Direction-dependent diffusion fMRI signals during hypercapnia and hyperoxia

T. Jin[1], and S-G. Kim[1]
[1]Neuroimaging laboratory, Department of Radiology, University of Pittsburgh, Pittsburgh, PA, United States

Introduction

Recently, diffusion-weighted fMRI (DfMRI) signals of brain water were reported to increase with the degree of diffusion sensitization during human visual stimulation, indicating a decrease of the apparent water diffusivity [1-2]; however, the interpretation of the signal origin was controversial. Le Bihan et al. attributed the activation-induced change of the apparent water mobility to a functional expansion of neuronal cell membrane [1]. Miller et al. found similar DfMRI signal change during a hypercapnia challenge, which was also dependent on the direction of diffusion-sensitizing gradients, thus suggesting that the DfMRI signal change might be due to residue intravascular signals [2]. In this preliminary study, we measured the direction-dependent change of DfMRI signal i) during intravascular susceptibility change without changes in vascular physiology by the intravascular injection of a small amount of iron oxide nanoparticle (Feraheme), and ii) during global hypercapnia and hyperoxia stimulations in anesthetized rats after the suppression of the intravascular signals.

Methods

All MRI experiments were performed on a 9.4-T magnet. Sprague-Dawley rats were anesthetized under 1.3-1.5% isoflurane and scanned with a 1.7-cm diameter surface coil. A double-refocused spin-echo EPI sequence with interleaved pairs of bipolar diffusion gradients was used for the diffusion MRI measurement [1-2]. Imaging parameters were: field of view 2.56 × 2.56cm^2, matrix size 64 × 64, slice thickness 4mm, TR = 2 s, and TE = 40 ms. Three *b*-values of 5, 1000 and 2000 s/mm^2 were applied, and the diffusion gradients were applied in two orthogonal directions (+X+Y and +X-Y) for *b* = 1000 and 2000 s/mm^2. 1) In dynamic susceptibility change experiments (n = 4), two doses of 1 mg/kg iron oxide particles were injected in a 13-minute run. 2) For global stimulations studies, 5 mg/kg of iron oxide particles was injected to suppress the intravascular signals. Two types of gas challenge were used: inhalation of 8% CO_2 for 3 minutes (n = 4) or 60% O_2 for 4 minutes (n = 4).

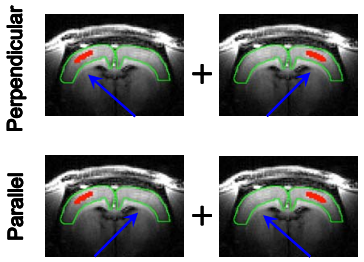

Fig. 1. Selection of cortical regions of interest for direction-dependent DfMRI data analysis. Arrows: gradient directions.

Cortical regions of interest (ROI) were selected for quantitative analysis of the direction-dependent data (red pixels, Fig. 1). To improve sensitivity, the two ROIs where the cortical tangential direction were approximately perpendicular or parallel to the direction of diffusion-sensitizing gradients (indicated by the blue arrows) were combined together and referred to as perpendicular or parallel cases, respectively.

Results

MR signals dropped during the two doses of iron oxide injection (arrows, Fig. 2A and 2B), and ΔS/S was dependent on the strength of the diffusion gradient (different color traces) but independent of diffusion gradient direction (Fig. 2A vs. 2B). Our data suggest a direction-independent decrease in the apparent diffusion coefficient (ADC), as expected for cortical gray matter, where the vasculature orientation should be fairly random.

To test whether direction-dependent ADC changes were detected, hypercapnia and hyperoxia were used. In hypercapnia, susceptibility-induced fMRI signal changes are relatively small because of two competing effects: the decrease of deoxyhemoglobin content due to the BOLD effect and the increase of iron oxide content due to vessel dilation. For hyperoxia, the susceptibility-induced fMRI signal change was much larger because of the additive effects of the BOLD and vessel constriction responses. Thus, the effect of the susceptibility-induced DfMRI change is expected to be minimal in our hypercapnia data but quite large in hyperoxia. In our DfMRI studies, the MR signal changes during both gas challenges were dependent on the direction of the diffusion sensitization. During hypercapnia (Fig. 2C and 2D), ΔS/S increased with *b*-value for parallel case but not for perpendicular ROIs. During hyperoxia (Fig. 2E and 2F), the signal change decreased with increasing *b*-values—more significantly in the parallel case. This indicates direction sensitive responses in the apparent water mobility during stimulation.

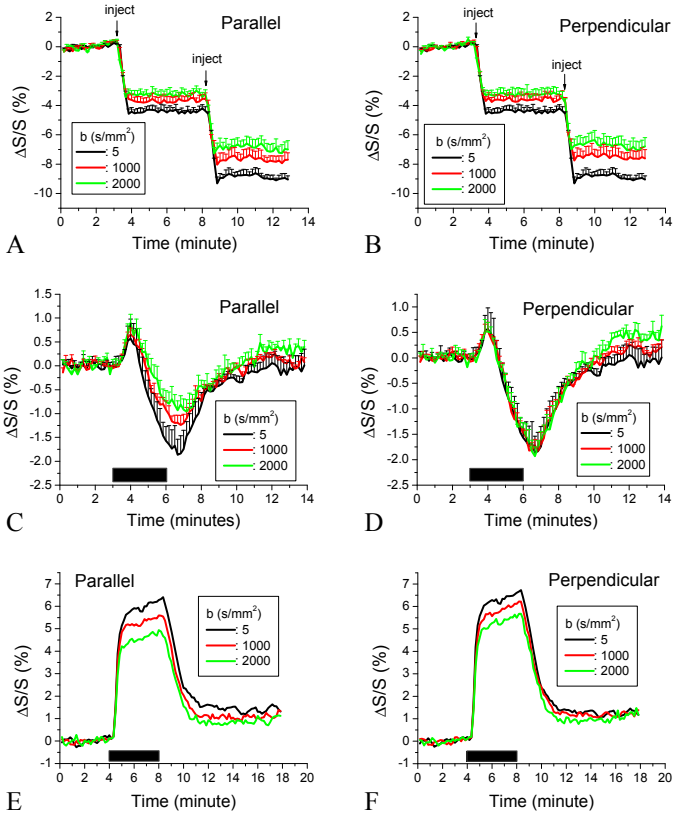

Fig. 2 Time courses of diffusion-weighted signals at b-values of 5, 1000, and 2000 s/mm^2 during two iron oxide injections (A, B), 3 minutes of hypercapnia challenge (C, D), and 4 minutes of hyperoxia (E, F). Data were compared for the parallel case (A, C, E) and perpendicular case (B, D, F).

Discussion

Hypercapnia and hyperoxia are known to induce dilation and constriction of blood vessels, respectively [3]. Their effects in the microstructure of cortical neuronal cells are expected to be small and should not have significant anisotropy. With suppression of intravascular signals, the directional dependence of diffusion fMRI signals during gas challenges indicates that changes in apparent water diffusivity occur in the extravascular space and are likely induced by the dilation or constriction of blood vessels. Our results suggested that the DfMRI change observed during neuronal activation might also have a contribution from the vascular response. Further study is necessary to understand the mechanism of how vessel dilation or constriction may cause a direction-dependent change in the extravascular water mobility.

Acknowledgments: This work is supported by NIH grants EB008717, EB003324, EB003375, and NS44589.
References: [1]. Le Bihan D et al, PNAS 103:8263 (2006). [2]. Miller K et al., PNAS 104:20967 (2007). [3]. Lu, J et al., NeuroImage 45 :1126 (2009).