

**FUNCTIONAL BRAIN IMAGING AND OPTOGENETIC
MANIPULATIONS FOR THE STUDY OF PLASTICITY**

by
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Abstract

Cortical reorganization has been found in patients with injury to the peripheral or central nervous system. The degree of plasticity determines the extent of recovery after injury, and therefore may provide useful means for rehabilitation therapy. However the underlying mechanism for plasticity after peripheral nerve injury is not fully understood. The goal of this thesis was to study cortical plasticity and to develop recovery strategies by modulating cortical neuronal behavior following peripheral nerve injury. The work involves two distinct but tightly related technical aspects to fulfill the overall goal: (i) functional brain imaging techniques to measure brain activities, and (ii) optogenetic techniques to perturb and control neuronal behaviors.

I first developed a laser speckle contrast imaging (LSCI) system, a minimally invasive optical interference technique to map full field (on the order of millimeters) cerebral blood flow (CBF) with high spatial resolution (on the order of micrometers). I further advanced the LSCI technique to detect multiple hemodynamic responses and designed experiments using LSCI and blood level dependent (BOLD) functional magnetic resonance imaging (fMRI), which provide complementary information about functional brain responses in cortex, both ipsilateral and contralateral to peripheral

stimulation.

Next, with the above advanced functional imaging techniques and electrophysiological recording approaches, I characterized the neuronal and hemodynamic responses associated with cortical functions induced by optogenetic manipulations. Cortical plasticity has been demonstrated to take place in a laminar specific manner within the cortex. Accordingly, I investigated laminar specific cortical processing in response to channelrhodopsin-2 (ChR2) stimulation on excitatory neurons in the rat somatosensory cortex (S1). I also directly compared the neuronal and hemodynamic responses throughout the large spatial area of S1. The results showed that the neuronal activation in response to ChR2 stimulation was limited to the stimulation site while the extent of the corresponding CBF and BOLD changes remained beyond 1 mm from the stimulation site. These results indicate an inherent spatial limit for the hemodynamics-based functional imaging techniques.

Then I studied neuronal plasticity to develop recovery strategies following peripheral nerve injury in a rat forepaw denervation model. I inhibited the excitatory neurons located in the healthy somatosensory cortex by optogenetic manipulations, and measured the modulation output from the whole brain network, to micro-vessel and to single cell level by using fMRI, LSCI, and electrophysiological recording. I investigated in depth both the neuronal and hemodynamic responses that occurred in the healthy and deprived cortices following the forepaw denervation. This work could have a great impact on the next generation of rehabilitation strategies following peripheral nerve injury.