

On the age effect of the BOLD signal in rat fMRI using electrical mystacial stimulation

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Introduction:

Functional magnetic resonance imaging (fMRI) using the blood oxygenation level-dependent (BOLD) technique is a powerful means to noninvasively investigate brain activity. The characterization of BOLD signal change in the animal model is an essential step toward a better understanding of neuroscience research, such as cortical reorganization after surgery (1) and hemodynamic alternation during stroke recovery (2). These studies emphasize the importance of longitudinal follow-up. Therefore, it is inevitable to include senescent rats. For this reason, it is critical to understand how normal aging may affect the BOLD characteristics in the animal model, yet this has not been discussed before. In this study, we aimed to investigate the age-related change in the BOLD response to mystacial pad stimulation by including 3- and 9-month-old rats.

Materials and Methods:

Two-month-old Lewis rats ($n=6$) were kept under standard conditions until 3 and 9 months of age. Rats were initially anesthetized with 4% ISO, and needle electrodes were inserted under the skin of the right mystacial pad. Each rat was secured in a head holder and breathed spontaneously without mechanical ventilation. Then, anesthesia was reduced to 1%-1.2% ISO. MRI images were acquired on a 7T animal MRI scanner (Bruker ClinScan 70/30). The pulse sequences of gradient echo EPI for fMRI were as following: TR/TE=1000 ms/25 ms, slice thickness=1mm, number of slices=7, matrix size=64x64, FOV=30mmx30mm, and flip angle=90 degrees. For the mystacial pad stimulation, the rats were stimulated with the current of 3mA, pulse duration of 330 us, and frequency of 3 Hz. The stimulation paradigm consisted of 75 scans during rest and 15 scans during stimulation, which was repeated five times. Each rat was scanned twice at the age of 3 month (3M) and 9 month (9M), respectively. The task-based BOLD data were processed using Matlab and SPM5. Averaged BOLD percentage changes were calculated in a region of interest (ROI) within the primary somatosensory barrel field cortex (S1BF) and secondary somatosensory cortex (S2) identified by the structural MR image. In addition, we acquired the hemodynamic response (HDR) from a single voxel with the largest t value so that each HDR would be in the best correlation.

Results:

The group activation maps induced by the mystacial pad stimulation are displayed in Fig. 1. The top row shows the rat brain atlas, and the middle and bottom rows respectively show the activation maps of 3M and 9M rats. Both 3M and 9M groups exhibited pronounced activation in thalamic ventral posterior nucleus (VPM), S1BF, S2 as well as the primary somatosensory cortex upper lip region (S1ULp). The spatial extent of activation was similar between the two groups. We found no clusters in which activation was significantly different between groups. Figure 2 shows the mean BOLD signal changes of two groups. The increased BOLD signals in S1BF were $2.27\pm 0.52\%$ (mean \pm S.E) and $2.22\pm 0.35\%$ for 3M and 9M rats, respectively. The increased BOLD signals in S2 were $0.91\pm 0.22\%$ and $1.06\pm 0.17\%$ for 3M and 9M rats, respectively. Paired Student t -test showed that those did not reach the significant level. The HDRs obtained from the single voxel with the highest t value are present in Fig. 3. All voxels from two groups show flat prestimulus baselines and well-defined HDRs. The general forms of the HDRs were similar across the groups. Furthermore, the amplitudes of HDR between stimulations were similar (ANOVA analysis: $P>0.05$).

Discussion and Conclusion:

In this study, we had examined age-related changes in the animal fMRI studies for the first time. Our results showed that in terms of the spatial extent of activation and the BOLD signal changes, both 3M and 9M possessed the similar characteristics. This implies that the cortical area of S1BF may remain unaltered during aging. Furthermore, the synaptic transmission and synaptic integration generally function well within this age range. In the HDR aspect, the general forms were similar across the groups. Our result is consistent with the human study, which found that no significant difference in HDR between younger and older subjects (3). In summary, BOLD responses to a mystacial pad stimulus were similar in the spatial extent, signal changes and HDR between 3M and 9M rats. These results indicate that rodent fMRI studies are feasible in populations composed of rats aging up to 9-month-old. The further age-related correlation is not needed in the rodent fMRI studies.

References:

1. Pelled et al, *NeuroImage*, 2007; 37: 262-273. 2. Kim et al, *JCBFM*, 2005; 25: 820-829. 3. Huettel et al, *NeuroImage*, 2001; 13: 161-175.

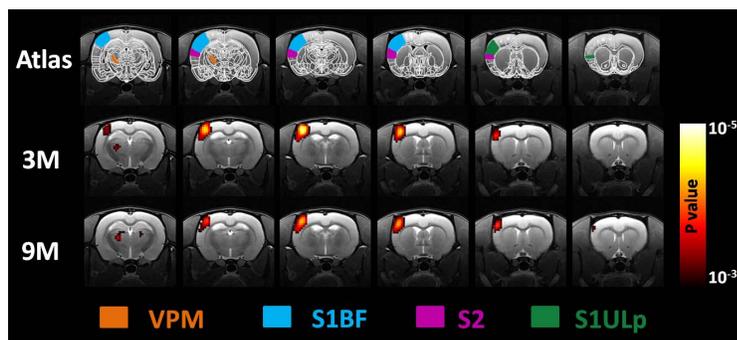


Fig. 1. Comparison of the group activation pattern between 3- (3M) and 9- month (9M) groups. The significant activations in VPM, S1BF, S2 and S1ULp associated with mystacial pad stimulation were found in both groups. No activation clusters were significantly different between groups.

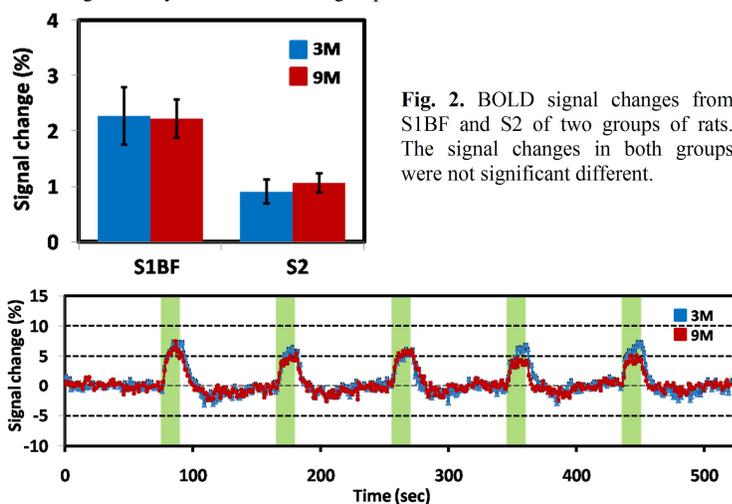


Fig. 2. BOLD signal changes from S1BF and S2 of two groups of rats. The signal changes in both groups were not significant different.

Fig. 3. The HDRs in the single most-significant voxel in 3M and 9M groups. The shaded regions indicate the 15s stimulation period. The general forms of the HDRs were similar across the groups. No significant differences in the amplitudes of HDRs between stimulations ($P>0.05$).