Can diffusion weighted spectroscopy (DWS) in brain white matter become a viable clinical tool? A re-producibility/robustness study at 3T and 7T

Ece Ercan[1], Emily T. Wood[2,3], Andrew Webb[1], Daniel S. Reich[2], and Itamar Ronen[1]

[1]*C. J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center, Leiden, Netherlands,* [2]*Translational Neuroradiology Unit (NINDS), National Institutes of Health, Bethesda, Maryland, United States,* [3]*Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States*

Target Audience: Clinicians and researchers interested in studying tissue microstructure with diffusion weighted spectroscopy (DWS).

Purpose: DWS assesses the diffusion properties of intracellular metabolites such as total N-acetylaspartate (tNAA), creatine and choline compounds.[1] Compartmental localization of these metabolites means that diffusion metrics can reflect cell-type specific structure and physiology. For example the diffusion properties of tNAA have been shown to be sensitive to intraneuronal/axonal damage in a variety of pathologies, such as stroke,[2-3] tumor[3] and multiple sclerosis,[4] giving rise to changes of 30%-50% in diffusion properties of tNAA. In order to assess the diagnostic utility of DWS, the robustness and reproducibility of the technique need to be established. In this study, we have investigated the inter- and intra-subject variability of the diffusion properties of tNAA in the human corpus callosum (CC). Subsequently, we used a jackknife-like resampling approach to explore the variance of these properties in data subsets reflecting different total scan duration as well as different choices of b-values. In this fashion, we aimed to validate the DWS method for clinical studies and to help experimenters choose the optimal combination of scan parameters within the limitations of hardware and available scan time.

Methods: 6 healthy volunteers (3 men 3 women, ages 34±8 years) without known neurological abnormalities were scanned in 5 separate sessions:3 on a 3T Philips Achieva with an 8-channel head coil: 3 on a 7T Philips Achieva with a 32-channel head coil. *Data Acquisition:* The scan protocol consisted of a 3D T_1-w image (res≈1x1x1mm^3), DTI (res≈2×2×2mm^3, b=0 image, 32 DW images with b=800s/mm^2 at 3T and 15 DW images with b=1000s/mm^2 at 7T) followed by a single volume DWS scan planned on the anterior body of the CC (Fig.1). For DWS scans, PRESS with bipolar diffusion gradients was applied with 7 b-values in 2 directions: along the RL of the VOI (b=191-3050s/mm^2 at 3T and b=80-3905s/mm^2 at 7T) and perpendicular to the CC fibers (b=381-6101 s/mm^2 at 3T and b=160-7811s/mm^2 at 7T). DWS scan parameters for 3T: VOI=3.6mm^3, TR/TE: 2 cardiac cycles/110ms, spectral width=1.5kHz, 1024 sample points, 72 spectra per diffusion condition. DWS at 7T: VOI=3mm^3, TR/TE: 3 cardiac cycles/121ms, spectral width=3kHz, 1024 sample points, 40 spectra per diffusion condition. *Data Analysis:* DWS data were analyzed with custom MATLAB routines in which eddy-current, phase and frequency-drift corrections were performed. Averaged spectra were subsequently analyzed with LCModel.[5] tNAA estimates at each diffusion condition were used to calculate parallel diffusivity (D_{par}, sensitive mostly to properties of the intra-axonal medium, e.g. tortuosity) (Fig.1 panel d) and perpendicular diffusivity (D_{perp}, mostly sensitive to e.g. axonal diameter) (Fig.1 panel b) from the monoexpoential decay of the signal as a function of b-value in each direction. The empirical diffusion coefficient (D_{avg}) was calculated based on the average of these two diffusivity coefficients. Cytosolic diffusion coefficient (D_{model}) was derived through a modeling routine, which accounts for the macroscopic curvature of the fiber tract within the VOI.[6] *Variability Analysis:* For inter-subject and across-session variability analysis, the entire data set from each session was used. Subsequently, a jackknife-like subsampling procedure was applied to data from all 5 sessions from two participants, one from each scanner. Within-session subsets of these data sets were randomly resampled without replacement prior to averaging. These averaged spectra were then used to calculate D_{par}, D_{perp}, D_{avg} and D_{model} for increasing number of signal averages. To investigate the effect of the choice of b-values on the variance of D_{avg} and D_{model}, these measures were calculated for various selections of b-values, shown in Fig.3, where 1 corresponds to the lowest b-value per direction.

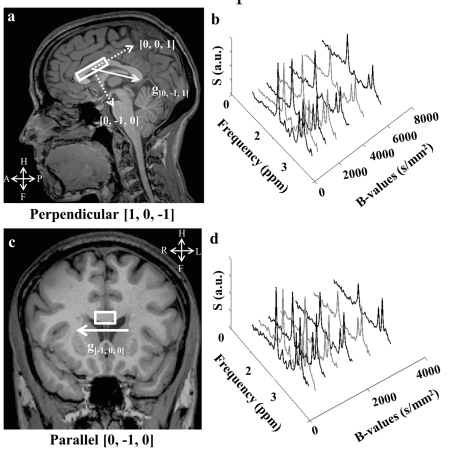

Fig.1 Planning of the VOI with perpendicular (a) and parallel (c) gradient directions. Spectra shown as a function of b-value for perp (b) and par (d) gradient directions at 3T.

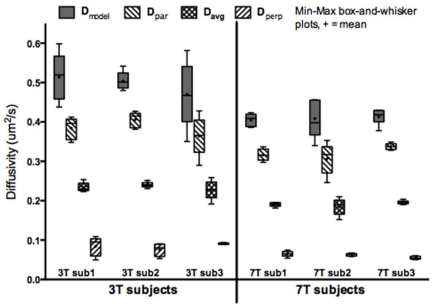

Fig.2 Across subject and across session variability of all diffusivity values from 3T (left) and 7T (right) sessions.

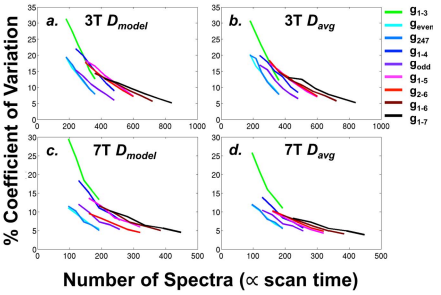

Fig.3 The coefficient of variation of D_{model} (panels a,c) and D_{avg} (panels b,d) for different b-value combinations, determined by the gradient strength g, shown as a function of number of co-added spectra

Results and Discussion: Cramér–Rao lower bounds for the tNAA peak from all spectra were between 6% and 20% at 3T and between 3% and 14% at 7T. Fig. 2 shows inter-subject and across-session variability for all participants. No significant differences in D_{par}, D_{perp}, D_{avg} and D_{model} were observed between subjects at the same field strength when one-way ANOVA with multiple comparisons was applied to the data. This, taken with the low across-session variability at 7T (average coefficient of variation 6%-8% for all measures) indicates good reproducibility of the method at 7T. At 3T, the average across-session coefficient of variation was somewhat higher (6%-11% for D_{par}, D_{avg} and D_{model} and 17% for D_{perp}). tNAA diffusivity values between patients and control in the literature[2-4] were typically substantially higher than the standard deviation in tNAA measures on both scanners, suggesting good reliability of DWS for case-control studies in both field strengths. The standard deviations of D_{avg} and D_{model} critically rely on the choice of b-values for the experiment. Fig. 3 shows the coefficient of variation (C_v) for different b-value schemes. The C_v decreases when sampling a wide b-value range. This implies DWS experiments can be performed within clinically relevant scan times (in our example, ~10 minutes for the g_{247} combination at 7T) while retaining low variance (~5%), by using a proper combination of low and high b-values.

Conclusion: Here we have shown the reproducibility of the diffusivity measures obtained through DWS experiments. Statistical assessment of the intra-subject variability shows the importance of using higher b-values for getting robust DWS measurements. Our results suggest that by choosing a combination of low and very high b-values, one can use a low number of b-values acquired and get robust results while keeping acquisition time short. **References: 1.** Nikolay, K. et al. NMR Biomed (2001) **2.** Zheng, D. et al. AJNR Am J Neuroradiol (2012) **3.** Harada et al. NMR Biomed. (2002) **4.**Wood, E.T. et al. J Neuroscience (2012) **5.** Provencher, S. MRM (1993) **6.** Ronen, I. et al. Brain Struct Funct (2013).