Time dependent diffusion and kurtosis of human brain metabolites using DW-MR spectroscopy on the Connectom

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Target audience: Scientists and clinicians interested in new imaging biomarkers for the in vivo characterization of the human brain microstructure.

Purpose: The aim of this work is to provide first estimates of metabolites diffusion and kurtosis time-dependence in vivo in the human brain. Measurements of the diffusion-time dependent DW-MR signal have been shown to provide information on the brain tissue inter-compartmental exchange[1], structural disorder[2] and restrictions[3]. Several studies[4-6] have shown that the diffusivity of purely intracellular metabolites (e.g., NAA, Cr and Cho) at very short diffusion times (<10 ms) can be used to infer unique information on the cytoplasmic viscosity of different cell types (e.g. neurons versus glia). More recently, Mougel et al.[7] have measured brain metabolites apparent diffusion (ADC(t)) and kurtosis (K(t)) time-dependence up to 500ms in vivo in the mouse brain gray matter and shown promising results supporting their potential as specific imaging biomarkers of brain cell microstructure. Here, we provide first measurements of intracellular brain metabolites ADC(t) and K(t) from short (~6 ms) to long (~250 ms) diffusion time in vivo in the human brain gray matter exploiting the ultra-high gradients of the Connectom scanner at 3T. Moreover, given the challenges of reliably estimating ADC(t) and K(t) at 3T in humans, we also developed a new denoising strategy based on deep learning to improve data SNR and estimation robustness.

Methods: Data acquisition: Measurements were acquired on a 3T Connectom-A MR scanner (Siemens Healthcare, Erlangen, Germany) with 300mT/m per gradient axis using a 32-channel receive headcoil. Voxel positioning and brain segmentation was performed on T1 images acquired with MPRAGE at 1mm³ isotropic resolution. Brain metabolite diffusion was measured by diffusion weighted MR spectroscopy (DW-MRS) at: (i) short to intermediate diffusion times (TDs) with semiLASER localization[6] (TE/TR: 76/3000ms) using oscillating and pulse gradient diffusion encoding at TDs of 6, 21, 37ms; and (ii) intermediate to long TDs with STEAM localization[8] (TE/TR: 37/3000ms) using pulsed gradient diffusion encoding at TDs of 50, 100, 250ms (**Fig. 1A**). Diffusion encoding was applied with equal gradient strength along x,y-direction, but not along z to prevent table vibrations. The b-values for semiLASER covered 200, 1000, 2000, 3000s/mm² (G_{max}: 254mT/m) and for STEAM 200, 1000, 2000, 3000, 6000, 8000s/mm² (G_{max}: 151mT/m), with 32 individual transients in the lower b-value range (≤3000s/mm²) and 64 in the higher. Both sequences use FALIR for CSF suppression and metabolite cycling (MC) to measure water and metabolite diffusion simultaneously. Cross-terms were compensated by diffusion-gradient polarity inversion in successive transients. Six outer-volume-suppression (OVS) bands encompassing the volume of interest (VOI) were used to prevent lipids and spurious echoes. To exclude bias introduced by differences in sequence designs (spin-echo vs stimulated-echo) validation was performed in a NIST phantom[9] with free Gaussian diffusion (**Fig. 1B**). A macromolecular baseline (MMBG) was acquired for STEAM in a single subject at TD 50, 100, 250ms using metabolite nulling at an inversion time (TI) of 765ms and moderately high diffusion-weighting of 5000s/mm². Data processing: Beyond coil-channel averaging, phase-offset, frequency-drift and eddy-current correction, the inherent water reference was used for motion compensation (MoCom) to restore signal amplitudes to a reference level presumably unaffected by motion[10]. Subjects: Scans were performed in accordance with the competent ethical review boards. Six healthy subjects (4 female, 33.1±2.3years) were recruited and measured with a VOI of 9.6±1.5mL in the posterior cingulate cortex (PCC). Grey matter fraction within the VOI was maximized to 71.7±1.5% (**Fig. 2**). Cardiac triggering at each 3rd RR cycle with a trigger-delay of 180ms was applied in the last two DW-MRS measurements to study the effect of motion induced signal drop at high b-values. Novel denoising: Metabolic basis-sets for Asp, tCr, GABA, Glc, Gln, Glu, Gly, tCho, GSH, mI, Lac, NAA, NAAG, PE, sI and Tau were calculated for particular TDs with MARSS[11], taking real RF pulse profiles and sequence chronograms into account. These basis sets combined with the MMBG were superimposed with Gaussian noise, phase, frequency, linewidth distortions to generate sets of realistic synthetic data, to train a neural network[12] with six convolutional layers for data denoising (**Fig. 3A**). Noisy and denoised spectra were exported for sequential linear-combination modeling (LCM) at individual b-values and TDs with FiTAID[13] using the aforementioned metabolite basis-sets and MMBG. Data analysis & Fitting: A cohort average was calculated for each TD at a particular b-value using the inverse variance of the inherent water references as weights to further reduce remaining motion artifacts. Two diffusion representation models were implemented in MatLab: (i) a monoexponential diffusion model in the low b-value range (≤3000s/mm²) to fit metabolite apparent diffusion coefficients (ADCs), and (ii) a kurtosis diffusion model to investigate the non-Gaussian diffusion at high b-values (>3000s/mm²) depending on TD.

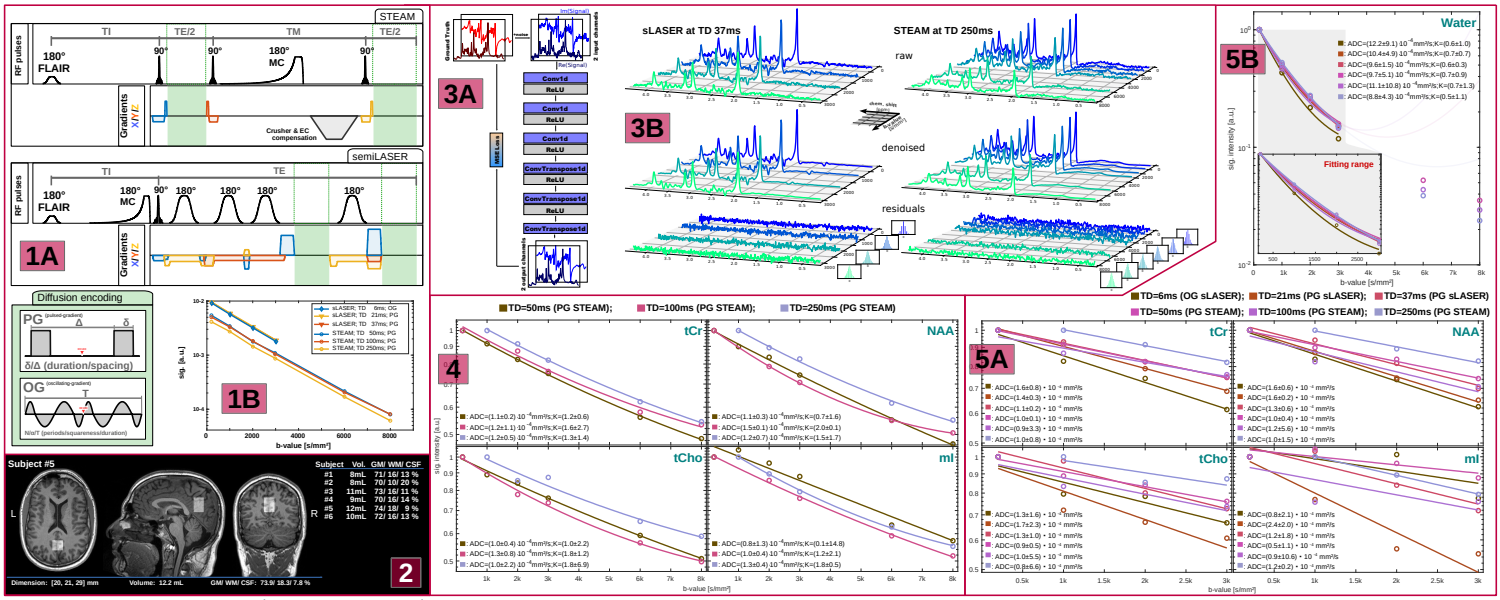

Fig1: A: Sequence diagrams of STEAM/semiLASER with pulsed/oscillating diffusion encoding. B: Sequence validation in NIST phantom. **Fig2:** Voxel position in PCC, volumes, and segmentation. **Fig3:** A: Autoencoder network for denoising. B: Spectra with and without denoising. **Fig4:** Kurtosis fit for brain metabolites (b_{max}: 8k s/mm²). **Fig5:** A: ADC fit for brain metabolites (b_{max}: 3k s/mm²). B: Kurtosis fit for water (b_{max}: 3k s/mm²).

Result: Novel denoising: **Fig. 3B** shows exemplarily spectra of semiLASER and STEAM before and after the new proposed denoising at TDs of 37 and 250ms, respectively, where residuals obey a Gaussian noise characteristic. This was found reproducibly for all datasets, where K(t) and ADC(t) modeling was more robust, with lower confidence intervals after denoising (not shown). Metabolites K(t): The kurtosis of the major brain metabolites tCr, NAA, tCho and mI increases with TD (**Fig. 4**). Metabolite ADC(t): Metabolite ADCs are highest for TDs <21ms and plateauing at TDs >50ms (**Fig. 5A**). The higher ADCs found in the kurtosis model might indicate a contribution of non-Gaussian diffusion even for b<3000s/mm². Water K(t) and ADC(t): Water kurtosis shows little to absent time dependence, even for TDs below 50ms (**Fig. 5B**). However, this result is probably affected by partial volume with CSF in our large spectroscopic VOI (**Fig. 2**). The ADC of water overall increases with decreasing TDs, as expected (**Fig. 5B**).

Discussion & Conclusion: We found increased kurtosis at long TDs for tCr, NAA, tCho and mI, in good agreement with results in animals, suggesting an elevated impact of cellular boundaries on the non-Gaussian diffusion for TDs>50ms. The observed constant kurtosis for water might originate from cross-compensating effects of water exchange between intra- and extracellular space at long TDs and significant partial volume CSF contamination of the VOI. This assumption is supported by the steady loss in signal for water at TDs>50ms at high b-values and the non-zero kurtosis at the longest TD. The elevated metabolite ADCs at low TDs indicate a shift in compartmental sensitivity towards smaller cellular structures as well as cytoplasmic viscosity, while the non-zero plateau at long TD underpins the hypothesis of metabolite diffusion rather in long branched cylinders than small restricting compartments (e.g., organells). It is important to note that these are preliminary data and validation in a larger sample size is needed. Applying denoising and cardiac triggering can help to stabilize ADC(t) and K(t) estimation and to obtain data even on a single subject level. Although reported in one recent animal study, metabolites ADC(t) and K(t), have remained uninvestigated in the human brain. Here, we demonstrated -by exploiting ultra-strong diffusion gradients, state-of-the-art DW-MRS sequences, post-processing, and novel denoising- that it is possible to measure metabolite ADC(t) and K(t) in vivo in the human brain.

References: [1] Jelescu et al 2022; [2] Novikov et al. 2014; [3] Palombo et al. 2016; [4] Ligneul et al. 2017; [5] Valette et al. 2018; [6] Döring et al. 2019; [7] Mougel et al. 2022; [8] Brandejsky et al. 2015; [9] Palacios et al. 2017; [10] Döring et al. 2018; [11] Landheer et al. 2019; [12] Rösler, https://github.com/frank-roesler/MRspecNET, 2022. [13] Adalid et al. 2017

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