Direct evidence for decreased intra-axonal diffusivity in ischemic human stroke

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INTRODUCTION: Diffusion MRI is a sensitive and a reliable clinical tool for the early detection and localization of acute and subacute stroke[1]. Within minutes after stroke onset, the diffusion coefficient is reduced in ischemic lesions by approximately 50% relative to normal tissue[2]. The origin of this effect is still under debate[3-6]. In addition, several recent studies using Diffusional Kurtosis Imaging (DKI), a clinically feasible extension of diffusion tensor imaging (DTI) that quantifies non-Gaussian water diffusion, have shown substantial increases in the kurtosis within ischemic lesions[7-11]. Recently, we introduced a white matter (WM) model[12], allowing a direct physical interpretation of the DKI metrics in terms of specific microstructural characteristics of WM[13] such as the axonal water fraction, the intra-axonal diffusivity D_{axon}, and the extra-axonal axial and radial diffusivities, $D_{e,\parallel}$ and $D_{e,\perp}$. In this work, we characterize the changes in these WM integrity metrics within ischemic lesions to help elucidate the underlying biophysical mechanism.

METHODS: Eight subjects (5 male; mean age 64 ± 14, range 50-92 yrs) with a clinical diagnosis of acute to subacute stroke with ischemic lesions in the WM were selected for this research study. All subjects were scanned on a 1.5 T Avanto Siemens MR scanner within 23 to 43 hours after symptom onset and were not treated with tissue plasminogen activator (tPA). DKI acquisition was performed with 3 b-values (0, 1 and 2 ms/μm^2) along 30 diffusion encoding directions using single-shot twice-refocused-EPI with NEX=1 (NEX=10 for b=0). Other imaging parameters were: acquisition matrix = 74 x 74, image resolution = 3 x 3 x 3 mm^3, TR/TE = 5.5 s/99 ms, BW/pixel = 1325 Hz, FOV 222×222 mm^2, parallel imaging factor of 2, 40 oblique axial slices. DKI parametric maps were calculated[14] and then used to derive WM parametric maps[13] of the axonal water fraction (AWF), the intra-axonal diffusivity (D_{axon}), extra-axonal axial diffusivity ($D_{e,\parallel}$), and extra-axonal radial diffusivity ($D_{e,\perp}$). For each subject, a single slice was selected that best showed the ischemic lesion in the WM. Regions of interest (ROIs) were defined in each WM lesion using the mean diffusivity (MD) and mean kurtosis (MK) maps, and ROIs of the same size were located on a corresponding area of the normal-appearing contralateral hemisphere using the fractional anisotropy (FA) map (see example in Fig. 1). Mean values of the four WM integrity metrics were obtained by averaging the maps over the ROIs. The percentage changes caused by ischemia were calculated according to:

$$\text{Percentage change} = 100 \times \frac{X_{\text{ischemia}} - X_{\text{contralateral}}}{X_{\text{contralateral}}}, \text{ where X represents an averaged WM metric.}$$

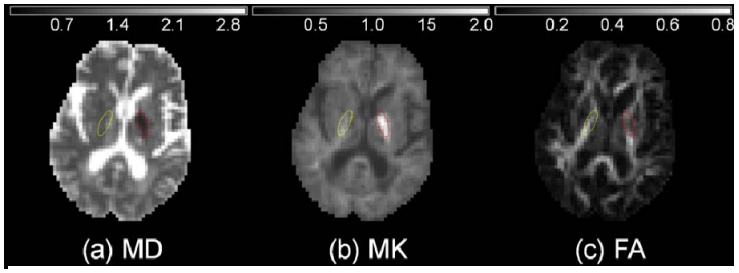

Fig. 1: Axial maps of three DKI metrics. The ischemic lesion in the white matter is hypointense on the MD-, and hyperintense on the MK-map. ROIs are drawn of the white matter lesion (red) and the corresponding area of the normal-appearing contralateral hemisphere (yellow).

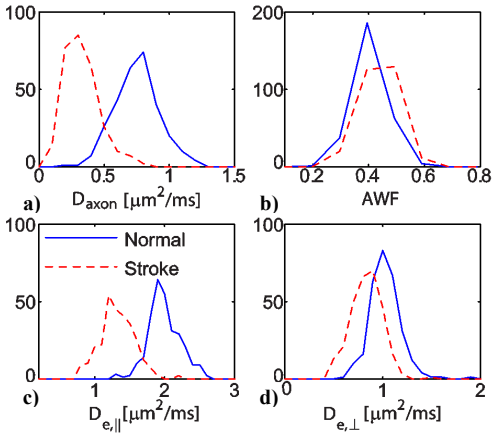

Fig. 2:Probability distributions for the WM integrity metrics for the ischemic ROIs, and contralateral ROIs of all 8 subjects: (a) intra-axonal diffusivity D_{axon}; (b) axonal water fraction (AWF); (c) axial extra-axonal diffusivity $D_{e,\parallel}$; (d) radial extra-axonal diffusivity $D_{e,\perp}$

RESULTS: An example of MD, MK and FA parametric maps is shown in Fig. 1. We observe that MD is hypointense, while MK is hyperintense in the ischemic lesion relative to the contralateral hemisphere. At the same time, FA does not demonstrate objective visual changes. Probability distributions for each WM metric from all 8 subjects are depicted in Fig. 2, showing significant shifts towards smaller values in D_{axon} and $D_{e,\parallel}$, $D_{e,\perp}$, while the AWF is only slightly increased within ischemic lesions compared to normal tissue. The percentage changes averaged over all 8 subjects are shown in Fig. 3: D_{axon}, $D_{e,\parallel}$ and $D_{e,\perp}$ were reduced in the ischemic regions by 55±7%, 34±3%, 20±6%, respectively, whereas the AWF is increased by 5±10%.

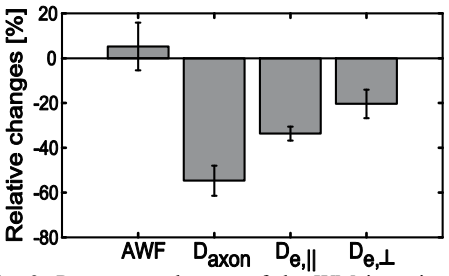

Fig. 3: Percentage changes of the WM integrity metrics in the ischemic ROI relative to the contralateral ROI, averaged over all 8 subjects. The error bars indicate standard errors.

DISCUSSION: By using the newly proposed WM integrity metrics, we find that the decrease in the diffusion coefficient observed in subacute ischemic human stroke is mainly due to a significant drop in the intra-axonal diffusivity D_{axon}. As both the intra- and extra-axonal diffusivities are reduced, it is possible that axonal beading[15] may modulate the diffusivity along axons and provide main restrictions to diffusion in the intra-axonal space, while also increasing the tortuosity of the extra-axonal space. In this respect, our *in vivo* results are consistent with the recent suggestion[6], based on DWI measurements under *in vitro* tensile stress, that axonal beading reduces the overall diffusivity along the fiber. As our analysis is able to separate the extra- and intra-axonal diffusivities, we provide the key evidence that the separate changes in diffusivities of both compartments are consistent with axonal beading, as is the slight increase in the AWF.

To summarize, we report for the first time the MRI-based direct evidence of the reduction in the intra-axonal diffusivity associated with acute to subacute ischemic human stroke. Our results are consistent with the axonal beading restricting the diffusion both inside and outside axons.

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