Subcortical Forepaw Stimulation fMRI Activations in Awake Rats

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Introduction

There has been increasing interest in fMRI studies with awake monkeys [1], rabbits [2], and rats [3]. fMRI of awake animals offers many distinct advantages over anesthetized models. *First*, the effects of anesthesia can be avoided. *Second*, neural activity is not compromised, which yields increased fMRI signal changes and potentially improved detection of activation. *Finally,* subcortical and higher order cognitive functions can be stimulated in an awake model. Such studies would be very difficult if not impossible under anesthesia. The disadvantages of performing awake fMRI studies are potential motion artifact and stress.

In this study, we showed that the CBF and BOLD fMRI responses under awake conditions are reasonably robust. CBF and BOLD fMRI responses under awake conditions were investigated using forepaw electrical stimulation. Reasonably robust and enhanced fMRI responses were observed in conscious animals. Furthermore, subcortical activations and high order functions were observed under awake conditions and were abolished by anesthesia. Potential movement artifacts and functional contrast-to-noise ratios were discussed.

Method

Sprague-Dawley rats (n = 4) were anesthetized with 2% isoflurane and secured in a rat restrainer with ear-, nose-, tooth-, shoulder-bars, and a body restraining tube. Before the real experiment, the rats were trained twice in the same secure setup on the bench and were given recorded MR gradient sound. Needle electrodes were inserted under the skin of both forepaws. Then Isoflurane was turned off. Rectal temperature was maintained at 37±1°C and respiration rate was monitored. Two forepaws were stimulated simultaneously in series using 3 mA, 0.3 ms pulse duration at 3 Hz.

MR experiments were performed on a 4.7T/40cm magnet. Combined CBF and BOLD measurements were made using the continuous arterial spin-labeling technique using single-shot, gradient-echo EPI with matrix=64x64, FOV=2.56 x 2.56 cm^2, and 1.5-mm slices, TE= 16 ms, and TR =2s. Activation maps were calculated using cross-correlation analysis and superimposed on echo-planar images.

Results & Discussion

In general, the baseline fluctuations of MR signals were higher under awake relative to the anesthetized conditions. This was not necessary due to increased movement artifact, which usually manifested into large spikes in the MR signal time courses in cases where the animals were not properly restrained. When the animals were properly restrained, few or no large spikes in the MR signal time courses were observed. The larger baseline fluctuations of MR signals were likely due to increased basal neural activity and/or physiological "processes" associated with being awake.

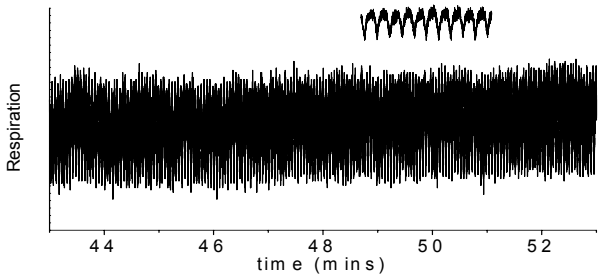
Figure 1 shows the recorded resperation waveform over 10 mins of a representative awake experiment, the insect fiugre shows the detailed waveform. It shows that the animal was secured very stablely, very few spikes could be seen.

Figure 2 shows the CBF and BOLD response at different cross-corelation levels. Robust responses were observed at primary somatosensory cortex. And when lower the CC value, subcortical area (e.g., secondary somatosensory contex and caudoputamen) responses were observed, which hardly can be observed in anethetized conditions. CBF showed better localized response than BOLD. BOLD showed higher cross correlation, but much more closer to the cortex surface than CBF repsonses.

Figure 3 summarized the percent change of BOLD and CBF at three typical response locations: pramary somatosensory cortex (S1), secondary somatosensory cortex (S2), and caudoputamen (cPU). The BOLD response for S1, S2, and cPU were 2.8±0.3%, 1.5±0.2% and 1.1±0.2%. The S1 response is about double that of under isoflurane anethetized condition and 6mA current stimulation [5]. The CBF response for S1, S2, and cPU were 39±3%, 26±4% and 23±4%.

Comparable or improved functional contrast-to-noise ratios were observed under the awake relative to the anesthetized conditions.

Fig. 1



Conclusion

These results demonstrate that CBF and BOLD fMRI changes in awake animals are reasonably robust, though at a marginally higher failure rate. Potential motion artifact and stress associated with performing awake fMRI could be alleviated with proper restraint and acclimation; these factors are currently under investigation. The ability to study *subcortical and higher order cognitive* functions justifies further development of awake animal models for fMRI studies.

References [1] Logothetis, *Nat Neurosci* 1999, 2:555. Zhang, *Brain Res* 2000, 852: 290. Ferris, *NeuroRep* 2001, 12:2231. Vanduffel et al. *Neuron* 2001, 32:565. [2] Wyrwicz et al. *MRM* 2000, 44:474. [3] Lahti et al. *J Neurosci Meth* 1998, 82:75. Peeters et al., *MRI* 2001, 19:821. [4] Tenney, ISMRM 2003. Liu et al. MRM 2004, 52: 277

Fig. 2

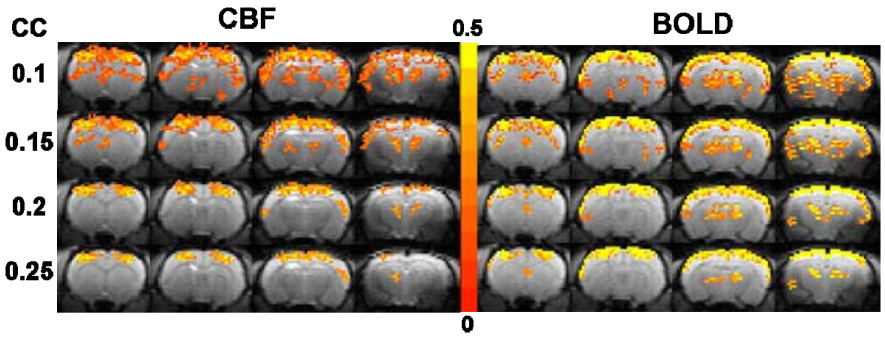


Fig. 3