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Imaging optically induced neural activity in the brain

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Abstract— **Infrared neural stimulation (INS) is well characterized for the peripheral nervous system; however, translation to the central nervous system (CNS) presents a new set of challenges which require us to consider different anatomy, multiple cell types, and the physiology associated with structures in the CNS. This study presents our first attempt to translate INS to *in vivo* stimulation of the CNS and to image the related response. The results from this study show that INS generates intrinsic optical signals of similar magnitude and shape associated with well characterized mechanical stimuli. The implications of this work could lead to neural implants which allows for single cell stimulation making it possible to design closed loop neural prosthetics.**

I. Introduction

A. Overview of Neural Stimulation

Neural stimulation is the process of using an external source to activate ion channels causing depolarization of the neural membrane and evoking an action potential to propagate down the axon of a stimulated neuron. Electrical, thermal, chemical, optical and mechanical methods have been reported to generate action potentials in both the central nervous system (CNS) and peripheral nervous system (PNS) [1]. Electrical stimulation has been the gold standard for the stimulation of neurons for both clinical and basic research applications. Neural stimulation using infrared light has recently been characterized as a novel method to stimulate peripheral nerves with higher spatial precision than electrical stimulation. Additionally, optical stimulation is contact free and has been shown to stimulate without damaging neural tissue; however, optical stimulation has not been previously achieved in the brain due to complexity of neuronal networks.

B. Definition of Infrared Neural Stimulation

Infrared neural stimulation (INS) is defined as the direct induction of an action potential in response to a transient targeted deposition of infrared energy into neural tissue [2]. Previous studies by our group have shown that a temperature gradient (dT/dz or dT/dt) is required for pulsed infrared light to generate an action potential [3]. It is important to note that INS differs from other optical methods used to modulate the excitability of nerves [4] or from the use of low-level light therapy where low irradiance levels of weakly absorbed light is continuously applied over several minutes to obtain a physiological response [5]. In this work, we will demonstrate the application of INS to induce neural activity in the rat somatosensory cortex in vivo and discuss our ability to detect the resulting response using different methods.

C. INS in the Central Nervous System

INS research thus far has been confined to the peripheral nervous system. The next natural step in the progression of this research was therefore to ask the question of whether it is possible to directly stimulate neurons in the brain using this technique. Possible applications of INS in the CNS, if found successful include cortical mapping during awake craniotomies, tumor resection, and deep brain stimulation. All three potential applications stand to benefit from the lack of electrical field spread associated with INS and cortical mapping and tumor resection procedures could benefit from contact free delivery of infrared light reducing the possibility of mechanical damage to healthy tissue. Thus the next step in the development of INS is to achieve and optimize this method for the CNS, specifically the brain.

The differences in geometry and physiology of the brain compared to the PNS imply that a different wavelength of infrared light may be needed to achieve stimulation in the CNS. Previous work by our group has demonstrated that INS can activate neurons contained within a brain slice model. It was found that the advantages identified for PNS stimulation were preserved; however, stimulation was best carried out using higher repetition rates than what was used for PNS stimulation. The results from the brain slice study provided the necessary data needed to move forward to an *in vivo* model. In this study, we employ the use of optical imaging techniques to study the effects of INS on the rat somatosensory cortex.

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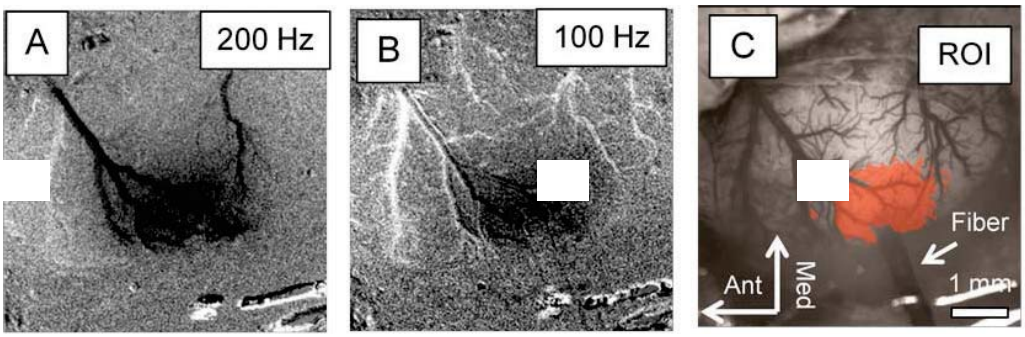

Figure 1: Infrared irradiation of cortex produces intrinsic signals as measured by optical imaging. The intrinsic response for vibrotactile stimulation is inhibited while interleaved with laser stimulation A.) Blank subtracted map at a laser repetition rates of 200 Hz, B) Blank subtracted map at a laser repetition rates of 100 Hz, and C) Blood vessel map with ROI overlayed. ROI generated from t-test between 100 Hz stimulation and blank condition. Fiber location illustrated by white rectangle. Laser stimulation parameters: λ=1.875 µm, spot size=400 µm, radiant exposure = 0.55 J/cm^2, pulse width = 250 µs, pulse train duration = 500 ms. Imaging parameters: 40 Trials, 5 f/s.

II. Results and Discussion

In vivo optical stimulation experiments were performed in the rat somatosensory cortex using hemodynamic optical imaging to detect cortical activation. Optical stimulation was performed using pulsed infrared laser energy in the range of 1.85-1.94 microns to target different layers of cortex. Optical energy was used to stimulate the somatosensory cortex at varying laser parameters and the effect on neural activity was detected using optical imaging techniques. Initial results from this study indicate optical stimulation produces similar intrinsic activation maps and signal time course plots when compared to vibrotactile stimulation of the contralateral forepaw. Additionally, activation of motor cortex was imaged using Ca^{2+} sensing dye fluorescence in response to optical stimulation of somatosensory cortex.

The optical imaging results made during INS were correlated with physiological activity using traditional electrophysiology. Single unit recordings made in barrel field cortex indicated statistically significant local inhibition during INS and had a duration of approximately one second after stimulation onset. This result indicates a physiological response was evoked by the pulsed infrared light delivered

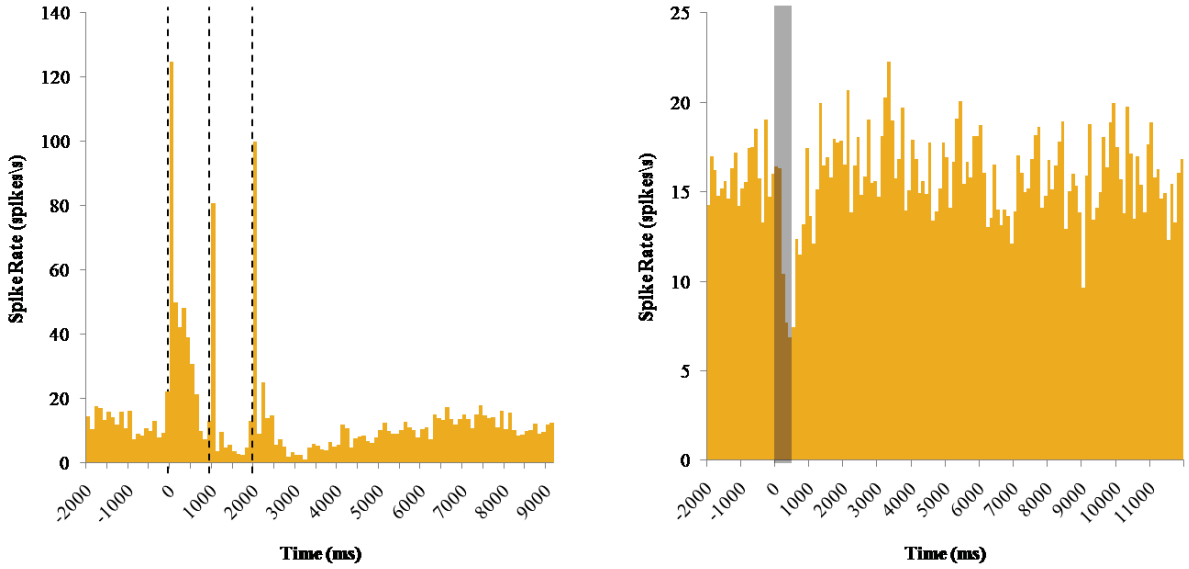

Fig 2. Electrophysiological analysis of INS shows inhibitory response in contrast to excitatory response associated with mechanical stimulation. A.) PSTH generated by 3 sec. train of 1 Hz piezoelectric stimulation of contralateral whiskers.(dashed lines indicate piezoelectric pulse) B.) PSTH of inhibitory response related to INS (gray box indicates stimulus onset). INS parameters: λ=1.875 µm, 500 ms pulse train length, 0.019 J/cm^2, 250 µs pulse width.

during INS. In contrast, vibrotactile stimulation of a whisker indicated excitatory activation suggesting two separate mechanisms by which INS and tactile stimulation generate intrinsic responses. To further elucidate the mechanism behind the intrinsic signal associated with INS and source of inhibition, calcium dye imaging was used to study the effects of infrared light on intracellular calcium dye dynamics in somatosensory cortex.

This study demonstrates the INS can be used to inhibit neuronal activation *in vivo*. Infrared neural stimulation generates intrinsic optical signals with timecourses that are similar to signals generated by vibrotactile stimulation. The heat associated with laser irradiation could cause changes in the de-oxyhemoglobin content through vasodilating blood vessels in the cortex. This would increase blood flow leading to an intrinsic signal that may not be related to neuronal activity. The PSTH contained in fig 2b demonstrates that INS inhibits neuronal activity for approximately 1 second after onset of stimulation. In contrast, all prior studies, mainly in the PNS, have demonstrated excitatory responses that are frequency locked with the laser.

III. Conclusions

In this study, we have shown that optical imaging techniques can be used to image to neuronal activity in response to INS. The presence of astrocytes and interneurons in superficial cortical layers offer a possible explanation for the observed inhibitory response generated by INS.

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