Limits on Activation Induced Temperature and Metabolic Changes in the Human Primary Visual Cortex

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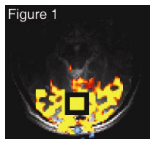
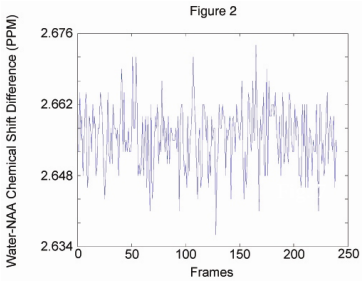
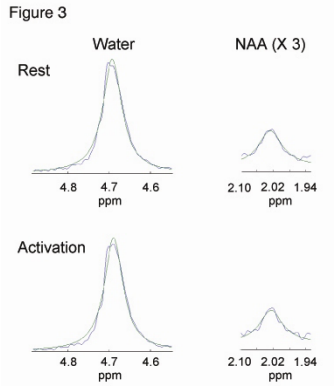
Background: In activated regions of the brain, blood flow and glucose consumption increase substantially more than oxygen consumption (Fox et al 1986; Fox et al 1988; Ginsberg et al 1988). These changes, along with changes in cerebral blood volume, lead to the blood oxygenation level dependent (BOLD) contrast in functional magnetic resonance imaging (fMRI) (Ogawa et al 1992). Broad investigations have been concerned with the possible mechanisms that underlie these phenomena and their relation to neuronal activation. Proton magnetic resonance spectroscopy (^{1}H-MRS) can be sensitive to temperature, oxygenation, metabolism, and neurotransmitter concentrations. ^{1}H-MRS was employed to constrain changes of these quantities in the visual cortex of normal volunteers during 32 second blocks of visual stimulation. Previous ^{1}H-MRS studies of metabolism and temperature during visual and other stimulation paradigms used prolonged stimulation duration (4 - 48 min) (Frahm et al 1996; Prichard et al 1991; Richards et al 1999; Richards et al 1997; Sappey-Marinier et al 1992; Urrila et al 2003; Yablonskiy et al 2000). However, long slow changes are prone to systematic errors. The contribution of drifts to systematic errors can be diminished using a block design paradigm. We chose multiple 32 s blocks as an optimal timing for following the BOLD response, neuronal oxidative glucose metabolism, and astrocytic anaerobic glycolysis (Kasischke et al. 2004; Logothetis et al. 2001). The same block design behavioral paradigm was used for both the fMRI and the ^{1}H-MRS parts of the study in order to explore the metabolic and physiologic correlates of brain activation.

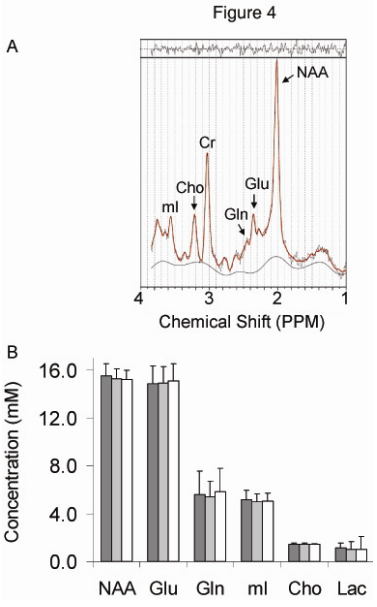
Methods: Nine subjects underwent MRI, fMRI, and partially water-suppressed single-voxel short-echo-time (35 ms) ^{1}H MRS at 3 Tesla (Signa VH/i, GE Healthcare, Waukesha, WI) with a transmit body coil and receive only 7.8 cm surface coil. Informed consent was obtained in accordance with the guidelines of the institutional review board. The ^{1}H-MRS voxel (2 x 2 x 1, 4 cm^3) was positioned using T_2-weighted images, at the site of activation (revealed by the fMRI BOLD response statistical map) as shown in **Figure 1**. The visual stimulation paradigm involved 12 repetitions of 40 s of darkness, 32 s of black and white checkerboards alternating at 8 Hz, and 32 s of darkness, with 46 s for rest between the repetitions (with 2 repetitions for each of the fMRI scans at the start and end of the study and 10 repetitions for the MRS investigation). The NAA signal was used here as a control for non-thermal frequency changes. The difference between the water and NAA chemical shift was used as a measure of temperature (Cady EB et al1995 and Corbett et al 1997). The chemical shift difference between the central resonance frequencies of these signals was calculated using either the peak of the signals in single frames or a least square fitting on average spectra (4 frames, 8 s of acquisition) using a Lorentzian line shape $(L(\omega)=(1/T_2^*) / ((1/T_2^*)^2+(\omega-\Omega)^2$, where Ω is the center of resonance). Fitting results of $R^2>0.9$ were considered for temperature and T_2^* calculations. Analysis of metabolite and neurotransmitter concentration was performed using LC-Model (Provencher S. 1993). For each cycle (4 dummy scans and 48 MRS frames), the frames were grouped into three block categories according to the stimulation paradigm: 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 (**Figure 4A**), stimulation, and post-stimulation. Metabolite concentrations were calculated assuming 10 mM Cr.





Results: The time course of the chemical shift difference between the water and the NAA signals in one of the volunteers is shown in **Figure 2**. The chemical shift difference was calculated in each frame and the results of every second acquisition frame are shown. The first 8 frames were acquired during rest, the subsequent 8 frames were acquired during stimulation, and the subsequent 8 frames were acquired during the post-stimulation period, with this order repeating for 10 cycles. The chemical shift difference between the water signal and the NAA signal was found to be stable throughout the time course of the experiment and not strongly correlated to the stimulation paradigm. Typical curve fitting of the water and the NAA signals in the primary visual cortex of one of the volunteers at rest and during stimulation is shown in **Figure 3** (The NAA signal was enlarged 3 fold relative to the water signal). Curve fitting of these signals enabled robust determination of their central resonance frequency and T_2^*. The local temperature at the visual cortex (35.7 ± 0.8 ºC at rest) was similar at rest and during stimulation (ΔT = 0.1 ºC, P = 0.09, 95% confidence interval (CI) = 0.0 to 0.2 ºC), suggesting that the change in the temperature of the visual cortex during activation was not strongly significant. In the period post-stimulation, the temperature remained unchanged. The T_2^* values that were calculated using the curve fitting of the water (77 ± 14 ms) and the NAA (64 ± 9) did not significantly change during stimulation (mean difference = -0.4 ms and 0.4 ms, P = 0.5 and 0.7, 95% CI = -1.6 to 0.9 ms and -2 to 3 ms, respectively) as well as post-stimulation. The concentration of the metabolites and the neurotransmitters in the primary visual cortex is shown in **Figure 4B**. The mean results (+ standard deviation) during rest (dark gray), stimulation (light gray), and post stimulation (white) are shown. The concentrations of N-acetylaspartate (NAA), glutamate (Glu), glutamine (Gln), myo-Inositol (mI), choline (Cho), and lactate (Lac) were not significantly affected by activation. Specifically, the mean difference in lactate concentration during stimulation was -0.08 mM (P=0.8, 95% CI = -0.65 to 0.49 mM).





Discussion: Our constraints on temperature change during activation suggest important increases in heat production during activation. Except for very near the edge of the brain, temperature control is determined predominantly by local heat production and inflow of blood at approximately 0.3°C lower temperature than brain parenchyma (Collins et al 2004; Yablonskiy et al 2000). Visual stimulation induces 50% increases in blood flow and glucose utilization across a relatively large volume of visual cortex (Fox et al 1988). A 50% increase in flow should induce a 0.1°C temperature drop in the absence of increased heat production. Our constraints on temperature change, however, suggest an increase in heat production proportional to or even greater than the increase in flow. Were this increase to result from metabolic consumption of the increased glucose utilized, almost completely aerobic metabolism of this glucose would be required because of the limited heat produced by glycolysis. The elevated oxygen consumption required, however, would be in disagreement with almost all studies of oxygen utilization changes accompanying activation. Alternatively, neural activity itself may be exothermic (Howarth et al 1968; Ritchie et al 1985) While any heat produced during activity must eventually be replaced by glucose metabolism, the timescale for full replenishment of cellular ion concentrations could be many hours. The approximately proportionate increases in heat production and flow indicated by our results suggest flow elevation during activation may serve primarily to remove increased heat and regulate temperature during activation. Limits on lactate concentration changes were too weak to constrain theories of the metabolic use of elevated glucose consumption during stimulation and emphasize the challenges of measuring even large lactate changes accompanying stimulation. Limits on T_2^* changes of the water and the NAA signals were within the relative range of previously published results (Hennig et al 1994 and Zhu et al 2001).