A Protocol for Longitudinal BOLD-fMRI Imaging Deep Brain Stimulation Response in the Rat Brain

Tzu-Hao Chao[1], Jyh-Horng Chen[2], and Chen-Tung Yen[1]

[1]*Institute of Zoology, National Taiwan University, Taipei, Taiwan,* [2]*Interdisciplinary MRI/MRS Lab, Dept. of Electrical Engineering, National Taiwan University, Taipei, Taiwan*

Introduction

Functional MRI (fMRI) provides global spatial activation pattern of the brain. Recently, there has been growing interest in investigating adult brain plasticity by fMRI study in rodent models [1-4]. To date, most rodent fMRI studies use limb or whisker stimulation model under α-chloralose anesthesia. Yet, α-chloralose is very harmful to animal, and is not suitable for longitudinal study of the same individual subject. Moreover, peripheral stimulation models limit the brain regions that can be studied. Multisynaptic processing from peripheral to brain also causes uncertainty of interpretation. Recently, a noninvasive rodent fMRI protocol using the A2-adrenoreceptor agonist medetomidine as sedative has been proposed. In the current study, we further combined medetomidine based fMRI protocol with chronic implantation of MRI compatible stimulation electrode in the thalamus, and sought to longitudinally follow thalamocortical responses in the rat brain.

Materials and Methods

Adult Long Evens rats were used. A bipolar tungsten stimulus electrode was implanted into the right ventroposterior nucleus of the thalamus (VP), targeting the left forepaw representation area, and allowing one week for recovering. The stimulation electrode set was custom-made in the lab by aligning two tungsten microwires (0.0014 in., California Fine Wire Co., Grover Beach, CA, USA) in parallel (300-400 μm inter-electrode separation). The electrode was bended 90 degree and extended along the skull surface to allow the placement of MRI surface receiver coil over the head (Fig. 1A). The connector and the wire set were fixed in place by dental cement (Fig. 1B). The connector was placed far from the recording side to minimize signal distortion by the metal in the connector (Fig. 1C). BOLD-fMRI tests were performed in two repeated sessions with 1 week interval to determine the long-term reproducibility. For BOLD-fMRI study, animal anesthesia was induced by 5% isoflurane. A bolus injection of dexmedetomidine was given subcutaneously (Dexdormitor®, 0.025 mg/kg) followed by a continuous subcutaneous infusion (0.05 mg/kg/h) 15 min later for the whole scanning period. Imaging data were acquired on a 7 Tesla scanner (Bruker Biospec 7030 USR, Ettlingen, Germany). BOLD-fMRIs were acquired with single shot EPI (10 coronal slices, thickness=1 mm, TR=2000 ms, TE=22 ms, matrix size=80 x 80, FOV=25 x 25 mm, bandwidth=200 kHz). Monophasic square wave electrical stimulation (0.4 ms, 100-300 μA, 6-12 Hz) was applied in 5 blocks of 20 seconds on / 20 seconds off cycles. 10 dummy scanning and 10 additional images for baseline were acquired, resulted in a total 120 images. Statistical activation maps were created by statistical parametric mapping packages (SPM8; www.fil.ion.ucl.ac.uk/spm). The region of interested (ROI) analysis using the mean signal intensity of selected significantly activated region to get the time-series of BOLD signal intensity, and then normalize the time-series of signal changes to the first control block to get the percent BOLD signal change, finally, the evoked response intensity was calculated by the mean difference between stimulating and resting condition.

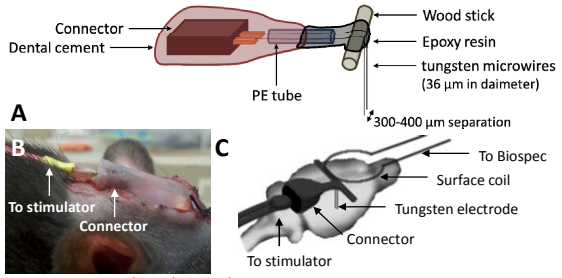

Figure 1: Stimulus electrode setup

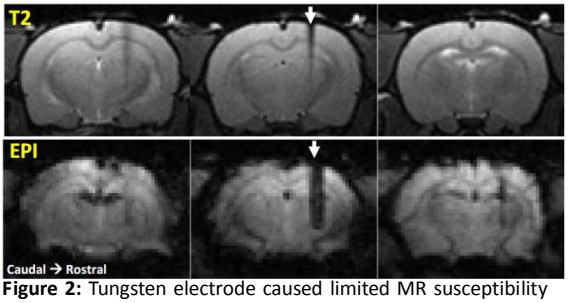

Figure 2: Tungsten electrode caused limited MR susceptibility distortion (arrow)

Results and discussions

The tungsten electrode caused limited distortion to MR signal around the electrode in T2 anatomical images (upper panel, Fig. 2) and in EPI images (lower panel, Fig.2). In each panel, 3 serial scans from caudal (left) to rostral (right) are shown. The white arrows indicate the electrode track (Fig. 2). Figure 3 shows original data of longitudinal BOLD responses from 3 representative experiments. Each rat was scanned two times with an inter-session interval of 7 days. Similar dynamic BOLD responses were observed between session 1 (blue trace) and session 2 (red trace) within the primary somatosensory cortex (SI) under the stimulus parameter of 200 μA, 9 Hz. The response amplitude in the SI in session 1 and session 2 correlated significantly with a correlation coefficient of 0.89 ($P < 0.001$, n=5) (Fig. 4). Here we provided a reliable method for longitudinally following VP stimulation-evoked BOLD response in the rat brain. Since plasticity change of brain circuitry occurs in many diseases, for examples, chronic pain, Parkinson disease, depression…etc, our method is potentially useful to probe the plasticity change in the brain during the development of these chronic diseases, and help to understand the neurobiological mechanism of these diseases. Additionally, deep brain stimulation (DBS) has been used in many clinical treatments such as essential tremor, Parkinsonism disease, dystonia, Tourette syndrome, chronic pain, depression and obsessive compulsive disorder [5]. Our method will be useful for the study of the neurobiological mechanism of DBS and for optimizing the treatment parameters.

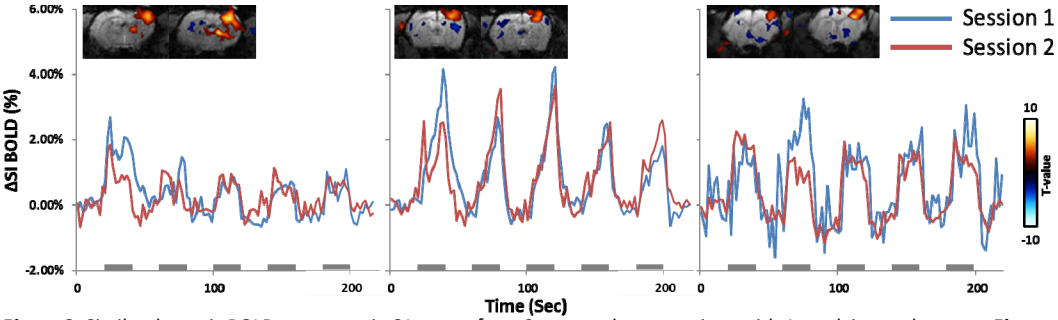

Figure 3: Similar dynamic BOLD responses in S1 cortex from 2 repeated scan sessions with 1 week interval

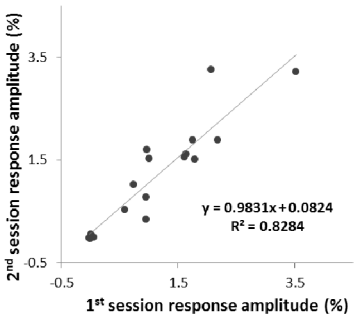

Figure 4: Reproducibility of the BOLD response amplitude in the S1 cortex from 2 repeated sessions

Conclusion

We provided a new protocol that enables us to study the long-term plasticity of specific neural circuit in the brain.

References

[**1**] Yu X, *Neuron.* 2012;74(4):731-742; [**2**] Yu X, *NeuroImage.* 2010;49(2):1667-1676; [**3**] Dijkhuizen RM, *Proceedings of the National Academy of Sciences.* 2001;98(22):12766-12771; [**4**] Pelled G, *NeuroImage.* 2007;37(1):262-273; [**5**] Perlmutter JS, *Annu. Rev. Neurosci.* 2006;29:229-257