In Vivo Observation of Time-Dependent Diffusion in White Matter in Humans

Lauren Burcaw[1], Jelle Veraart[2], Dmitry S Novikov[1], and Els Fieremans[1]

[1]*New York University School of Medicine, Bernard and Irene Schwartz Center for Biomedical Imaging, Department of Radiology, New York, NY, United States,* [2]*Vision Lab, Department of Physics, University of Antwerp, Antwerp, Belgium*

Target Audience: Researchers interested in exploring the microstructure of white matter (WM) using diffusion MRI.

Purpose: By varying the diffusion time, and thus the resultant diffusion length, one can glean information about WM structure, such as axonal dimensions and cell packing. In this abstract, we are concerned with the diffusion in both the axial and radial direction of major WM fiber tracts. The presence of restrictions to diffusion will manifest as a decrease in $D_{ax}(t)$ and/or $D_{rad}(t)$ with increasing diffusion time, t. The evidence is conflicting: both Stanisz *et al.*[1] and Assaf *et al.*[2] have observed this decrease in *ex vivo* measurements of bovine optic nerve on an NMR spectrometer. However, human *in vivo* measurements on a clinical scanner performed by Nilsson *et al.*[3] and Clark *et al.*[4] did not observe any effect. Here we perform *in vivo* diffusion tensor imaging (DTI) on 3 volunteers in order to study the time-dependence of both axial and radial diffusion.

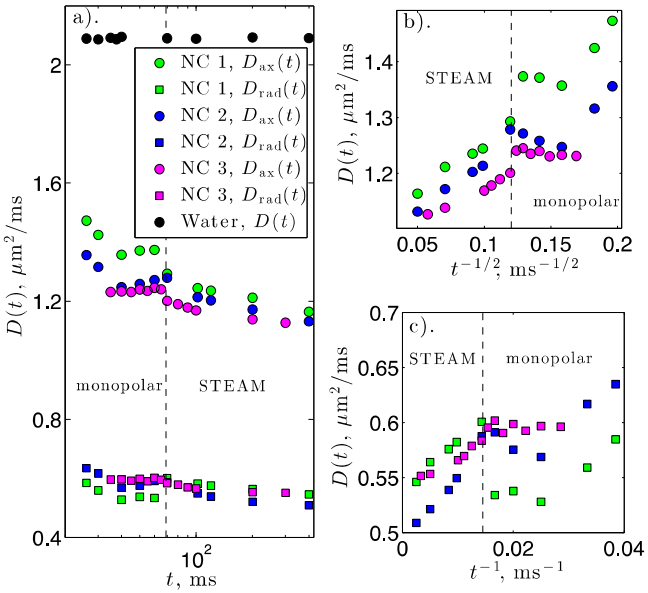

Figure 1: a). The axial and radial diffusion for 3 subjects. b). $D_{ax}(t)$ plotted with respect to $t^{-1/2}$. c). $D_{rad}(t)$ plotted with respect to t^{-1}.

Methods: Diffusion measurements are performed on 3 normal controls (NC) comprised of a 32 y/o female (NC 1), a 37 y/o male (NC 2), and a 30 y/0 male (NC 3) on a 3T Siemens Trio magnet using a 32 channel head coil. The WIP511 sequence as provided by the vendor is utilized to measure the time-dependent diffusion coefficient, $D(t)$. The protocols used are summarized in the table below.

Table 1: Summary of the diffusion protocols used.

	NCs 1 and 2			NC 3		
	***t* (ms)**	**b (s/mm^2)**	**TE (ms)**	***t* (ms)**	**b (s/mm^2)**	**TE (ms)**
monopolar	26 30 40-60	0,250, 500 0,350, 700 0, 1000	60 67.6 78.8-88.8	35-65	0,1000	78.8-95.6
STEAM	70 102-400	0, 1000 0, 1000	72.8 98.8	70-300	0,1000	73.2-51.2

Subjects are registered to the standard 1 mm^3 MNI FA template in FSL and a global WM region of interest was created by selecting voxels with FA > 0.4 and MD < 2 μm^2/ms (to avoid CSF contamination).

Results and Discussion: No time dependence is found in the water phantom. Overall, $D_{ax}(t)$ was observed to decrease over time for all subjects, while a less pronounced decrease was seen for $D_{rad}(t)$ (figure 1a). Restriction in the axial direction could be due to the presence of glial cells in the extra-axonal space, and/or due to nodes of Ranvier or axonal varicosities[5,6]. Since the axial diffusivity is effectively one-dimensional, and the restrictions along the axial direction are randomly placed[6], we would expect $D_{ax}(t)$ to follow the relationship $D(t) \cong D_\infty + ct^{-1/2}$, Ref. [7]. Indeed, in figure 1b, we plot $D_{ax}(t)$ with respect to $t^{-1/2}$ and see a reasonably linear dependence on $t^{-1/2}$. Similarly, restriction in the radial direction could be attributed to glial cells and/or the disordered axonal packing within a bundle. As radial diffusion is effectively two-dimensional, and the restrictions are also randomly placed, the radial diffusivity $D_{rad}(t)$ is expected[8] to take the form $D(t) \cong D_\infty + A\ln(t/t_0)/t$ which is fairly close numerically to $D(t) \approx D_\infty + B/t$. Indeed, plotting $D_{rad}(t)$ vs. t^{-1} shows an approximately linear trend for the STEAM data. Confounding factors include a noticeable trend in our data between 35 and 60 ms where the monopolar axial difusion for all subjects *increases* with respect to time. This effect could potentially be caused by the increasing TE (Table 1) and different compartment T2 values within the WM. Another feature of the data is a sharp decrease in diffusion with respect to time in NC 1 and 2 at the earliest time points t = 26 and 30 ms. It is unclear if this decrease is due to the differing b-values in these two time points compared to the rest of the data, cf. Table 1. Further work will focus on disentangling the effect of the b-value and varying TE on the observed diffusion values.

Conclusions: Using a clinical system, we observed a more pronounced time-dependence in $D_{ax}(t)$ compared to $D_{rad}(t)$. Future work will include refining the protocol to eliminate possible sources of contamination such as the varying TE times and b-values.

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