Metabolite concentration changes in the human auditory cortex using functional Magnetic Resonance Spectroscopy (fMRS) at 7 Tesla

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Introduction: Signal-to-noise ratio (SNR) and chemical shift dispersion increase at high magnetic field, allowing the investigation of the human brain metabolism using MR spectroscopy (MRS) with improved accuracy and precision. Functional MRS (fMRS) takes advantage of high field to study metabolite changes during neuronal activation by continuously acquiring MR spectra during a functional task. In addition to the increased spectral resolution, the characterization of the small observed transient changes (around 0.2µmol/g) requires high MR sensitivity for a high time resolution. Recently, fMRS studies performed at 7 T [1-3] reported similar metabolite changes, in particular a lactate increase around 10-20% during visual activation. More recently, Schaller *et al.* [4] detected a similar increase of lactate during motor activation. Thus, it is of interest to further characterize the relationship between neuronal activation and energy metabolism, in other brain areas, such as the auditory cortex in the human brain investigated here for the first time.

Materials and Methods: Seven healthy subjects (3 men, 4 women aged 18 to 27 years) were enrolled in the fMRS study. All the subjects gave informed consent according to the procedure approved by the local ethics committee. The experiment were performed on 7T/68cm scanner (Siemens) with the use of a single channel quadrature transmit and 32-channel receive coil. To mitigate the limitations imposed on B_1^+, a dielectric pad filled with a solution of D_2O and barium titanate was placed on subject's head (above the auditory cortex). A preliminary fMRI experiment was first performed where the subjects were asked to carefully listen to an auditory stimulation (20s ON, 20s OFF, TA=2min30s, sounds of different frequencies). The overlap of the anatomical images (MP2RAGE [5]) and the activation map guided the placement of the VOI for the subsequent fMRS scans (inset in Fig. 1). First- and second-order shims were adjusted using FAST(EST)MAP. During fMRS, each subject underwent an auditory task similar to that described in the preliminary fMRI experiment with the following timing: 2min rest period followed by four alternate periods of 5min of auditory stimulation and rest (22min total). ^{1}H MR spectra were continuously acquired using the semi-adiabatic SPECIAL sequence (TR/TE=7800/12ms, BW=4000Hz, vector size=2048 pts, VOI=17×20×17mm^3, 84×2 scans) [6] preceded by VAPOR and outer volume suppression [7]. The individual MR spectra were frequency corrected to compensate for small B_0 drift. To determine that the placement of the VOI minimized partial volume effect, ^{1}H MR spectra from the last 4 min of each period were summed separately between activation (NT = 60) and rest (NT = 60) and then subtracted to yield a difference spectrum. To validate the statistical significance of the metabolite changes, a paired two-tailed student t-test was performed using the quantification of the aforementioned summed activation spectra and the summed rest spectra for each subject. For the time courses, MR spectra were summed over the 7 subjects in blocks of 14 spectra (2 scans per subject) and then moving averaged (kernel of 8 points). All spectra were fitted and quantified using LCModel [8] with a basis set of simulated spectra of 21 metabolites.

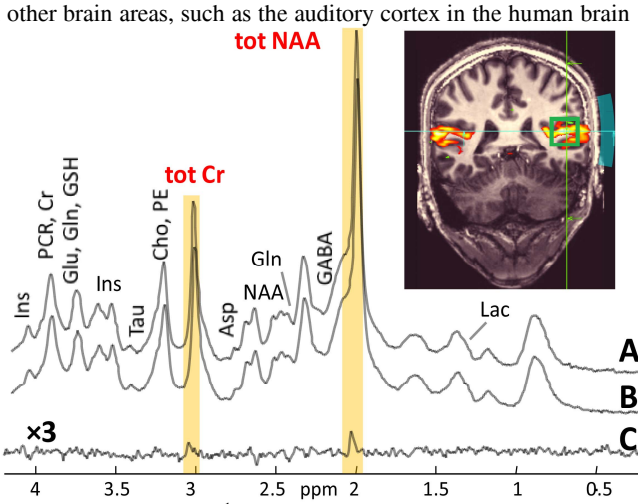

Figure 1: *Representative ^{1}H spectrum of a single subject acquired during stimulation* ***(A)*** *and rest* ***(B)*** *periods (NT=60 scans).* ***(B)*** *was subtracted to* ***(A)*** *to yield a difference spectrum* ***(C)****. Inset: Overlap of the anatomical scans and the activation map guided the placement of the voxel (green square). Dielectric pad (blue bar) was placed above the auditory cortex.*

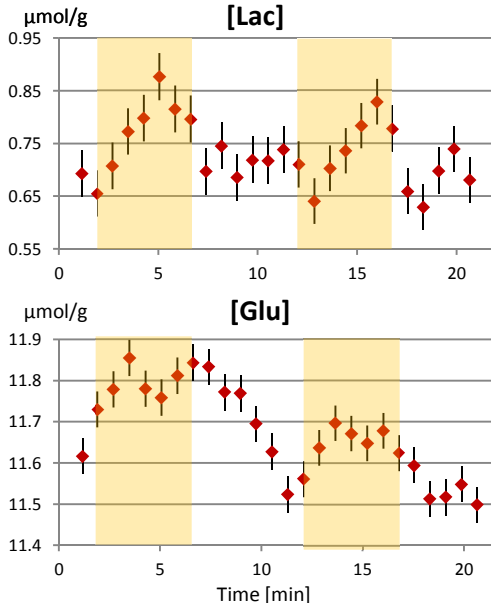

Figure 2: *Time courses for [Lac] and [Glu] in the human auditory cortex. Data are mean±CRLB*

Results and Discussion: Shimming resulted in typical water linewidths of 13.8±0.7Hz (mean±sd, n=7). Stable and reproducible spectra were acquired during the fMRS experiment and no signal contamination, due to extraneous lipid, was observed in the spectral region 1-2 ppm (Fig. 1A and B). Residual water signal was minimized below the height of the NAA peak. SNR of NAA resonance was typically 47±7 (mean±sd, n=7, NT=2). The use of the semi-adiabatic SPECIAL sequence at 7T and the dielectric pad (inset in Fig. 1) yielded sufficient sensitivity to investigate the metabolite changes during auditory stimulation, as judged from CRLB of lactate (Lac) and glutamate (Glu) with CRLB < 30 % and 2 % (NT = 14). Linewidth narrowing of the ^{1}H MR spectra, which are induced by the BOLD effect [8], resulted in a mean increase of the creatine peak height of 4% during activation periods, which confirmed the position of the voxel in the activated area. The influence of the physiological activation on the ^{1}H MR spectra was also observed on the difference spectrum of a single subject (Fig. 1.C). The linewidth narrowing caused by the BOLD effect was clearly visible in the difference spectrum at the singlet resonances of totCr (3.03 ppm) and totNAA (2.01 ppm). Spectra were averaged between the subjects allowing a native time resolution of 15.6s for the metabolite time courses and then moving averaged (Fig. 2). The time courses illustrated a new steady state reached by the metabolites. Statistically significant increases of Lac by 11±4% ($p<0.02$,) and of Glu by 2±1% ($p<0.007$) were found (n=7, mean±sem).

We conclude that activation results in transient Lac and Glu increases to a new steady state in the human auditory cortex, similar to increases reported during visual and motor stimulations [1-4]. Therefore, we propose that Glu and Lac increases may be a general manifestation of neuronal activation.

References and Acknowledgements: [1] S. Mangia, JCBFM, 2007 [2] B. Schaller, JNR, 2013 [3] Y. Lin, JCBFM, 2012 [4] B. Schaller, 21st ISMRM, 2013 [5] Marques JP Neuroimage, 2010 [6] L. Xin, MRM, 2012 [7] I. Tkac, AMR, 2005 [8] S. Provencher, MRM, 30, 1993 [9] Zhu and Chen, MRM, 2001. Supported by CIBM of the UNIL, UNIGE, HUG, CHUV, EPFL, the Leenaards and Jeantet Foundations and SNF grant 131087.