Laminar-specific output- to input-layer connections between cortical areas V1 and MT observed with high-resolution resting-state fMRI

J. R. Polimeni[1], B. Fischl[1,2], D. N. Greve[1], and L. L. Wald[1,3]

[1]Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Charlestown, MA, United States, [2]Computer Science and AI Lab (CSAIL), Massachusetts Institute of Technology, Cambridge, MA, United States, [3]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, United States

Introduction: Accelerated image encoding and increased sensitivity afforded by highly-parallel receive arrays and ultra high-field (7T) systems have enabled sub-millimeter isotropic resolution studies of the functional architecture of the human brain. Several studies have imaged the spatial patterns of columnar systems along a small, flat section of cortex, demonstrating that the specificity of the hemodynamic response is controlled *tangential* to the cortical surface at a local level sufficient to resolve columnar features [1,2]. Further studies have noted that cortical Layer IV exhibits a stronger BOLD response than other layers [3,4], suggesting that the BOLD signal may contain a laminar-specific component. The relative increase at Layer IV could, however, simply reflect the higher CBV in this layer rather than local, laminar-specific control of CBF. To distinguish these two scenarios with fMRI, a laminar-specific stimulus is needed, rather than one which broadly drives all neurons in a cortical column.

In this study, we demonstrate a laminar-specific BOLD response using resting state measurements of functional connectivity within visual cortex by exploiting the known anatomical connectivity pattern between Layer II/III in cortical area V1 and Layer IV in area MT previously observed by invasive studies [5]. The presence of known "output layer to input layer" connections (V1 Layer II/III to MT Layer IV) and expected lack of the reverse connection (MT Layer II/III to V1 Layer IV, or "input to input" (IV to IV) or "output to output" (II/III to II/III) connections between V1 and MT are examined using 0.75 mm isotropic fMRI at 7T. Examination of the laminar correlation matrix between each combination of layers in V1 and MT shows large correlations between the shallowest layer abutting the pial surface, presumably reflecting correlated BOLD signals in or around large draining veins, but also a pattern of increased "output to input" resting-state correlations compared to the other laminar combinations in agreement with the known anatomical connections between V1 and MT. The laminar-specific resting state correlations demonstrate the ability of high-resolution rs-fMRI to probe laminar-specific connections and provide evidence that the BOLD signal is controlled, to some degree, on the laminar level.

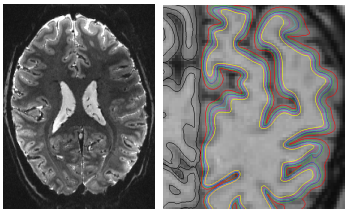

Fig. 1: (L) Example 0.75 mm EPI slice (10 averages). (R) Family of laminar surface reconstructions.

Methods: Four healthy subjects were studied with a 7T Siemens scanner equipped with AC84 head gradients (80 mT/m, 400 T/m/s) and a custom-built 32-channel receive array. The BOLD acquisition consisted of 750μm isotropic resolution GE single-shot EPI with 52 oblique-transverse slices parallel to the calcarine sulcus, 0.75-mm thick, no slice gap with TR/TE/flip=4000ms/27ms/90º, FOV=192mm×192mm, 256×256 matrix, 6/8 partial Fourier, bandwidth=1502 Hz/pixel, *R*=3 GRAPPA acceleration yielding an effective EPI echo-spacing of 0.27 ms. Four 5 min 20 sec scans were acquired each session with eyes-open fixation.

The position of area MT was identified with a 5 min functional localizer with a standard low-contrast motion stimulus. The position of V1 was predicted in each subject offline with a surface-based atlas [6]. The resting-state data was corrected for slice timing, motion corrected, then temporally low-pass filtered with a cutoff of 0.08 Hz. Average signals from the whole brain, ventricals, and white matter together with the motion parameters were regressed out of the time series data [7]. For each subject, surface reconstructions of the inner and outer boundaries of the cortical gray matter were generated by FREESURFER from 1 mm MPRAGE data collected in a separate 3T scan session, generating a family of 11 intermediate surfaces evenly spaced throughout the cortical depth. The functional volumes were aligned to the surfaces with a boundary-based registration method [8] and functional voxels at each depth were painted onto its corresponding surface. Thus the correlation between two areas, such as left V1 to left MT could be computed for any combination of cortical depths, resulting in an 11×11 laminar correlation matrix between the areas. To better show off-diagonal asymmetries, a given row and column were normalized to their diagonal element. The procedure started in the top left corner (pial layer to pial layer) and was repeated for each remaining sub-matrix. This processing removed symmetric offsets in the matrix. To quantify significance of the effect of depth on the matrix pattern, a permutation test on each data set was performed by randomly shuffling the depths independently at each surface vertex.

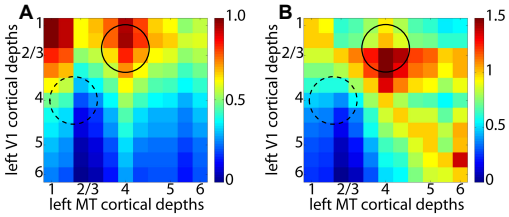

Fig. 2: Laminar correlation matrices. Solid circle indicates location of V1 output and MT input, and dashed circle indicates location of inverted connection. (A) Normalized V1 to MT correlation. (B) Matrix normalized to diagonal elements.

Results: Fig. 2 demonstrates the pattern of laminar correlations between V1 and MT, which exhibits a local peak at the position representing the known output Layer II/III of V1 to the input Layer IV of MT. Although the peak is seen in the data prior to the removal of symmetric offsets (Fig. 2A), removal of the diagonal symmetric offsets shows that the peak value in the asymmetric component is a correlation between V1 at ~Layer II/III and MT at ~Layer IV (output layer of V1 to input layer of MT) and that little correlation exists for the reversed connection. The permutation test (200 trials) indicated that the correlations were highly significant (p<0.01), although more trials may be needed for increased significance estimation accuracy. Fig. 3 shows that this input-output pattern was absent from the inter-hemispheric correlation computed between left V1 and right V1.

Discussion: The observed bias in the correlations between V1 and MT towards the lamina of known anatomical connections suggests that the BOLD signal contains some layer-specific component attributable to laminar-level blood flow regulation. While the inputs and outputs are known to be segregated into specific layers, the anatomical connections between V1 and MT are also known to be organized topographically [9] and therefore should increase if correlations were measured only in retinotopically corresponding locations. The known connection "signature" between output layers in one cortical area to input layers in another provides the equivalent role of a precise laminar specific activation in fMRI allowing us to directly test laminar-specific CBF control, and strengthens earlier findings suggesting peak BOLD signals in Layer IV. This laminar functional connectivity approach could also be used to infer the directionality of connections observed in rs-fMRI.

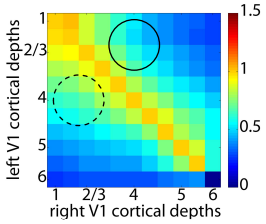

Fig. 3: Laminar correlation matrix with diagonal normalization for left V1 to right V1.

References: [1] Yacoub *et al.* (2008) *PNAS* 105:10607-12. [2] Cheng et al. (2001) *Neuron* 32:359-74. [3] Zhao *et al.* (2004) *MRM* 51:518-24. [4] Koopmans *et al.* (2009) *Proc ISMRM* 1558. [5] Felleman & Van Essen (1991) *Cereb Cortex* 1:1-47. [6] Hinds *et al.* (2009) *NeuroImage* 46:915-22. [7] Van Dijk *et al.* (2008) *Soc Neurosci Abs* 885.24. [8] Greve & Fischl (2009) *NeuroImage* 48:63-72. [9] Weller & Kaas (1983) *J Comp Neurol* 220:253-97.

Acknowledgements: Supported by NCRR P41 RR14075 and NIBIB R01EB006847.