Feasibility of detecting differential layer specific activations in humans using SE BOLD fMRI at 7 T

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Background:

Studying layer-dependent neural activity is important because in all species cells, cortical afferents and projection neurons are arranged with reference to different depths in the gray matter. A basic understanding of the different computations of the underlying neuronal circuitry can be best revealed through investigations of inter-laminar connections. Like studying the basic characteristics of cortical columns, the study of cortical layers is extremely important. Thus far, there have been several studies investigating laminar specificity (1-6).The investigation of layer specific functional activation in humans has been demonstrated using GE BOLD at 3 T (4). To date, however, *differential* layer specific activation (i.e. paradigm dependent layer profiles) has not been demonstrated in *any* model. Prior observations of layer specific activations could be attributed to vascular density differences between the layers observed via the vascular dependent BOLD response. However, differential layer specific activation would suggest the intrinsic ability of fMRI to observe basic *neuronal* inter-connections. The development of high field magnets has proven beneficial for functional MRI with respect to spatial specificity and functional sensitivity, offering significant advantages over conventional lower field studies. In this work we aimed to capitalize on these advantages at high fields for the purpose of demonstrating layer and differential layer specific functional activations in humans.

Methods:

Studies were conducted on 2 subjects using a 7 T magnet (Magnex Scientific, UK) equipped with a Siemens console (Erlangen, Germany) and Avanto body gradient set capable of 45 mT/m and a maximum slew rate of 200 T/m/s. BOLD fMRI data were acquired using a 2D T_2 weighted slab selective reduced FOV acquisition (TR/TE 2000/50 ms). Single shot EPI readouts were employed using: 0.5 mm in plane resolutions, matrix size: 22 x 384, FOV: 1.1 x 19.2 cm^2 and a 2.5 mm slice. A small quadrature surface coil was used for reception and a separate large quadrature coil was used for transmission. A coronal slab was selected in order to better visual activations through the layers, furthermore, since the cortical thickness is only a few millimeters, the phase FOV (SI direction) could be cut to ~ 1 cm, permitting single shot EPI with 0.5 mm in plane resolutions. Subjects used a bite bar to minimize motion. In addition, image registration was used to correct small amounts of motion within and between scans. The visual stimulus (presented via a rear projection setup) consisted of flickering hemi-field checkerboards alternating between the left and right side of the display in 12s blocks. On alternate scans subjects were cued either to monitor the fixation point for size changes, or to monitor the checkerboards for brief pauses in the animation. For anatomical scans, an MP-RAGE pulse sequence was used with 1 mm isotropic resolutions, TR/TI; 3s/1.5s. A proton-density weighted volume, acquired with parameters identical to the MP-RAGE acquisition, but without the inversion pulse, was used to flatten the T_1 images (7) (allowing for automated tissue segmentation).

Results:

Robust BOLD activation was achieved from single 4 min. fMRI scans, which were repeated several times to increase sensitivity. Using only anatomical metrics generated from automated tissue segmentation of the flattened MPRAGE data, estimates of the activation profiles through the gray matter were computed and are shown in the figure below for 1 subject. Each voxel was assigned a 'partial volume' value (i.e. 1 = white matter, 2 = gray matter, 1.5 = 50% gray/white matter) and a distance value (with 0 marking the center of the gray matter, negative values approaching the white matter surface, and more positive values approaching the gray matter surface). To generate the activation profiles shown below, voxels in V1 (defined by retinotopy), in the pre-selected gray matter slab, were binned/averaged with other voxels having similar relative distances with respect to the middle of the gray matter and the surfaces. Additionally, only voxels quantified as being mostly gray matter were used in the plot. *No* activation dependent requirements (only anatomical) were used in the analysis. The plot shows an increase in the activation when the center of the gray matter is approached and an even larger increase at the gray matter surface (observable on **single** scans), suggesting a sensitivity to both the middle layers and the cortical surface, in agreement with animal studies, and in apparent disagreement with the only human study on the topic (4). In the presence of large vein contamination, differential maps of layer specific functional responses (due to attention) would in the worst case be spatially biased toward superficial layers. The differential activation would, however, still distinguish between input and output layers of the cortex. Interestingly, though, we did not observe any significant laminar or global level changes in V1 activity due to a shift in attention. Feedback effects in V1 have been controversial (8), and, with this paradigm, the global changes in V1 (related to attention) are not significant and consistent with the lack of any layer specific functional differences. We are currently pursuing alternate paradigms which may induce measureable feedback effects in V1.

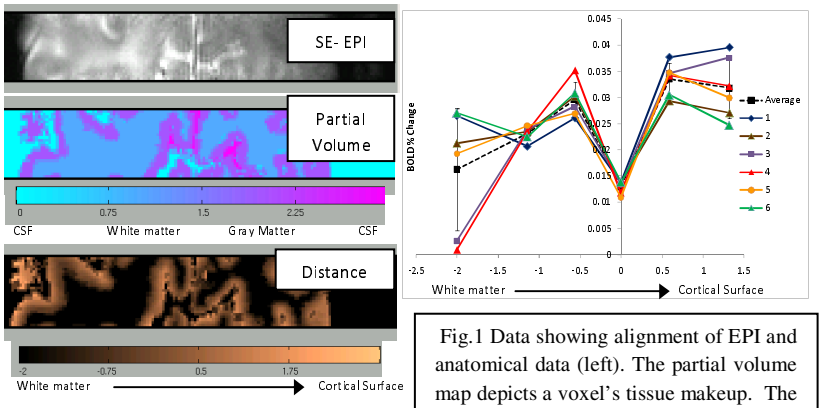

Fig.1 Data showing alignment of EPI and anatomical data (left). The partial volume map depicts a voxel's tissue makeup. The distance map shows a voxel's relative distance to the white matter and/or cortical surface. The plot (above) represents the profile through the gray matter of BOLD changes (from 6 scans) for voxels which are mostly gray matter. Peaks are present near the middle of the gray matter *and* on the cortical surface and are reproduced between scans.

References: **1.** Goense et al 2006 MRI. **2.** Harel et al 2006 NImage. **3.** Zhao et al 2006 Nimage. **4.** Ress et al 2007 NImage **5.** Lu et al 2004 MRM. **6.** Yang et al 1998 PNAS. **7.** Van de Moortele et al 2007. **8.** Posner et al 1999 PNAS.

Acknowledgements: R01MH70800, R01EB000331, P41-RR008079, P30 NS057091, The Keck Foundation, The MIND institute.