About differences of the transverse relaxation time (T_2) of 18 brain metabolites in gray and white matter at 3T

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Target Audience: Scientists and clinicians interested in MR spectroscopy, Neuroscience and in measuring absolute metabolite concentrations

Introduction: The specific measurement of the transverse relaxation time constant T_2 of brain metabolites is a prerequisite for reporting quantitative MR spectroscopy results in the millimolar concentration range and also allows for conclusions about molecular tumbling rates (1). If a metabolite's T_2 varies across different tissues, the degrees of freedom for movement of these molecules is different, e.g. the environment of the molecule is altered. The more the molecular motion is restricted, the smaller T_2 becomes. The assessment of the T_2 relaxation times of 18 brain metabolites at 3T was recently enabled by ProFit2.0 (2) and investigated in a large volunteer cohort in a gray matter rich voxel (3). **This investigation** is the first to explore differences in T_2 relaxation times of 18 metabolites between gray and white matter at 3T and to evaluate the quantitative results with respect to the molecular environment.

Methods: In addition to the 83 gray matter T_2 relaxation time measurements from (3), T_2 relaxation times from white matter have been measured in 9 healthy volunteers. The gray matter voxel was positioned in the bilateral pregenual anterior cingulate cortex (pACC) (amount of white matter <15%).The white matter spectroscopic voxel (25x20x20 mm^3) was located in the periventricular white matter area (Fig.1) based on a highly resolved 3D T_1 weighted scan (1x1x1 mm^3). With a maximum echo J-resolved ^{1}H MRS (JPRESS) protocol (4) in combination with inner volume saturation (5) and VAPOR water suppression, the T_2 relaxation characteristics of brain metabolites at 3T (Achieva, Philips Healthcare, Best, The Netherlands) were resolved. The J-coupling evolution was tracked by increasing the echo time (TE) by 2ms over 100 steps (starting at TE=28ms, 8 averages/step and 1 w/o water suppression for phase and eddy current correction, TR=1.6s, 8-channel sense head coil (Philips Healthcare, Best, The Netherlands) used). JPRESS data were evaluated using ProFit2.0 (2) including metabolite basis sets of acetate (ace), ascorbic acid (asc), aspartate (asp), choline (cho), creatine (cr), gamma-amino-butyric acid (gaba), glucose (glc), glutamine (gln), glutamate (glu), glutathione (gsh), glycine (gly), lactate (lac), myo-inositol (mi), N-acetylaspartate (naa), N-acetylaspartylglutamate (naag), phosphoethanolamine (pe), scyllo-inositol (scy), and taurine (tau). T_2 values were calculated from ProFit's metabolite specific line broadening parameter ϑ ($T_2 = \frac{1}{\pi \cdot \vartheta}$), which is part of the fit model. Own MATLAB-based scripts incorporating the Statistical Parametric Mapping (SPM; Wellcome Trust Centre for Neuroimaging, London, UK) segmentation routine were used to calculate the voxel composition (CSF, gray and white matter). The statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 20) and Two-Tailed Independent-Samples T-Tests were applied to identify differences in mean and standard deviation of the metabolites' relaxation times between both mainly gray and mainly white matter (normal distribution check with Kolmogorov-Smirnov for each metabolite; Levene's Test for Equality of Variances applied). Effects for multiple comparisons were corrected by applying Bonferroni correction ($p = \frac{0.05}{18} = 0.003$).

Results and Discussion: The voxel composition of the 83 mainly gray matter measurements was gray matter (71%±4%), CSF (18%±4%) and white matter (11%±3%). Measurements in the periventricular white matter area revealed mainly white matter (98%±2%) with residual gray matter (2%±2%). Mean and standard deviation of T_2 relaxation times in white (15 metabolites) and gray matter (18 metabolites) are shown in Tab 1, which may enable better quantification in the future. The concentrations of gaba, tau and ace in the periventricular white matter area were too low to be fitted reliably (CRLB>20). Cr, glc, asp, pe and asc show rather similar T_2 values in white and gray matter. However, significant differences ($p<0.001$) are found for naa, cho and mi. Additional metabolites, such as glu ($p=0.005$) and naag ($p=0.005$) have highly significant differences, but do not pass the strict Bonferroni correction criterion. Naa and naag have higher T_2 relaxation time in white matter, whereas cho, mi and glu have lower T_2 values. An explanation could be that the motion of cho, mi and glu molecules is more and of naa and naag less restricted in white matter tissue, indicating different functions and integration of these metabolites in their environment. The altered T_2 value may therefore be an indicator of different cell compartments or a difference in interaction with enzymes. The measurements in the periventricular white matter area were robust, but still a larger cohort and other brain areas are to be measured in the future to confirm exact T_2 values and to increase statistical power.

Conclusion: T_2 values are important for correction algorithms in absolute quantification of metabolites. There exist different T_2 values in white and gray matter for multiple metabolites, which should be considered and precisely evaluated for. Differences may reveal a variation of cell compartments or interaction between molecules and enzymes.

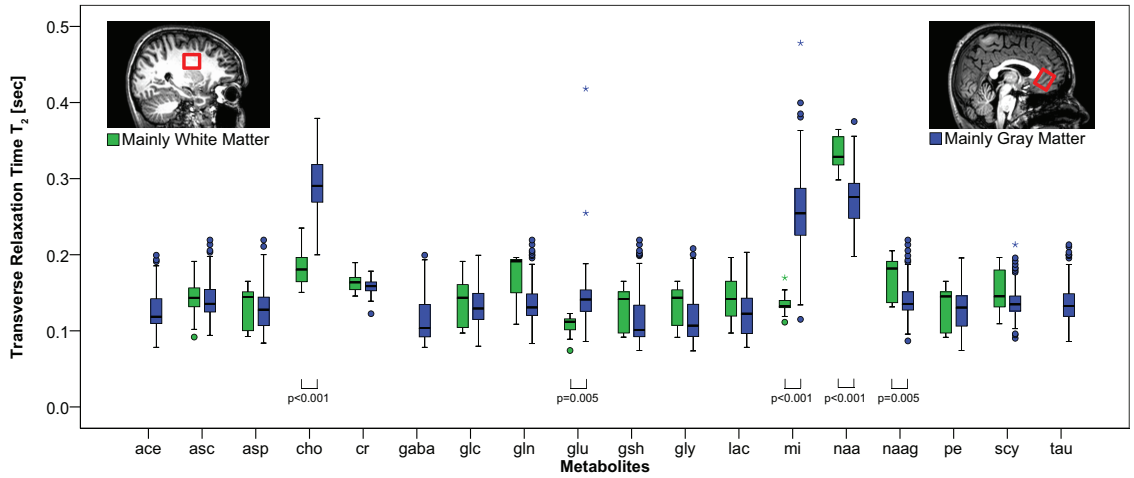

Fig 1: *Red marked voxel of interest (VOI) in periventricular white matter area (left) and in the pregenual anterior cingulate cortex (right). Boxplots for comparison of T_2 values of different metabolites in mainly white matter (green) and mainly gray matter (blue). Outliers are denoted by circles and extreme outliers are denoted by asterisks.*

Tab.1*: T_2 relaxation time for 18 metabolites in mainly white matter (upper line) and mainly gray matter (lower line) tissue (*: significant differences)*

Met:	ace	asc	asp	cho*	cr	gaba	glc	gln	glu*	gsh	gly	lac	mi*	naa*	naag*	pe	scy	tau
T_2 (ms) in WM	-	141 ±31	129 ±29	186 ±28	163 ±14	-	138 ±34	165 ±49	106 ±16	128 ±29	133 ±27	144 ±35	136 ±18	333 ±22	168 ±30	132 ±30	151 ±33	-
T_2 (ms) in GM	128 ±28	142 ±28	131 ±31	293 ±39	158 ±10	116 ±32	133 ±30	138 ±31	144 ±38	117 ±36	117 ±33	125 ±31	258 ±61	272 ±34	140 ±27	131 ±30	139 ±23	138 ±30

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