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BOLD matches neuronal activity at the mm scale: A combined 7 T fMRI and ECoG study in human sensorimotor cortex

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ABSTRACT

High resolution BOLD fMRI has the potential to map activation patterns of small neuronal populations at the scale of cortical columns. However, BOLD fMRI does not measure neuronal activity, but only a correlate thereof, since it measures blood dynamics. To confirm that BOLD activation maps reflect neuronal population activity patterns, a direct comparison with neuro-electrophysiological data from the same cortical patch is necessary. Here, we compare BOLD activation patterns obtained with fMRI at 7 T to electrophysiological patterns obtained with implanted high density electrocorticography (ECoG) grids in the same patch of human sensorimotor cortex, and with similar resolution (1.5 mm). We used high spatially sampled high-frequency broadband (HFB) power from ECoG, which reflects local neuronal population activity. The spatial distribution of 7 T BOLD activation matched the spatial distribution of ECoG HFB-power changes in the covered patch of sensorimotor cortex. BOLD fMRI activation foci were located within 1–3 mm of the HFB-power ECoG foci. Both methods distinguished individual finger movement activation within a 1 cm cortical patch, revealing a topographical medial to lateral layout for the little finger to index to thumb. These findings demonstrate that the BOLD signal at 7 T is strongly correlated with the underlying electrophysiology, and is capable of discriminating patterns of neuronal population activity at a millimeter scale. The results further indicate the utility of 7 T fMRI for investigation of intra-area organization of function and network dynamics.

Introduction

Blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has the potential to map activation patterns of small scale neuronal ensembles such as cortical columns (Yacoub et al., 2007, 2008) or cortical layers (Goense et al., 2012; Koopmans et al., 2011; Olman et al., 2012), as shown by a number of studies, predominantly in human primary visual cortex and at high field strength (7 T). Hemodynamic changes are influenced by different components of the neurophysiological signal (Hermes et al., 2012a; Magri et al., 2012; Scheeringa et al., 2011). As inferences are drawn from fMRI BOLD activation about the functional anatomy at such a fine scale, a sound understanding of the spatial relationship between neuronal activity and evoked BOLD responses becomes critically important.

Previous research using BOLD fMRI or electrical stimulation has demonstrated that activations from individual finger movements can show large overlapping regions in primary motor cortex (Indovina and Sanes, 2001; Rao et al., 1995; Sanes et al., 1995; Schieber and Hibbard, 1993). When considering the *foci* of the differential activation (contrast map of activation of the movement of a finger versus the movements of the other fingers), several BOLD fMRI studies have observed a fine scale topographic organization in primary motor cortex (Beisteiner et al., 2001; Dechent and Frahm, 2003; Hlustik et al., 2001; Kleinschmidt et al., 1997). Single neuron recordings in non-human primates have indicated that different fingers have largely overlapping representations in motor cortex (Schieber, 2001; Schieber and Hibbard, 1993), suggesting that the fine-scale topographic organization in the BOLD response may not be present in the neuronal response. Previous electrocorticography (ECoG) work, however, has shown that separate finger representations exist in populations of neurons spaced ~1 cm apart (Miller et al., 2009b), and that individual finger movements can be decoded adequately using ECoG (Chestek et al., 2013; Kubanek et al., 2009). We hypothesize that the BOLD signal measured with high-resolution fMRI measures these individual finger representations present specifically at the neuronal population level. Moreover, we hypothesize that the high-resolution BOLD signal further corresponds to neuronal population activity at the even finer scale of mm.

Most studies that have combined BOLD fMRI with intracranial electrophysiology have focused on the temporal aspect of both modalities, comparing changes in BOLD activity with changes in electrophysiological

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measures such as event-related potentials (Huettel et al., 2004) or spectral power changes (Ekstrom et al., 2009; Engell et al., 2012; Goense and Logothetis, 2008; Hermes et al., 2011, 2014; Khursheed et al., 2011; Lachaux et al., 2007; Logothetis et al., 2001; Meltzer et al., 2008; Mukamel et al., 2005; Ojemann et al., 2010; Scheeringa et al., 2011; Vansteensel et al., 2010). These studies have concluded that BOLD amplitude correlates most strongly with changes in the high frequency broadband power (HFB-power, also often referred to as 'high gamma'), a frequency range associated with local neuronal processing, and correlated with local spike rate (Crone et al., 1998; Manning et al., 2009; Miller et al., 2009a; Nir et al., 2008; Ray and Maunsell, 2011; Siero et al., 2013). Studies focusing on the exact spatial correspondence between hemodynamic and electrophysiological measures generally compared fMRI with neurophysiology over different sites that were about a centimeter apart (Brovelli et al., 2005; Disbrow et al., 2000; Hermes et al., 2012a; Lachaux et al., 2007), not allowing to test whether differences in BOLD changes from millimeter to millimeter in an individual subject reflect noise, or measure hemodynamic changes, or are an indication of neuronal activity patterns.

It thus remains unclear whether BOLD and HFB-power changes correspond on a much finer spatial scale. Here we investigate the spatial specificity of BOLD fMRI as compared to HFB-power changes in the human primary sensorimotor system, in the case of individual finger movements. The approach in the current study was to compare differential activation maps obtained with state of the art 7 T BOLD fMRI pre-operatively, and high-density small-sized ECoG grids after implantation. BOLD fMRI at 7 T allows for high spatial resolution and subsecond sampling times, and, therefore, efficient mapping of finger-specific BOLD signal changes. Further, BOLD fMRI at 7 T has an increased capillary specificity compared to lower field strengths, and is therefore more weighted towards the hemodynamic demands of active neuronal tissue (Yacoub et al., 2001). A prerequisite for comparing BOLD fMRI activation with ECoG HFB-power for a fine spatial functional organization is to have sufficient and similar spatial resolution in both techniques. The employed high-density ECoG grids (electrode-to-electrode distance 3 mm, diameter 1 mm) have a spatial resolution that is on the same order as the 7 T BOLD fMRI measurements (1.5 mm). The activity patterns in HFB-power of the high-density ECoG grids are taken as reflecting the organization of neuronal populations in sensorimotor cortex. This setup allows for a direct link between techniques and evaluation of the BOLD spatial specificity with respect to the underlying electrophysiology in the case of individual finger activations.

Materials and methods

Subjects and procedure

Three right handed subjects (1 female, 2 male; mean age: 27 years; range: 19–43) participated in the study, approved by the Institutional Review Board of the Utrecht University Medical Center, after giving written informed consent in accordance with the Declaration of Helsinki 2008. All subjects had normal hand function and were scheduled for ECoG grid implantation for the clinical purpose of epilepsy monitoring. The pathological region of the subjects did not extend to the sensorimotor cortex. On average 125 electrodes were implanted, 32 of which corresponded to a high resolution grid of 8×4 electrodes located on the left sensorimotor cortex (see Fig. 1B), implanted for medical research purposes. The high resolution grid has an inter-electrode distance of 3 mm center-to-center (pitch) and each electrode has a spherical measurement surface of ~1 mm diameter per electrode. For each subject, the electrodes were localized using a method presented previously (Hermes et al., 2010); the electrodes were identified on a high resolution CT scan (Philips Tomoscan SR7000) and projected to a cortical surface rendering that was generated from a presurgical T1-weighted (T1w) anatomical MRI scan that was acquired with a 3 T MR system (Philips 3 T Achieva, Best, The Netherlands): 3D TFE, an isotropic voxel size of 1 mm^3, TR/TE = 8.4/3.8 ms, flip angle = 8°, and FOV = $225 \times 225 \times 175$ mm^3. Fig. 1B shows the 3D rendering of the T1w anatomical scan, together with the projected electrode grid, for subject 1. Unfortunately, the electrode grid for subject 3 did not cover the multiple individual finger representations of sensorimotor cortex, leading to the exclusion of this subject from further analysis. Functional and anatomical MRI data were obtained using a 7 T MR System (Philips 7 T Achieva, Cleveland, Ohio).

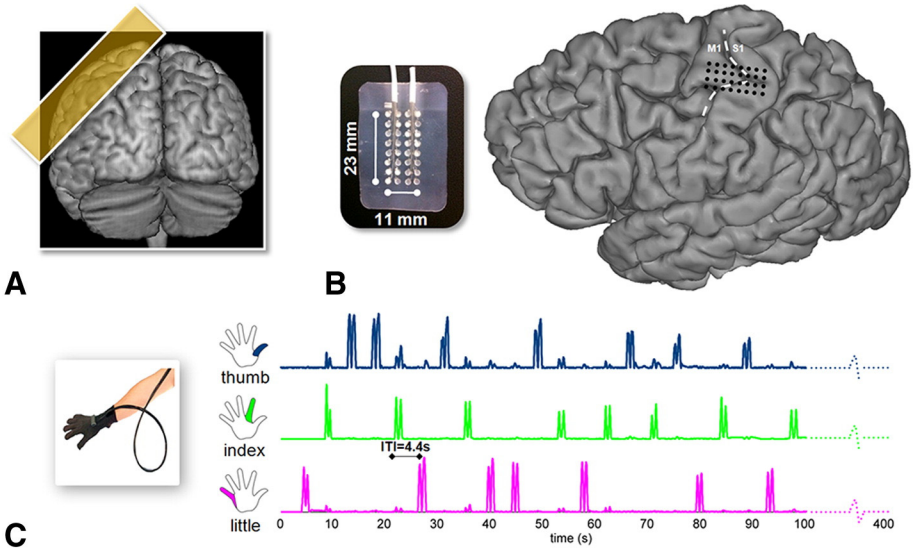

Fig. 1. Overview of the experimental setup: comparing BOLD and ECoG HFB-power activation maps for individual finger movements. We acquired (A) presurgical BOLD fMRI at 7 T and (B) electrophysiological data using intra-cranial high density ECoG grids post-implant from the same patch of sensorimotor cortex in the same subjects. Panel B shows the position of the ECoG grid in black for subject 1. The white line indicates the central sulcus. (C) Subjects performed a finger movement task; on a visual cue the subjects were instructed to move their thumb, index and little finger in a randomized event-related design. One trial consisted of two flexions of the appropriate finger. The inter-trial interval (ITI) between two successive finger movements was 4.4 s as indicated in panel C. In both BOLD fMRI and ECoG sessions individual finger movements were recorded using a digital dataglove (see time courses in panel C). The dataglove recordings were used to compute BOLD and ECoG HFB-power differential activation maps for each finger.