The Contribution of Vascular Reactivity in Layer-Specific Hemodynamic Response

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Introduction Cortical layer-specific hemodynamic responses measured with high-spatial resolution fMRI have been shown to resemble the neural response from the cortical layers (1), generating a strong interest in studying inter-laminar cortical processing of sensory neurons. However, recent reports have raised questions about whether laminar hemodynamic response and laminar neural activity are tightly coupled to each other (2,3). A possible confounding factor is the layer-specific vascular reactivity, which also affects the laminar hemodynamic response (4). To investigate the role of vascular reactivity in layer-specific hemodynamic response, we performed two cerebral blood volume (CBV)-weighted fMRI studies with visual stimulation and hypercapnic stimulation. Carbon dioxide is a potent vessel dilator and hypercapnia in normal subject can be used to access the vascular reactivity without altering the neural activity (5). By comparing the layer profile of hemodynamic response from both experiments, we can examine the contribution of vascular reactivity in the layer-specific hemodynamic response induced by visual stimulus.

Materials and Methods Three adolescent cats weighing 1.32 - 1.86 kg were used under a protocol approved by the Institutional Animal Care and Use committee at the University of Pittsburgh. Cats were mechanically ventilated and maintained under 0.7 – 0.8% isoflurane in a mixture of N_2O/O_2 = 0.65/0.35. Animals were placed inside a 9.4-T/31-cm horizontal bore magnet (Varian, Palo Alto, CA, USA) and a custom-built surface coil placed on top of the visual cortex. fMRI was acquired using four-shot GE-EPI sequence with slice thickness = 1 mm, FOV = 20 x 20 mm^2, matrix size = 128 x 128 zero-filled to 256 x 256, TE = 10 ms, and TR = 0.5 s per segment. To measure the CBV-weighted MRI signal, a bolus of 10 – 15 mg/kg of MION (Massachusetts General Hospital, Boston, MA, USA) was administrated intravenously along with ~1.5 ml/kg 10% dextran-40 solution. The visual stimulation paradigm consisted of 40 s of square-wave grating with temporal frequency = 2 Hz and spatial frequency = 0.2 cycle/degree. The hypercapnic stimulation was induced by inhaling a CO_2 mixture for 20 s, resulting in an end-tidal CO_2 reaching a maximum of 7%. Activation maps were calculated using t-Test ($p<0.05$) in STIMULATE with minimum cluster of four. To generate the CBV-weighted layer profiles in the cortical depth dimension, the average distance within quadrangular region of interests from the surface of the cortex to the gray/white matter boundary was determined in area 18 of each animal. Data were then spatially interpolated with the linear re-sampling method to average depth resolution of 78 μm. The CBV weighted signal were normalized to the minimum response of hypercapnia challenge or regular visual stimulus for each animal and averaged along the surface dimension at the same relative cortical depth.

Results and Discussion In Fig 1A, peak CBV responses span along the middle of the primary visual cortex during hypercapnia challenge for one cat. In addition, excessive responses can also be found in the pial surface outside the visual cortex, indicating the non-neural specific nature of the stimulus. Fig 1B shows normalized layer profiles of the CBV response to hypercapnia compared to the response elicited by visual stimulation within parenchyma. In spite of a small difference in the shape of the two laminar profiles, the depth of the peak responses to hypercapnia and to visual stimulation co-localized to the middle layer (~0.9 mm from the cortical surface). Therefore, although it is believed that the layer-specific hemodynamic response induced by visual stimulus represents the underlying neural activity, contribution from the vascular reactivity cannot be ignored, as both of them peaked at the same cortical depth. In conclusion, caution should be taken in interpreting fMRI data as reflecting neural responses in laminar scale.

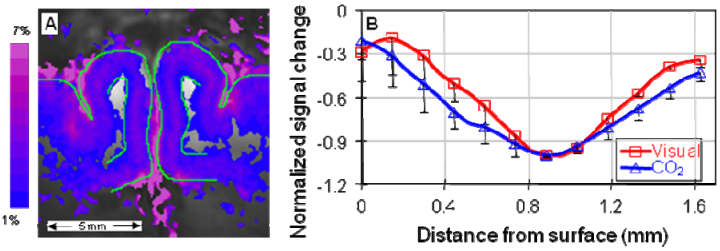

Figure 1 (A) The percentage change map of CBV weighted signal masked by t-Test ($p<0.05$) of one cat (green contour delineated part of the parenchyma) (B) Normalized layer profile of CBV weighted signal averaged across three cats (Error bar = S.E.M.)

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