In vivo proton MR spectroscopic (^{1}H-MRS) investigations of metabolic changes in human brain associated with unspecific low back pain

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PURPORSE: Chronic back pain is associated with a dramatic decline of life quality and causes high costs for health care systems as it often requires a lifelong therapy. However, due to the multimodal and individually variable origin of this disease, therapeutic methods are mostly rather unspecific. Especially, dysfunctions that occur at the level of the central nervous system are widely unexplored. *In vivo* ^{1}H-MR spectroscopically detected metabolic changes in the brain of these patients may provide deeper understanding of the neuronal biochemical processes associated with chronic pain and may potentially help to improve therapy [1]. Several, recently published *in vivo* ^{1}H-MRS studies on patients with chronic low back pain described a relation between prolonged pain perception and metabolic changes in cortical pain processing areas [2-5]. The aim of the present work was to investigate whether metabolic changes in patients with unspecific chronic low back pain (*uLBP*) are detectable in the brain pain processing regions *anterior cingular cortex (aCC)*, *anterior insula (aI)*, and *thalamus (Th)* by means of quantitative ^{1}H-MRS at 3 T.

MATERIAL AND METHODS: Six right-handed *uLBP*-patients (one male and five female, age: 45±11 years) and 6 age- and weight-matched healthy controls participated in this study. Averaged over all patients subjective pain intensity amounted 4.3±2.8 on the visual-analogue pain scale (VAS), which ranges from 1 ("no pain") to 10 ("worst pain imaginable") [6]. All MR measurements were performed with a whole-body 3 T MR Scanner (Magnetom Trio TIM, Siemens Medical Solutions, Germany) and a 12 channel *receive only* head matrix coil. ^{1}H-MR spectra with (NEX: 128) and without (NEX: 16) water suppression were acquired in three voxels (see Fig. 1), located in the *aCC* (V_{ACC}: 2 ml), in the *left aI* (V_{aI}: 3.8 ml) and in the *left Th* (V_{Th}: 3.2 ml), respectively, with a single-voxel PRESS sequence (TR/TE: 5000/30 ms, manual shim). Voxel locations were selected by means of T_1-weighted 3D MRI data (MP-RAGE; TR/TE/TI: 2300/3.03/900 ms; α: 9°; 192 sagittal 1 mm thick slices, $FOV_{AP\times FH}$: 256×256 mm²), acquired prior to MRS. Water suppressed spectra were automatically corrected for eddy current distortions and φ_0-offsets by using the corresponding water unsuppressed spectra [7]. Metabolite and water intensities (I_M, I_W) were quantitated with the LCModel [8]. Metabolite concentrations (in mmol/l) of N-acetyl aspartate *(NAA)*, creatine (*Cr*), total choline (*tCho*), *myo*-inositol (*mI*) and glutamat (*Glu*) were calculated by multiplying the I_M/I_W ratios with the brain tissue water concentration [9]. Individual distributions of tissue composition within the MRS voxel were automatically extracted from the tissue segmented MP-RAGE data to account for partial volume effects due to CSF as well as for the different water concentrations [9] and T_1- and T_2-induced signal relaxations in grey and white matter [10, 11].

RESULTS: Whereas all six data set pairs (patient *vs*. volunteer) from *aCC* and *aI*, and three data set pairs from *Th* had sufficient SNR and narrow spectral line widths (mean SNR_{NAA}: 15.3±2.7; mean $FWHM_{NAA}$: 4.5±1.0 Hz), three data set pairs from *Th* suffered from low spectral resolution (FWHM: >10 Hz) and were excluded from further analysis. CRLB values, calculated with the LCModel for *NAA*, *Cr*, *tCho*, *mI* and *Glu*, were below 15%. *Fig. 1* shows distributions of absolute metabolite concentrations in the investigated cortical areas for patients (black stars in blue boxplots) and controls (black stars in green boxplots). *Table 1* summarizes metabolite concentration differences as well as corresponding *p*-values (two-tailed *t-test*) obtained from the comparison between controls and patients. In general, patients exhibit lower metabolic concentrations in all cortical regions, except for *Glu* in *Th*. However, this difference was only significant for *Glu* in *aCC* (see *Fig. 1b*).

Table 1: *Metabolite concentration differences between controls and uLBP-patients in aI, aCC and Th as well as corresponding p-values obtained by a t-test based comparison between patients and controls*

		NAA	*Cr*	*tCho*	*mI*	*Glu*
left aI	dif [%]	-8.1±12.4	-8.0±27.1	-15.7.0±30.0	-12.6±30.0	-5.8±29.5
	p-value	0.224	0.41	0.146	0.525	0.41
aCC	dif [%]	-8.2±15.2	-8.5±16.6	-13.3±11.6	-16.3±20.7	**-16.3±11.2**
	p-value	0.096	0.19	0.231	0.096	**0.02**
left Th	dif [%]	+8.9±6.5	-12.2±9.5	-13.6±16.8	-11.8±26.5	-36.2±44.7
	p-value	0.527	1.137	0.144	0.324	0.137

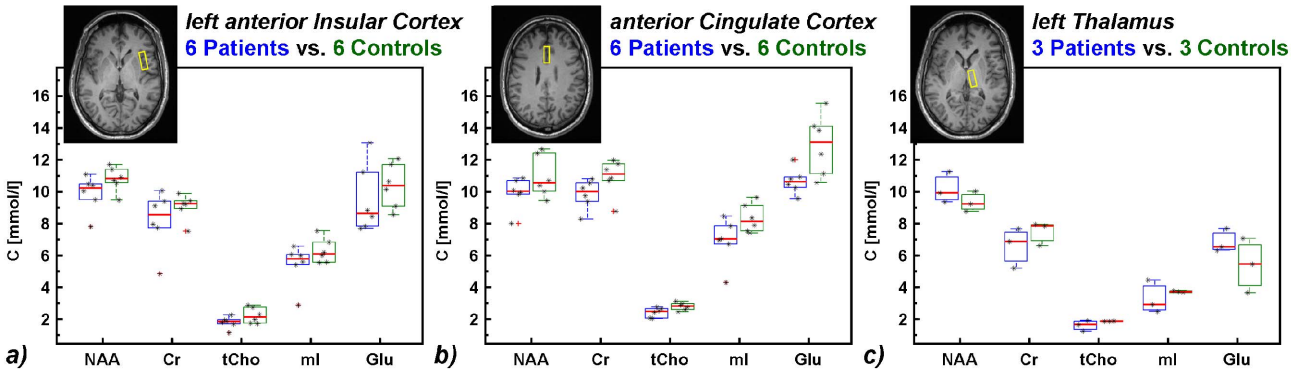

Fig. 1: *Distributions of NAA-, Cr-, tCho-, mI- and Glu-concentrations, obtained in left aI (a), aCC (b) and left thalamus (c), for uLBP-patients (blue boxplots) and healthy controls (green boxplots). Red lines in the boxes represent median values, whereas the upper and lower box limits correspond to the 75th and 25th percentile, respectively. Whiskers indicate outliers. Individual concentrations of single persons are depicted by black stars in the boxplots.*

DISCUSION AND CONCLUSION: Our results demonstrate that ^{1}H-MRS may be able to track *in vivo* metabolic alterations in the brain induced by chronic pain. In contrast to recent, comparable studies [2-5], we used a higher B_0 field strength, enabling higher quantitation accuracy, especially for *Glu* and *mI*, whose spectra overlap with other metabolites. Furthermore, we accounted for the individual tissue distribution in the voxels, thus considering potential alterations of the CSF content due to chronic pain associated morphological changes [1]. Finally, we extended these examinations to three cortical regions to regard the multifocal nature of pain processing in the human brain. Similar to our recent ^{1}H-MRS study of healthy controls during acute pain stimulation [12], altered Glu concentrations in *uLBP*-patients may be ascribed also to neurotransmitter turnover changes due to pain perception. The observed reductions of *NAA* and *mI* are in agreement with recent studies by *Fukui et al.* [3] and *Pattany et al.* [2], who explained the decrease of these metabolites in *Th* of chronic patients to disease associated neuron and glia cells reshuffle. Investigations of larger patient populations and correlation with VAP values and morphologic changes are currently planned to confirm statistical significance of these results.

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