presentation I will present our efforts on leveraging in-vivo recordings in non-human primates (NHP) to study the TMS electrophysiological response.
We focus on the following problems: 1) Disentangling direct neural TMS effects from peripheral origin (auditory, sensory), 2) Demonstrating a TMS dose-response and spatial specificity. We use a NHP model with implanted depth electrodes. We record electrical activity from three electrodes spanning from visual area (V2) to frontal eye field (FEF), auditory (AUD) and temporal (TEM) regions. We stimulate five different brain regions with different intensities and a sham protocol. In addition, a control stimulation site over the right hemisphere was used to demonstrate spatial specificity. Our key findings are a dose-dependent effect of TMS evoked potentials (TEP) at 50 ms in frontal contacts in FEF and TEM electrodes and coil location-dependent effect of center of activation.
These initial results support the premise that TMS induces direct neural responses in a dose-dependent and targeted manner. Our results have key implications for the utility of TMS-EEG in humans to measure direct physiological responses to TMS.

S3A.02

DECIPHERING THE DYNAMICS OF NEURONAL ACTIVITY EVOKED BY TRANSCRANIAL MAGNETIC STIMULATION

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Abstract
Transcranial magnetic stimulation (TMS), a non-invasive method for stimulating the brain, has been used for more than 35 years.
Since then, there have been many human studies using sophisticated methods to infer how TMS interacts with the brain. However, these methods have their limitations, e.g. recording of EEG potentials, which are summation potentials from many cells and generated across many cortical layers, make it very difficult to localize the origin of the potentials and relate it to TMS induced effects. However, this is necessary to build accurate models that predict TMS action in the human brain.
In recent years, we have developed a method that allows us to demonstrate nearly the direct effect of a TMS pulse at the cellular level. We transferred a TMS stimulation protocol from humans to a rat model. In this way, we were able to gain direct access to neurons activated by TMS, thereby reducing the parameter space by many factors. Our data show that a single TMS pulse affects cortical neurons for more than 300 ms. In addition to temporal dynamics, there are also spatial effects. These effects arise at both local and global scale after a single TMS pulse. The local effect occurs in the motor cortex and is very short-lived. It is characterized by a high-frequency neuronal discharge and is reminiscent of the I-wave patterns described in humans at the level of the spinal cord. The global effect occurs in many cortical and subcortical areas in both hemispheres and is characterized by an alternation of excitation and inhibition. Both effects either occur together or only the global effect is present. Next, we are planning to correlate these neurometric data with induced electric field modeling to create detailed TMS-triggered neuronal excitation models that could help us better understand cortical TMS interference.
Keywords: Transcranial magnetic stimulation (TMS), Animal models, I-wave, Electrophysiology

S3A.03

EFFECTS OF TMS AT THE SINGLE NEURON LEVEL IN NON-HUMAN PRIMATES

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Abstract
The effects of TMS are studied with a variety of approaches across species, but the clinical goal is to improve the technology to help humans. One pathway to improvement is establishing what TMS does to single neurons and circuits in the brain. This biological information, complemented by computational modeling, provides a more rational basis for the design of stimulation protocols to target cell types and networks associated with disease. In the lab, the animal model most homologous to humans is the macaque. In collaboration with Drs. Angel Peterchev and Warren Grill, my lab develops and applies methods to study the influence of TMS on neural activity in awake macaques. Our approach is to record from single neurons in the intracranial, TMS-induced electric field. Custom TMS coils deliver the stimulation and permit the insertion of microelectrodes through their center into the brain. Signals are recorded through amplifiers designed to mitigate the stimulation artifact, allowing for detection of action potentials shortly after the TMS pulse. Models based on MRI of each monkey's head simulate the electric field at every recording site. We have recorded 290 neurons from the motor cortex of two macaques using this paradigm while systematically varying stimulation intensity in both standard and sham configurations. Using action potential waveforms, we classify the recordings as putatively derived from inhibitory neurons, excitatory neurons, or axons. We find that TMS causes a triphasic pattern of neural response consisting of a short-latency burst, a pause, and a rebound that returns to baseline. In putative inhibitory neurons and axons, the rebound can persist for several seconds, providing a potential mechanism for cumulative inhibition during repetitive TMS. The data are informing large scale biophysical models of TMS effects that may help to translate the insights from macaques to predictions for patients.
Keywords: TMS, Macaque, Single neuron recording, Modeling

S3A.04

REPETITIVE MAGNETIC STIMULATION INDUCES SYNAPTIC PLASTICITY THROUGH COOPERATIVE PRE- AND POSTSYNAPTIC ACTIVATION

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Abstract
Repetitive TMS (rTMS) induces changes in cortical excitability. However, the cellular and molecular mechanisms which underlie rTMS-induced plasticity remain incompletely understood. Using a combination of functional optical imaging, electrophysiological recordings, and multi-scale computational modeling we study how the physical input parameters of rTMS affect the ability of neurons to express synaptic plasticity. Our experiments in pyramidal neurons of mouse organotypic tissue cultures show that a cooperative pre- and postsynaptic activation during stimulation asserts metaplastic effects, which result in robust LTP-induction. At the molecular level we demonstrate that these effects depend on the activation of NMDA receptors, L-type voltage gated calcium channels and functional intracellular calcium stores. Finally, a computational model that is based on a voltage-dependent STDP rule with fast BCM-like metaplasticity reproduces our findings, and predicts biological differences between 10 Hz and iTBS protocols. These results confirm and expand upon our previous work on rTMS-induced synaptic plasticity in animal models. They provide a framework towards the development of multi-scale computational models that can predict biological effects of rTMS.