The apparent diffusion coefficient response during brain activation: a gradient-echo EPI study at 9.4 T

T. Jin[1], and S-G. Kim[1]

[1]Department of Radiology, University of Pittsburgh, Pittsburgh, PA, United States

Introduction Transient ADC decreases have been observed in human visual stimulation using moderate to high diffusion weighting (*e. g.* $b > 200$ s/mm^2), and was hypothetically attributed to activation-induced neuronal cell swelling [1]. More recently, such an ADC decrease was also found to be temporally faster than the conventional BOLD response, and was explained by a small expansion of a slow diffusion water pool in neuronal cells [2]. If this mechanism can be confirmed, it may potentially offer improved spatial localization of brain activation compared to hemodynamic based contrasts. A high spatial resolution study can better localize the site of this ADC decrease and may help to understand its signal source. We have recently studied the ADC response in a cat visual stimulation model at 9.4 T [3]. Stimulation-induced ADC changes were not observed in the brain parenchyma for $b > 200$ s/mm^2, while very small ADC decreases were detected at the cortical surface. Because the pulsed gradient spin echo (PGSE) sequence we used in that study is affected by the changes in field inhomogeneity [4], we measured the ADC response using a diffusion-weighted gradient-echo (GE) EPI sequence in this report. The sensitivity of the GE-EPI to the susceptibility gradient is experimentally examined.

Materials and methods All MR experiments were carried out on a 9.4T/31-cm magnet (Magnex) interfaced to a Unity INOVA console (Varian). A 1.6-cm diameter surface coil was used for both excitation and reception. To compare the effect of the susceptibility gradients to the ADC measurement in GE-EPI and PGSE-EPI sequence, rat experiments (n=5) were performed with various doses (between 0 to 10 mg/kg) of superparamagnetic contrast agent (MION) injection. For GE-EPI, a pair of bipolar diffusion weighting gradients was inserted between the excitation pulse and acquisition train, and TR/TE=1 s/21 ms. For PGSE-EPI, a double spin-echo sequence was used, and two unipolar diffusion gradients were placed on both sides of the second 180^0 refocusing pulse, and TR/TE = 2 s/45 ms. Four diffusion weightings of b = 200, 600, 1000 and 1500 s/mm^2 were used for the ADC measurement. For fMRI studies, cats were anesthetized and kept under normal physiological conditions. A coronal slice was chosen with imaging parameters: 2×2 cm^2 FOV, 2 mm slice thickness, and 64×64 matrix size. A single-shot GE-EPI sequence was used with TR/TE = 0.5 s/18 ms (n=6). Three b-value series of 5, 200, and 1000 s/mm^2 were acquired sequentially in each run; the effective temporal resolution was 1.5 s for three b-value images. The images with same diffusion weighting were grouped together, and then linear temporal interpolation was performed to take into account their different time origins. The order of the b values was pseudo-randomized for different studies. The visual stimulus is a high contrast black and white square-wave drifting grating. The stimulation paradigm is 30 s control, 30 s stimulation, and 30 s control, and ~60 runs were averaged. Two series of ADC images were calculated: one from images with b = 5 and 200 s/mm^2 and the other from images with b = 200 and 1000 s/mm^2, respectively. We also performed experiments with TR/TE= 1 s/18 ms. For this study we used b-values of 200 and 1200 s/mm^2, and a flip angle about half that of the three b-value study. The temporal resolution was 2 s for ADC images (n=3). The stimulation paradigm is 30 s control, 30 s stimulation, and 40 s control, and ~90 runs were averaged. A Gaussian filter with a full width at half maximum of one pixel was applied to all ADC images. Student's t-test was performed on a pixel-by-pixel basis to detect the activated area. A t-value threshold of 2.4 ($p<0.01$) and minimal cluster size of three pixels was applied.

Results In a GE-EPI sequence with bipolar gradients, the coupling between the bipolar gradients and the field inhomogeneity gradients is significantly reduced compared to a PGSE sequence [5]. Fig. 1 shows the normalized ADC values measured on a cortical ROI by GE-EPI and PGSE-EPI sequences at modulated field inhomogeneity levels, reflected by the ΔR_2* values. Our results confirm that the ADC measured by a PGSE-EPI sequence is influenced by the field inhomogeneity, while the GE-EPI sequence is much less sensitive. The ADC decrease vs ΔR_2* is nearly linear for PGSE-EPI, and can be fitted as: $\Delta ADC/ADC = 1 - 0.002 \cdot \Delta R_2$* ($\Delta R_2$* in s^{-1} unit).

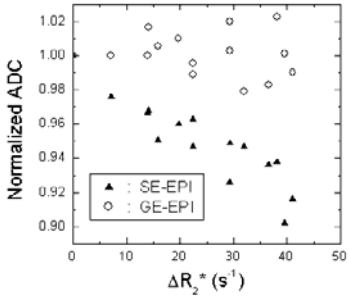

Fig. 1 Normalized ADC values measured by the GE-EPI and PGSE-EPI sequences (n = 5) as a function of susceptibility change caused by various doses of contrast agent injection.

For functional studies measured with GE-EPI sequence, Fig. 2a shows the t-map of GE-BOLD (at b = 5 s/mm^2) for a representative animal. A large area of signal increase is observed at the primary visual cortex, depicted by the green contour. The ADC response obtained from small diffusion weighting (b = 5 and 200 s/mm^2, Fig. 2b) shows activation-induced ADC increase. The activated pixels at the brain parenchyma originate from the functional increase of blood flow and volume of the arterial blood [3]. There are also highly activated pixels at the cortical surface, which is likely due to the inflow effect since our repetition time (0.5s) is not enough to reach full T_1 recovery. The average ADC increase is ~1% at the middle of the cortex, agreeing with our previous results obtained with a SE-EPI sequence [3]. With higher diffusion weighting (b = 200 and 1000 s/mm^2, Fig. 2c), the ADC response shows both positive and negative activated pixels. Many pixels at the surface of the cortex show positive ADC changes, where these pixels were also highly activated in the BOLD map and in the ADC map of the small b-value pair. Similar characteristics were observed in all six animals. The origin of these positive pixels is likely due to residue intravascular blood signal which is not fully crushed by the b = 200 s/mm^2 gradients. These positive pixels were significantly reduced when a longer TR of 1s and a smaller flip angle was used, as shown for another animal (b = 200 and 1200 s/mm^2, Fig 2d). In Fig. 2c (and 2d) the negative ADC change located at the parenchyma as well as at the cortical surface, but is smaller in extent than both the BOLD map and the ADC map obtained from the small b-weightings (Fig. 2a and 2b). The averaged SNR of the ADC image calculated from large b-weightings is 264 ± 68 (n=9), and the averaged number of negatively activated pixels detected on the cortex is 80 ± 40 (n=9).

Discussions Our results show that the ADC measurement using diffusion weighted GE-EPI sequence is insensitive to the background susceptibility effect, while a SE-EPI sequence is linearly dependent on the ΔR_2*. For typical ΔR_2* value of ~1 s^{-1} for anesthetized cat visual stimulation at 9.4 T, the results of Fig. 1 indicate that in our previous PGSE-EPI experiments, the relative ADC decrease due to the susceptibility effect is small (~ 0.2%) [3]. Using GE-EPI, transit ADC decrease is observed with much smaller spatial extent compared to the BOLD functional map. However, the ADC-decreasing pixels appear at the parenchyma as well as the cortical surface, and are not as well localized to the middle cortical layer as those obtained by the CBV-weighted fMRI results [6]. Furthermore, the time course obtained from these negatively activated pixels are similar to that of a hemodynamic response (not shown). These results suggest that source of the ADC decrease we observed may be complicated and can still be hemodynamic-related. Our results also suggest that b = 200 s/mm^2 may not fully suppress the intravascular signal. In order to detect ADC changes truly from the extravascular space, it is necessary to ensure that the intravascular signal is eliminated, such as by injection of contrast agents.

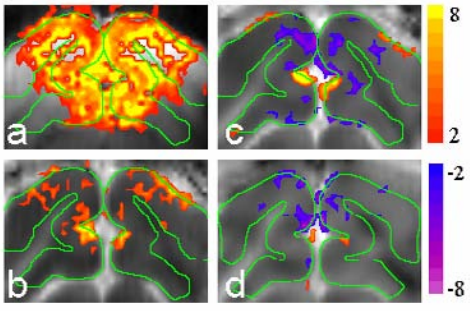

Fig. 2 (a): BOLD (b = 5 s/mm^2) t-map for a representative animal. ADC t-maps calculated from b = 5 and 200 s/mm^2 (b), and 200 and 1000 s/mm^2 (c). (d): ADC t-map calculated from 200 and 1200 s/mm^2 with reduced inflow-effect, from another animal. The t-values are represented by the colors as shown except in (a) where t is from 5 (red) to 15 (yellow).

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References: [1] Darquie A et al., *PNAS* 98:9391-9395 (2001). [2] Le Bihan D et al., *PNAS* 103:8263-8268 (2006). [3] Jin T et al., *Magn. Reson. Med.* In press (2006). [4] Does MD et al., *Magn. Reson. Med.* 41:236-240 (1999). [5] Song AW et al., *NeuroImage* 20:955-961 (2003) [6] Zhao F., et al., *NeuroImage* 30:1149-1160 (2006).