

Identifying common-source driven correlations in resting-state fMRI via laminar-specific analysis in the human visual cortex

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Introduction: Functional connectivity analyses in fMRI provide a means to infer anatomical connections in human subjects by correlating “resting-state” or spontaneous fMRI (rs-fMRI) signals between brain regions [1]. A limitation of the approach is the difficulty of differentiating a true connection between two cortical areas from correlations arising from a common source that drives the two areas synchronously. For example, inter-hemispheric rs-fMRI correlations are often observed from human area V1 in one hemisphere to its contralateral counterpart [2,3], despite the lack of callosal connections in human V1 [4]. These correlations are perhaps attributable to common feed-forward signals driven from the visual input at the retina and conveyed via the LGN and require, at best, regression using a common source model to detect.

In this work, we utilize high-resolution (750 μ m isotropic voxels) 7T rs-fMRI together with laminar analysis on the folded cortex [5] to assess the ability of laminar-specific comparisons to differentiate resting state correlations due to direct anatomical connections from correlations arising from a common-source input. For example, where cortical connections in the visual system are known they are expected to have an “output layer to input layer” signature. We show that the Layer II/III “outputs” of human V1 are more highly correlated to the Layer IV “inputs” of area MT than to other layers, as expected from the known laminar-specific anatomical connections in non-human primates [6]. In contrast, we show that the V1 to contralateral V1 correlations do not show this signature: each layer of V1 within one hemisphere is maximally correlated with the same layer in the V1 of the opposite hemisphere, as would be expected from (i) a common drive from the retina and (ii) similar processing within a cortical column on both hemispheres. This finding suggests that laminar analysis of functional connectivity can help identify correlations that may be attributable to indirect connections through common inputs.

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 750 μ m 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/90°, FOV=192mm \times 192mm, 256 \times 256 matrix, 6/8 partial Fourier, bandwidth=1502 Hz/pixel, R=3 GRAPPA acceleration yielding an effective echo-spacing of 0.27 ms. Four 5 min 20 sec scans were acquired each session with eyes-open fixation.

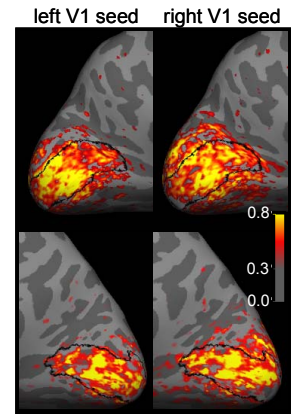


Fig. 1: Correlation maps in V1 displayed on the inflated cortical surface. Strong inter-hemispheric correlation is apparent. (Maps were smoothed for visualization.)

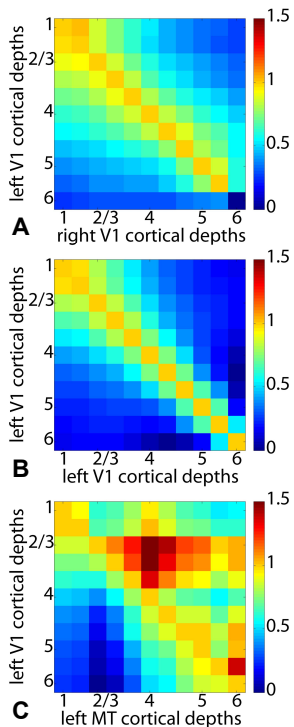


Fig. 2: Laminar correlation matrices (normalized by diagonal to remove depth offset). (A) Cross-hemisphere correlation in V1. (B) Within-hemisphere correlation in V1. (C) Within-hemisphere V1 to MT correlation.

The position of area MT was identified with a 5 min functional localizer with a standard motion stimulus. The position of V1 was predicted in each subject offline with a surface-based atlas [7]. 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, ventricles, and white matter along with the motion parameters were regressed out of the time series data [8]. 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 [9] and functional voxels at each depth were painted onto its corresponding surface. Thus the correlation between two areas, such as left V1 to right V1 or left V1 to left MT could be computed for any combination of cortical depth, resulting in an 11 \times 11 laminar correlation matrix between the areas. To better highlight 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.

Results: Fig. 1 shows strong correlations to the contralateral hemispheres in V1 when either the left or right V1 is seeded despite the lack of direct callosal connections in V1 [5]. The laminar connection matrix both within and across hemispheres in V1 ROIs demonstrated a symmetric pattern with the peak along the diagonal (see Fig. 2A & B), indicating that the BOLD signal in each layer was maximally correlated with the corresponding layer. In contrast, the laminar correlation matrix between left V1 and left MT (Fig. 2C) shows a distinct peak between the output layers of V1 (Layer II/III) and the input layer of MT (Layer IV), suggesting a direct anatomical connection. The laminar correlation matrix between right V1 and right MT showed a similar pattern. A permutation test showed a significant effect in all subjects.

Discussion: After removing symmetric biases from the pial surface, peak correlations between the known output layers of V1 and the input layers of MT can be measured with high-resolution rs-MRI with a surface-based laminar connectivity analysis. All layers within V1 are equally correlated with their counterparts in the opposite cerebral hemisphere, suggesting that no such causal relationship exists and that the cross-hemisphere correlations are likely to be due to a common input source such as feed-forward activity in the retina relayed through the LGN. Furthermore, the causality of functional connections may assist graph-theoretic analyses of brain networks by incorporating the direction of information flow between connected areas [10].

References: [1] Biswal et al. (1995) *MRM* 34:537-41. [2] Lowe et al. (1998) *NeuroImage* 7:119-32. [3] Tian et al. (2007) *NeuroImage* 36:684-90. [4] Clarke & Miklosy (1990) *J Comp Neurol* 298:188-214. [5] Polimeni et al. (2009) *Proc ISMRM* 1559. [6] Felleman & Van Essen (1991) *Cereb Cortex* 1:1-47. [7] Hinds et al. (2009) *NeuroImage* 46:915-22. [8] Van Dijk et al. (2008) *Soc Neurosci Abs* 885.24. [9] Greve & Fischl (2009) *NeuroImage* 48:63-72. [10] Hagmann et al. (2008) *PLOS Biol*

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