Observation of functional ADC decrease in the extravascular tissue: a fMRI study with suppression of intravascular signal

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Introduction

fMRI signal changes have been found to increase at high diffusion weightings ($b \geq 600$ s/mm^2) in both human and cat visual stimulation [1,2]. Because the high diffusion sensitizing gradients presumably crush the signal from the blood, this finding suggest a change of water diffusion characteristics in the extravascular tissue and has been hypothetically attributed to the activation-induced neuronal cell swelling [1]. In contrast, a recent human hypercapnia study suggested that vascular contribution might dominate the observed change in the diffusion weighted fMRI [3]. We have recently studied the response of the apparent diffusion coefficient (ADC) for a cat visual stimulation model using a gradient echo sequence [4]. When the blood signal was eliminated by the injection of an intravascular contrast agent, stimulation-induced ADC changes could not be observed with b <1050 s/mm^2 in the brain parenchyma, whereas ADC decreased at the surface of the visual cortex suggesting an activation-induced change of the partial volume of cerebrospinal fluid (CSF). In this work, we investigated the diffusion weighted fMRI response for higher b-values using a double spin-echo sequence [1,3]. Experiments were performed with and without the suppression of intravascular signals by a contrast agent, monocrystalline iron oxide nanoparticles (MION).

Materials and methods

All MR experiments were carried out on a 9.4 T Varian scanner. Five adolescent cats were anesthetized under isoflurane and kept under normal physiological conditions, and were scanned using a 1.8-cm diameter surface coil. A single-shot double spin echo EPI sequence was used, and an interleaved pair of bipolar gradients was applied on all the three axes for diffusion weighting [1,3]. For fMRI, a transverse slice was chosen with imaging parameters: 2×2 cm^2 FOV, 2 mm slice thickness, 64×64 matrix size, TE = 36 ms, and a repetition time (TR) of 1 s. Without MION (n=3 studies), an fMRI run of images with three b values of 500, 1500, and 2500 s/mm^2 were acquired sequentially thus the effective TR is 3 s for the same b-value image, and the order of the b value is pseudo-randomized for different runs. Experiments were also performed after intravenous injection of 3-7 mg/kg MION (n=4 studies) to fully suppress the blood signal, where three b values of 50, 1000, and 2000 s/mm^2 were applied. The visual stimulus was a high contrast black and white square-wave drifting grating. The block-design stimulation paradigm was 30 s control, 30 s stimulation, and 45 s control. The experiments with and without MION were performed in separate studies. For data analysis, all images were smoothed by a Gaussian filter with a full width at half maximum of 1.5 pixel. To improve the SNR of ADC images, the data with the two higher b-values were averaged and one series of ADC response was calculated. Student's t-test was performed on a pixel-by-pixel basis to detect the activated area; a threshold of $p<0.05$ and a minimal cluster size of 3 pixels were applied. Two ROIs were drawn on anatomical image, one from the tissue area and the other from the cortical surface where there are large vessels and a significant partial volume of parenchyma and CSF [4]. Signal time courses were obtained from all pixels of these ROIs *regardless of* whether the pixels met the activation criteria.

Results and discussions

Without MION injection, the averaged diffusion weighted signal time courses show very similar responses at both the tissue ROI and the cortical surface ROI (Fig. 1), indicating negligible change of ADC at both areas. In contrast, the results after MION injection show percent signal change increases with b-value at the tissue ROI. This agrees with findings in human, however the difference in $\Delta S/S$ between b = 50 and 2000 s/mm^2 in our study (less than 0.3%) is much smaller compared to those human data [1,3], which may partly be due to that our ROI is obtained from anatomical image rather than functional maps. Note that the $\Delta S/S$ at b-value of 50 s/mm^2 became very small after the injection of MION. This is because during brain activation the effect of blood volume dilation nearly cancels the BOLD effect for our small MION dose [4]. At the cortical surface, the signal changes of b = 1000 and 2000 s/mm^2 are similar in magnitude, and both are significantly larger than the $\Delta S/S$ of b = 50 s/mm^2. This indicates a decrease of ADC at the cortical surface for b–value between 50 and 1000 s/mm^2, in agreement with the results in our previous study using a GE sequence [4]. This decrease of surface ADC can be explained by an activation-induced reduction in the volume fraction of CSF in voxels where tissue and CSF coexist, which can be caused by the dilation of surface vessels. Such a functional change of CSF partial volume has also been found in our recent spin-locking fMRI experiments [5]. For b > 1000 s/mm^2, there is almost no b-value dependence in $\Delta S/S$ for the surface ROI because the CSF signal is almost suppressed at such high b-value.

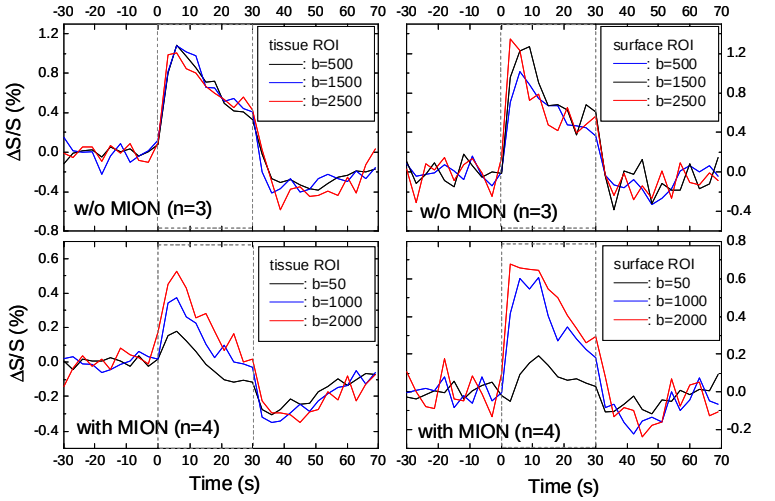

Fig. 1 Without MION, percent signal changes at the two ROIs show very similar time courses for three different b-values. With MION, $\Delta S/S$ increases with b-value at the tissue ROI. At the surface ROI, the signal changes at b = 1000 and 2000 s/mm^2 are similar and are significantly larger than that of b = 50 s/mm^2.

Our functional ADC maps without MION (n=3) show few activated pixels (not shown), which appear in disagreement with previous human results [1,3]. Nonetheless, the ADC map after the injection of MION shows decrease of ADC in the parenchyma as well as the cortical surface (Fig. 2), although the pixels were scattered due to low contrast to noise ratio. The difference in the ADC maps with and without MION suggests that there may be intravascular signal even when very high diffusion weighting ($b \geq 1000$ s/mm^2) is applied. A functional change of residual intravascular signals may induce a decrease or an increase of ADC, dependent on baseline blood velocity and its change; in our cat studies, a small ADC decrease in tissue can be masked by a small ADC increase originated from blood. When intravascular signal contribution is suppressed by MION injection, a small extravascular ADC change is observed. However, the exact signal source of extravascular ADC decrease is still uncertain and further study may be needed to clarify whether this is caused directly by effects of neural cell swelling.

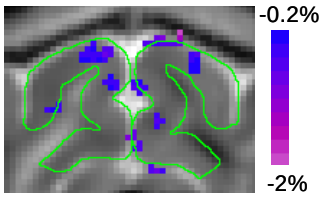

Fig. 2. The map of ADC percent change with MION injection shows decrease in ADC at both the parenchyma (outlined in green) and the cortical surface area.

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