# UNCOUPLED COUPLINGS: COMBINED FMRI AND 1H-MRS FOR THE STUDY OF THE NEUROVASCULAR AND NEUROMETABOLIC COUPLING

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## Purpose

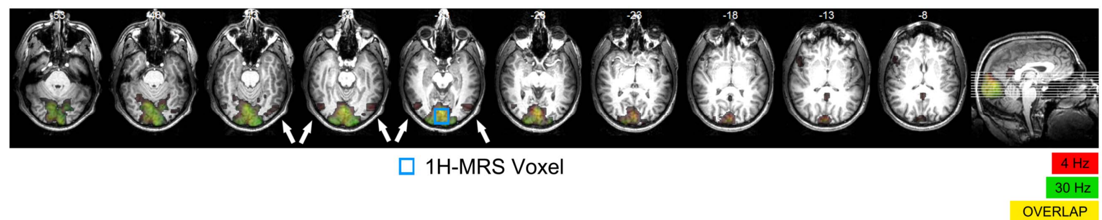
Functional magnetic resonance imaging (fMRI) is the tool of choice for mapping brain function. Unfortunately, the blood oxygenation level dependent (BOLD) contrast is essentially a vascular effect and hence only an indirect measure of neural activity. Accordingly, BOLD is found to reflect synaptic, more than spiking, activity and it is potentially independent on energy requirements [1]. As such, the exact relationship between BOLD fMRI signal and neural processes (action potentials and inhibitory/excitatory postsynaptic potentials) is still elusive. Here we combined fMRI with proton magnetic resonance spectroscopy (1H-MRS) to study the vascular and metabolic response of the brain by activating different pathways within the central visual system. The aim of the present study is to examine the neural events underlying functional brain images and the metabolism of the activated tissue.

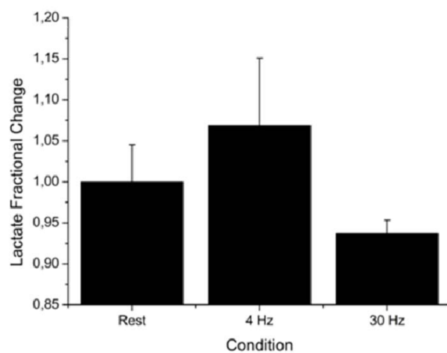
## Methods

Five healthy subjects (age 34 +/- 6) participated in this study. Visual stimulation consisted of full-contrast circular sinusoidal gratings (0.4 cycles/deg) drifting at either 4 Hz (low-frequency) or 30 Hz (high-frequency). We acquired fMRI data using GRE-EPI sequence (TR/TE=1000/30 ms, FOV 192x192 $mm^2$) prior to MRS voxel positioning. Localization of the volume of interest (VOI) within V1 was guided by realtime fMRI analysis. Single voxel (voxel size 20x20x25 mm) 1H-MRS was performed using short echo time STEAM sequence (TR/TM/TE=2000/10/10 ms, 1024 @ 2 kHz bandwidth). Functional images were analyzed (realign, slice-timing, smoothing, GLM fitting, thresholding $p<0.05$ FWE, 25-voxels clustering, and inference) using SPM5 software. Spectra were postprocessed (phasing, $B_0$ drift, eddy-current correction, truncation, zero-filling, Gaussian 3Hz apodization) using MRUI software, and subsequently quantified by means of a tailored basis-set (13 metabolites) using LCMODEL quantification algorithm. Further analysis was performed on metabolites with CRLB<20%.

## Results

We found task-related fMRI signal increases in primary visual cortex (V1) both during low- and high-frequency stimulations. However, only the low-frequency stimulus was found to activate extrastriate areas (see figure). Since BOLD signal reflects local synaptic activity (i.e. input) [1], this is consistent with a suppression of spiking activity of V1 during the high-frequency stimulation, likely corresponding to reduced perception of the stimulus due to intracortical inhibition [2]. The communication between V1 and higher-order visual areas (that is, spiking activity in V1) was not compromised during low-frequency stimulation. Noticeably, MRS revealed increased tissue lactate concentration only in this condition, while no accumulation of lactate was observed during the high-frequency stimulation (see figure).




## Discussion

By acting on the temporal selectivity of the primary visual cortex (V1), we partly disentangled spiking and synaptic activity *in vivo*. As previously demonstrated in animal studies [3], high-frequency flickering/drifting visual stimulations result in significant intracortical inhibition within V1, consistent with our fMRI results showing reduced BOLD activation in extrastriate areas, but not in V1, during high-frequency stimulation. Importantly, the specific activation of the central visual pathways results in different non-oxidative metabolic response. Our results show that, within the activated area (V1), similar changes in BOLD signal are accompanied by different changes in tissue metabolism, confirming that the energetics of the stimulated brain contains more information than that revealed by fMRI alone [4]. Regardless of the rationale for the observed rise in lactate level during the low-frequency stimulus, our preliminary results indicate that the neurovascular coupling (as revealed by fMRI) and the neurometabolic coupling are, in fact, uncoupled between each other.

## References

1. Logothetis N.K et al. Nature. 2001;412:150-157. 2. Shady S. et al. Proc Natl Acad Sci USA. 2004;101:5170-5173. 3. Viswanathan A. and Freeman R.D. Nat Nauroscі. 2007;10:1308-1312. 4. Gjedde et al. J Cereb Blood Flow Metab. 2002;22:1-14.