

## High-Field MRI of Brain Activation and Connectivity

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The research is to develop advanced high-field MRI technologies for the study of brain activation and functional connectivity. The specific aims of this research are: 1. Develop effective and reliable functional MRI techniques through mapping of sensory functions; 2. Develop rat model to correlate fMRI contrast with electrophysiological activity in the fore-brain; 3. Develop diffusion tensor MRI techniques to reconstruct cerebral white matter trajectories. We have successfully achieved the specific aims to develop effective and reliable functional MRI techniques for both human and animal studies; Correlative studies have been successfully done with multiple channel ensemble single-unit recording and fMRI activation pattern. As for the connectivity imaging, we have implemented and validated the diffusion tensor imaging (DTI) as well as diffusion spectrum imaging (DSI) to reveal the fiber connectivity and cytostructure imaging of the brain activation. Applied these techniques, one can study the brain function with fMRI, diffusion spectrum brain connectivity/cytostructure imaging and simultaneous fMRI and electrophysiological activations recording in the same lab. This opens up a possible avenue for us to monitor the dynamic change of neuronal structure and connectivity caused by brain lesions or associated learning experiences.

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### I. INTRODUCTION

Emerged from 1992, functional magnetic resonance imaging (fMRI) [1, 2], with its high spatial and temporal resolution, provides a new window to map brain function under more realistic condition without the limitation of radiation exposure. This method has been applied to various fields ranging from psychology, physiology, pharmacology, to clinical medicine [3–5]. The most successful mechanism for MRI to detect brain function is based on the blood oxygen level dependent (BOLD) contrast [1]. In the brain cortex, task activation or cognitive processes introduce local blood flow variations that alter oxy/deoxyhemoglobin distributions in the active regions. This change in blood oxygen level alters tissue magnetic susceptibility that, in turn, produces a contrast change in the  $T_2^*$  weighted image. Typically, the MRI signal is increased by a few percent in the active brain region due to a sharp increase in oxygen supply.

A major strength of fMRI, when applied to the study of human cognitive function is to unveil correlation between brain activation and mental function. At first glance, studying anesthetized animals with fMRI might totally defeat this purpose because the anesthetic will obliterate most explicit behavior. However, evidence has shown that the nervous system in an anesthetized or a sleeping state is by no means deprived of all mental functions. First of all, under anesthesia various brain regions are still responsive to external stimulation. As a matter of fact, most of electrophysiological data are collected in anesthetized animals. To assume that such neural activation plays no functional role simply because it gains no access to the consciousness will be deserting a fertile ground. Inquiry into the functional significance of neural activity recorded in an anesthetized state and related it to possible mental activity is by all means a legitimate scientific issue and has been addressed by several previous studies. Such findings suggest that under anesthesia some kind of learning is still possible. It is interesting to note that some forebrain structures engaged by noxious stimuli, such as the amygdala and cingulate cortex, have been implicated in acquisition and/or expression of fear conditioning [6, 7].

Relations between functional activation patterns and structural properties of axonal fiber pathways are essential to the understanding of working mechanisms of human brain function. This information has been obtained from animal models using invasive tracer techniques [8, 9]. Unfortunately, these techniques cannot be performed in living humans, and animal results shed limited light on human cognitive functions. Diffusion tensor MRI, proposed by Basser, samples direction-dependent diffusivity of water molecules in tissues and produces images that indicate integrity and orientation of local tissues at each location [10]. Typically, integrity of a local tissue is represented by Trace ADC (a scalar equivalent to the mean diffusivity) or fractional anisotropy of diffusion (a scalar representing directional bias of water molecular mobility), whereas local tissue orientation is represented by the principal direction of the diffusion tensor [11]. This technique has been used for in vivo study of cerebral white matter, myocardium, and other tissues [12]. It provided information about normal tissue architecture, and helped assess disease conditions that perturb tissue structural coherence, such as ischemia, acute infarct, multiple sclerosis, schizophrenia, gliosis, and tumor growth in the brain [13, 14].

In this research, Interdisciplinary MRI/MRS Lab at National Taiwan University played the role as a resource center to provide 3T MRI/MRS facilities, MR techniques and professional skills. Our team has significant progress on fMRI artifact removal, Diffusion Spectrum connectivity/cytostructure imaging (DSI), simultaneous recording and correlation of fMRI activation and electrophysiological recording in the same rat during fMRI activation. These developments strengthen our long-term efforts to map neural connectivity using registered fMRI and DSI.

## II. EXPERIMENTAL DETAILS

In this research, fMRI techniques developed and been applied to other subprojects includes: 1. Model-free fMRI Analysis Platform; 2. Coil Design: surface coils, head coils

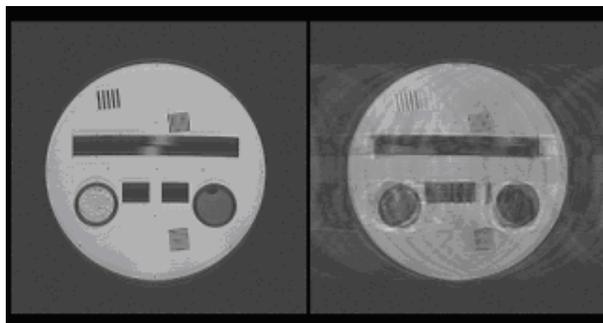


FIG. 1: MR images with Motion artifact (right) and with proposed 3D motion correction (left). Artifacts are significantly reduced in this study.

and phased array coil; 3. fMRI Motion correction optical system; 4. fMRI database; 5. Automatic eddy-current compensation for EPI; 6. Active Noise Cancellation systems; 7. Image Registration system using deformable model; 8. Pulse Sequencing for original acquisition: DSI, Spiral, interactive shimming and pre-emphasis sequences.

### III. RESULTS AND DISCUSSION

In this study, we have developed a reliable and robust fMRI technique through technical development and optimization. The results are the following: 1. developing physiological motion correction technique to increase the sensitivity and specificity on fMRI; 2. addressing the problems of magnetic field inhomogeneity; and 3. optimizing visual specific fMRI paradigms based on the developed motion correction (Fig. 1) and field inhomogeneous compensation techniques. Overall, this study has achieved its main goals to support convincing BOLD-fMRI techniques; Physiological artifact removal system for human study have draw international attentions, Susceptibility signal void will be reduced using parallel imaging acquisition; Current spiral sequence has shown good results on reducing this problem.

In the electrophysiological part, the most important finding is that somatosensory fMRI activation pattern correlated not as well with evoked field potential. Instead, it correlated the best with ensemble single-unit activation pattern. We have made preliminary trial with salt solution filled glass micropipette implanted into the primary somatosensory cortex of the rat. Noise analysis shows that most of the magnetic field induced artifacts can be eliminated with suitable filtering, differential recording setup, and special attention to the sensor material and arrangements.

With the setup of the microscopic system and the optimization of the activation sequence, we have successfully mapped fMRI activation pattern of electrical stimulation of the hindpaw of the rat (Fig. 2). Correlative studies have been successfully done with multiple channel ensemble single-unit recording and fMRI activation pattern. Simultaneous recording of fMRI and electrophysiological activations are actively pursued. And we can

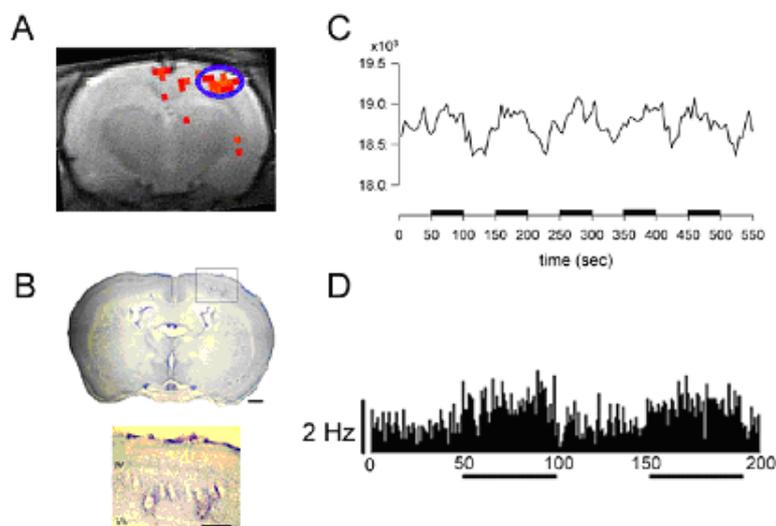


FIG. 2: A representative comparison of BOLD activation correlation map (A, C) and ensemble multiple single-unit recording data (B, D). (B) is the microphotographs of a representative implanted rat brain. The microelectrodes were placed in the infragranular layers of the primary somatosensory cortex as better seen in the enlarged boxed area. The ensemble activities (D) were summed from 10 well isolated single-units whose receptive fields were in the left hindpaw. Note the same on-off pattern similar to that in (C). 3 Hz, 2 ms, 2 mA constant current pulses were applied to the left hindpaw in the underlined periods. IV: layer IV. VIb: deep layer VI.

combine the simultaneous recording, correlation of fMRI activation and electrophysiological recording in the same rat during fMRI activation. In here, we will concentrate on documenting the change of amygdala, cortex and thalamus in various experiences, including the fear condition.

There are three results in DTMRI: 1) to optimize DTMRI schemes, 2) to validate DTMRI in white matter tracking by histology (Fig. 3), and 3) to obtain registered MRI of brain activation and connectivity in vivo. To optimize DSI data sampling scheme, we developed two DSI data acquisition schemes, a spherical encoding scheme and a half Fourier encoding scheme, to reduce the acquisition time. Our results showed that the diffusion cross terms can be calculated from the data acquired with lower b values. Mapping of the first eigenvector of the diffusion tensor and mapping of motor cortical activation under finger tapping were spatially co-registered. We are currently undertaking development of a 3D tractography algorithm to establish the connectivity between pre-motor cortex and an activated region in the contra-lateral cerebellum.

#### IV. FUTURE WORK

These developments strengthen our long-term efforts to map neural connectivity using registered fMRI and DSI. Moreover, parallel imaging capability will be installed recently,

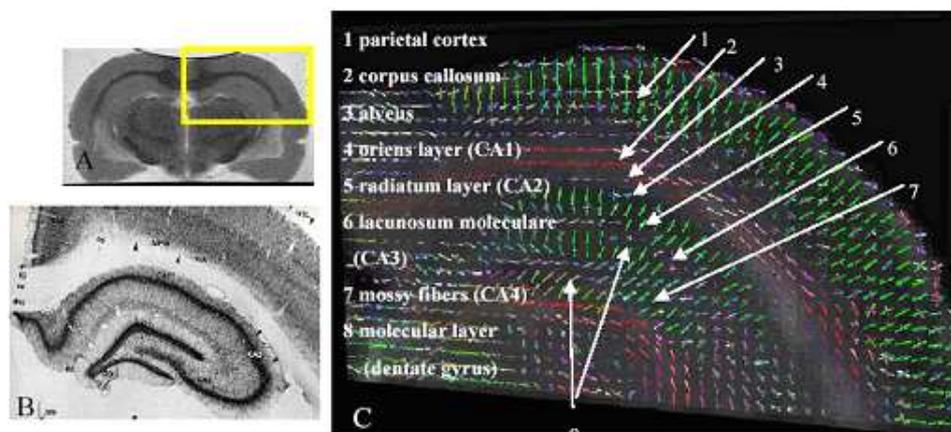


FIG. 3: T2WI of rat brain in coronal section (A), histology with parvalbumin preparation of the rat hippocampus (B), and DSI of the rat hippocampus (C). Segments in each pixel represent orientations of PDF. Each segment is color-coded according to its polar angle: green in radial and red in circumferential.

novel bioactivated calcium-selective contrast agents for magnetic resonance imaging is under development, if incorporated with fMRI, dynamic nature of a functional brain and its relation to fMRI contrast can be investigated. Current direction is to apply parallel imaging capability to animal experiment using the same published approach for event-related fMRI in the future.

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