Contributions of spiking activity to the fMRI response in the rat olfactory bulb

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Target Audience: fMRI scientists, clinicians and neuroscientists.

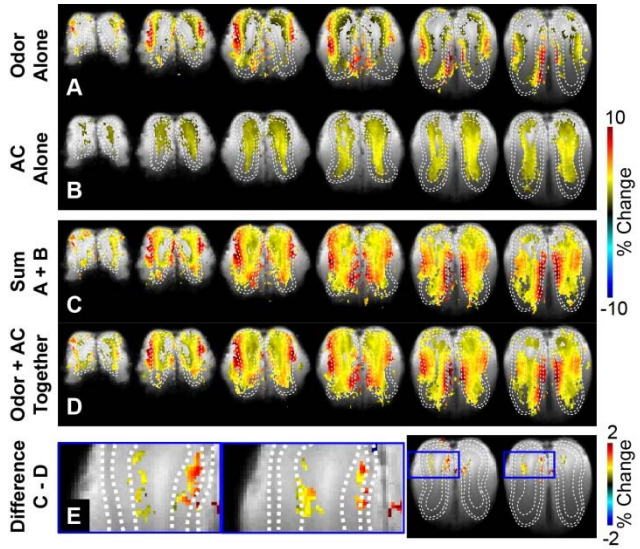

Figure 2: Group CBVw fMRI signal changes (n = 6 rats). CBV increases were observed in superficial layers for odor (A), in deep layers for AC (B) and across all layers for the sum of individual (C) and simultaneous stimulations (D). A small difference (E) is observed in layers around MCL (output layer) that may be attributed to mitral cell spiking activity. The white contours represent the inner and outer boundaries of GL and the outer boundary of MCL. Cluster level family-wise error corrected at $p < 0.01$ (A-D) and $p < 0.05$ (E).

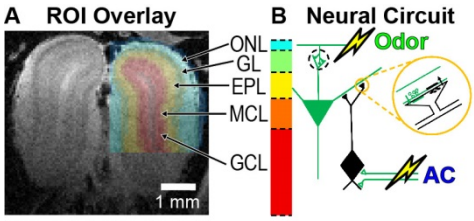

Figure 1: (A) Anatomical T2-weighted image with ROI overlay to show laminar definitions. (B) Experimental paradigm in which mitral cell spiking (green cells) increases with odor stimulation but is suppressed by AC stimulation of inhibitory granule cells (black cells).

Introduction: Activity of a neuron can be separated between the local integration of synaptic input and its translation to spiking output to target neurons. Although both processes require energy, previous studies in the cortex observed that the hemodynamic response, as measured by fMRI, is better correlated to the synaptic activity[1-3]. However, both spiking and synaptic activities are manipulated in these paradigms and not completely dissociated. To directly examine this issue, we chose the rat olfactory bulb model because spiking activity from mitral cells (output neurons) can be selectively decreased while controlling synaptic activity. In particular, odors excite olfactory receptor neurons that project to the olfactory bulb through the olfactory nerve layer (ONL) and form excitatory synapses with the apical dendrites of mitral cells in the glomerular layer (GL), which descend through the external plexiform layer (EPL) and initiate spiking to cortical targets at the mitral cell layer (MCL). In addition, inhibitory granule cells in the granule cell layer (GCL) are excited by anterior commissure (AC) stimulation, which form dendro-dendritic synapses with mitral cells in EPL and inhibit mitral cell spiking (Fig. 1B, orange circle). Therefore, odor evoked mitral cell spiking is reduced by simultaneous AC stimulation, which we used to directly determine the contributions of spiking activity to the cerebral blood volume-weighted (CBVw) fMRI response. CBVw fMRI was used for its increased sensitivity and specificity to neural activity in the olfactory bulb compared to BOLD[4].

Methods: Six male Sprague-Dawley rats were induced with 45 mg/kg α-chloralose (40 mg/kg/hr maintenance) and a tungsten stimulating electrode was positioned to the left AC. Odor delivery (5% amyl acetate), AC micro-stimulation (-200 µA, 200 µs duration, 40 Hz) and simultaneous odor plus AC stimulation were interleaved in a block design experiment (120-s off, 64-s on, 120-s off). For CBV weighting, 15 mg/kg MION was intravenously injected. fMRI data were acquired at 9.4 T with a compressed-sensing, gradient-recalled echo technique. Imaging parameters were TR = 125 ms, TE = 8 ms, 9 slices, 110 x 110 µm^2 in-plane resolution, 500 µm slice thickness, reduction factor of 4, and temporal resolution = 2 s. Percent change maps were calculated with SPM using a general linear model with a CBV-specific hemodynamic response function. The sign of the CBVw percent change was reversed so that positive signal changes represent blood volume increases. Group fMRI maps were calculated with SPM.

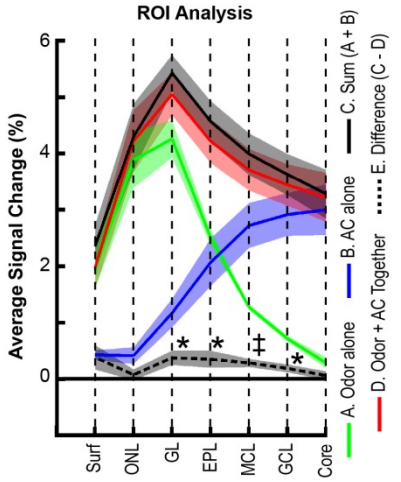

Figure 3: CBV fMRI responses peaked in GL for odor (green) and in GCL for AC (blue) stimulations. The sum of individual (black) and simultaneous stimulations (red) had small but significant differences (dashed black) in layers surrounding the spiking output layer MCL. * $p < 0.05$, ‡ $p < 0.01$ (uncorrected).

Results and Discussion: We observed CBV increases to individual odor (Fig. 2A) and AC (Fig. 2B) stimulations that were specific to the layer of neural activation. Specifically, odor evoked CBV increases were observed in superficial layers, while AC increased in deep layers. Odor evoked mitral cell spiking is not affected in the sum of these individual activations ("Odor Alone" + "AC Alone"), but is reduced during simultaneous stimulation ("Odor + AC Together"). Therefore, the relative contributions of mitral cell spiking activity to the hemodynamic response can be determined from the difference ("Odor Alone" + "AC Alone" – "Odor + AC Together"). We observed large CBV increases that spread across all bulb layers for the sum of the individual stimulations (Fig. 2C). The simultaneous stimulations (Fig. 2D) showed qualitatively similar activation patterns. However, a small difference (Fig. 2E) was observed in MCL and adjacent layers when examined at a lower threshold. To quantify these effects, a regions-of-interest (ROI) analysis was performed without a threshold by averaging all of the pixel-wise fMRI changes for each laminar ROI that were manually determined from the anatomical images. We observed similar laminar patterns from the ROI analysis (Fig. 3), whereby the CBVw increases were greatest in superficial layers for odor stimulation (green, ONL: 3.9 ± 0.5%, GL: 4.3 ± 0.3%) and in deep layers for AC stimulation (blue, GCL: 2.9 ± 0.4%, core: 3.0 ± 0.5%). In addition, the sum of individual stimulations (black) had a similar laminar shape as the simultaneous stimulations (red), but the difference (dashed black) was statistically different from zero in GL, EPL, MCL and GCL (one-sample t-test, $p < 0.05$), with the most significant difference occurring at the site of output spiking activity (MCL: $p = 0.007$, 0.28 ± 0.08% CBVw fMRI signal change). At this layer, 3.71 ± 0.37% signal change is attributed to an inseparable combination of spiking and synaptic activities.

Conclusions: Our results indicate that odor evoked spiking activity of mitral cells, the primary output neurons of the olfactory bulb, slightly contribute to the CBV fMRI response. However, the majority of the signal changes may still be attributed to synaptic activity. Further study is needed to directly suppress post-synaptic activity without altering pre-spiking activity.

References: 1. Logothetis N, Pauls J, Augath M, Trinath T and Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001; 412:150-157. 2. Viswanathan A and Freeman R. Neurometabolic coupling in cerebral cortex reflects synaptic more than spiking activity. Nature Neurosci. 2007; 10: 1308-1312. 3. Yen CC, Fukuda M and Kim S-G. BOLD responses to different temporal frequency stimuli in the lateral geniculate nucleus and visual cortex: Insights into the neural basis of fMRI. Neuroimage 2011; 58: 82-90. 4. Poplawsky A and Kim S-G. Layer-dependent BOLD and CBV-weighted fMRI responses in the rat olfactory bulb. Neuroimage 2014; 91:237-251.