BOLD impulse response functions and baseline-dependent response adaptation

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INTRODUCTION

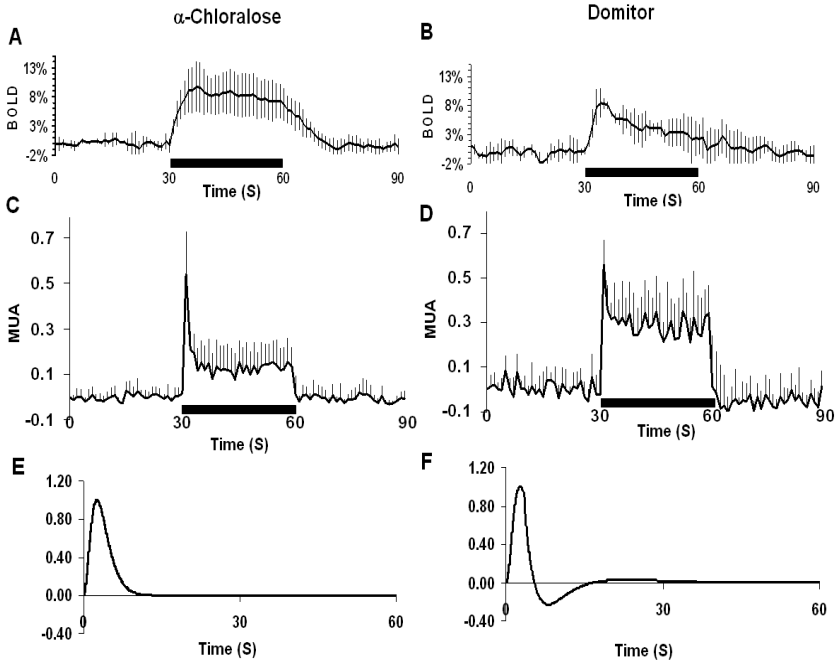
It is well known that the BOLD impulse response functions (IRFs) show some degree of variability – primarily represented by either a presence or absence of a delayed undershoot – across different stimuli and/or regions. However a mechanistic basis of the BOLD-IRF variability is unknown. We hypothesized that BOLD-IRFs could be different due to the system's variable adaptive properties because some prior studies have shown that adaptive properties of sensory systems are affected by the baseline state [1,2]. We conducted electrophysiology and fMRI studies in rats with domitor and α-chloralose anesthesia as two differing baseline states represented by presence and lack of high frequency neural signaling, respectively. Extracellular data were compared with BOLD signal during forepaw stimulation to reveal that while BOLD-IRFs were nearly identical in the early phase, they were significantly different in the late phase. Domitor, where responses are more adapted than in α-chloralose, featured a long time-constant undershoot in the BOLD-IRF. We propose a testable hypothesis that the late phase of the BOLD-IRF could represent differences in adaptive properties across states.

MATERIALS and METHODS:

Animal preparation: Sprague-Dawley rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation isoflorane (3 - 4%) used for induction. Intraperitoneal lines were inserted for administration of α-chloralose (46±4 mg/kg/hr) or domitor (0.1mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment. ***Forepaw stimulation***: Stimulation was achieved by insertion of thin needle copper electrodes under the skin of the forepaw. Electrical stimulation (2mA) consists of 0.3ms square wave pulses provided with an isolator stimulator (World Precession Instruments, FL, and USA). Variation of functional response is achieved by varying the frequency (1 – 24 Hz) of the stimulus. The stimulus was controlled with a computer by custom written script with 30s off 30s on block design. ***fMRI (n=16):*** All fMRI data were obtained on a modified 11.7T horizontal-bore spectrometer using a ^{1}H surface coil (Ø = 1.4 cm). The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15). ***Extracellular measurements (n=8):*** The rat was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes above the contralateral and ipsilateral somatosensory regions [4.4 mm lateral and 1.0 mm anterior to bregma] were thinned and tungsten microelectrodes (FHC inc, Bowdoinham, ME) were inserted up to layer 4 with stereotaxic manipulators (Kopf). All signals were then digitized (>20 kHz) with a μ-1401 interface using SPIKE-2 software. ***BOLD-IRF***: The transfer function, or IRF, between the MUA/LFP and the BOLD signal was modeled by a gamma variate function [3]. The input function was defined as the average of the LFP/MUA series, where individual events were normalized to the first evoked potential (in the middle cortical layer).

RESULTS and DISCUSSION:

As suggested by prior studies [1,4], the forepaw stimulation frequencies which evokes the maximal BOLD and neural responses are different for α-chloralose and domitor. All experimental comparisons of IRFs were done with these maximal stimuli (3 and 9 Hz, respectively). The BOLD time courses for α-chloralose (3 Hz) and domitor (9 Hz) are shown in Figs. A and B, respectively. There were significant differences in shape and amplitude of the BOLD responses. The amplitude of the BOLD responses were larger and sustained throughout the stimulation period (30 s) under α-chloralose, whereas with domitor the responses returned faster to baseline during the stimulation period. Baseline MUA and/or LFP recordings under α-chloralose and domitor showed very different powers in the γ band range of neural activity, which presumably reflects different arousal states (data not shown). MUA/LFP responses under both anesthetics are shown in Figs. C and D. Note specifically that the α-chloralose state allows far more neural adaptation than does the domitor state. We then calculated BOLD-IRFs for both α-chloralose and domitor, as shown in Figs. E and F, respectively. There were no significant differences in the BOLD-IRFs calculated with LFP or MUA, for either state [4]. The BOLD-IRFs were nearly identical in the early phase but different in the late phase. Overall, the distribution of the domitor BOLD-IRF compared to α-chloralose BOLD-IRF was nearly 70% accurate (i.e., early phase correspondence, both peaking at ~2.5s), whereas the remaining disagreement accounted for a small negative peak and even a very small late positive peak, both present in domitor but not α-chloralose. Together these results suggest that the early phase represents active neurovascular coupling which is similar across both states. However the late phase could potentially characterize a state-dependent difference in the neural system which may be already be adapted (as in domitor). Future studies including blood flow (CBF) and volume (CBV) measurements could provide further the proposal that IRFs of CBF and CBV are also baseline-dependent.



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