In Vivo Investigation of Restricted Diffusion in Human Brain Using Oscillating Diffusion Gradients

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INTRODUCTION – In the presence of cellular barriers, such as tissue membranes and different organelles, diffusion in biological tissue is restricted. The microstructural composition and the restrictions it imposes on diffusive motion lead to apparent diffusion coefficient (ADC) measurements that depend on the "shutter speed" of the diffusion probing tool (a.k.a. the diffusion time). The dependence of diffusion on the motion probing time allows one to infer further microstructural details beyond conventional ADC measurements. As the motion probing interval increases, ADC measurements will reveal increased diffusion restrictions due to an increased likelihood for spins to be affected by cellular obstacles within their diffusion trajectory. Theories have been developed relating the time dependent behavior of the ADC to geometric parameters of tissues [1]. Experiments on mice have been successfully carried out with ultra-shot diffusion times and relatively high b-value in animal MRI scanners to validate these theories and promise a new type of contrast [2,3]. However, to our knowledge, previous *in-vivo* human studies [4,5] have not been able to observe the time dependency of ADC (measured at constant b-value) due primarily to the relatively long minimum diffusion time used. The goal of the current study was to achieve short minimum diffusion time (4 ms) at an acceptable b-value and echo time on a standard 3 T human MRI system and to investigate the time dependency of the ADC in human brain *in vivo* by using cosine-modulated diffusion-encoding gradients.

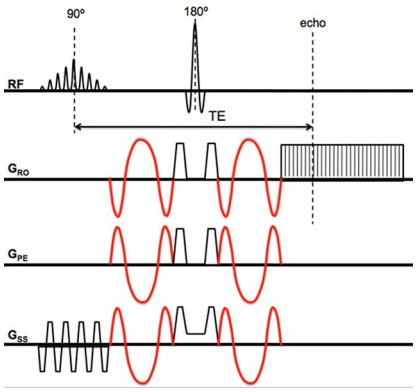

Fig. 1 *– Sequence diagram.*

METHOD – Apodized cosine-modulated gradients were designed to replace the traditional trapezoid diffusion-encoding gradients in a 2D spin-echo diffusion sequence (Fig. 1). As in [2,3], the apodization was performed by replacing half of a cosine period with two halves of a sine period at twice the frequency of the cosine straddling each diffusion block. The cosine gradient waveform was chosen because of its better performance in revealing the time dependency characteristic of ADC than the sine and repeated trapezoid waveform [2,6]. The bipolar gradient waveform usually has a very low diffusion-attenuation effect. Thus, to maximize gradient performance, a tetrahedral diffusion-encoding scheme was used. The diffusion-encoding parameters were: TE = 116 ms, b-value = 150 s/mm^2, diffusion times of 4 ms, 6 ms, 8 ms, and 10 ms, corresponding to the cosine gradient frequencies of 62.5 Hz, 41.7 Hz, 31.3 Hz, and 25 Hz. Phantom studies were carried out to verify the achieved b-value across different diffusion times. Other imaging parameters were: 2x2x5mm^3 resolution, 3-shot EPI readout, GRAPPA R=3, partial Fourier acquisition with 24 over scan lines, spatial-spectral pulse for water excitation, NEX=10. The study was IRB approved. Three healthy volunteers were scanned on a 3T GE system (G_{max}= 50mT/m, S_{max}=200 mT/m/ms) after written informed consent was obtained.

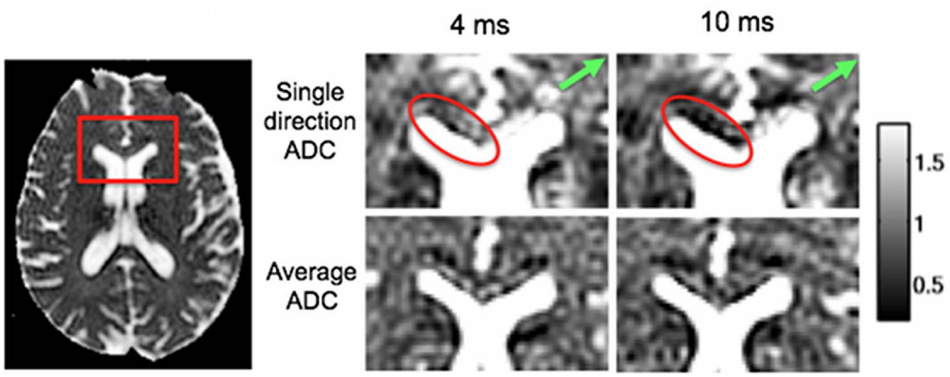

Fig. 2 *– ADC maps (in unit of 10^{-3} mm^2/s). Left: full FOV average ADC map at 4 ms diffusion time. Right: Zoom-in ADC maps approximately in the ROI pointed out by the red rectangle on the left. Top row: single direction ADC map from subject 1. Bottom row: average ADC map from subject 2.*

RESULTS & DISCUSSION – Figure 2 (left) shows an ADC map obtained from averaging all four gradient directions. To illustrate the observed diffusion time dependence of the ADC, zoomed ADC maps are shown for the shortest (4 ms) and longest (10 ms) diffusion time. When ADC maps were computed from a single diffusion direction (top row), the long diffusion time result shows significantly low ADC values at locations where fibers are running predominantly perpendicular to the diffusion-encoding direction (the in-plane diffusion encoding direction is shown by the green arrow on the top right corner of each sub figure). At a shorter diffusion time (4 ms), the measured ADC in these fibers increases. However, the ADC is still lower than ADC values measured on the contra-lateral side, where fibers run predominantly parallel to the gradient. This suggests that the effects of diffusion restriction imposed by boundaries just starts to increase the ADC at a diffusion time of 4 ms. When multiple diffusion directions are averaged, also the time-dependency effect is mostly drowned by the high diffusivity along fibers, but it is still observable in the genu of the corpus callosum (Fig. 2). Fig. 3 plots the changes of the ADC obtained from a single diffusion encoding direction in an ROI in one side of the genu of the corpus callosum of one subject showing the decreasing trend of the ADC as the diffusion time increases.

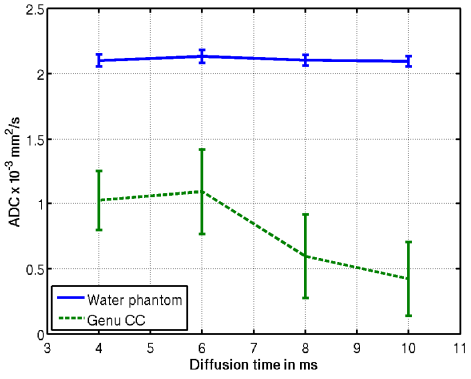

Fig. 3 *– Time dependency of the measured ADC from a single diffusion direction in one side of the genu of the corpus callosum on a subject. ADC measured in a water phantom at the same diffusion times is shown for reference.*

CONCLUSION – The use of cosine-modulated diffusion gradients at a reasonably low diffusion times has been shown for the first time in *in vivo* human studies without the use of high-performance gradients. The added microstructural information that can be inferred from the time-dependency of ADC may have utility in early detection of degenerative disease of the brain, such as AD, or in MS.

References:[1] Mitra et al, Phys Rev B. 47: 8565-74, 1993; [2] Does et al, MRM. 49: 206-15, 2003; [3] Aggarwal et al, MRM. In press, 2011; [4] Le Bihan et al, Neuroreport. 4: 887-90, 1993; [5] Clark et al, MRM. 45: 1126-29, 2001; [6] Parsons et al, MRI. 21: 279-85, 2003.

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