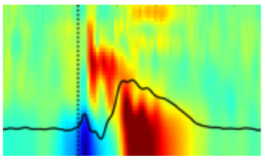
Stanford | Keller Laboratory

PERSONALIZING NEUROTHERAPEUTICS



Novel methods, mechanistic insight, and personalized treatment for mental health disorders

List of large-scale goals (with individual projects and contact person):

1. Closed-loop, personalized brain stimulation (R01MH126639)

TMS is FDA-cleared and clinically effective for depression and other psychiatric disorders. However, TMS is still applied in a one-size-fits-all manner without reference to an individual's brain abnormalities, ongoing brain activity, or changes during treatment. Likely as a result, TMS is only effective for some and can be greatly improved. We are working to develop a fully-automated, fully-personalized, adaptive form of TMS. This new treatment methodology will use closed-loop machine learning techniques to assess ongoing brain activity recorded with simultaneous TMS and EEG ('TMS-EEG') to update or modify treatment parameters. This platform can be used for any brain biomarker, whether it be local excitability measured in response to pulses of TMS or reaction time for a behavioral task relevant to the circuit of interest. This fully personalized closed-loop approach will likely result in stronger and faster brain changes and improved clinical symptom response.

- **Development of closed-loop TMS treatment for depression** (Chris C). TMS is FDA cleared for several neuropsychiatric disorders, but treatment is still a one-size-fits-all open-label approach. This project combines EEG biomarkers, real-time visualization, and machine learning to develop fully personalized TMS treatment algorithms for mental health disorders.

- **Exploring the stimulation parameter space of TMS** (Chris C, Jessica). TMS treatment has only been investigated with 10Hz, 1Hz, and theta burst stimulation patterns, and little is known about how other stimulation parameters modulate brain activity. This project combines TMS and EEG to investigate how frequency, amplitude, duration and other stimulation parameters modulate brain activity, both on an acute and sustained timescale.

- **Evaluation of TMS artifacts and neural responses to DLPFC stimulation** (Juha, Chris C). TMS has been applied to many subregions of the dorsolateral prefrontal cortex (dlPFC), but we still lack an understanding of how stimulation site affects the location and strength of brain excitability and connectivity. This project investigates how single pulses of TMS, applied to different locations, angles, and intensities within the dlPFC, affect stimulation-induced artifacts and EEG measures of brain excitability and connectivity.

- **Suppression of sensory evoked responses** (Jessica, Manjima). TMS-EEG recordings represent one of the only non-invasive, causal measures of brain excitability, but off-target sensory artifacts from

TMS mask many of the underlying neural signals of interest. In this project, we derive a new and more effective form of sensory suppression using a combination of noise dampening, auditory masking, and timed predictability of TMS pulses.

- **Neuromodulation of prefrontal cognitive processes** (Jade, Jessica). EEG measures of brain excitability/connectivity are powerful tools, but understanding how neuromodulation also affects cognitive processes is equally important. In this project, we gain an understanding of how TMS stimulation parameters modulate cognitive processes that engage the dlPFC and associated circuitry.

- **Automated motor hotspotting and thresholding using closed-loop control** (Austin, Chris C in collaboration with Scott Linderman in Statistics). Determining the motor hotspot and threshold is an essential component of every TMS treatment and/or research study, but it is a manual and time-consuming process. In this project, we use computational tools to develop an automated algorithm to perform motor hotspotting and thresholding, as a proof of concept for more sophisticated closed-loop methods.

- **Automated real-time TEP optimization** (Sara, Chris C). Obtaining TMS-evoked potentials (TEPs) with high signal-to-noise is a critical component of every research study, but currently is performed in an open-loop manner (and in many groups without any modification) to boost signal and reduce noise. In this project, we combine TMS-EEG and real-time monitoring to develop a fully-automated method to derive robust TEPs with maximal signal-to-noise ratio.

2. Noninvasive, real-time monitoring of brain networks (1R01MH129018)

TMS is clinically effective, but determining where and how to stimulate is currently a blind and one-size-fits-all approach. The dlPFC is a nexus of brain networks, including the *fronto-cingulate-insular 'saliency' network* and the *fronto-parietal 'dorsal attention' network*. Being able to determine the subregion within the dlPFC that maximally activates the brain network of interest for each patient is critical for more effective treatment. In an effort to target the frontoparietal attentional network for TMS treatment, using a large database of intracranial brain recordings, we will first identify the subdivision of the dlPFC most connected to the parietal node of the frontoparietal attention network. Next, we will use these findings in combination with TMS-EEG to noninvasively develop in-clinic, individualized markers of the frontoparietal attention network grounded in neurophysiology. More broadly, this algorithm can be adapted to identify any brain network of interest in the clinic for treatment or research purposes.

- **Intracranially-derived measures of non-invasive effective connectivity** (Sara in collaboration with Olivier David at Aix-Marseille University). TMS-evoked potentials (TEPs) represent powerful tools for non-invasively measuring causal inter-regional relationships, but neural effects directly related to the TMS pulse are mixed with stimulation artifact and off-target sensory effects. In this project, we use intracranial stimulation and recordings as a 'roadmap' to derive neurophysiology-grounded components of the non-invasive TEPs.

- **Sensing cortical and subcortical activity with non-invasive brain measurements** (Ajay and Austin in collaboration with Andrea Pigorini at University of Milan). Non-invasive EEG is a powerful tool to monitor brain activity in a clinical setting to stratify treatment options, optimize treatment algorithms, and predict relapse, but our understanding of these signals is critically lacking with

regard to the underlying neural mechanisms. In this project, we use jointly-recorded intracranial and non-invasive EEG to develop non-invasive predictors of cortical and subcortical activity.

3. Intracranial mechanisms underlying non-invasive brain stimulation (pending NIMH R01)
Clinical TMS is rapidly expanding and is now FDA-cleared for depression and other psychiatric disorders. Despite this, we still lack knowledge of how TMS treatments modulate the human brain. Specifically, we are unsure if and how TMS modulates brain activity at regions local to the stimulation site (dlPFC) or if it affects downstream functionally connected regions. Noninvasive fMRI has poor temporal resolution and scalp EEG has poor spatial resolution. In contrast, intracranial EEG recordings provide high spatiotemporal resolution to resolve this outstanding question. In this work, we pair TMS with intracranial brain recordings in surgical patients undergoing electrode implantation and examine the local and downstream effects of single pulse and repetitive TMS. These findings will provide important insights regarding the neural mechanisms underlying TMS-induced brain plasticity.

- **Characterization of intracranial neural effects of TMS** (Jeff Wang, in collaboration with Aaron Boes at University of Iowa). TMS is a powerful non-invasive tool, but to date we lack an understanding of the neural effects of TMS in humans. In this project, we combine TMS with intracranial EEG recordings in humans to better understand the local and downstream effects of TMS.

4. Non-invasive monitoring of cortical and subcortical activity in humans (unfunded, R21 to be submitted)
Noninvasive brain monitoring tools have revolutionized human neuroscience and hold great potential to help diagnose, evaluate disease severity, or monitor treatment outcome for neuropsychiatric disorders. EEG measured on the scalp can be easily monitored in outpatient clinics. A critical missing component is that it is unknown which frequency bands and groups of electrodes in scalp EEG relate to specific brain activity in cortical and subcortical regions. Methodology exists to estimate the intracranial sources of scalp EEG recordings with computational models built from anatomical MRIs, but this approach is limited by a number of requisite assumptions and unknown accuracy. Instead, a direct comparison between invasive and noninvasive brain activity is needed to provide objective evidence of these relationships. In this work, we develop a model between intracranial and noninvasive brain recordings in humans, exploring 1) a global evaluation between spatial location, oscillatory activity, and brain state changes; 2) evaluation of the neural correlates of published scalp EEG brain biomarkers in psychiatry; and 3) a targeted evaluation focused on the scalp EEG projections derived from depression-related cortical and subcortical regions. This work has the potential to 1) gain insight into the distributions and frequency content of intracranial brain activity captured on the scalp; 2) determine the neural correlate to known scalp EEG biomarkers; and 3) develop scalp EEG projections of cortical and subcortical brain activity that can be tracked in the clinic.

5. Investigating the neural mechanisms of TMS-induced plasticity in a rodent model (unfunded, R21 to be submitted)
While we investigate the neural mechanisms underlying TMS-induced brain plasticity in humans, we recognize that these neuroscientific investigations have limits. Noninvasively, it is difficult to definitively connect scalp EEG to specific brain regions or neural events. Intracranial investigations are only possible in a surgical epilepsy population, often time-limited, and without standardized electrode placement. In contrast, animal models provide standardization in genetics, environmental factors, and electrode placement. Furthermore, experiments are less time-limited and allow the measurement of single neurons. Animal studies have examined how single neurons are modulated with single pulses of TMS, but an exploration into the short- and long-term neural effects of trains of TMS in animals have not been well explored with human translation in mind. Here, pairing TMS with single neuron and local field potential recordings, we plan to investigate 1) how

single TMS trains modulate neural activity, 2) how sequential TMS trains build to induce longer-lasting effects, and 3) how changes in neural activity relate to biochemistry markers (c-fos, BDNF).

- **Investigating the neural mechanisms of TMS-induced plasticity in a rodent model** (Corey in collaboration with Windy McNerney at Palo Alto VA). Intracranial and non-invasive recordings following brain stimulation in humans are powerful tools, but are lacking in control with respect to electrode placement, stimulation duration, and types of neural recordings. In contrast, in this project we combine miniaturized TMS with intracranial EEG recordings in a rodent model to explore the stimulation parameter space, better understand underlying mechanisms of acute and sustained effects of stimulation, and study the relationship of stimulation-induced neural and behavioral effects.

Ancillary projects not associated with above goals:

- **Optimizing offline analysis of effective connectivity measures** (Chris M). TEPs are a powerful tool to measure excitability and connectivity, but typically each TEP feature is examined in isolation and no algorithm combines components of the TEP. In this project, we combine TEPs with computational techniques to develop a novel multivariate approach that incorporates measures of amplitude, latency, and morphology of each response and leverages metrics of validity to extract the most relevant features of the TEP.

- **Development of a noninvasive depression biomarker** (Austin in collaboration with Scott Linderman). Closed-loop adaptive treatment requires real-time monitoring of treatment progress using a biomarker. Non-invasive measurements are particularly amenable as they can be easily recorded in an outpatient clinic. In this project, we leverage a large publicly available dataset (EMBARC study) coupled with machine learning techniques to develop EEG biomarkers for depression diagnosis and severity.

- **Evaluation of Hebbian plasticity in humans** (Saachi, Naryeong in collaboration with Ashesh Mehta at Feinstein Institute). The motto of Hebbian plasticity, "cells that fire together wire together," is taught worldwide, yet a direct demonstration of this in humans has not been performed. In this project we demonstrate that intracranial stimulation can induce a form of cortical plasticity that is specific in time, space, and frequency.

- **Behavioral and neuronal correlates of human mood states** (Danny in collaboration with Josef Parvizi). Clinical mood scales rely on subjective state and EEG is difficult to distribute outside of the clinic, but video and audio can be readily obtained in the natural world. In this project, we combine intracranial recordings, mood scales, and video to derive behavioral and neural metrics that track human mood states.