Direct Quantitative Comparison between Cross-Relaxation Imaging and Diffusion Tensor Imaging of the Human Brain

H. R. Underhill[1], C. Yuan[1], and V. L. Yarnykh[1]
[1]University of Washington, Seattle, WA, United States

Introduction: Diffusion tensor imaging (DTI) has been proven to be an effective tool for the visualization of white matter fiber tracts in the human brain based on the anisotropic diffusion effect. DTI also provides quantitative information about white matter architecture, which is typically expressed as the fractional anisotropy (FA) index [1]. Another quantitative imaging method, which was recently shown to be highly sensitive to regional white matter organization is cross-relaxation imaging (CRI) [2]. CRI produces quantitative maps of key parameters describing the magnetization transfer effect in tissues – the macromolecular proton fraction (*f*) and the cross-relaxation rate constant (*k*) [2]. The patterns of elevated macromolecular proton fraction *f* were demonstrated to be in close association with major fiber tracts in the human brain [2]. While literature data suggest that DTI and CRI provide specific contrast features highlighting fiber tract architecture, it remains unclear whether both modalities deliver similar or different information about brain tissue organization. In this study, we sought to conduct direct quantitative comparison between the CRI parameters *k* and *f* and the principle scalar metric of DTI, FA, in the human brain *in vivo*.

Methods: : Five healthy volunteers (4 male, 1 female, mean age 36.6 years, range 28 – 53 years) were imaged at 3.0 T (Philips Achieva, Release 2.1.1, Best, Netherlands) with a transmit/receive head coil. CRI data acquisition was performed according to the previously described time-efficient four-point method [2] adapted for 3T imaging. Four pulsed *Z*-spectroscopic data points with variable offset frequencies (Δ) of the off-resonance saturation pulse (effective flip angle 990°; Δ = 1, 2, 4, 8 kHz, duration 19 ms) were acquired with a 3D spoiled gradient echo sequence (TR/TE = 43/2.3 ms, α = 10°). A complementary R_1 map necessary for parameter fitting was obtained using the variable flip angle (VFA) method with a 3D spoiled GRE sequence (TR/TE = 20/2.3 ms, α = 3, 10, 20, and 40°). All *Z*-spectroscopic and VFA images were acquired with spatial resolution 1.5x1.5x3.0 mm (zero-interpolated to 1.0x1.0x1.5 mm) and one signal average. Scan time was 3.5 minutes and 2 minutes per point for *Z*-spectroscopy and VFA, respectively. To account for effects of B_0 and B_1 heterogeneity, whole-brain B_0 and B_1 maps were acquired using previously described techniques [3, 4] to establish actual offset frequencies of the saturation pulse and determine actual flip angles for parameter fitting. Total scan time for the entire imaging protocol was < 30 minutes. Data were fitted to a constrained model of magnetization transfer [2] to produce whole-brain *k*- and *f*-maps.

DTI was performed using a single-shot 2D echo-planar sequence (TR/TE =11824/60, α=90°, EPI factor = 119, 32 gradient directions, b = 0 and 1000 s/mm^2). Images were acquired with in-plane resolution 2.0x2.0 mm (zero-interpolated to 1.0x1.0 mm), slice thickness 3 mm, and one signal average. Diffusion-weighted images were processed using DTIStudio (Johns Hopkins University) to produce FA-maps. Pearson's correlation coefficient, *r*, was used to compare results from different anatomic structures between cross-relaxation parametric images and FA.

Results: Mean ± SD (standard deviation) values for *k*, *f*, and FA for both grey and white matter structures are detailed in Table 1. Sample parametric maps from an axial image are presented in Figure 1. For all structures, there was a good correlation (r = 0.61, p=0.001; Figure 2A) between FA and *k* and a strong correlation between FA and *f* (r = 0.75, p<0.001; Figure 2B). For grey matter structures, FA was strongly correlated to both *k* (r = 0.93, p<0.001) and *f* (r = 0.89, p=0.001). For white matter structures, a significant association was not present between FA and *k* (r = –0.12, p=0.62) and FA and *f* (r = 0.35, p=0.15).

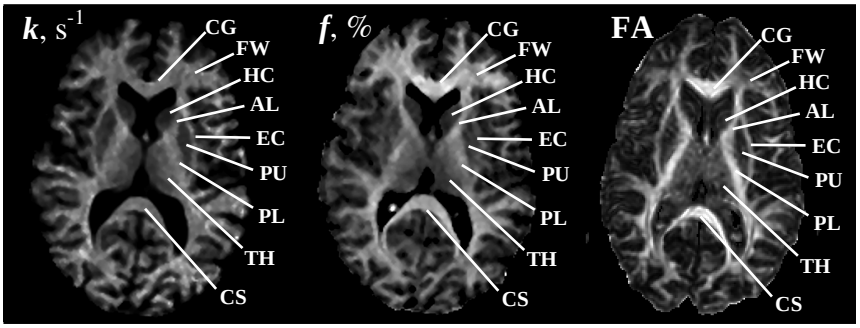

Figure 1. Quantitative cross-sectional images derived from magnetization transfer data (*k* and *f*) and diffusion anisotropy (FA). AL = anterior limb, internal capsule; FW = frontal white matter; CG = corpus callosum, genu; CS = corpus callosum, splenium; EC = external capsule; HC = head of caudate; PL = posterior limb, internal capsule; PU = putamen; TH = thalamus.

Table 1. Mean±SD of cross-relaxation parameters and fractional anisotropy from different anatomic structures.

	k, s^{-1}	*f*, %	FA
Cerebellar cortex	1.35±0.18	6.5±1.1	0.15±0.04
Frontal cortex	0.96±0.27	5.8±0.5	0.11±0.01
Globus pallidus	2.33±0.28	7.9±0.5	0.23±0.08
Head of caudate	1.28±0.30	6.1±0.9	0.12±0.03
Insular Cortex	1.22±0.28	6.9±1.8	0.11±0.01
Putamen	1.44±0.19	7.0±0.8	0.11±0.03
Red nucleus	3.04±0.61	8.9±1.3	0.50±0.06
Substantia nigra	2.13±0.84	8.3±0.8	0.34±0.04
Thalamus	2.25±0.22	7.8±0.6	0.25±0.02
Anterior commissure	2.03±0.47	9.8±0.6	0.58±0.08
Frontal white matter	3.07±0.23	12.7±0.3	0.33±0.03
Cerebral peduncle	4.19±0.54	10.3±1.2	0.77±0.04
Cingulum	2.80±0.37	13.9±1.4	0.63±0.06
Corona radiata	3.39±0.56	11.4±1.6	0.55±0.06
Corpus callosum, genu	3.30±0.92	14.5±0.7	0.71±0.06
Corpus callosum, splenium	3.25±0.50	12.3±0.7	0.86±0.04
Corpus medullare	3.50±0.66	9.9±1.3	0.24±0.01
External capsule	3.77±0.53	8.8±0.6	0.51±0.03
Gyrus rectus	4.54±1.18	9.5±1.3	0.28±0.04
Internal capsule, anterior limb	2.90±0.47	11.6±0.7	0.54±0.03
Internal capsule, posterior limb	3.23±0.29	11.3±0.7	0.69±0.10
IFO/ILF	3.69±0.24	12.6±0.6	0.62±0.07
IFO/UNC	3.46±0.65	10.6±1.0	0.54±0.06
Middle cerebellar peduncle	4.40±1.00	10.7±0.8	0.64±0.07
Optic radiation	3.98±0.83	11.6±0.9	0.54±0.06
Orbital gyrus	4.20±0.75	10.6±1.1	0.30±0.08
Occipital white matter	2.98±0.15	10.6±0.6	0.35±0.07
Superior longitudinal fasciculus	2.80±0.30	14.2±1.0	0.50±0.06

Grey matter structures in **bold print**; IFO=inferior fronto-occipital fasciculus; ILF=inferior longitudinal fasciculus; UNC=uncinate fasciculus

Discussion: The lack of association between CRI and FA in white matter is consistent with differences in the underlying physical principles between the two techniques. While FA is driven by directionality, fiber density may have the predominant effect on CRI. For example, the anterior white matter and the splenium of the corpus callosum had similar values of *k* and f, but substantially different FA (Table 1). Frontal white matter marks an anatomic location of dense fiber tracts, but the low coherence of fiber directionality results in a low FA. The strong agreement between FA and *k* and *f* in grey matter may be a reflection of the variable axonal density unique to each structure. For example, the red nucleus is known to have substantial white matter efferent/afferents, which may have driven the observed elevation in FA, *k* and *f*.

Conclusions: Our findings suggest that whole-brain CRI provides unique quantitative information compared to diffusion anisotropy. Since CRI parameters are not subjected to the directionality limitations, they may prove constructive as quantitative biomarkers in diseases, which affect brain structures that lack directional uniformity, such as gray matter diseases (e.g. Parkinson's disease, Alzheimer's disease) and diffuse white matter pathology, (e.g. multiple sclerosis, traumatic brain injury).

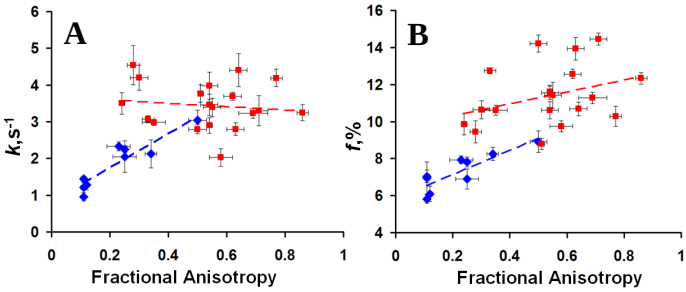

Figure 2. Comparison of fractional anisotropy to *k* (A) and *f* (B). blue = grey matter; red = white matter; bars = standard error; dashed lines correspond to best fit of data through either grey (blue) or white (red) matter.

References: **1.** Basser et al, Biophys J 1994,66;259. **2.** Yarnykh and Yuan Neuroimage 2004,23:109. **3.** Skinner and Glover MRM 1997;37:628 **4.** Yarnykh MRM 2007,57:192.