High *b*-value diffusion-weighted imaging on human spinal cord *in vivo*: Investigation of signal dependence on diffusion time

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Purpose: The goals of this study were (a) to acquire very high *b*-value images to study molecular diffusion *in vivo* in human cervical spinal cord (SC), and (b) to study the effect of increasing diffusion time (Δ) on parameters, such as the apparent diffusion coefficient (ADC), that are used to characterize the diffusion signal decay. High *b*-value diffusion-weighted (DW) images were acquired within clinically acceptable scan durations using stimulated echo acquisition mode (STEAM[1]) followed by echo planar imaging (EPI) acquisition. The results from this study are expected to provide a context to aid in the understanding of pathology resulting from spinal cord injury.

Methods: An EPI sequence was modified to acquire DW images with STEAM. Diffusion-weighting gradients were applied before the second RF pulse and after the third RF pulse. The mixing time (TM), defined as the duration between second and third RF pulses, was user-selectable with a maximum possible value of 2 seconds and corresponding $b \sim 31{,}000$ s/mm^2.

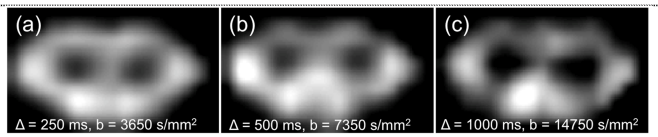

FIGURE 1: DW-STEAM images with maximum possible b-values for diffusion times (Δ) of (a) 250 ms, (b) 500 ms, and (c) 1000 ms. Window and level settings were adjusted independently for each image.

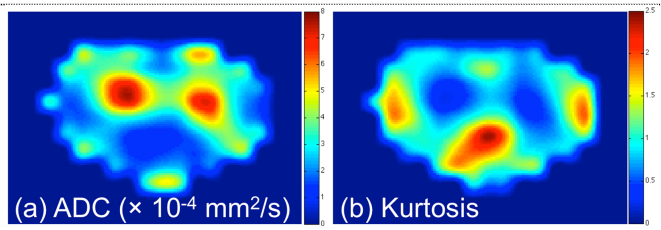

FIGURE 2: (a) ADC and (b) kurtosis maps using DK fit on bmax data acquired with Δ = 1000 ms on one volunteer.

The DW STEAM EPI imaging sequence was used to acquire axial images of the cervical spinal cord (C4-C5) in six healthy volunteers (3 female, age = 18–32 years), using the upper six channels of a twelve-channel cervical-thoracic-lumbar (CTL) RF receiver coil array. TM was progressively increased so that Δ = 250, 500, and 1000 ms. For each Δ, twelve images were acquired with increasing diffusion weighting and the following imaging parameters: TR = 2500 – 4000 ms, TE = 60 ms, 8-12 signal averages, FOV = 12 cm, acquisition matrix = 96 × 48 (reconstructed matrix of 128 × 64), left-to-right frequency direction, phase FOV = 0.5, slice thickness = 10 mm, with spatial saturation bands placed anterior and posterior to the slice and diffusion sensitization in the right-left direction. The maximum possible *b*-values corresponding to increasing Δ were 3650, 7350, and 14750 s/mm^2, and increased spacing was used between the higher *b*-values.

Images were reconstructed from the raw *k*-space data. After subtraction of the noise floor, a region of interest (ROI) was selected to include the entire spinal cord. For each volunteer and Δ, the signal decay curve (S_b) obtained from the selected ROI was input to two fitting equations using a non-linear least-squares algorithm: the mono-exponential fit (ME[2], $S_b = S_0 e^{-bD}$), and the diffusional kurtosis fit (DK[3], $S_b = S_0 e^{-bD+(bD)^2 K_{app}/6}$), where S_0 is the signal at $b \sim 0$ s/mm^2, D is the ADC, and K_{app} is the excess kurtosis of the diffusion displacement probability function. All models were implemented using MATLAB. The ROI analysis was performed on the entire dataset (called bmax) and on a subset of the data (called b3500) using the signal decay curves corresponding to $b = 0 \sim 3500$ s/mm^2. This resulted in 12, 8, and 5 points in the b3500 datasets for Δ = 250, 500, and 1000 ms, respectively. Parameter maps were generated for the ROI.

Results: Figure 1 shows example DW images from one volunteer, with increasing Δ and corresponding maximum *b*-value. The images show the contrast between anterior horns of gray matter (GM) and surrounding white matter (WM) increasing with *b*-value, particularly at $b = 14750$ s/mm^2, where the posterior horns of gray matter are also visible. This observation was supplemented by the parameter maps (Fig. 2), which show variations not only between GM and WM as expected, but also among WM regions in the SC. Consistent results were obtained across subjects for each fitting approach (Table 1), with generally decreasing variation as *b*-range increased. Pairwise *t*-tests showed statistically significant differences between Δ = 1000 ms and Δs of 250 and 500 ms in the bmax data. Analysis of b3500 data showed no statistically significant differences between Δs, indicating that the variations in fitting parameters in the bmax data are due primarily to differences in the *b*-value ranges rather than intrinsic diffusion differences across this range of Δ.

Discussion and Conclusions: STEAM EPI allows the acquisition of DW images with long Δ (and therefore large *b*-values) with less signal loss related to T_2 relaxation. Our results indicate that larger *b*-ranges can provide greater consistency to the fitting. However, the ME and DK equations suffer from *b*-value limitations[4], indicating the need for other robust models that account for signal decay independent of *b*-range and incorporating properties intrinsic to the tissue being studied, e.g., AxCaliber[5]. No dependence of the diffusion signal decay on diffusion time was observed in this range of Δ in healthy volunteers. To our knowledge, this is the first time the human cervical spinal cord has been studied *in vivo* with such high *b*-value and long Δ ranges. Future work includes analyses of other regions of SC, with the use of gating or compensation for cardiac and respiratory motion in thoracic and lumbar sections of the SC.

TABLE 1: ME and DK fitting parameters (mean ± inter-subject standard deviation) generated from ROIs in bmax and b3500 datasets, showing statistically significant differences in ADCs obtained across pairs of Δ in the bmax data (given by *, #). The b3500 data does not show significant differences across this range of Δ.

Δ (ms) / b_{max} (s/mm^2)	--- Monoexponential fit ---		---------- Diffusional Kurtosis fit ----------			
	ADC (bmax) (× 10^{-4} mm^2/s)	ADC (b3500) (× 10^{-4} mm^2/s)	ADC (bmax) (× 10^{-4} mm^2/s)	ADC (b3500) (× 10^{-4} mm^2/s)	K_{app} (bmax)	K_{app} (b3500)
250 / 3650	4.09 ± 1.25#	4.09 ± 1.25	6.25 ± 1.83#	6.25 ± 1.83	1.21 ± 0.28	1.21 ± 0.28
500 / 7350	2.82 ± 1.1*	3.64 ± 1.05	4.79 ± 1.22*	5.54 ± 0.49	1.04 ± 0.24	1.15 ± 0.59
1000 / 14750	1.61 ± 0.46*#	3.27 ± 0.57	3.04 ± 0.61*#	5.13 ± 0.9	0.92 ± 0.17	1.2 ± 0.18

References: (1) Frahm *et al.*, *J Magn Reson*, 64:p81, 1985 (2) Le Bihan *et al.*, *Radiol*, 161:p401, 1986 (3) Jensen *et al.*, *Magn Reson Med*, 53:p1432, 2005 (4) Jensen *et al.*, *NMR Biomed*, 23:p698, 2010 (5) Assaf *et al.*, *Magn Reson Med*, 59:p1347, 2008.