Limits on Activation Induced Temperature Related Frequency Changes in Primary Visual Cortex

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Introduction

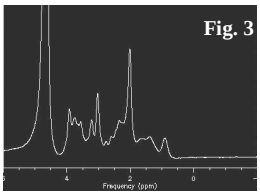
Stimulus induced water frequency changes attributed to changes in local brain temperature have been reported by Yablonsky et al. (*1*). Such a finding could have important implications for metabolic and flow changes accompanying brain activation. There are, however, numerous other potential causes of frequency shifts in-vivo including magnetic field drifts and susceptibility changes. NAA has been suggested as a standard for temperature measurement since its frequency change with temperature is much smaller than that of water (*2*). Here we report the simultaneous measurement of the water and proton metabolite frequency shifts using partially water-suppressed, single-voxel magnetic resonance spectroscopy in the primary visual cortex. In order to explore the variations of the MR signal during a time frame of a typical fMRI study, MRS and fMRI were performed using the same behavioral paradigm.

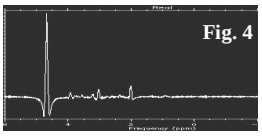
Materials and Methods

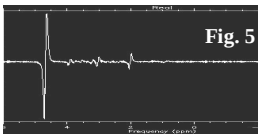
9 subjects (5 men and 4 women, 28 to 57 years of age) underwent MRI, fMRI, and MRS of the brain. Informed consent was obtained in accordance with the guidelines of the institutional review board of the Beth Israel Deaconess Medical Center. The studies were performed on a 3T scanner (Signa LX, General Electric, Waukesha, WI) equipped with a body coil (transmit) and a 7.8 cm diameter surface coil (receive). The subjects entered the scanner in a supine position with the calcarine fissure positioned at the center of the coil. Axial T_2-weighted images as well as EPI T_2*-weighted images were recorded with the same graphic prescription. fMRI data were analyzed using a Real Time Image Processing software (RTIP, GE Medical Systems). 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 using the T_2-weighted images, at the site of activation observed in the RTIP images. PRESS spectra were acquired using a repetition time of 2 sec, time to echo of 35 msec, spectral width of 5000 Hz, and 2048 time points. The MRS acquisition and the stimulation paradigm were synchronized and repeated 10 times with a period of 46 sec for rest between runs.

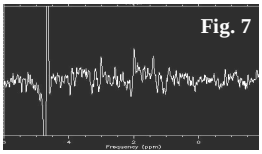
Spectral processing was performed using SAGE (GE Medical Systems) and MATLAB (The MathWorks, Inc., Natick, MA). The FIDs were phase-corrected, zero-filled to 16,384 points, and Fourier transformed. For each cycle, the frames were grouped into three categories (16 frames each): rest, stimulation, and post-stimulation.

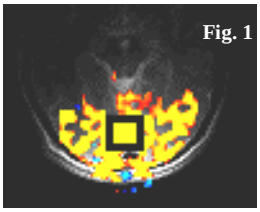
Results











All of the volunteers showed a strong BOLD response to the stimulus in the striate cortex as well as in the extrastriate cortices, as demonstarted by a typical example in **Fig. 1.** The MRS voxel is indicated by a black square. This response was recorded at the end of the experiment, ruling out acclimation to the stimulus as a result of the consecutive MRS recordings. The frequency variations of the water resonance did not correlate with the stimulation paradigm. However,the frequency variations of the water resonance were matched by the frequency variations in the resonances of choline (Cho), creatine (Cr), and N-acetyl-aspartate (NAA), and appeared to occur on a longer time scale than that of the stimulation paradigm. **Fig. 2** demonstrates the time course of frequency variations in one of the volunteers. The vertical scale is in units of -0.305 Hz (the spectral resolution of the spectrum) and the horizontal scale correponds to averages of 16 frames, starting with the first rest period of the experiment and ending with the last post-stimulation period. The frequency of the 1st cycle was significantly higher than that of the 10th cycle for all the investigated resonance (P= 0.021, 0.0058, 0.013, 0.0041, for water, Cho, Cr, and NAA, respectively, two-tail paired t-test, n=9 volunteers). The average frequency shift, estimated from the difference of the mean frequency in the 1st and 10th cycle for each volunteer, was 0.11 ± 0.12 Hz/min for the water resonance (n = 9). Similar frequency shifts were found for Cho, Cr, and NAA, (0.13 ± 0.11, 0.13 ± 0.12, 0.13 ± 0.10, respectively).

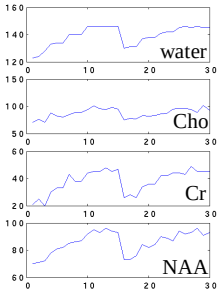


Fig. 2

Potential linewidth chages during stimulaiton were investigated using a difference technique. **Fig. 3** demonstrates an averaged spectrum (10 cycles in 9 volunteers, 1440 frames, 48 min total) of the primary visual cortex at rest processed with a linebroadening (LB) of 3 Hz. The effect of linewidth decrease is demonstrated in **Fig. 4**: the averaged spectrum processed with no LB was subtracted from the same spectrum processed with LB of 0.1 Hz. **Fig. 5** demonstrates the effect of a frequency decrease: the averaged spectrum processed without a shift was subtracted from the same spectrum shifted by 1 point (0.305 Hz). In the boundries of the averaged water-signal's linewidth, the relative amplitude difference was linear with the change in linewidth (**Fig.6 right**) and with the frequency shift (**Fig. 6 left,** frequency decrease). **Fig. 7** shows the experimental difference between stimulation to rest (average of 9 volunteers, 10 cycles each). The spectrum was enlarged to show the metabolite region. The spectra at rest and stimulation were both processed with LB of 3 Hz prior to subtraction to reduce the noise in the metabolite region. In this spectrum it is visible that there is a component of frequency shift in the data and possibly a linewidth change as well. Using calibration plots (such as shown in Fig. 6), the linwidth change during activation was found to be 0.088 Hz for the water signal and 0.070 Hz for the NAA signal. However, the linewidth change could not be conclusively determined due to the dominant effect of frequency shift in the spectra.

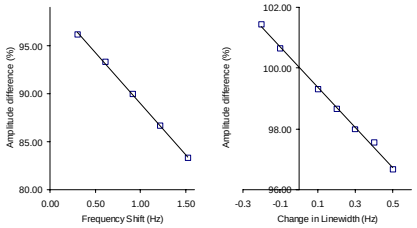


Fig. 6

Discussion and Conclusions

Determination of linewidth changes using difference spectroscopy, that utilizes a continuous dimension of the measurement, may be more sensitive and accurate than conventional spectroscopic analysis which is discrete and depends on the spectral resolution in Hz/Point. However, since frequency shifts were also present in the data, the results of the difference analysis provided an upper limit for the linewidth change and not an absolute determination. Previously, a decrease of 1.7 to 2.3% in the linewidth of the metabolites and water signals during stimulation was reported at 4T(*3*). This observation was in agreement with the reported increase in T_2* during stimulation (from 58 msec to 61 msec), that was measured by MRS at 2T (*4*). Here, the linewidth at rest was of the order of 8 Hz and the upper limit for a linewidth change corresponded to about 1 % of the linewidth.

Previously, MRS of prolonged activation revealed a change in frequency of the MR signal (up to 0.2 Hz/min, at 1.5 T) and this change has been attributed to a change in temperature during activation (*1*). However, in the same report it appears that during a shorter activation period (< 1 min) this phenomena was not observed. Here, the frequency shifts of the MR signal were not correlated to the stimulation paradigm. However, a decrease in frequency larger than that of the magnet drift (0.068 Hz/min) had been observed. Because the same frequency shift was found for the water and the metabolite resonances we conclude that the source of these frequency shifts is not thermal.

References 1. D. A. Yablonskiy et al., Proc Natl Acad Sci **97**, 7603-7608 (2000). 2. E. B. Cady et al., Magn Reson Med **33**, 862-867 (1995). 3. X. H. Zhu et al., Magn Reson Med **46**, 841-847 (2001). 4. J. Hennig et al., Magn Reson Med **31**, 85-90 (1994).