Brain parenchymal fMRI signals during cortical spreading depression

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Introduction

Recently, there has been interest in performing alternative functional magnetic resonance imaging (fMRI) methods to detect neuronal or metabolic activity via water signal (1). One of these methods is the spin-lock (SL) fMRI, utilizing spin-lattice relaxation rate in the rotating frame (R1ρ). Several in vitro studies have established that SL-technique is sensitive to solute properties (pH), chemical-exchange processes (hydroxyl and amino-acids) and dipolar fluctuations which constitute a large part of the parenchymal *in vivo* imaging contrast (2, 3). Since these properties are closely associated with tissue homeostasis and energy status a perturbation in homeostatic equilibrium may be translatable into changes in parenchymal endogenous signals detectable using SL-fMRI. The aim of the present study was to find out parenchymal fMRI signals evoked by strong brain activation. To address this possibility, cortical spreading depression (CSD), a self-propagating wave of cellular activation, was used as a stimulation paradigm in combination with SL-fMRI technique.

Materials and Methods

Male Sprague-Dawley rats, (340 ± 40 g) were initially anesthetized with isoflurane for surgical preparation. Cranial window was made in the parietal bone above visual cortex and meninges was carefully removed to expose cortical surface for KCl application, which evokes CSD. A catheter was inserted for blood gas sampling. After surgery, anesthesia was switched to urethane (i.p. 1.25 g/kg). The experiments were performed on a 9.4 T horizontal magnet system interfaced to a DirectDrive console (Agilent inc., Palo Alto, CA). Half-volume quadrature coil was used to achieve high sensitivity and to obtain high B_1 fields. Anatomical reference images were obtained using fast spin-echo imaging. All fMRI experiments were performed with single shot spin-echo EPI using 22 ms echo time, 2 s repetition time, 64 x 64 matrix, 25 x 25 mm FOV and 2-mm slice thickness. For fMRI runs the interleaved data acquisition scheme consisted of three images: control image without SL preparation and two images with a 50 ms spin-lock time using the low (500 Hz) and high (6000 Hz) $B_{1,SL}$ fields.

Results

Application of K^+ onto the visual cortex initiated CSD and large spatiotemporal fMRI changes were observed (Fig. 1a). As the CSD propagated through the ipsilateral cortex, initial positive (warm colors) response was followed by negative (cold colors) BOLD fMRI signal, which did not return to baseline during the 45 minute scan. The low (Fig. 1b) and high (Fig. 1c) B_1 SL-sensitizing increased CSD-associated fMRI signal changes. The relative time-course of BOLD fMRI is shown in Figure 1d (n = 5, trials 14). Both, low and high B_1 SL-weighted BOLD signals showed prominent differences when compared with BOLD fMRI signal (Fig. 1d). The positive signal changes 3.2 ± 1.3% ($p < 0.05$) and 4.3 ± 0.9% ($p < 0.01$) for low and high B_1 SL-weighted BOLD, respectively, were substantially larger than 2.2 ± 1.0% BOLD response (Fig. 1f). To visualize the signal change contributing to SL period, the differences between BOLD and SL-weighted BOLD signals are plotted in Figure 1e. In agreement with activation maps, relative SL time-courses exhibited earlier increases in magnitude when compared with BOLD.

Since blood presumably influenced SL-fMRI results we next performed CBV-weighted experiments (n = 5, trials 12, USPIO 8 mg/kg). Low $B_{1,SL}$ weighting had negligible effect on CBV-weighted fMRI signal (Fig. 2a, b), thus the aforementioned BOLD low $B_{1,SL}$ may be ascribed to partial volume effects. In contrast, the high $B_{1,SL}$ CBV-weighted time-course exhibited substantial increases in signal intensity. Tentatively, the temporal characteristics of this SL signal resemble in shape previously published pH time-courses (4), supporting a predominantly pH origin of the signal change.

Conclusions

The present study shows activation related changes in the brain parenchymal fMRI contrast obtained with R1ρ technique. The high $B_{1,SL}$ signals were likely mediated via pH sensitive water proton chemical-exchange processes changed by enhanced brain metabolism. This approach may have wide applications in biology and medicine, however, further research is mandatory to clarify the mechanisms of SL fMRI.

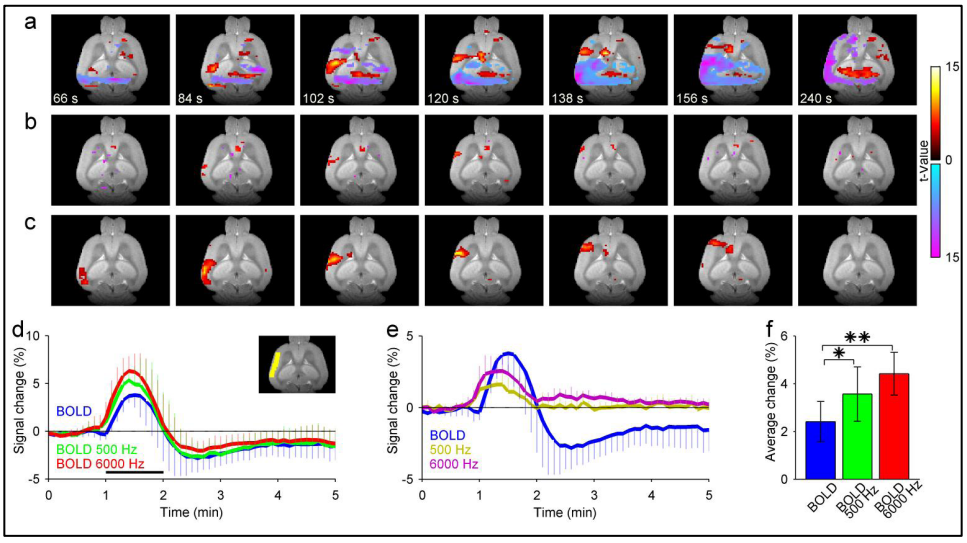

Figure 1

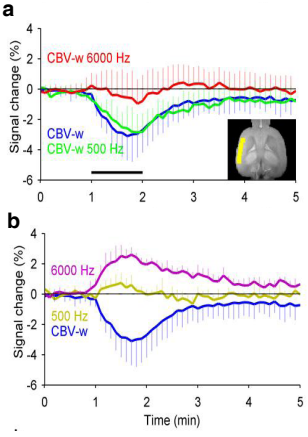

Figure 2

References: [1] Magnotta et al, PNAS 109: 8270-8273 (2012). [2] Mäkelä et al, BBRC 289:813-818 (2001). [3] Jin et al, MRM 65:1448-1460 (2011). [4] Mutch et al, JCBFM 4:17-27 (1984).