Slice-selective FID acquisition of proton spectroscopic imaging to access functional metabolic changes during GABAergic stimulation with µl resolution in the mouse brain

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Introduction Spectroscopic imaging (SI) provides quantitative metabolic information in the brain. Methods based on slice selective pulses in three directions such as PRESS [1] or STEAM [2] are routinely used clinically and more recently also on the rat brain [3]. However, poor SNR related to the use of long echo times impairs spatial and temporal resolution, which imposes significant limitation when studying dynamic processes in small species such as mice. Moreover, at high field conventional SI suffers from large chemical shift artifacts due to limitations in the maximum achievable pulse bandwidth. Slice selective FID acquisition has been demonstrated to yield excellent SNR and very small chemical shift artifacts at high field in clinical applications [4]. In this work, slice selective FID spectroscopic imaging was applied in the mouse brain using a cryogenic four-element phased array coil. The method was applied to monitor changes in the cerebral metabolic profile in the mouse brain upon systemic infusion of the $GABA_A$ antagonist bicuculline.

Method All experiments were carried out using a BioSpec 94/30 (Bruker BioSpin MRI GmbH, Ettlingen, Germany) small animal MR system operating at 400 MHz. A four-element receive-only cryogenic phased array coil (2x2 geometry, overall coil size 20x27mm^2) was used in combination with a linearly polarized room temperature volume resonator for transmission. The cryogenic array coil was provided by Bruker BioSpin AG, Fällanden, Switzerland. All *in vivo* experiments were carried out in strict adherence with the Swiss law for animal protection. All mice were anesthetized using 1% isoflurane in an oxygen/air (20% / 80%) mixture, intubated and artificially ventilated. In the SI experiments the FID was acquired after a slice selective excitation using following parameters: TR: 2500ms ; FOV: 2.2x1.4cm; matrix: 22x14; reconstructed size: 32x32; slice thickness: 1.3mm; acquisition time: 13min. Scans were performed using VAPOR water suppression interleaved with six saturation slices for fat suppression. Field maps were used for shimming. The acquisition was weighted using a Hanning filter. SI scans were repeatedly acquired, one time pre-injection and four times post-injection of bicuculline, with a temporal resolution of 13 min. Bicuculline (Molekula) was infused in two different doses (0.6 and 1.2 mg/kg), with 0.04ml/min for the first 2 min and with 0.004ml/min for the next 10 min [5]. All mice were paralyzed using pancuronium (1mg/kg). All spectra were individually phase corrected to ensure optimal SNR during reconstruction. Relative quantification was performed using LCModel [6].

Results The SI data obtained in the mouse brain in 13min using slice selective FID acquisition enabled the quantification of more than 10 metabolites in most of the voxels included in the region of interest (fig 1.a.). The Cramer-Rao lower bounds (CRLB, LCModel) were found less than 20% even for weak signals such as GABA, lactate (Lac) and glutamate (Glu) (fig 1.b). The metabolite maps obtained from the integration over individual metabolite signals correlate well with the brain anatomy (fig 1.c, acquired pre-injection). Striatum, thalamus, hippocampus and parts of the midbrain display high creatine (Cre) and N-acetylaspartate (NAA) levels. During the control state Lac was found particularly high in the ventricles. The response to bicuculline showed the expected behavior: Lac was increased by more than 100% in hippocampus and thalamus immediately following the injection of the high dose of Bicuculline (fig 2). Choline and GABA signals were decreased up to 30% and 24 % respectively in hippocampus and thalamus (fig 3.b, c). Similarly, Glu and NAA were decreased, while taurine and myo-inositol remained mostly unchanged.

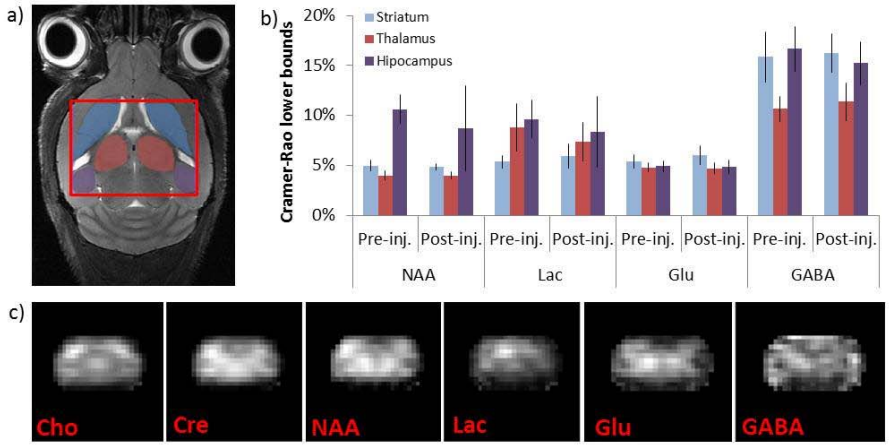

Fig 1: SI data has been acquired from one slice in the coronal orientation, comprising striatum, thalamus, hippocampus, ventricles and part of the midbrain (a). The Cramer-Rao lower bounds were below 20% for at least 10 metabolites, ensuring reliable quantification (b). Metabolite maps (pre-injection) obtained from integration over the metabolite signals show metabolite specific distributions (c).

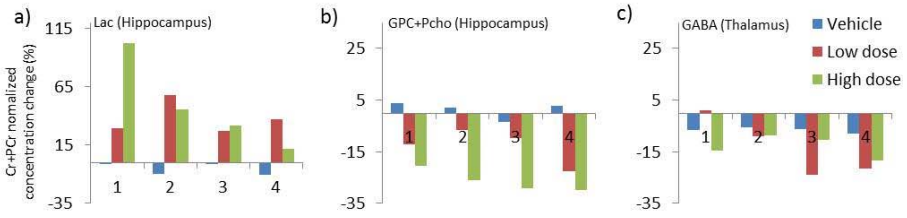

Fig 3: Brain metabolite response to bicuculline in two different doses compared to the vehicle solution for four time points (1, 2, 3 and 4) acquired with 13 min temporal resolution. Lactate (Lac) is strongly increased in the whole brain, especially in the hippocampus and the thalamus (a). Choline is decreased in hippocampus (b), GABA is decreased in the thalamus (c).

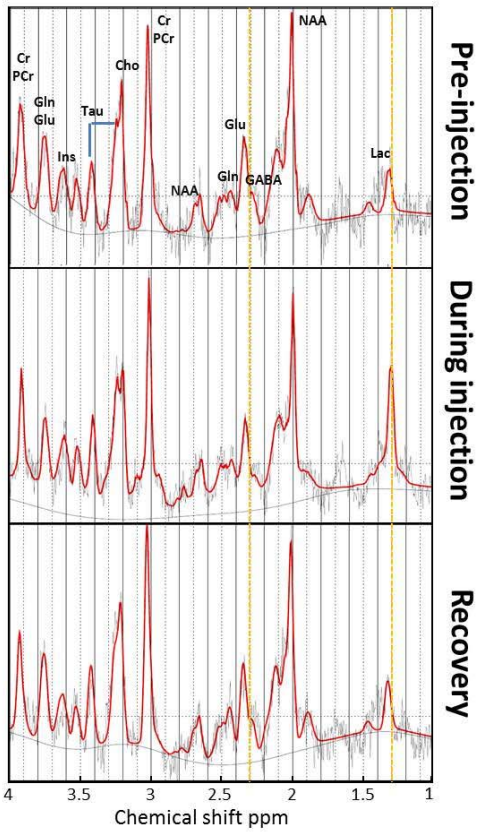

Fig 2: Spectra of a voxel located in the thalamus before injection of bicuculline (high dose), during injection and during recovery.

Conclusion & outlook Metabolic maps with voxel dimensions of 1 µl have been recorded from mouse brain with an acquisition time 13min. using slice selective FID acquisition. Most of the metabolites were reliably quantified over the region of interest. The quality of spectral information derived from individual voxels was excellent. Quantitative analysis yielded CRLB of less than 10% for NAA, Lac, Glu and less than 15% for GABA. The temporal resolution allowed the assessment of transient changes induced by the administration of a $GABA_A$ antagonist. Spectral changes were found to be dependent on the dose of bicuculline. The SI protocol has also been applied in the axial orientation in order to include cortical regions (data not shown). Extension of the work will go in two directions. Local spectral changes will be correlated with drug induced changes in functional MRI scans for both bicuculline stimuli and vehicle. Also the use of a phased array coil allows for accelerated data acquisition which should further enhance the temporal resolution.

References [1] Frahm J, Bruhn H, Gyngell ML, Merboldt KD, Hanicke W, Sauter R. Magn.Reson. Med. 1989; 9(1):79–93. [2] Provencher SW. Magn. Reson. Med. 1993; 30(6):672–679. [3] Mlynárik V, Kohler I, Gambarota G, Vaslin A, Clarke P, Gruetter R. Magn Reson Med. 2008; 59(1):52–58. [4] Henning A, Fuchs A, Murdoch JB, Boesiger P. NMR Biomed. 2009;22(7):683-96. [5] Mueggler T, Baumann D, Rausch M, Rudin M. Magn Reson Med. 2001 Aug;46(2):292-8. [5] Provencher SW, Magn Reson Med 1993;30:672–679.