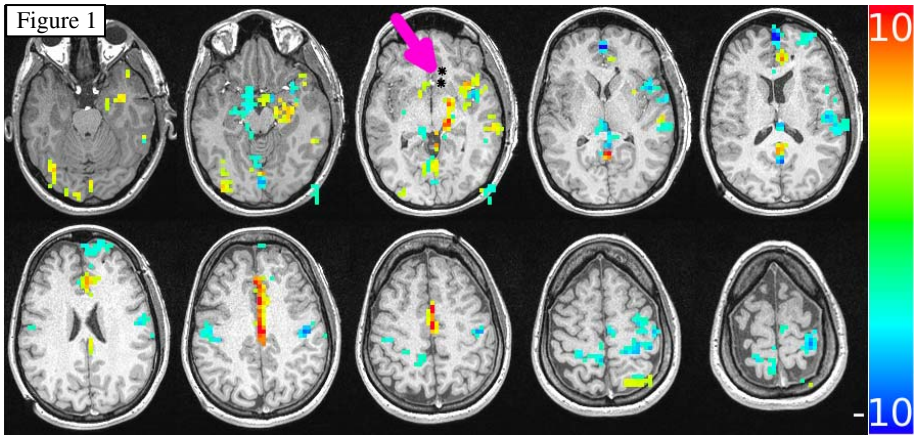
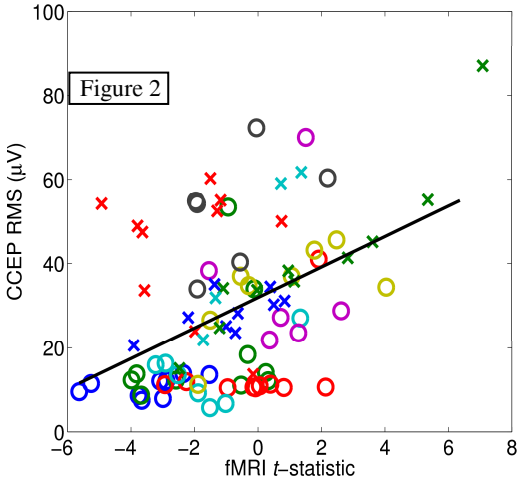
Target audience: Foundations of fMRI, epilepsy, stimulated electrode connectivity, intracranial electrodes

Purpose: Cortico-cortical evoked potentials (CCEPs) use intracranial electrical stimulation and recording to study electrophysiological (EP) connectivity within the brain[1]. 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 activity[2]. 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. IRB approval was obtained and 3 patients have been imaged to date.

Results:





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 CCEPs strength (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.

Discussion: While some patterns of stimulated fMRI networks conform to known anatomy, we observe some discordant patterns. In addition, the stimulated response of a putative EZ was seen to be both less than or greater than a control stimulation. Altogether, this new technique raised numerous questions regarding the meaning of stimulated fMRI networks. Further experiments are underway exploring the patterns and strength of stimulated networks, for example stimulated frequency, current, and event-repeated vs block paradigms. We observe the correlation was highest when CCEPs RMS was taken over longer time periods (300 ms), suggesting that fMRI protocol is more sensitive to integrative neural processes.

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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[2] Phillips, M. D., Baker, K. B., Lowe, M. J., Tkach, J. A., Cooper, S. E., Kopell, B. H., & Rezai, A. R. (2006). Parkinson Disease: Pattern of Functional MR Imaging Activation during Deep Brain Stimulation of Subthalamic Nucleus—Initial Experience. *Radiology*, *239*(1), 209-216.