An approach to high resolution diffusion tensor imaging (DTI) in fixed brain tissue

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Introduction

There is growing interest in MRI of fixed neural tissue. Recent DTI studies have shown that while the brain's T_1, T_2 and ADC values are reduced by tissue fixation, diffusion *anisotropy* is preserved (1-3). We have developed an approach for acquiring high resolution 3D DTI of fixed brain tissue using a relaxation agent gadopentate dimeglumine to provide optimal SNR within the scanner hardware limitations.

Methods

Brain Specimens

Formalin fixed brain tissue (whole and tissue sections) was obtained from an ongoing study of stroke in nonhuman primates (de Crespigny, 2005). We only evaluated the contralateral, non-ischemic hemisphere. The optimum Gd concentration for contrast enhanced DTI studies was calculated based on T_1, T_2 and T_2^* relaxivity (2.5mm coronal sections of the normal occipital lobe of one animal). Sections were soaked in phosphate buffered saline (PBS) and either 0, 1, 5 or 10mM gadopentetate dimeglumine (Magnevist) at 4ºC for 4 days prior to imaging. Whole brains (6 adult male macaques, M. Fasicularis, 7-9kg) were placed in a solution of 2% PBS mixed with Gd. Brains were placed in a dedicated plexiglass sealable chamber, held immobile with a moulded thermoplastic base and cap, the chamber filled with Fomblin liquid and air bubbles evacuated.

MR Imaging

Brain sections were imaged on 4.7T and 9.4T/20cm horrizontal bore, and 14T/89mm vertical bore Bruker systems with the following imaging parameters: **T_1;** slice selective inversion recovery fast spin-echo sequence, 2ms sech inversion pulse, 9 inversion times between 5ms-2s. Shorter inversion times for the higher Gd concentrations. **T_2;** multi-slice multi-echo spin-echo sequence, 8 echoes, echo spacing 10ms (up to 1mM Gd) or 5ms (5, 10mM Gd). **T_2^*;** multi-echo gradient echo sequence, 8 echoes, echo spacing of 7 (up to 1mM Gd) or 5ms (6, 10mM Gd).

Relaxivity Measurements

3D spin-echo diffusion weighted EPI sequence (0.45mm voxels, δ=5.2ms, Δ=16.5ms, b=4100s/mm^2, 20 directions (4)).

Whole brain scans were acquired using the following; 4.7T/33cm bore Oxford magnet interfaced to a Bruker Biospec Avance console (ParaVision 3.0.1), a 12cm i.d. Bruker gradient set, Bruker 72mm i.d. birdcage coil, a standard 3D spin-echo Stejskal-Tanner diffusion imaging sequence, b_{max}=4025s/mm^2, δ=6.9ms, Δ=10.4ms, TR 250ms, minimum TE=31.7ms, maximum diffusion gradient strength=380mT/m. δ 6.9ms, Δ 10.4ms, 20+2 directions, 425μm or 440μm isotropic resolution, scan time about 25 hours.

Data Processing

Images were processed with MRVision software (MRVision Co.) for T_1, T_2, T_2^*, ADC and FA maps. DTI tractography used the FACT algorithm DTIStudio Software, Jiang and Mori, Johns Hopkins University, MD).

Results

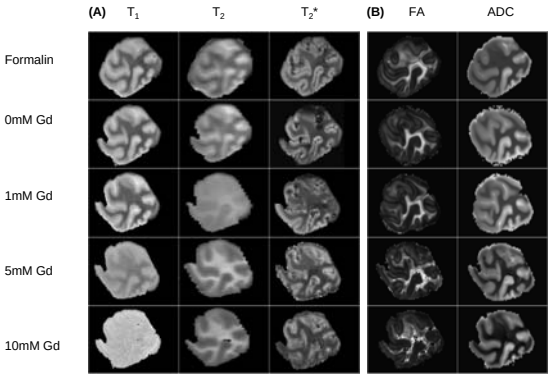
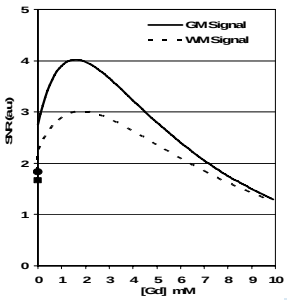


Figure 1. (A) Relaxation maps and (B) diffusion maps(ADC) in normal occipital cortex Relaxation times were greatly reduced with increasing Gd concentration,images *individually* window/leveled. With increasing Gd concentration, gray-white T_2 and contrast decreased to zero, T_2^* contrast decreased somewhat, while T_1 contrast reversed. FA and ADC maps (*same* window/level settings for all Gd concentrations). Gray and white matter FA was, virtually unchanged with increasing Gd concentration. Gray matter ADC changed little while white matter ADC decreased at concentrations of 5 and 10mM.



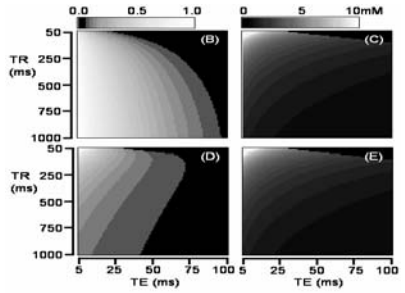


Figure 2. (A) Variation of relative spin-echo SNR with gadolinium concentration at 4.7T for gray and white matter soaked in Gd/PBS, TR of 250ms, TE 32ms. Values for gray (●) and white (■) matter in Formalin also shown. (B) Log plot of the peak SNR (i.e. the maxima of curves such as (A)) against TE and TR for white matter at 4.7T (assuming all other pulse sequence parameters are held constant). (C) The optimum gd concentration which gives the peak SNR shown in (B) (i.e. the position of maxima in curves such as (A)). (D) Peak SNR per unit time and (E) corresponding optimum Gd concentration. Plots for gray matter and higher field strengths are qualitatively similar.

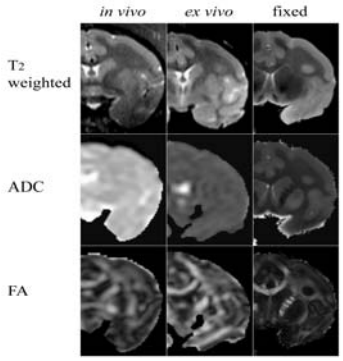


Figure 3. Images showing the normal hemisphere of approximately the same coronal section in the same brain scanned *in vivo*, at 2.5 hours post mortem and after Formalin fixation. *In vivo* and 'freshly' *ex vivo* data was acquired at 1.5T using multislice spin-echo (T_2-wt) and EPI (ADC, FA) sequences. The Formalin fixed brain was scanned at 4.7T using a 3D spin-echo sequence.

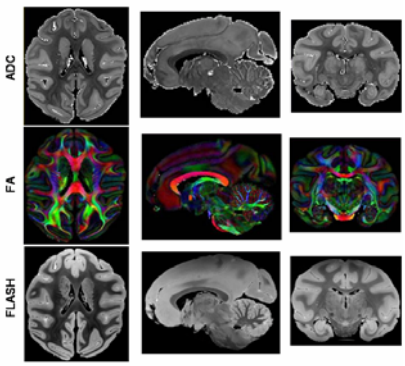


Figure 4. Othogonal planes through 425μm trace ADC maps, FA maps, and gradient echo FLASH (175μm) images of a fixed macaque brain. Voxel color in the FA maps encodes princple eigenvector direction in the usual way (red=LR, green=AP, blue=SI).

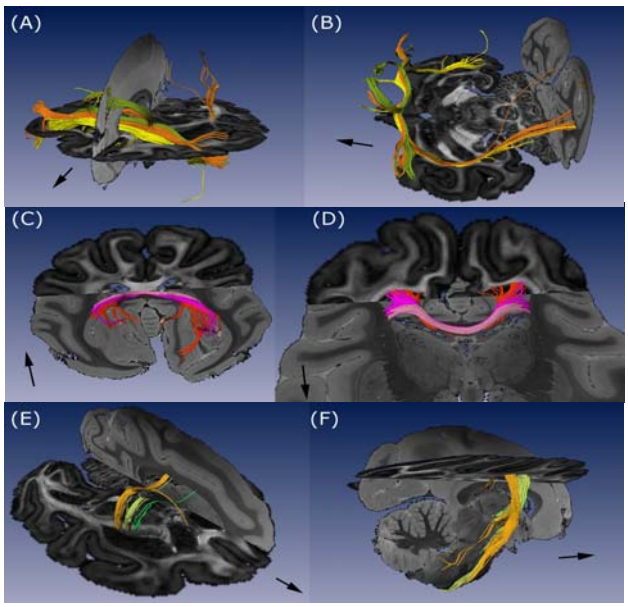


Figure 5. Left, DTI tractography whole brain. Background images are FA maps and coregistered structural (FLASH) images. Arrows indicate the direction of the front of the brain. Fiber bundles are color coded according to the seed ROI. Sets of three adjacent seed regions were placed manually in the left hemisphere in (A,B) forceps minor and (C,D) forceps major of the corpus callosum, and the (E,F) posterior limb of the internal capsule.

Conclusions

- Relaxation properties of fixed tissue can be modified to suit scanner hardware limitations.
- At least double the SNR per unit time for *Gd-soaked* 3DFT DTI scans on our 4.7T system.
- Diffusion anisotropy preserved, ex-vivo brains compared to in-vivo brains.
- High resolution DTI tractography possible in whole primate brains which will facilatate the process of 'validation' of tractography results by direct comparison with more traditional measures of fiber architecture.

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