Effect of muscimol on BOLD and local neuronal activity in awake animals

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Introduction

Blood oxygenation level-dependent (BOLD) contrast functional magnetic resonance imaging (fMRI) has become an important tool for studying brain function. This technique relies upon the coupling between electrical activity and both regional cerebral metabolic events, such as changes in oxygen or glucose utilization, and hemodynamic changes, such as changes in blood flow and volume. Despite the wide utilization of fMRI to detect activation related to stimulus-based, task-related, or cognitive paradigms, many questions remain about the link between the modulations in local cellular metabolic and hemodynamic properties measured by fMRI and the underlying neuronal electrical activity. Although previous studies have begun to investigate this relationship through simultaneous BOLD and electrophysiological measurements [1,2], no previous work has examined the effect of direct modulation of neuromediators. The neuronal electrical activity in both the baseline and modulated states depends heavily upon the level of neuromediators, the two most important of which for excitatory and inhibitory function in the cerebral cortex are glutamate and GABA, respectively.

In this study, we examine the changes in both BOLD and electrophysiological response produced by localized changes in the level and efficiency of GABA. In order to explore these changes, we performed simultaneous BOLD and electrophysiological measurements in the somatosensory cortex during whisker stimulation in the awake rabbit. Somatosensory activity in both the baseline and stimulates states was examined before and after the effects of the locally-injected GABA agonist muscimol.

Methods

Two Dutch-Belted rabbits were chronically implanted with manipulators containing a single bundle of four microwire gold-silver electrodes and injection cannula aimed at the whisker barrel cortex. Neuronal activity was recorded using the Neuralynx system, and blocks of gradient interference were removed prior to analysis MR imaging was performed using a 4.7 T Bruker BioSpec imaging spectrometer. Four contiguous slices (1 mm thickness) which included the somatosensory cortex and thalamus were imaged using a single-shot gradient-echo EPI pulse sequence (TR=2 sec; TE=20 ms) with a 94 x 94 matrix size, corresponding to an in-plane resolution of 210 x 210 µm. Images were registered using a 2-D affine method and analyzed using cross-correlation method. The stimulus consisted of a 75 Hz vibration delivered to three whiskers (A1, A2, and A3) on the left side by means of a nylon band coupled to an oscillating magnetic coil [3] and monitored in real time by an infrared sensor [4] to ensure consistent amplitude and frequency of the vibration.

Each session consisted of two trials, with 60 images acquired in each trial. The stimulation paradigm for each trial consisted of 20 baseline images followed by 20 images during which the whisker stimulus was presented, and 20 post-stimulation images. Between trials the subjects received a local injection of the GABA agonist muscimol (1 µl, 3.5 nmol/µl) into the whisker barrel cortex. The second trial began ten minutes after drug administration. Control experiments were also performed using the same parameters but with injection of saline.

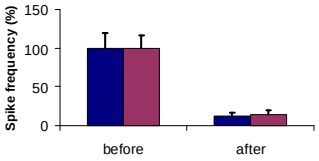

Figure 1. Baseline (blue) and modulation (red) neuronal activity before and after muscimol injection (N=8, mean±standard deviation). Note the large decrease of baseline activity after muscimol injection. Values are normalized to preinjection baseline (blue) or modulation (red) levels.

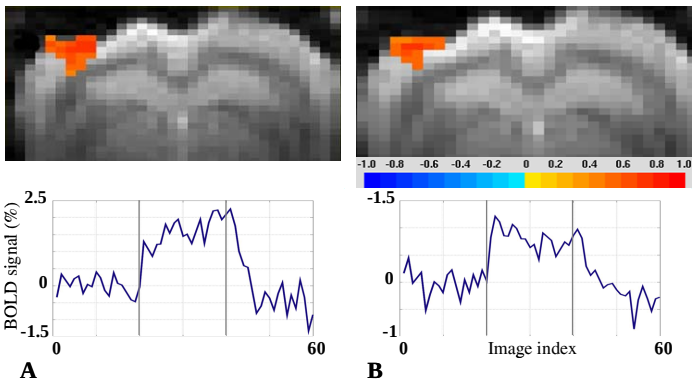

Figure 2. Functional activation maps and temporal profiles of the whisker stimulation of before (A) and after (B) local muscimol injection. The BOLD temporal response magnitude decreased to approximately 60% of the preinjection level, and little change can be seen in the activated area. The color bar represents magnitude of correlation coefficient. Gray bars indicate the timing of the stimulus presentation.

Acknowledgements:

Supported by: R01 NS44617, S10 RR15685, S10 RR019920

Results

The GABA agonist muscimol injected locally into brain tissue affected both neuronal activity and BOLD signal. Baseline and modulation of single units decreased to 10% of preinjection level (figure 1), and modulation of local field potential (LFP) decreased to 80% of preinjection level (data not shown). Two types of cells were distinguished during electrophysiological recording which produced distinct behavior under the effect of mucsimol. The response of low-frequency cells (presumably pyramidal neurons) to stimulus modulation was abolished after drug injection. In contrast, high-frequency cells (presumably interneurons) showed no response to stimulus modulation before injection, but exhibited a strong response after injection.

The magnitude of the BOLD temporal response decreased to 60% of the preinjection level (figure 2), and little change was observed in the area of activation detected by cross-correlation analysis. Injections of the saline control produced no significant changes in either neuronal activity or BOLD signal.

Discussion

The relatively small local change in BOLD response in the somatosensory cortex after muscimol injection were surprising, considering large reduction in single unit activity. However, the relatively high level of LFP activity after drug injection suggests that if single unit activity is artificially decreased, LFP may be a major component of the BOLD signal. This result suggests that the relationship between BOLD, single-unit, and LFP activity may be quite complex, and significantly dependent upon the experimental modulation. Figure 1 also illustrates that the baseline and modulation components of the single-unit activity experience similar levels of relative change in response to muscimol injection. Thus, these data could suggest that the preservation of this relative difference, despite the decrease in absolute baseline and modulation activity after injection, could maintain the level of BOLD response.

Future work will examine the effect of further pharmacological manipulations, such as the GABA antagonist picrotoxin as well as glutamate antagonists, on the BOLD signal in order to gain a more comprehensive understanding of the relationship between BOLD activation and underlying neuronal activity under the effect of neuromediators.

References:

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