# Baseline and Functional Vessel Size Index Imaging in Cat Visual Cortex: Insights into Hemodynamic Regulation

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## INTRODUCTION

Tight coupling between neural activity and hemodynamic response is the basis of modern functional brain imaging techniques. During increased neural activity, cerebral blood volume (CBV) is increased. However, the size of vessels responsible for the CBV increase is not clear. It is well-known that gradient-echo (GE) MRI is sensitive to vessels of all size, while spin-echo (SE) MRI selectively depicts microvessels [1-5]. Data from both techniques can be combined to yield vessel-size-index (VSI, an index of the weighted-mean vessel radius) [6, 7]. Baseline VSI has been measured in animal and human brain [6 -11]. In this abstract, both baseline VSI and functional VSI changes during visual stimulation were measured in cat visual cortex using both the GE and SE MRI techniques by combining data acquired before and after intravenous injection of blood-pool contrast agent, MION (monocrystalline iron oxide nanoparticles).

## METHODS

Cats (n = 5) were maintained under ~1.3% isoflurane. Blood pressure, arterial blood gases, end-tidal $CO_2$ and rectal temperature were kept within normal ranges. NMR measurements were performed on a 9.4 T / 31 cm Varian system with a 1.6-cm diameter surface coil. A single 2-mm thick imaging slice was selected perpendicular to the surface of the visual cortex in area 18. Images with 128x128 matrix size and FOV of 2x2 $cm^2$ were obtained with the 4-shot echo planar imaging technique. Maps of baseline $R_2$ and $R_2$* changes ($\Delta R_2$* and $\Delta R_2$ from GE and SE data, respectively) induced by MION provide indices of baseline total and microvascular CBV distribution, respectively. Relative VSI at the baseline condition is calculated by $(\Delta R_2^{*}{}_{MION} / \Delta R_{2\,MION})^{3/2}$ (see Eq. [14] in [7]). Functional data were obtained before (BOLD) and after (CBV-weighted) the injection of MION by both GE and SE fMRI with visual stimulation. Binocular visual stimuli consisted of drifting high-contrast square-wave gratings [12]. For both GE BOLD and GE CBV-weighted fMRI studies, each run consisted of 10 control - 10 stimulation - 10 control image acquisitions with TR = 4 s. For both SE BOLD fMRI and SE CBV-weighted fMRI studies, 7 control – 5 stimulation – 5 control images were acquired with TR = 8 s. Quantitative analysis was performed on pixels with a t-value ≥ 2 and active cluster size ≥ 4. Stimulation-induced relaxation rate changes ($\Delta R_2^{*}{}_{stim}$ and $\Delta R_2^{*}{}_{stim+MION}$ for GE measurements without and with MION, and $\Delta R_{2\,stim}$ and $\Delta R_{2\,stim+MION}$ for SE measurements without and with MION, respectively) were calculated from the percentage signal changes as –(ΔS/S)/TE for both BOLD and CBV-weighted studies under the assumption that the intravascular contribution is minimal. A map of relative VSI for vessels undergoing dilation induced by neural activity can similarly be determined by $((\Delta R_2^{*}{}_{stim+MION} - \Delta R_2^{*}{}_{stim}) / (\Delta R_{2stim+MION} - \Delta R_{2\,stim}))^{3/2}$. For cortical depth-specific signal analysis, two quadrangular sections in area 18 within each hemisphere of the visual cortex were selected, and pixel values along lines perpendicular to the dorsal surface were determined without using any statistical threshold. Averaged signals across cortical layers were plotted as a function of distance from the cortical surface.

## RESULTS AND DISCUSSION

The map of Fig. **A** shows $(\Delta R_2^{*}{}_{MION} / \Delta R_{2\,MION})^{3/2}$ (i.e., *relative* VSI) at the baseline condition, which was calculated on a pixel-by-pixel basis from measurements of $\Delta R_2$* and $\Delta R_2$ induced by MION in GE and SE techniques, respectively. Clearly, at the surface of the cortex, high values of relative VSI were observed due to a higher ratio of large to small vessels and a longer diffusion coefficient of cerebral spinal fluid. Interestingly, the white matter area (indicated by red contours) also has high values of relative VSI, which can be explained by the relatively higher ratio of large to small vessels as compared to gray matter (the diffusion constants in both gray matter and white matter are known to be similar). A map of relative VSI for vessels undergoing dilation induced by neural activity (Fig. **B**) can similarly be determined from the pixels activated in either GE or SE data. The middle of the cortex has smaller relative VSI values as compared to the lower cortical area, indicating that a higher ratio of small to large vessels is contributing to the CBV change. Profiles of relative VSI across cortical layers were obtained from each animal for baseline and stimulation conditions from the two quadrangular ROIs within area 18 outlined in yellow in Fig. **A**. Average relative VSI values from five animals were plotted in Fig. **C** as a function of depth from the surface of the cortex. Baseline relative VSI (squares in Fig. **C**) decreases with cortical depth, with an average value of 7.23 ± 1.64 (n = 5) over the "middle of the cortex" (region shown in blue). Generally, stimulation VSI values (circles in Fig. **C**) are higher than baseline values. In the middle of the cortex, the average relative VSI value for vessels undergoing dilation during visual stimulation is 19.99 ± 7.79 (n = 5). The average ratio of stimulation to baseline values (relative VSI) in the middle of the cortex is 2.80 ± 1.08 (n = 5). If as an example the mean vessel radius was 2 - 5 µm in the middle cortex, then the corresponding mean vessel radius responding to stimulation would be ~6 - 14 µm. This is qualitatively consistent with previous vessel diameter measurements during hypercapnic stimulation (see Fig. 8 in [13]). Our data strongly suggest that the dominant changes during neural activity occur in vasculature with diameters larger than capillaries.

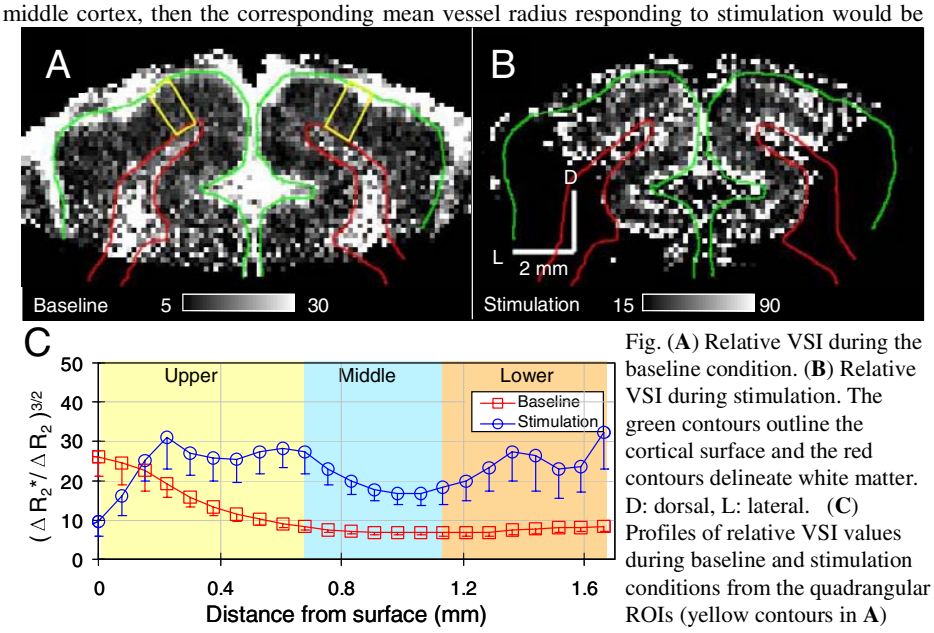


Fig. (**A**) Relative VSI during the baseline condition. (**B**) Relative VSI during stimulation. The green contours outline the cortical surface and the red contours delineate white matter. D: dorsal, L: lateral. (**C**) Profiles of relative VSI values during baseline and stimulation conditions from the quadrangular ROIs (yellow contours in **A**)

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