Separate assessment of diffusion properties of NAA and NAAG at 7T

H. E. Kan[1], M. J. van Osch[1], M. J. Versluis[1], A. Techawiboonwong[2], M. A. van Buchem[1], A. J. Webb[1], and I. Ronen[2]

[1]Leiden University Medical Center, Leiden, Netherlands, [2]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, United States

Background: Diffusion-weighted imaging (DWI) is a common technique in the characterization of tissue microstructure in health and disease. The explanatory power of DWI results is weakened, however, by the lack of compartment specificity of water as a "tracer". By using diffusion weighted spectroscopy (DWS) of metabolites, compartment specific information has been obtained in several studies (e.g. 1, 2, 3), revealing subtle differences in cytoarchitectonics and compartmentation of these metabolites. Recently, DWS has been successfully used to probe the changes in metabolite diffusivity upon anesthesia with isoflurane (4), indicating that subcellular structures may have a significant role in dictating the diffusion properties of metabolites. N-Acetyl aspartate (NAA) is an intra-neuronal metabolite and is the most prominent peak in the brain ^{1}H spectrum. N-Acetylaspartylglutamate (NAAG), is a neuropeptide neurotransmitter that is packed in synaptic vesicles and released to the synaptic cleft in a calcium-dependent manner.(5). At clinical field strengths, the singlet of the CH3 group of NAAG almost completely overlaps that of the much higher concentration NAA, making it impossible to obtain separate diffusion measurements of both compounds. At field strength of 7 T, the signals for NAA and NAAG are partially separated due to the increased spectral resolution. In this study we lay the groundwork for separately studying for the first time the diffusion properties of NAA and NAAG, which are expected to be different due to their different compartmentation.

Methods. ^{1}H DWS of the parietal white matter was performed in 4 healthy subjects on a 7T Philips Achieva 58 cm clear bore scanner (Philips Healthcare, Best, The Netherlands) using a 16-channel Nova Medical phased array head coil. Partially water suppressed PRESS spectra were acquired with the center frequency on the NAA/NAAG region from a voxel in the parietal white matter (15 x 15 x 20 mm, 2 KHz bandwidth, 1024 points, TR=2s, TE=110ms) (fig 1A). Subsequently, a non water suppressed spectrum was acquired with the central frequency on water, to avoid a large chemical shift artifact between water and NAA. Diffusion weighting was accomplished by incorporating diffusion gradients (3) and applied in three directions ([1 1 0], [1 0 1] and [0 1 1]) with the following diffusion parameters: Δ = 43 ms and δ = 24.6 ms and g-values of 0, 1.4 and 2.2 g/cm. This resulted in b-factors of 0, 591 and 1461 s/mm^2. Data were acquired as single scans (64 for the metabolite scans, 7 for the non-water suppressed scans), corrections for phase and frequency shifts were applied using the partially-suppressed water resonance (3) and eddy current correction was performed using the unsuppressed water spectrum via a custom written program in Matlab®. Thereafter, the individual spectra were averaged. Peak fitting was applied in jMRUI on the averaged spectra of the three diffusion directions. Resonances for NAA, NAAG and water were fitted to Gaussian line shapes, with prior knowledge on the relative peak position of NAAG compared to NAA (Δ= 0.04 ppm). Line widths of the NAA and NAAG peaks were fixed to the average value for all three diffusion weightings. Peak areas of NAA, NAAG and water were plotted against the b-value and used to calculate trace/3 ADCs according to: $\ln(S)=\ln(S_0)-b*D$ where S is the signal intensity at a given b-value, S_0 is the signal intensity in the absence of diffusion weighting and D is the diffusion coefficient.

Individual trace/3 ADCs for all subjects

Subject	ADC(NAAG) mm^2/s x 10^{-3}	ADC(NAA) mm^2/s x 10^{-3}	ADC(water) mm^2/s x 10^{-3}
1	0.31	0.23	0.6
2	0.17	0.22	0.58
3	0.17	0.30	0.68
4	0.22	0.35	0.64

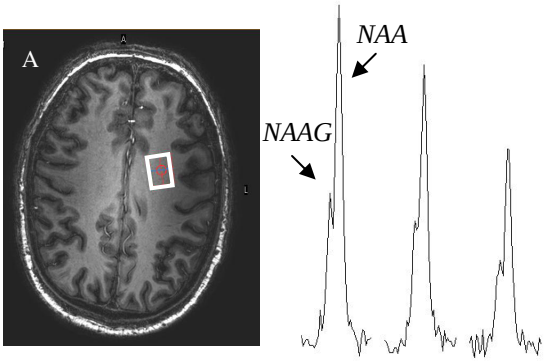

Fig 1.Voxel location (A) and NAA and NAAG signals in the corresponding ^{1}H MR spectra with increasing diffusion weightings. Spectra are the average of three diffusion directions, the left spectrum has no diffusion weighting

Results. In all subjects, a separation between the NAA and NAAG signal was visible before and after diffusion weighting (fig 1B). Assessment of the separate trace/3 ADCs of both compounds based on all thee b-values resulted in $0.21\pm0.07\times10^{-3}$ mm^2/s for NAAG and $0.27\pm0.06\times10^{-3}$ mm^2/s for NAA (table). Calculation based on the first 2 b-values did not significantly differ.

Discussion and conclusion. Our very preliminary results show that even at relatively low b-values, a difference in the diffusivity of NAA and NAAG can be detected, where the apparently lower ADC(NAAG) may be due to the NAAG compartmentation within synaptic vesicles. At this very initial stage of our study, the quantitative value of our results is limited and the inter-individual variability is considerable. As the diffusion attenuation of both NAA and NAAG signals is not monoexponential, a difference in compartmentation may be reflected by the shape of the diffusion curve and more b-values are needed for accurate characterization of the diffusion properties of both metabolites. Finally, it is essential to extend this study to include gray matter volumes where the concentration of both metabolites is expected to be higher and the release of NAAG to the synaptic cleft may significantly alter the diffusion profile of NAAG.

References. *[1]. Posse S, et al. Radiology 1993;**188**(3):719-725. [2].Ellegood J, et al. Magn Reson Med 2005;**53**(5):1025-1032. [3].Upadhyay J, et al. Neuroimage 2008;**39**(1):1-9. [4] Valette, J., et al, J Cereb Blood Flow Metab.* 2007 Mar;27(3):588-96. [5].Neale JH, et al. *J Neurochem* 2000;**75**(2):443-452.