Investigation of metabolic changes in human visual cortex during neuronal activity using functional Proton Magnetic Resonance Spectroscopy at 7T

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Introduction

Magnetic Resonance Spectroscopy (MRS) has become a powerful tool to investigate metabolism in the human brain during activation [1-5]. ^{13}C-MRS studies [2] have showed that the cerebral metabolic rate of oxidative glucose, CMRglc(ox), is correlated to the glutamate/glutamine neurotransmitter flux and Shulman *et. al.* hypothesized that during stimulation the increase in CMRglc(ox) will lead to an increase in the levels of glutamate (Glu) and glutamine (Gln), without change in the lactate (Lac) level. However, it has been suggested that the initial energy demands during activation is met predominantly through glycolysis in astrocytes[5]. Several Proton MRS studies have provided evidence supportive of non-oxidative metabolism with markedly increased Lac concentration at the early onset of neuronal activation and remains constant thereafter [1,4]. Unfortunately, the feasibility of measuring Lac changes under stimulation has been challenged by other authors: Merboldt *et. al.* (1992) could not detect any Lac increase during several kinds of visual stimulation; Christine *et. al.* [3] failed to detect the Lac signal during visual stimulation. The purpose of the present study was to use the improved SNR and spectral resolution available at 7T to study changes in ^{1}H metabolite levels in the visual cortex during visual stimulation. Specifically, the aim was to confirm and quantify the increase in Glu/Gln levels suggested by Shulman[2] and reported by others[4], and to investigate further any Lac response to visual stimulation.

Methods

Nine healthy subjects (six males, three females, 23 to 29 years old) participated in this study. All MR measurements were acquired using a Philips Achieva 7T MR system and a 16-channel SENSE head coil（Nova Medical）.The visual stimulus was delivered with Light Emitting Diode (LED) goggles flickering at a frequency of 8 Hz. The paradigm comprised of two 10 minute stimulation periods interleaved with two 10 minute rest periods. A STEAM sequence (TE/TM/TR=15/17/3000ms, spectral width 4000Hz, 4096 time points) was used for acquiring the metabolic data, with water suppression. Spectra were collected in blocks of 32 averages, with 6 blocks per 10 minute period. 1 scan without water suppression was acquired for every 32 water suppressed spectrum. An initial fMRI scan (EPI, TE=26ms, TR=2200ms, spatial resolution 2×2×2mm^3) was performed prior to spectroscopic acquisition in order to determine the activated region in the visual cortex. A cubic VOI of 2cm^3 was positioned inside the activated region for functional MRS acquisition. Spectral pre-processing was done in MATLAB and summed spectra for visual stimulus off (the control period) and visual stimulus on were analyzed separately using Subtract-QUEST in jMRUI, with basis-set simulated with NMR-SCOPE [6]. Spin parameters were taken from Govindaraju *et. al.*[7]. 19 data points were omitted and background signal was estimated from the first-points of the MRS signal using Subtract-QUEST method. For each subject, the water signal was used as an internal reference and the levels of Lac, Glu, Gln as well as other brain metabolites were monitored and compared. A Wilcoxon signed rank test was conducted to compare the relative metabolites change. Results were considered to be significant when p <0.05.

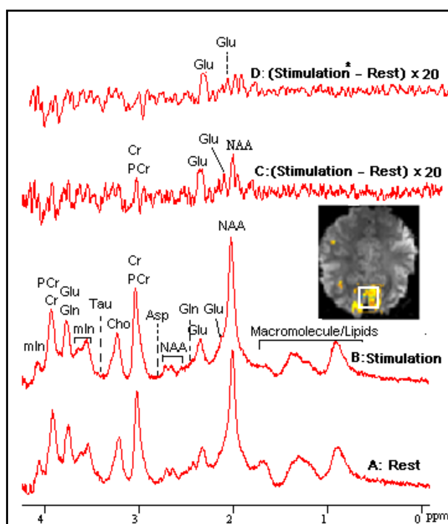

Fig.1 A representative 7T proton spectrum from a single subject:(A) averaged spectrum acquired at rest; (B) averaged spectrum acquired during stimulation; (C) difference between (A) and (B). The peaks seen at 2.01, 2.10, 2.35 and 3.03ppm in the difference spectrum are attributed to linewidth changes due to the BOLD effect as well as concentration changes of metabolites. (D) same as (C), but the spectrum acquired during stimulation was linebroadened by 0.6Hz to match the linewidth of the spectrum acquired at rest, in order order to eliminate the linewidth changes due to BOLD effect. Glutamate peaks at 2.10 and 2.35ppm survive this procedure. Inset: An example acquired BOLD response. The voxel position is indicated by a white square.

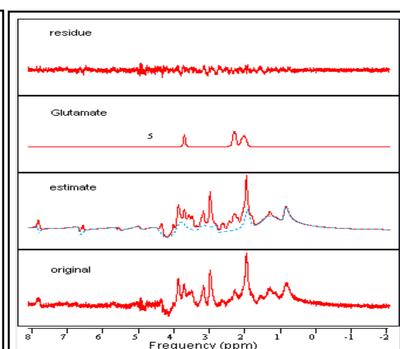

Fig.2 jMRUI QUEST Quantitation result window. From bottom to top, original spectrum; estimated spectrum and background (dashed line) using Sub-QUEST; selective Glutamate spectrum; and residue.

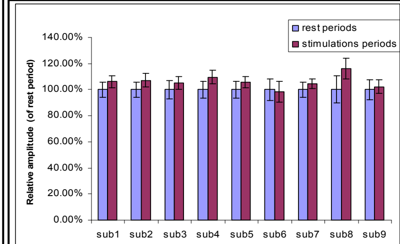

Fig.3 Relative Glutamate amplitude between rest and stimulation for nine subject measured by Sub-QUEST.

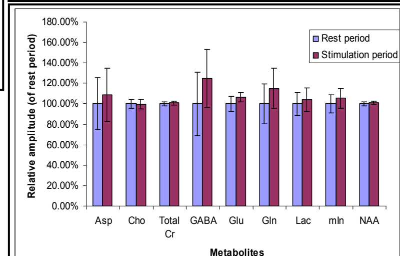

Fig.4 Averaged relative metabolites amplitude over nine subjects between rest and stimulation measured by Sub-QUEST.

Results

Fig.1 shows an example of ^{1}H NMR spectra acquired at 7T from a single subject. Fig.2 presents the resulting fit from Subtract-QUEST in jMRUI. As can be seen, the estimated background fits the lipid peaks at 0.89 and 1.3 ppm well. The averaged NMR signals acquired during the rest periods were normalized to 100%. The mean values and the corresponding standard deviations of the metabolites estimated as relative amplitude are expressed as a percentage of the estimated rest concentrations. Fig.3 shows a significant (p=0.01) Glu increase in visual cortex during activation. Fig.4 shows the averaged relative amplitude over nine subjects for the measured metabolites between rest period and stimulation period. The highest significance increase during stimulation was found for Glu, with an average increase during stimulation of 6.13%±4.6%. No statistically significant difference can be seen for Gln, Lac, N-acetyl aspartate (NAA), choline (Cho),creatine/phosphatecreatine (total Cr), myo-inositol (mIn), aspartate (Asp), gamma aminobutyric acid (GABA).

Discussion

Using a short echo time STEAM sequence at 7T, it was possible to acquire ^{1}H spectra from the visual cortex with excellent spectral resolution, such that the amino acids Glu, Gln and GABA, as well as many other neuro metabolites, could be quantified. We found a significant increase in Glu of 6.13%±4.6% on visual stimulation, similar to that reported by Mangia et al [4]. However, we do not find evidence for an increase in Gln and Lac on activation, nor do we observe a decrease in Asp. This may be due to poor signal to noise for the low concentration metabolites (Fig.4), but the changes if present are certainly small (less than 0.2µmol/g [4]). This information will be important in the metabolic modelling for the 7T ^{13}C MRS studies of visual activation currently being planned in our laboratory.

References: [1] Frahm, J, et al. Magn. Reson. Med. 35,143-148 (1996). [2] Shulman R G et al., Proc Natl Acad Sci 95, 11993-11998(1998). [3] Christine C et al. Eur Radiol. 15:47-52(2005). [4]Mangia, S et al. Journal of Cerebral Blood Flow & Metabolism, 27,1055-1063 (2007). [5] Lin AL, et al. Neuroimage. 36(SI),381 (2007). [6]. Graveron-Demilly D et al. J Magn Reson A.101: 233–239(1993). [7] Govindaraju V, et al. NMR Biomed 2000. 13:129-153.