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Contrast mechanisms in vessel-scale human fMRI: Ultra-slow post-stimulus “ringing” oscillations in cortical arteries

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Synopsis

Keywords: Task/Intervention Based fMRI, Blood vessels

Motivation: In-vivo microscopy of brain hemodynamics have observed resonance phenomena in pial arteries in mouse cerebral cortex, however similar observations in human fMRI are anecdotal. Vessel-scale fMRI has the potential to reconcile these observations.

Goal(s): Characterize arterial resonance phenomena in human pial vessels.

Approach: Vessel-scale fMRI sensitive to blood velocity and vessel diameter changes to track responses of individual pial vessels to visual stimulation.

Results: Reductions in inflow enhanced signal are seen in many arterial responses, suggesting a reduced velocity corresponding to increased vessel diameters. Responding vessels exhibit “post-stimulus ringing”, i.e., slow oscillations (~0.1Hz) phase-locked to stimulus presentation, after the main response.

Impact: We demonstrate a post-stimulus ringing phenomenon in vessel-scale fMRI responses in individual cortical arteries when responding to visual stimulation. This suggests a trial-locked oscillation that is consistent with observations of arterial resonance seen in in-vivo microscopy studies.

Introduction

Neural activity triggers the dilation of nearby arteries and functional hyperemia. Arteries can also dilate spontaneously: excised vessel segments show diameter oscillations (spontaneous vasomotion) around 0.1 Hz[1]. Similar ultra-slow oscillations are observed in vivo in recent microscopic imaging studies, where pial vessels behave as a network of connected oscillators[2,3], but detection of spontaneous vasomotion in human imaging studies remains so far somewhat elusive[4-6].

Independent development of a damped oscillator theory for arterial dynamics led to anecdotal observations of hemodynamic ringing in human imaging studies, where ~10-s oscillations follow functional hyperemia[7,8]. Interestingly, clear post-stimulus oscillations were incidentally reported in single-vessel measurements using vessel-scale fMRI in rat[9] and human[10]. Here we leveraged vessel-scale fMRI[10-13] optimized for blood velocity and vessel diameter sensitivity to investigate these intriguing non-canonical oscillatory arterial dynamics in humans.

Methods

Five healthy adult volunteers (2 males) provided written informed consent prior to scanning, following all policies of our institution’s Human Subjects Research Committee. MRI data were acquired using a whole-body 7T scanner (Terra, Siemens) and an inhouse-built 1Tx/64Rx brain array coil. Anatomical MEMPRAGE and TOF guided prescription of a oblique-coronal slice through the calcarine sulcus. Slice prescription was automatically updated between runs[14].

Vessel-scale fMRI used an inflow-weighted modified FLASH protocol (TR/TE=8.4/3.68ms; R=4; voxels=0.4x0.4x1.2mm3; FA=40; BW=390Hz/Px). Resolution-matched six-echo FLASH data (TE=4.3-30.0ms; 0.4x0.4x1.2mm^3) were collected to identify arteries vs. veins based on T2* decay.

fMRI data were collected in ~5-min runs at 1/0.84-s sampling rate with 0.84-s- or 5.04-s-duration full-field flashing-checkerboard visual stimulus repeated every 47.9s. Participants performed a fixation task to maintain/monitor alertness. Timeseries were corrected for within-plane motion using AFNI (3dAllineate). Activation maps (FDR<0.05) and trial-triggered response time courses were obtained with AFNI’s 3dDeconvolve. Multitaper spectral analysis used an adaptation of Chronux[15,16]. Analysis performed on a full-run timeseries reflects power or coherence irrespective of oscillation phase relative to trial onset. Our trial-triggered version of the multitaper analysis excludes timeseries data[17,18] outside a time window specified relative to each trial onset and averages out oscillations with phases inconsistent across trials.

Results

Visual responses were mainly observed in vessels. Sinus and extracerebral vessel activations were observed less consistently (Fig. 2). Stable measurements of 62 vessel cross-section ROIs across 5 subjects were achieved. Of these, 53 were responsive (at least one significant voxel; 24/27 arteries, 25/29 veins and 4/6 ambiguous) and exhibited three main activation patterns: (i) positive response centered on the vessel, (ii) center-negative response surrounded by positive responses and (iii) negative and positive responses flanking the vessel center. Pattern (i) dominated venous responses (12/23 veins vs. 1/20 arteries), while patterns (ii) and (iii) dominated arterial responses (15/20 arteries vs. 1/23 veins).

We found robust evidence for ultra-slow (~0.1Hz) oscillations in individual vessels. In the time domain, these were readily observable as “ringing” of the post-stimulus response--several ~10-s oscillations after the main response peak--averaged across all vessels in 2/4 subjects, in at least one vessel for 3/4 subjects, and most strongly in arteries. In the frequency domain, ultra-slow oscillations manifested as high power and coherence around the 0.1-Hz vasomotion frequency. Importantly, our trial-triggered analysis that used only data 23.5 s after stimulus onset, and that averages out oscillations with inconsistent phases across trials, removed stimulus-related peaks but retained power around 0.1Hz in all subjects, suggesting that ultra-slow oscillations are modulated by stimulus-driven hemodynamics, but outlive the latter by at least 20s.

Discussion

Vessel-scale fMRI provides a new means to investigate single-vessel hemodynamics in humans and thereby perform measurements analogous to ground-truth *in vivo* microscopy, helping to bridge species and modalities. Still questions remain regarding contrast mechanisms. We demonstrated a

consistent “center-surround” phenomenon in inflow-weighted fMRI of arteries, which is compatible with a contrast mechanism whereby the vessel dilates (dynamic partial volume generating positive signal change) and blood velocity decreases (decrease velocity-related signal enhancement) while volumetric flow is maintained or increases.
This fMRI approach revealed conspicuous “ringing” in the post-stimulus response, reported previously[7-10]; arteries show stronger post-stimulus low-frequency oscillations than veins while not always showing stronger stimulus related harmonic signal. This is a trial-locked oscillation at the same frequency as spontaneous vasomotion, which suggests an arterial resonance undergoing phase reset at the beginning of each trial. Ongoing work is further testing this theory of arterial resonance in animals and humans.

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Figures

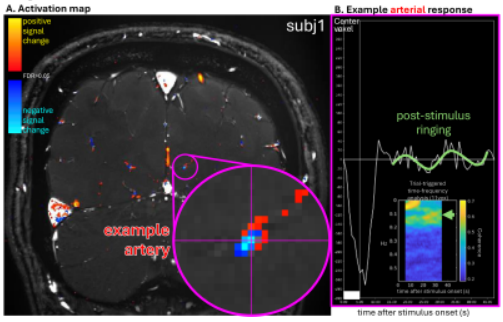

Figure 2: "Center-surround" arterial activation and post-stimulus ringing. (A) Activation map showing a negative response at the vessel center and a positive response in surrounding voxels, likely due to partial voluming between bright vessel and dark tissue, compatible with dilation and velocity decrease while volumetric flow is maintained or increases. (B) Responses from voxel highlighted in A. Main activation is followed by ~2 cycles of 10-s oscillations. A coherence peak is observed around 0.1 Hz (arrowhead) and is present after the canonical hemodynamic response.

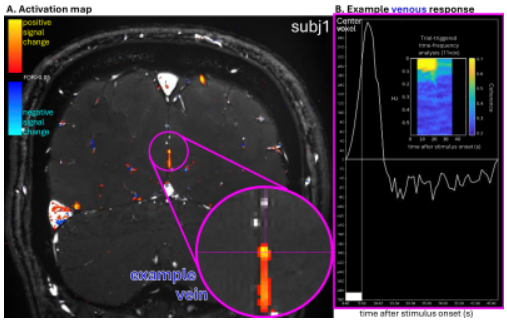

Figure 3: Positive venous activation. (A) Activation map shown in Figure 2, now highlighting a representative vein (inset). Contrary to arteries, almost all veins showed this simple positive activation pattern. (B) Example response from the single voxel highlighted in A. Post-stimulus oscillations are less clearly observed, both in the time domain and frequency domain (inset). This suggests either reduced post-stimulus oscillation in passively responding veins, or an active mechanism present only in arteries.

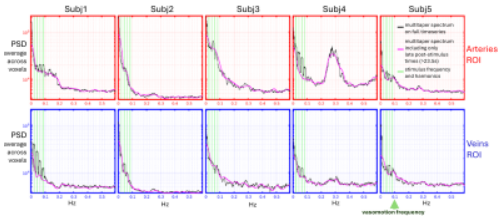

Figure 5: Spectral analysis of post-stimulus oscillations. Multitaper spectral analysis (black) on catenated runs, averaged within ROI. Power <0.2 Hz is partly attributable to stimulus harmonics (green lines). Excluding the first 23.5s after stimulus onset (magenta) still show ~0.1Hz power (arrowhead). This latter analysis averaged out inconsistent phase across trials, indicating low-frequency power corresponds to stimulus-locked oscillations. Arteries show stronger post-stimulus ringing, while not always showing stronger stimulus-related responses (see Subject 1).

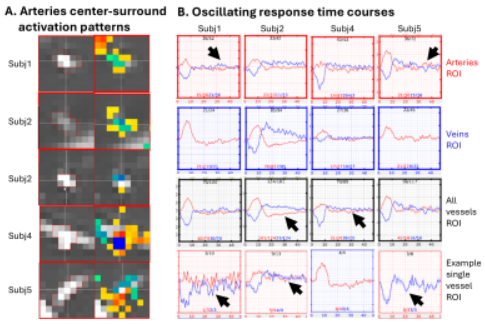

Figure 4: (A) Arterial activation often exhibited positive and negative voxel activation arranged in a center-surround pattern. One example is shown per subject. Active voxels identified using canonical HRF, FDR-corrected for the number of voxels in square ROI surrounding vessel center of mass. (B) Post-stimulus oscillations across vessels and subjects. Positive (red traces) and negative (red traces) response voxels are plotted separately. Post-stimulus oscillations were most conspicuous in Subject 5 (last column), but visible to some degree in all subjects (black arrows).

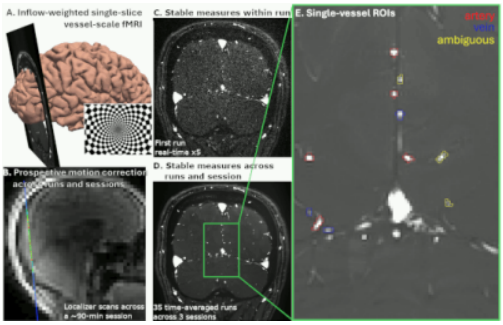

Figure1. Vessel-scale human fMRI. A. Single slice targeting cross-sections of pial vessels in occipital cortex and minimizing vulnerability to through-plane motion. Example visual stimulus in inset. (B) Scout scans allowed automatic slice-prescription update to varying head positions across runs and sessions. (C, D) Stable measurements of vessels (green outline), within and across runs and sessions, using combined prospective slice updates and retrospective within-plane motion correction, from experienced MRI participants. (E) Manually drawn vessel ROIs.