Functional Proton Magnetic Resonance Spectroscopy of the Human Primary Visual Cortex: Metabolite and Neurotransmitter Concentrations

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Introduction

The neurochemical correlates of the BOLD response in fMRI studies of the brain are not fully understood. Previous ^{1}H-MRS studies of the human primary visual cortex have shown that during prolonged photic stimulation (4 to 48 min), lactate is elevated (*1-3*) and glucose is decreased(*3, 4*). Lactate elevation has been reported during other sensory and cognitive activation as well. These findings were in support of the hypothesis of selective activation of anaerobic glycolysis during cortical stimulation. However, the prolonged activation time in previous studies prohibits the correlation to typical fMRI studies in which the activation time is shorter (of the order of 30 sec). On the other hand, ^{13}C-MRS studies showed that the cerebral metabolic rate of oxidative glucose consumption, CMRglc(ox), is correlated to the glutamate/glutamine neurotransmitter flux with a stoichiometry of about 1:1 (*5*), which would suggest that this glucose utilization pathway is dominant. We hypothesized that during stimulation the increase in CMRglc(ox) will lead to an increase in the levels of glutamate and glutamine, and the level of lactate will not be affected. To test this hypothesis, in the time frame of typical fMRI studies, we used ^{1}H-MRS because of its higher sensitivity compared to other nuclei. To further improve the sensitivity of the exam, we used a high-field magnet (3 T) and a short echo time and optimized the order of the ^{1}H-MRS localization gradients (*6*) and the RF coil dimensions. Using this optimized ^{1}H-MRS acquisition, the levels of lactate, glucose, glutamate, and glutamine as well as other brain metabolites were monitored at rest, stimulation, and after stimulation of the human primary visual cortex, using the same visual stimulation paradigm for ^{1}H-MRS and fMRI.

Materials and Methods

9 subjects (5 men and 4 women, 28 to 57 years of age) underwent MRI, fMRI, and ^{1}H-MRS of the brain. Informed consent was obtained in accordance with the guidelines of the institutional review board of the Beth Israel Deaconess Medical Center. The studies were performed on a 3T scanner (Signa LX, General Electric, Waukesha, WI). The subjects entered the scanner in a supine position. For surface coil acquisitions, it was verified that the calcarine fissure was positioned at the center of the coil. Axial T_2-weighted images and EPI T_2*-weighted images of the brain were recorded with the same graphic prescription. EPI was analyzed using a Real Time Image Processing software (RTIP, GE Medical Systems). The visual stimulation was delivered through LCD goggles equipped with corrective lenses. The visual stimulation paradigm included 40 sec of darkness, 32 sec of alternating checkerboards (at 8 Hz), and 32 sec of darkness. The MRS voxel (2 x 2 x 1 cm^3) was localized on the T_2-weighted images, at the site of activation observed in the RTIP images. The spectra were acquired using the PRESS sequence with a repetition time of 2 sec, time to echo of 35 msec, spectral width of 5000 Hz, and 2048 time points. ^{1}H-MRS acquisition was synchronized to the stimulation paradigm and both were repeated 10 times with a period of 46 sec for rest between runs. The spectra were stored in a frame-by-frame mode which allowed flexible post-processing. At the end of the spectroscopy part, two more fMRI data sets were acquired using the same stimulation paradigm to confirm continued activation. Spectral analysis was performed using SAGE (GE Medical Systems) and LC-Model, a frequency domain fitting algorithm that uses prior knowledge of the chemical shift and chemical formula of brain metabolites(*7*). For each cycle (4 dummy scans and 48 ^{1}H-MRS frames), the frames were grouped into three categories according to their time of acquisition: rest, stimulation, and post stimulation. For each volunteer, the spectra of the 10 cycles were combined according to their category, yielding three averaged spectra, each of 160 frames (5.3 min) of rest, stimulation, and post-stimulation. Metabolite to creatine (Cr) ratios were determined using LC-Model analysis of these three spectra, for each volunteer. Metabolite concentrations and SNR were calculated assuming 10 mM Cr.

Results

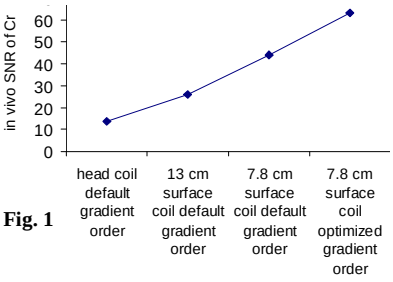
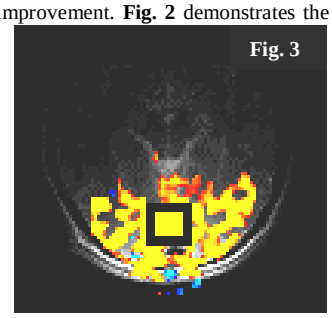


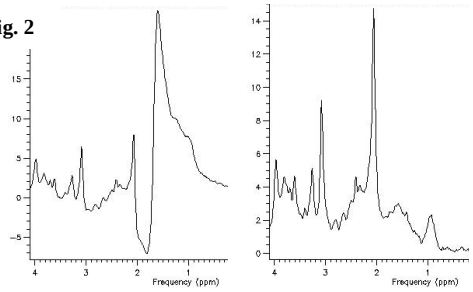
Fig. 1

The ^{1}H-MRS exam was optimized in terms of SNR increase and artifact reduction. **Fig. 1** demonstrates the improvement in SNR that was obtained through the use of surface coils (with body coil transmission) compared to a volume head coil, and the furter improvement obtained using a 7.8 cm surface coil instaed of a 13 cm one. The SNR was calculated from in vivo spectra for the Cr signal per 48 frames (1.6 min) per 4 cm^3 voxel. The default slice selection gradient order of the PRESS sequence was sagittal-coronal-axial. This order was optimized for the location of the primary visual cortex focusing on artifact reduction as well as on further SNR improvement. **Fig. 2** demonstrates the artifacts that may be obtained using a non-optimized localization gradient schemes such as coronal-axial-sagittal (left panel). The optimum gradient order was found to be sagittal-axial-coronal (right panel). The SNR improvement that was obtained using the optimized gradient order is shown in Fig. 1.



All volunteers showed a strong BOLD response in the striate cortex as well as in the extrastriate cortices. **Fig. 3** demonstrates a typical example of the BOLD response to the stimulus in one of the volunteers. The statistical map was overlaid on the T_2-weighted image. The MRS voxel is indicated by a black square. The concentration of brain metabolites in the primary visual cortex at rest (in mM, n = 9) were: N-actyl-aspartate compounds 16 ± 1, choline metabolites 1.4 ± 0.1, myo-inositol 5.2 ± 0.7, lactate (upper limit) 1.1 ± 0.5, glucose (upper limit) 0.50 ± 0.88, glutamine 5.6 ± 1.9, glutamate 15 ± 2. These concetrations did not alter significantly during stimulation and post-stimulation.

Fig. 2



Discussion and Conclusions

Optimized ^{1}H-MRS acquisition at 3T resulted in a SNR of 4.0 per mM per min acquisition per 4 cm^3 voxel (determined using the Cr signal). Thus, for the lactate signal, which is a doublet, the SNR would be 2.0. Assuming a 1 mM of lactate in the human brain, accurate determination of this content (SNR of least 10) would require an acquisition time of 25 min which is impractical for activation studies. Since the ^{1}H-MRS signals of glucose are more complex multiplets, an even longer time would be required for an accurate determination of the glucose content. Thus, the concentrations reported here for lactate and glucose in the primary visual cortex are given as a measure for an upper limit and not as absolute concentration. Because a significant increase in lactate content during stimulation was not detected, the hypothesis that the brain's BOLD response is associated with a shift to anaerobic glycolysis could not be confirmed.

There were no significant changes in the level of glutamate and glutamine (within an error of 13 % and 33 %, respectively), thus contradicting our hypothesis. This result suggests that the proportion of glutamate synthesis during stimulation is small compared to the existing level of glutamate in the awake resting (or not specifically stimulated) brain, or that the level of glutamate and glutamine is tightly regulated by clearance mechanisms. ^{13}C-MRS studies suggested that the increase in neurotransmitter cycling rate during stimulation was only 10 to 20 % above the rate of this cycle in the awake resting brain (*5*). We can not exclude the possibility that despite the improved SNR conditions of our study, changes of that order of magnitude were not detected.

References 1. D Sappey-Marinier et al., J Cereb Blood Flow Metab **12**, 584-592 (1992). 2. J Prichard et al., Proc Natl Acad Sci **88**, 5829-5831 (1991). 3. J Frahm, et al., Magn Reson Med **35**, 143-148 (1996).4. KD Merboldt et al., Magn Reson Med **25**, 187-194 (1992). 5. RG Shulman et al., Proc Natl Acad Sci **95**, 11993-11998 (1998). 6. T Ernst et al., Magn Reson Med **36**, 462-468 (1996). 7. SW Provencher, Magn Reson Med **30**, 672-679 (1993).