Imaging dynamic neural network in rat brains using BOLD fMRI.

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[Introduction] BOLD-fMRI is the method of choice to map neural network of the entire brain. However, imaging dynamic neural network has been limited to human and some awake monkey fMRI studies. Although neural network connections in the rat brain had been well described in electrical recording and tracer studies, BOLD fMRI of rodents to date is limited to detecting predominantly the primary sensory cortices and very infrequently in the secondary somatosensory cortices (1). It is not understood why activations in higher cortical areas in the rat somatosensory stimulation model could not be detected. Imaging neural network on rodents is thus limited. The purpose of this study is to develop a rodent model for dynamic imaging of neural network in response to forepaw stimulation using BOLD fMRI.

[Methods] BOLD-fMRI studies were performed associated with electrical stimulation of unilateral forepaw under alpha-chloralose anesthesia in rats. MR experiments were performed on a 9.4T/20cm magnet (Varian) and 70mm volume transmit/12mm surface receive coil was used. The cradle with the animal was physically positioned such that the Bregma is within 0.5mm of the magnetic field gradient isocenter. Magnetic field homogeneity was optimized by the chosen 1-mm voxel to yield a H^1 spectral line-width of ~15Hz. A single 1mm slice was acquired using single–shot gradient-echo-EPI using TR=0.5s, TE=25ms, NEX=1, matrix 64x64 and FOV 2.56x2.56 cm^2. Approximately 16-24 transients were acquired for signal averaging. BOLD fMRI data were analysis using cross correlation analysis and activation maps and BOLD percent changes were calculated.

[Results] Following a unilateral 4-second forepaw electrical stimulation, multiple areas in the brain associated with the somatosensory stimulation were detected (Fig.1). These regions included the contra-lateral somatosensory cortex, bilateral striatum, bilateral thalamus and bilateral reticular formation. The BOLD responses at the contra-lateral side of each region were 9.8%, 1.4%, 3.2% and 1.4%, respectively. Surprisingly, a biphasic fMRI response was detected in the bilateral striatum. A negative peak at 3~4 seconds after stimulation corresponded to the time of the peak positive response in the other activated area. A subsequent positive peak at 6-8 seconds was consistently seen in the bilateral striatum in all animals. (Fig.2)

[Discussion & Conclusion] Variations in the magnitude and temporal dynamics of the BOLD responses over the entire brain is dependent on many factors, including but not limited to anesthetics, brain regions, different types of neurons involved, neurovascular coupling and the local microvasculature (2). The large difference in temporal dynamics at the striatum is remarkable, which is consistent with previous human PET studies (3). This is also consistent with the notion that striatum receives dense projections of various neurotransmitters from the brainstem and most cortical areas (4). The complex morphological and chemical integrations in the striatum and presence of excitatory and inhibitory inputs make it difficult to interpret the BOLD responses. Nonetheless, these results demonstrated that we can now elicit multiple activations throughout the somatosensory pathways, offering the opportunity to study neural network of the entire brain in the widely used rat model for fMRI.

In conclusion, we have extended the somatosensory stimulation model for dynamic imaging of neural network. To the best of our knowledge, this is the first report of BOLD fMRI that demonstrated robust detections of activations in bilateral striatum, bilateral thalamus and bilateral reticular formation. The ability to detect activations in higher brain functions beyond the commonly reported primary somatosensory cortices could have many important applications, offering the opportunity to study neural network and fMRI evaluation in rat stroke models.

[**References**] [1] Keilholz et.al MRM 2004 [2] Ogawa et.al Annu Rev Biophys Biomol Struct. 1998 [3] Shulman,et.al J. Cognit. Neurosci 1997, Raichle et.al PNAS 2001 [4] Pierce et al. Neuroscience 1995, Sesack et.al Ann N Y Acad Sci. 2003

Fig 1. Representative t-map (p<0.01) induced by unilateral forepaw electrical stimulation were superimposed on corresponding coronal anatomical images (A; somatosensory cortex and striatum, B; Thalamus and reticular system). Fig 1C shows the time courses of the averaged % BOLD signal changes. The shaded area indicates 4-second stimulus duration.

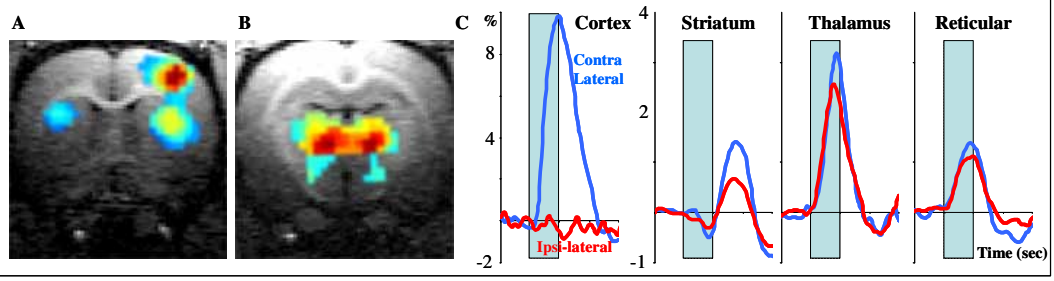

Figure 2: Time-binned Dynamic Activation tmap due to unilateral forepaw stimulation

Note that the negative BOLD response is detected over the bilateral striatum in the early stage, while the routine positive BOLD signal is observed in the contra-lateral cortex.