Relationship of BOLD response in SI of primate cortex to intensity of tactile stimulation

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Introduction: Although SI area has been studied intensively in the recent past [1, 2], the precise manner in which stimulus intensity is represented in SI cortex remains unclear. Recently we have demonstrated that positive BOLD signals at high field produced by subtle tactile stimulation can provide high spatial resolution functional images in non-human primates [3]. In addition, the resulting fMRI maps spatially correlate very well with intrinsic optical imaging and electrophysiology maps. To further evaluate the coupling of BOLD and electrophysiological signals, we have extended these studies to investigate the fMRI signal responses in SI areas to different stimulus intensities.

Method: Squirrel monkeys were anesthetized with ketamine hydrochloride and maintained with isoflurane anesthesia. Animals were incubated and artificially ventilated. Physiological states (respiration rate, temperature, SpO2, heart rate, ET-CO2) of each animal were carefully monitored. All scans were performed on 9.4T 21-cm bore Varian INOVA MI system using a 3cm surface transmit-receive coil secured over the sensory cortex. Gradient echo images (512x512 matrix) and GE-EPI (64x64 matrix) were used to acquire anatomical and functional images respectively. A custom-designed MR cradle with ear bars and eye bar was also used to reduce motion. The monkey's fingers were secured, leaving the glabrous surfaces available for vibro-tactile stimulation by a rounded plastic probe (2mm diameter) connected to a piezioelectric device. Piezos were driven by Grass stimulators at a rate of 8Hz. The displacement of the piezo is proportional to the driving voltage. Stimulation was synchronized to image acquisition. A block-designed stimulation pattern was used in this study (30s on/ 30s off). The repetition time TR on individual scans was adjusted (1.5s or 2s) to match the ventilator rate to minimize respiration-induced signal variations in the functional time-courses. Matlab was used for data analysis. A polynomial model was used for time course drift correction. Then data were spatially and temporally smoothed. Functional maps were generated by calculating the correlation of each functional time-course with a reference waveform. After the functional maps were created, a common region of interest was chosen and percent signal changes were calculated for each type of stimulus.

Fig.1. Activation Area for three different stimulus

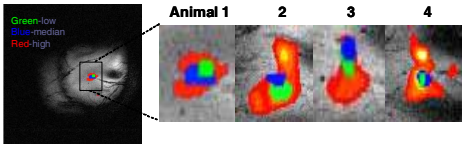


Fig. 3. Results of Optical imaging

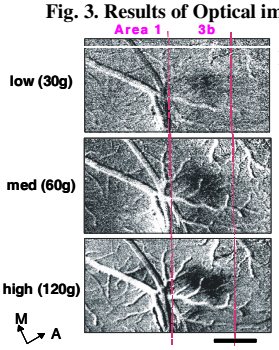
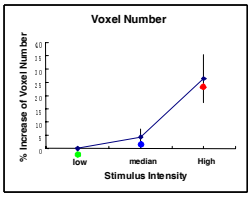
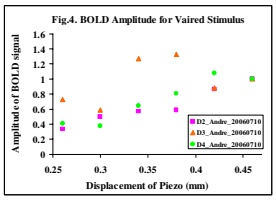


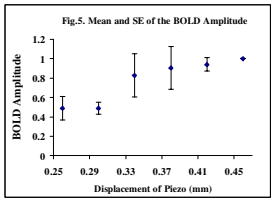
Fig. 2. % Voxel Number Change (fMRI results)

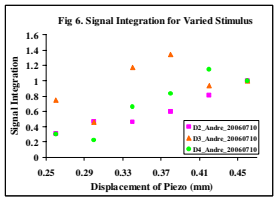


Results: **a) Activation Area:** To better compare with intrinsic optical imaging results, 3 types of stimuli (low, medium, and high) were used in the fMRI study for investigating activation areas. With the same threshold, activation areas for different stimulus strengths were picked and overlaid together and the results from 4 animals are shown in Fig. 1. Voxel numbers were calculated and normalized to the smallest stimulus repsonse and the percent voxel number increase was averaged over 4 animals as shown in Fig. 2. These are s also compared with optical imaging results as shown in Fig. 3 (Chen. L.M. et.al. unpublished)

b) BOLD signal: To investigate the relationship between BOLD signal and the stimulus intensity, we designed an experiment in which 6 stimulus intensities were applied (displacements: 0.26, 0.3, 0.34, 0.38, 0.42, 0.46mm). These stimuli were interleaved during each run, with 5 epochs for each type of stimulus, totalling 30 epochs in a single run. The results of a single monkey with 3 distinct digits stimulated separately (1 digit per run) are shown in Figs. 4-7. The amplitude of the BOLD signal, the integrated BOLD signal during the stimulation period (4.5s after stimulation to the end of stimulation), and the average BOLD signal during the stimulation period (data not shown here) were calculated for each stimulus intensity. All results were normalized to the highest stimulus (displacement of 0.46mm). The normalized results and the averaged value for these 3 cases (3 digits) are shown in Figs. 4-7.







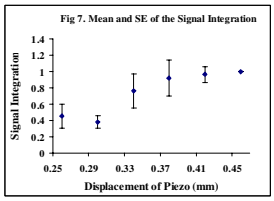
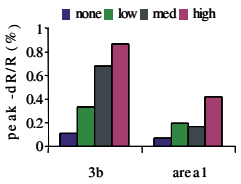


Fig. 8. Optical Imaging Signal



Discussion: Figs. 1 and 2. show that activated areas enlarged with increased stimulus intensity. For example, high stimulation caused the larger activation area (red area shown in Fig.1, and red dot in Fig. 2) than the low and median stimulation. Similarly, in optical imaging results, the activation area expanded as the stimulus increased.

Figs. 5-7 show that the BOLD signal did not change significantly until the stimulus reached a certain level. Once the stimulus is above this threshold, BOLD signal increased linearly within a specific range of stimulus strengths. This linear relationship is also observed in optical imaging results as shown in fig.8. However, when the stimulus is above an upper limit, the BOLD signal showed a ceiling effect (e.g. as shown in Fig, 5, the BOLD amplitude reached a plateau when the stimulus was over 0.42mm), or even slightly decreased in some cases, suggesting that some inhibiting mechanism may be relevant at high intensity stimulation. Our results are different from previously published data [2,3] in which SI signal was found to be linearly proportional to the stimulus intensity. Possible explanations include 1) different stimulation protocols (tactile vs. electrical stimulation), or 2) the way the ROI is chosen. Nonetheless, fMRI at high field is clearly able to provide new information on the organization of the cortex and our model permits correlations with other measures of activation.

References: [1] Nelson A, Staines W, Graham S, McIlroy W. *Cogn Brain Res.* 2004;**19**:174–184.
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[3] Turner G.H., Chen L.M., Friedman R.M., Gore J.C., Roe A.W., Avision M.J. Greg. ISMRM 2006, # 2134, p420.