Assessment of trace ADCs of several metabolites in grey and white matter in the human brain at 7T

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Introduction. Diffusion-weighted imaging (DWI) is a popular technique for measuring the diffusion properties of water in the brain. The diagnostic power of DWI is limited, however, by the lack of compartmental specificity of water. In contrast, diffusion weighted spectroscopy (DWS) of metabolites, which are mainly located in the intracellular space, yields microstructural information that is more specific to cellular geometry. DWS in human brain of the three main singlet signals in the 1H MR spectrum, N-acetyl aspartate (NAA), creatine and phosphocreatine (tCr) and choline containing comounds (tCho) has revealed subtle differences in cytoarchitectonics and compartmentation of these metabolites [1-7]. However, the apparent diffusion coefficients (ADC) of other metabolites such as myo-inositol (Ins) or glutamate (Glu), which could be different due to their different localization and/or compartmentation, have not been assessed in humans due to signal-to-noise and spectral resolution issues. In a study in rats, it was shown that ADCs of Ins and NAA changed in different ways to an ischemia/reperfusion challenge [8], indicating that glia cells show an altered response compared to neurons, thus showing the additional value of assessment of the ADC of Ins compared to NAA. Therefore, the aim of the present study was to obtain ADC values of a number of additional metabolites in the human brain, using bipolar gradients for diffusion weighting and dedicated spectroscopy data analysis, at a field strength of 7T.

Methods. 1H DWS of the parietal white matter (n=6) and the visual cortex (n=3) was performed in healthy subjects on a 7T Philips Achieva system (Philips Healthcare, Best, The Netherlands) using a 16-channel Nova Medical phased array receive head coil. Partially water-suppressed PRESS spectra were obtained from a voxel of 15 x 15 x 20 mm with the central frequency at NAA (2 kHz bandwidth, 1024 points, TR=2s, TE=115ms). Subsequently, a non-water-suppressed spectrum was acquired with the central frequency at water to enable phase, frequency and eddy current corrections [9]. Diffusion weighting was accomplished by incorporating bipolar diffusion gradients and applied in three directions ([1 1 0], [0 1 1] and [0 0 1]) at 8 different b-values (48 to 3059 s/mm2). Spectra were analyzed using the LCModel software package (9) and a simulated set of basis spectra to obtain peak integrals. Only metabolites with Cramer-Rao lower bounds (CRLB) of less than 20% at all b-values were included for further analysis. Trace/3 ADC values were calculated for glutamine (Gln), Glu, tCr, Ins, tCho, N-acetyl aspartate glutamate (NAAG) and NAA assuming a mono-exponential decay. In white matter, ADC values of all metabolites were compared with the ADC of NAA using a one-way ANOVA combined with a Dunnett’s multiple comparisons test. Differences between grey and white matter where compared with two-way ANOVA and post-hoc tested using a Bonferroni correction. Differences were considered significant at p<0.05.

Results. In parietal white matter, the quality of the MR spectra was sufficient to quantify not only the major signals of NAA, tCr and tCho but also NAA, Glu, Gln and Ins (Fig 1), as indicated by CRLB of less than 20%. As expected, CRLB values were lowest for NAA, tCr and tCho, with higher values for Ins and Gln. Calculation of trace/3 ADCs for all metabolites showed a high dispersion in values between the various metabolites (Fig 2). When compared to NAA, tCho, Glu and Ins showed significantly different diffusivities. Overall, grey matter ADCs were significantly lower than white matter ADCs, with only Glu showing a specific difference in the post-hoc test. In grey matter, NAAG, Ins and Gln could not be fitted with CRLB below 20% and were therefore excluded from the analysis.

Conclusion. In this study, we performed DWS of the brain in humans at a field strength of 7 tesla, using bipolar gradients and dedicated post processing and spectral analysis. The high SNR in these measurements allowed, for the first time in humans, determination of ADC values of not only the major brain metabolites NAA, tCr and tCho but, in white matter, also of Ins, Glu, Gln and NAAG. Interestingly, all ADC values were lower in grey matter compared to white matter, which is in agreement with previous results on NAA, tCr and tCho (3). The significantly lower ADC for Glu between grey and white matter is in agreement with DWS studies in monkey brain [10; 11] and could be due to the compartmentalization of Glu in neurotransmitter vesicles (10) and/or the higher density of mitochondria in grey matter resulting in more restricted diffusion (10).