Functional MRI of Cortico-Striato-Thalamal Circuit Using a Novel Flexible Polyimide-Based Microelectrode Array Implanted in Rodent Deep Brain

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Introduction Electrical stimulation of the brain is an important tool in the treatment of the neural disease. The major goal of this study is to develop a rodent model of Parkinson's disease (PD) to explore the therapeutic mechanisms of deep brain stimulation (DBS). Indeed, the investment in DBS research has spanned a diverse range of topics from how to assess and quantify efficacy of DBS in relieving movement dysfunction to the study of the psychological impact of DBS [1]. While few significant progresses have been made in recent years, a recurring point is the need to gain a better understanding of the pathophysiology of movement disorders, which appear to be manifested in disruptions of normal sensorimotor network function. In the present study, a novel microelectrode array has been developed, which is compatible with magnetic resonance imaging (MRI) system [2], and has the capability of stable electronic-stimulation/ signal recording in the deep brain as well. We will perform functional MRI to investigate the inhibition of subthalamic nucleus (STN) hyperactivity by chronic DBS and have comparisons between image patterns in PD rats and those in the normal and it is anticipated to disclose the resetting mechanism of the aberrant function of the cortico-striato-thalamal circuit.

Materials and Methods The MRI-compatible microelectrode array was designed for 16-channel electronic-stimulation/neural recording and its fabricating procedure were modified from a flexible probe [3]. Five Long-Evans rats were used and weighting 250-350 g. Rats were initially anesthetized with 4% isoflurane. A cannula was inserted into the femoral vein. We switch halothane to α-chloralose (initial: 80 mg/kg, maintain: 30 mg/kg/hr, i.v.) and medetomidine hydrochloride (initial: 0.05 mg/kg, i.v.). The animals were positioned in a stereotaxic frame and a small hole was drilled into the skull. A MRI-compatible microelectrode array was implanted into the thalamic ventral posterior medial (VPM) nucleus (target location: P 3.6 mm and L 3.2 mm with respect to the bregma, 5.6 mm from the surface of the brain). The fMRI experiments were performed by a 7T Biospec system (Bruker Biospec 7030, Ettlingen, Germany). A four elements phased array coil was used to receive the radio frequency signals and linear volume coil to transmit radio frequency pulses. Anatomical image were obtained using RARE sequence (TR=2500 ms, TE=62 ms, matrix size = 156×156, FOV = 25×25 mm, NEX = 2). Functional images were performed in the rat brain on 10 coronal slices of 1 mm thickness (FOV = 25×25 mm, matrix size = 80×80, Gradient-echo EPI: TR = 2000 ms, TE = 20 ms, bandwidth 200 kHz). A constant electrical current (0.4 ms, 300 uA, 3 Hz) was given through a microelectrode array. In a boxcar design, each session consisted of 110 scan images, including 5 stimuli blocks and 6 control blocks (A block consist of ten images: 20 sec.). The sets of images were analyzed by the custom-written software Functional MRI Analysis and Clustering Tools. Voxels with a cross-correlation coefficient higher than 0.3 (positive) or less than -0.3 (negative) were considered activated.

Results and Discussion The MRI-compatible microelectrode array was bonded onto a long polyimide-based cable with pins soldered into two rows of 8 in a wide Dual-Inline Pin (DIP) format. The MRI-compatible microelectrode array was constructed with integrated connector pads, a long shaft and recording sites with spacing at 66-μm interval [**Figure 1(A)**]. The *in vitro* and *in vivo* impedance of the 16 electrodes on the microelectrode array, measured by impedance spectroscopy, were 2.60 ± 0.52 MΩ and 0.86 ± 0.07 MΩ at 1 kHz, respectively. The punctured tracts were clearly found in MR coronal and sagittal images of rat brain as shown in **Figure 1(B)** and **Figure 1(C)**, respectively. These MR images with implanting microelectrode array reveled less susceptibility artifact. Furthermore, histological section of rat brain was shown the lesion tract caused by microelectrode array implanting [**Figure 1(D)**]. DBS of rat brain apparently activated both positive and negative BOLD changes in different brain areas as shown in **Figure 2**. Significant positive BOLD responses were observed in receptive field in upper lip region (S1ULp), barrel field (S1BF) and secondary somatosensory cortex (S2). Positive BOLD responses was also found surrounded the VPM area where was the DBS site. Negative BOLD responses were revealed in caudate putamen (CPu). In our case, positive and negative BOLD signals appeared in cortical areas and striatum, respectively, which was suspected a limbic cortico-striatal loop to form functional connectivity [4].

Conclusion The present study demonstrates a flexible microelectrode array based on polyimide substrate is capable of multichannel intracranial stimulation and neural recording. It also was designed to be compatible with hight MR field strengths, which cause little or no susceptibility artifact in MR images. Furthermore, we combined fMRI and intracranial stimulation to explore cortico-striato-thalamal circuit based on positive and negative BOLD signal changes.

References [1] J. Herzog *et al*., Mov Disord. 2003;18:1382-4. [2] J. F. Dunn *et al*., Magn Reson Med. 2009;61:222–8. [3] Y.Y. Chen *et al*., J Neurosci Methods. 2009;182:6-16. [4] H.J. Groenewegen *et al*., J Chem Neuroanat. 1999;16:167–85.

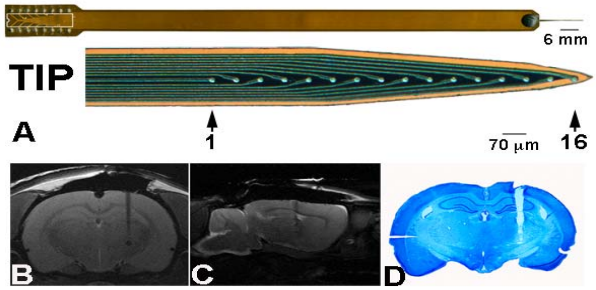

Figure 1. (A) An overall view of the MRI-compatible microelectrode array probe assembly. The MRI-compatible microelectrode array was constructed with integrated connector pads, a long shaft and 16 stimulating/recording sites. Photomicrograph of the tip (TIP) of the microelectrode array, which was designed with a 50° tapered angle. (B) Coronal T2 image with the implanted track. (C) Sagittal image, showing minimal susceptibility artifact. (D) Nissl stained section made of the same rat shows the location of microelectrode array.

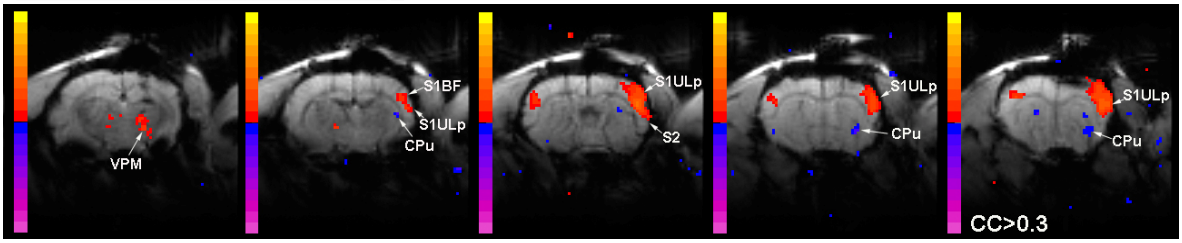

Figure 2. Example of fMRI BOLD responses to VPM stimulation. Activated areas such as ipsilateral S1BF, SiULp and contralateral S1ULp appeared positive BOLD signals. Negative activation was found in the ipsilateral striatum (CPu). MR signal changes were coded by hot and cold colors, respectively.