The role of GABA and glutamate neuromediators in generating the BOLD response

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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 glutamate and 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 stimulated states was examined before and after the local injection of the following drugs: (1) cocktail of GABA agonist muscimol and GABA antagonist picrotoxin, which should block GABA-ergic input without changing baseline neuronal activity, and (2) glutamate-antagonists.

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 4.7T or 9.4T 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 for 4.7T and TE=13 ms for 9.7T) with a 94 x 94 matrix size. Images were registered using a 2-D affine method and analyzed using cross-correlation. 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 into the whisker barrel cortex of one or more of the following drugs: the GABA agonist muscimol (1 µl, 3.5 nmol/µl), GABA antagonist picrotoxin (1 µl, 0.5-2.5 nmol/µl), NMDA glutamate antagonist MK-801 (1 µl, 20.8 nmol/µl) and AMPA and NMDA glutamate antagonist DGG (γ-D-Glutamylglycine, 1 µl, 0.39 µmol/µl). The second trial began ten minutes after drug administration. Control experiments were also performed using the same parameters but with injection of saline.

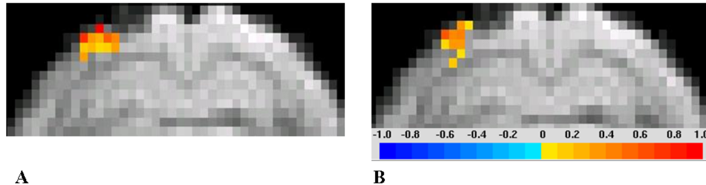

Figure 1. Functional activation maps of the stimulation of three whiskers (C1, C2, and C3) before (A) and after (B) local muscimol and picrotoxin injection. Activated pixels clusters in the rabbit barrel cortex are superimposed onto ss gradient-echo EPI images with 375x375 µm in-plane resolution and 1mm slice thickness. The color bar represents magnitude of correlation coefficient.

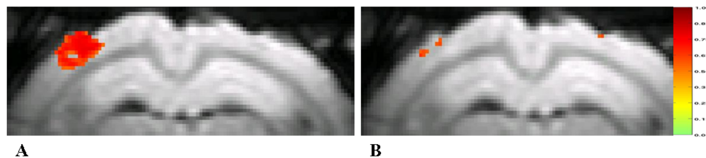

Figure 2. Functional activation maps of the stimulation of three whiskers (C1, C2, and C3) before (A) and after (B) local glutamate-antagonist injection. Activated pixels clusters in the rabbit barrel cortex are superimposed onto ss gradient-echo EPI images with 234x234 µm in-plane resolution and 1mm slice thickness. Data was collected on 9.4T imager. The color bar represents magnitude of correlation coefficient.

Results

The cocktail of GABA agonist muscimol and GABA antagonist picrotoxin did not significantly affect neuronal baseline but neuronal firing slightly increased during stimulation while of LFP slightly decreased. No change was observed in the area of BOLD response (Figure 1).

The effect of glutamate antagonists strongly depended on the type of receptors which were blocked. NMDA glutamate antagonist MK-801 decreased both single unit activity and LFP, and BOLD area and temporal response decreased to approximately half of the preinjection level. AMPA and NMDA glutamate antagonist DGG decreased single-unit activity and LFP by an even greater amount, and the BOLD respone was almost abolished (Figure 2).

Injections of the saline control produced no significant changes in either neuronal activity or BOLD signal.

Discussion

The cocktail of the GABA agonist and antagonist should remove stimulus-dependent GABA-ergic responses without affecting the neuronal baseline level. By removing the effects of interneurons from the circuit, this combination of drugs should allow observation of glutamatergic BOLD, driven only by direct input from the thalamus. The preservation of the BOLD signal under these conditions could reflect an increase in single-unit activity that compensates for the reduction in GABA-ergic LFP.

The effect of the glutamate antagonists on the BOLD signal was expected. These results suggest that analyzing the BOLD decrease due to the NMDA antagonist vs. the BOLD decrease due to both AMPA and NMDA antagonist can provide information about separate roles of the different glutamate receptors in the generation of the BOLD signal.

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