In vivo measurements of acute pain induced changes of GABA+ and Glx in the brain by using functional ^{1}H-MEGA-PRESS MR spectroscopy

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Target audience: Researchers and members of the Psychiatric MR Spectroscopy Study Group and of the Magnetic Resonance Spectroscopy Community.

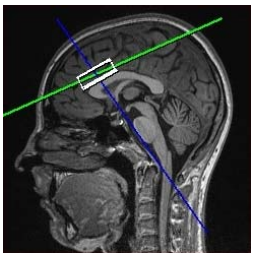

Fig. 1 Location of the MRS voxel in the aCC.

Purpose: ^{1}H-MR spectroscopic detection of pain associated metabolic changes in the human brain *in vivo* may be a method for objective evaluation of pain intensity and analysing interactions between the excitatory and inhibitory neurotransmitter systems. Ultimately, it may lead to a deeper understanding of neuronal pain processing mechanisms [1]. Recent *in vivo* ^{1}H-MRS studies performed during pain perception demonstrated a correlation between subjectively perceived pain intensities and local cortical glutamate (Glu) and glutamine concentrations [2, 3, 4]. The present study comprises results of time resolved measurements of acute heat pain induced changes in excitatory (Glx) and inhibitory (GABA+) neurotransmitter turnover in the anterior cingulate cortex (aCC) by using ^{1}H-MEGA-PRESS spectroscopy.

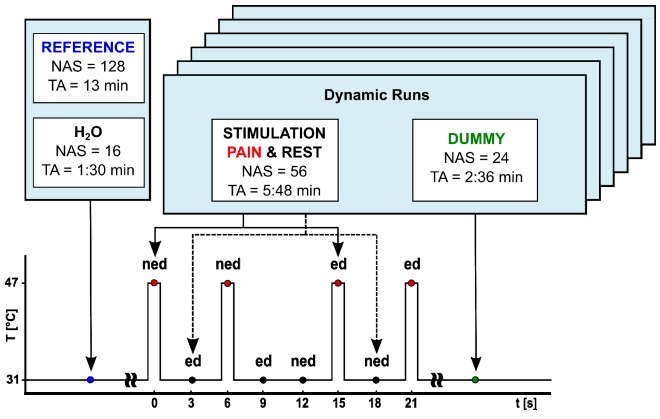

Fig. 2 Measurement protocol. Reference spectra were acquired (prior to stimulation) followed by six stimulation blocks. Each block consisted of two dynamic runs, applying heat stimuli only during the first. The bottom part shows the time points for the triggered heat application and spectra acquisition during the stimulation cycle.

Methods: The ^{1}H-MEGA-PRESS data (TR/TE: 3000/68 ms, manual shim) were acquired in the aCC (V = 8.6 ml, see Fig. 1) of 13 female, healthy volunteers (aged 22.7±0.5 years , right-handed) by using a clinical whole-body 3 T MR scanner (Magnetom TIM Trio, Siemens, Erlangen, Germany) and a vendor supplied 12-channel head matrix coil. During MRS cyclic painful heat stimuli were simultaneously applied to the left forearm by using a Medoc PATHWAY system with a CHEPS thermode (Ø 27 mm, Ramat Yishay, Israel). The protocol consisted of the following steps: First, T_1-weighted MR imaging data as well as reference spectra with (REF, NAS = 128) and without (NAS = 16) water suppression were acquired prior to stimulation. Next, MR spectra were collected in six blocks including two dynamic runs with 56 and 24 single acquisitions, respectively (Fig. 2). During the first run 2×22 cyclic heat stimuli were applied while simultaneously acquiring non-edited and edited MEGA-PRESS spectra. The second run was performed without applying any heat stimuli (DUMMY scans) to reduce habituation. The stimulation cycle consisted of the stimulation period with an individually adjusted maximal temperature (max. 47°C, 1 s), followed by a resting period at baseline temperature (31°C, 5/8 s). Using a trigger signal of the stimulation unit the acquired single MRS data could be assigned to two different time points within the stimulation sequence: PAIN (during heat stimulus) and REST (3 s after the heat stimulus). Mean PAIN and REST spectra (NAS = 128) were calculated by averaging the pooled data. Metabolic intensities of Glx and GABA+ were quantified in difference spectra (*edited – non-edited*) by using jMRUI [5] and normalised to the corresponding intensity of the total creatine signal (tCr) in non-edited spectra, applying CSF- and relaxation-correction to all metabolite intensities by using the segmented imaging data (*FreeSurfer* V 4.5.0, http://surfer.nmr.mgh.harvard.edu/). The Wilcoxon rank sum test was applied to evaluate the differences in GABA+ and Glx intensities in different paradigm conditions.

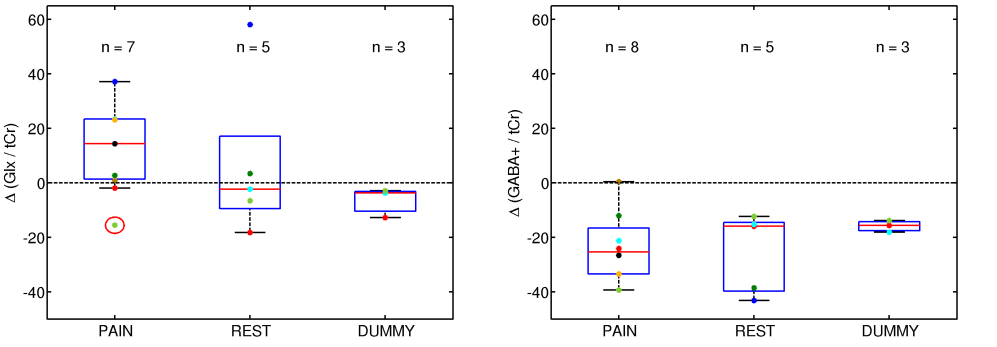

Fig. 3 Relative concentration changes of Glx/tCr (left) and GABA+/tCr (right) represented in boxplots normalized to the intra-individual REF-state (--) for each volunteer, which are represented in different colors of the diagram symbols, in aCC. The solid red line symbolizes the median value of the distribution. The lower and upper blue lines of the boxes represent the 25th and 75th percentile. The red encircled data point (left) was not included in the boxplot shown here.

Results: All volunteers reported painful sensations at the beginning of each stimulus cycle (rated 3-8 on a 10-point VAS [6]), but a subjectively perceived decreased pain intensity during the course of stimulations due to habituation. Only spectra satisfying previously defined quality criteria were analysed (line width < 0.07 ppm, SNR_{NAA} > 20, sufficient GABA+ and Glx fits). Compared to the REF-condition, Glx/tCr increased up to a median value of 14.2% in aCC (p = 0.017, excluding one data point due to insufficient Glx fit) in the PAIN state (Fig. 3). At the same time, GABA+/tCr decreased by a median value of 25.4% (p = 0.006). Intra-individually, Glx/tCr and GABA+/tCr showed no obvious trends during the REST and DUMMY period, whereas the median values had a tendency to return to the REF-condition.

Discussion and Conclusion: To our knowledge, our study demonstrates for the first time the possibility to quantify pain-induced neurotransmitter changes in the brain by using a functional ^{1}H-MEGA-PRESS technique. The Glx/tCr increase may be ascribed to the elevated glutamatergic turnover, while the decrease of GABA+/tCr may reflect reduced activity of the inhibitory system during pain processing in the aCC. However, ambiguous results of the REST and DUMMY state indicate slower processes in neurochemical regulation after pain perception. Therefore, further studies should aim to reduce measurement time and thus to avoid pain habituation by omitting the time resolved acquisition scheme.

References: [1] Borsook D et al., *Mol. Pain 2007*; 3: 25. [2] Gussew A et al., *Neuroimage. 2010*; 49: 1895–1902. [3] Mullins PG et al., *NeuroImage 2005*; 26: 642–46. [4] Siddall et al., *Anesth. Analg. 2006*, 102: 1164-8. [5] Stefan D et al., *Meas. Sci. Technol. 2009*; 20: 1-9. [6] Melzack R, *Pain 1975*; 1: 277-299.