Dependence of Fractional Anisotropy on Diffusion Time: A Frequency-Domain Analysis Using Temporal Diffusion Spectroscopy

J. Xu[1], H-K. Jeong[1], M. D. Does[1], A. W. Anderson[1], L. Chen[1], and J. C. Gore[1]

[1]Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States

Introduction: The relative values of the components of the diffusion tensor in white matter are expected to depend on the choice of diffusion time used in acquiring DTI data. However, it has been reported that the fractional anisotropy (FA) of human brain shows no significant changes with diffusion times in the range 8–80ms (1). Presumably, this is because these applied diffusion times are not short enough to allow water movements to be appear less restricted (2). The relevant diffusion lengths are still large, compared to cellular dimensions, and FA is almost constant in the applied diffusion time range. In the present work, the FA dependence on diffusion time was studied using temporal diffusion spectroscopy (3), which employs an oscillating gradient spin echo (OGSE) sequence and has the ability to probe much shorter diffusion times (~0.8ms for highest frequency, 300Hz used in this study).

Methods: *Theory*: In the frequency domain, diffusion weighted MR signals can be written as $S = S_0 \exp\left(-\frac{1}{\pi}\int_0^\infty \mathbf{F}(\omega)\mathbf{D}(\omega)\mathbf{F}(\omega)d\omega\right)$, where $\mathbf{F}(\omega) = \int_0^\infty dt \exp(i\omega t)\int_0^t dt'\gamma\mathbf{G}(t')$, **G** is the diffusion gradient and **D**(ω) is the diffusion spectrum.

Different effective diffusion times can be achieved by modulating **G** with oscillating waveforms, e.g., cos(ωt). Higher gradient modulation frequencies correspond to shorter diffusion times. For a cosine-modulated waveform, effective diffusion times in non-restricted media can be related to gradient frequencies by $t_{diff} = \pi/(2\omega)$ (3).

Brain specimens: Brain tissue was obtained from an adult male squirrel monkey (*saimiri sciureus*). One hemisphere was fixed by immersion in 10% formaldehyde solution for several months. Before the DTI measurements, the brain was washed by immersion in a solution of 2% phosphate buffer saline (PBS) for five days, each day with four times larger volume of PBS. This removes the free fixation solution in the tissue and the tissue T_2 returns close to those of normal tissues (4).

DTI experiments: DTI was implemented on a Varian 4.7T MRI system (Varian Inc. Palo Alto, CA) equipped with a micro-gradient coil providing a maximum amplitude =100G/cm. An apodised cosine-modulated gradient waveform (2) was used with diffusion gradients applied in six directions [(x, y,0), (x, 0, z), (0, y, z), (-x, y, 0), (-x, 0, z), (0, -y, z)]. Each gradient waveform has a duration of 20ms, b=500s/mm^2, TE=52ms, TR=3s, slice thickness 2mm, FOV=35×35mm, matrix size 128×128 and NEX=10. Six gradient frequencies were used, evenly ranging from 50Hz to 300Hz, corresponding to effective diffusion times from 5ms to 0.8ms.

Computer simulation: A computer simulation using the finite difference method (5) was performed to investigate the dependence of white matter (WM) FA on gradient frequencies. The WM was modeled as parallel cylinders on a square grid. The intra- and extra-cellular intrinsic diffusion coefficients are assumed to be 1.0 and 2.0μm^2/ms, respectively. The cylinders have a diameter of 1.96 μm, and the spacing of the lattice is 2.1μm, yielding a cylinder volume fraction 75.25%. Δx=0.1μm, Δt=1μs.

Results and Discussion: Fig.2 shows a clear dependence of measured WM FAs (top) on gradient frequency. FA decreases 28% from 0.69 to 0.49 in a frequency range 50Hz to 300Hz. This means the water molecules are much less restricted by boundaries/hindrance in some direction(s) at the shorter diffusion times. By contrast, there is no significant change of gray matter FA even when the frequency goes up to 300Hz. Fig.3 shows the WM FA dispersion curve obtained from computer simulations in a broader frequency range 50-10kHz. It is clear that FA in the model system decreases significantly with increasing gradient frequencies, especially at frequencies less than 1kHz. At higher frequencies (>4kHz), WM FAs are less than 0.2, which means most water molecules are unaffected by restricting (axon) boundaries and the diffusion is overall close to isotropic behavior. A limitation of the study is that even after washing with PBS five days, the WM T_2 of this brain was still low (23ms), which yields low SNRs with TE=52ms. In future studies, a tissue slice model (6) will be used to achieve larger T_2 and hence better SNRs.

Conclusion: Unlike previous studies using the conventional PGSE method with relatively long diffusion times, a temporal diffusion spectroscopy method has been used in the current work to achieve diffusion times as short as 0.8ms. A clear dependence of white matter factional anisotropy on effective diffusion time has been observed in a fixed monkey brain. The results were also predicted by computer simulations. The dependence observed in this study provides a means to probe diffusion restriction and hindrance at sub-cellular length scales, e.g. intracellular structures, and may provide insights into the microstructure of biological tissues and clarify the origins of anisotropy diffusion in white matter.

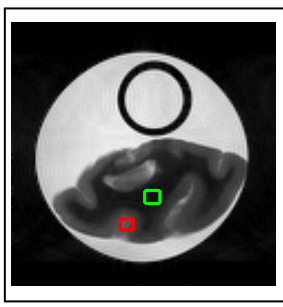

Fig.1 (left) T_2-weighted image of the monkey brain. Two ROIs for analyzing white matter (green) and gray matter (red). The plastic tube above the brain is to prevent tissue from vibration in scanning.

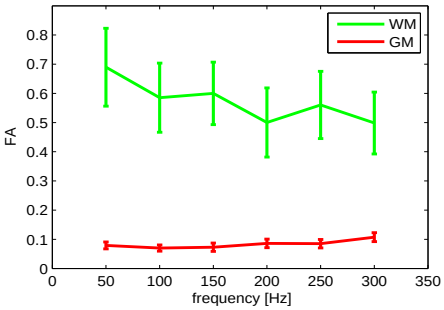

Fig.2 Measured white matter FA (top) and gray matter FA (bottom) change with gradient frequency. Error bars are standard deviations of the ROIs.

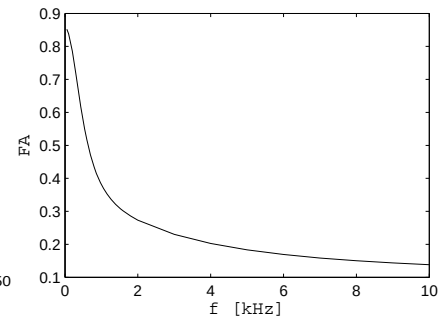

Fig.3 Simulated white matter FA dispersion curve.

References: (1) Clark et al. Magn Reson Med, 2001 (2) Does et al. Magn Reson Med, 2003 (3) Parsons et al. Magn Reson Med 2006 (4) Shepherd et al. Magn Reson Med 2009 (5) Xu et al. Phy Bio Med 2007 (6) D'Arceuil et al. Neuroimage 2007