MYO-INOSITOL INCREASE WITH AGE SHOWS *SCN1A* DEPENDENCY: A 3T MRS STUDY

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Introduction

Healthy aging is associated with structural, morphological and metabolic brain changes. The physiological and neuropsychological decline can be differently pronounced possibly attenuated or enhanced by lifestyle like physical activity versus sedentary lifestyle [1] or genetic disposition [2]. One of the most frequent Magnetic Resonance Spectroscopy (MRS) findings in white matter of aging brains is a reduced N-acetylaspartate (NAA) and an increased myo-Inositol (mI) concentration. In our study we wanted to investigate whether the gene variants of *SCN1A* (sodium channel voltage-gated, type I, alpha subunit) has any effects on the age dependent metabolites like NAA, Creatine (Cr), Choline (Cho) or mI in a sample of healthy volunteers with a wide age range. *SCN1A* is been seen as a novel gene candidate for cognitive decline, since the *C* allele of the *SCN1A* variant has been found associated with poor short-term memory performance in a genome wide association study [3].

Methods

In vivo proton spectroscopy has been performed on 49 healthy volunteers aged between 21 and 82 years, mean age: 46.8 ± 17 years (28 female). All MR measurements were acquired on a 3 T Siemens TRIO with a 12-channel head coil (Siemens Medical Solutions, Erlangen, Germany). A set of sagittal and transverse scout MR images was first obtained to determine patient position. Based on the scout images a 10x40x10 mm³ single voxel was positioned in the frontal white matter. Reduced water suppression localized spectra were obtained with a PRESS sequence using following parameters: TE = 30 ms, TR = 3000 ms. In addition six fully relaxed unsuppressed water spectra were acquired with TR = 10 s and different TE (30, 80, 276, 552, 1000 and 1500 ms) to extrapolate the absolute water signal at TE = 0 for waterscaling. For metabolite quantification LCModel with a simulated basis-set was used. Data were also corrected for partial volume effect by segmenting a T1-weighted MPRAGE including chemical shift displacement for different metabolites [4]. Blood samples for genotyping were taken from all subjects. Genotyping was accomplished using a pre-designed TaqMan 5' nuclease SNP genotyping assay (Applied Biosystems, USA). The genotypes *AC* and *CC* were together defined as risk group and the *AA* as non risk group.

Results

All Cramer Rao Lower Bounds (CRLB) for NAA, Cr and Cho were less than 6 and mI less than 12. For Glu we had to exclude eight subjects with CRLB > 20. Correlation analysis revealed a significantly negative correlation for age with NAA (N=49; R=-0.448, p=0.001) and Glu (N=41; R=-0.325, p=0.038); and a significantly positive correlation for Cr (N=49; R=0.349, p=0.014) and mI (N=49; R=0.494, p<0.001) with age. A T-test revealed no significant age and sex differences between the two genetic subgroups for SCN1A risk. MI was significantly different between the *SCN1A* risk (N=26) and non risk (N=23) group with higher mI values in the risk group (T=2.436, p=0.019).

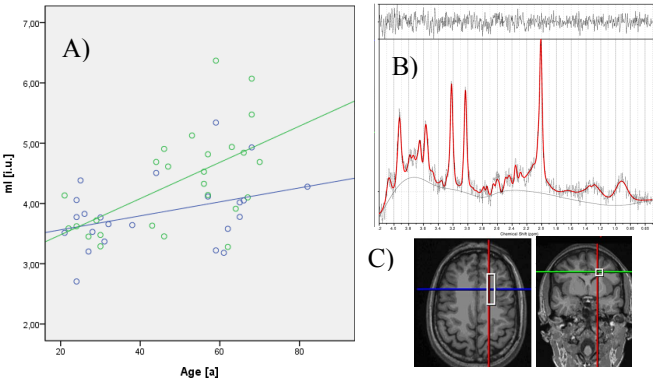

Figure 1: A) Correlation of myo-Inositol and age for *SCN1A* risk (green) und non risk (blue) group; B) MR sample spectra and C) voxel position in the left frontal white matter

Table 1: Age and gender characteristics and mean metabolite concentrations with SD

	SCN1A risk	
	no	yes
N	23	26
Age (SD) [a]	44.3 (19.2)	49.0 (16.2)
Age min [a]	21	21
Age max [a]	82	70
Sex/Female	15	13
NAA (SD) [i.u.]	6.24 (0.60)	6.11 (0.53)
Cr (SD) [i.u.]	4.45 (0.44)	4.51 (0.39)
Cho (SD) [i.u.]	1.54 (0.23)	1.56 (0.18)
mI (SD) [i.u.] *	3.84 (0.59)	4.35 (0.83)
Glu (SD) [i.u.]	4.00 (0.58); N=18	4.14 (0.74); N=23

Discussion

To our knowledge this is the first study investigating the relationship between MRS brain metabolites and *SCN1A* in the aging brain. We found increased Cr and mI and reduced NAA and Glu with age, confirming to the literature. Further studies will be needed to investigate whether *SCN1A* together with increased mI can be used as a biomarker for pathological aging.

References

[1] Bugg JM, Head D, Neurobiol Aging 2009; [2] De Jager PL, et al., Neurobiol Aging; [3] Papassotiropoulos, et al., Mol Psych 2009; [4] Weber-Fahr W., et al., Neuroimage 2002.