Monday, June 4

8:00 - 8:30 (B1) Contribution of persistent activity to cortico-hippocampal interaction in vivo

Mayank Mehta (UCLA), and Thomas Hahn

Cortico-hippocampal interactions are crucial for several forms of learning and memory, including long-term memory consolidation, thought to occur during slow-wave sleep. However, during slow-wave sleep, while the neocortex shows slow, synchronized oscillations, the hippocampus shows largely unrelated and irregular activity. The mechanism of this decoupling and its role are not understood. We hypothesized that this could occur due to the entorhinal cortex, which is a gateway between neocortex and hippocampus, with the medial and lateral entorhinal cortex layer III (MECIII and LECIII) neurons projecting directly to the hippocampal output area CA1. Hence, we measured their membrane potential (MP) in mice *in vivo* along with network activity from the neocortex and hippocampus during up-down state (UDS) oscillations. We developed Hidden Markov based analysis method to detect the precise timing of UDS. This data and analysis method revealed that while the LECIII UDS were always closely matched to neocortical UDS, MECIII neurons invariably persisted in the depolarized Up state well beyond the concurrent neocortical Up state, frequently for several cycles of the neocortical UDS. While the hippocampal CA1 neurons' spiking was weakly inhibited during the neocortical Up states, it was substantially enhanced during the persistent MECIII Up states. These results provide a major dissociation between MECIII and LECIII. Notably, during navigation, MEC neurons show grid cells but LEC neurons do not, which could be influenced by our observation of MEC selective persistent activity. The results also provide the first direct evidence for persistent activity in MECIII neurons *in vivo*. They further suggest that the decoupling between neocortical and hippocampal activities may be generated by the spontaneous persistent activity in the MEC, which could play a key role in working memory and long-term consolidation.

8:30 - 9:00 (B2) Integrated empirical and multiscale modeling of human sleep spindles

Eric Halgren (USCD)

Neural oscillations organize cortico-thalamic activity, and their role in memory, attention and sleep are a central focus of systems neuroscience. Sleep spindles are among the most prominent oscillations, and have been studied at many levels of investigation, from the biophysical level, where the low threshold calcium currents are implicated in the waxing-and-waning 11-15 Hz bursts of spikes that originate in the thalamus and recruit cortical circuits, to the systems level where the electroencephalogram (EEG) and magnetoencephalogram (MEG) measured outside the skull register largescale spatial and temporal coherence in the bursting pattern across the cortex (Destexhe and Sejnowski, 2001). Despite the wealth of physiological, anatomical and computational studies, major questions remain to be resolved: How do nearby parts of the cortex become synchronized during spindles? How are spindles propagated across the cortex? Why is there a discrepancy between the temporal patterns of spindles simultaneously observed in EEG and MEG measurements? What are the consequences of spindle activity in thalamocortical systems for cortical reorganization and memory consolidation during sleep? We will describe studies attack these questions with a range of experimental and modeling techniques that 1) link detailed models at the biophysical level to recordings from humans at the level of current source density analysis (CSD) and multiple single unit recordings from micro-electrode arrays; and 2) relate large scale reduced models of cortical circuits to EEG and MEG measurements in humans. By integrating empirical and modeling approaches at multiple scales, it is possible to understand the origin of macroscopic field measurements outside the scalp based on the specific biophysical mechanisms occurring in neurons located in different layers of the cortex and thalamus.

9:00 - 9:30 (B3) Parkinson's Disease: Mechanistic observations, and relevance to the improvement of PD DBS surgery

Ming Cheng (Alpert Medical School at Brown University), Uri Eden, Sridev Sarma, and Nancy Kopell

High-frequency stimulation (HFS) of the subthalamic nucleus (STN) is known to be effective in Parkinson's Disease (PD) patients, whereas low-frequency stimulation (LFS) is not. At last year's CRCNS meeting, we presented our findings demonstrating the dynamic pathological features of PD, specifically the greater beta oscillatory power, increased burstiness and elevated firing rate, from microelectrode recordings of single unit activity made in the contralateral STN during HFS and LFS of the STN. We hypothesized, and indeed found, that HFS drives a repetitive network-wide modulation that counteracts systemic pathologic neuronal activity; furthermore, this was not seen with LFS. We also demonstrated that this modulation was greatest in amplitude where DBS (with HFS) happens to make the greatest clinical impact, in the dorsal-most portion of the lateral and posterior portion of the STN, within the motor subunit. We call this location the "sweet spot" for STN PD DBS.

Our findings related to HFS disruption of pathological activity were robust due to two substantive improvements initiated by us in STN recording and interpretation. We were able to record in the contralateral STN during STN stimulation, where the stimulation pulses produces less artifactual interference in data from the recording zone. Combined with a technique to cluster and remove the stimulation-related artifact, we were able to better observe the HFS-induced reduction in pathological beta oscillation, burstiness, and firing rate. The patients with the most dramatic clinical improvements had their electrodes implanted within the "sweet spot," where the greatest degree of HFS-induced modulation of pathology was seen.

Having shown that HFS clearly disrupts the pathological network dynamics of PD, we may begin to ask how this is accomplished. For the first time, we report the following: 1) STN HFS appears to suppresses STN firing counteracting PD STN hyperactivity, whereas STN LFS does not reliably modulate firing rates; 2) firing rate suppression is accompanied by a stereotyped pulse-by-pulse decrement in the propensity to spike in the first 1-2 ms directly after each high frequency stimulation pulse; and 3) there is a stimulation frequency-locked increased probability to spike 3-4ms after each HFS pulse. These findings are not seen with LFS. We are now beginning the process of evaluating these findings upon PD pathological dynamics with biophysical modeling and control algorithms.

We believe that this work may lead to an explanation of how HFS, but not LFS, modulates the pathological dynamics of Parkinson's Disease in lockstep with the observed clinical benefit of HFS but not LFS in actual PD patients. Our results may inform our understanding of the mechanistic underpinnings of Parkinson's disease. Our findings are strengthened by the observation of a "sweet spot" that may be both physiologically and clinically relevant. Our logical "next step", our intended goal, is to attempt to improve PD DBS by developing closed-loop diagnostic systems that can effectively target this "sweet spot". The evaluation of PD dynamics in and around the "sweet spot," both during and after surgical electrode placement through the iterative adjustment of electrode or electrical field position, respectively, may result in substantive gains in the clinical efficacy of deep brain stimulation for Parkinson's Disease patients.

9:30 - 10:00 (B4) Fluctuating neural synchrony in the basal ganglia of parkinsonian patients: experimental observations, potential mechanisms, and functional implications

Leonid Rubchinsky (IUPUI and Indiana University School of Medicine), and Robert Worth

Motor symptoms of Parkinson's disease are associated with the excessive synchronized oscillatory activity in the beta frequency band (around 20Hz) in the basal ganglia and other parts of the brain. We study the dynamics of this synchrony in parkinsonian patients, as well as its potential mechanisms and functional implications with the computational models of basal ganglia circuits.

The study of neuronal units and LFP recorded in subthalamic nucleus of our group of patients revealed the specific temporal patterning of synchrony in time. If synchrony is present on the average, neural signals tend to go out of synch for a short (although potentially numerous) intervals. We developed time-series analysis approach, which quantifies this temporal patterning (and associated organization of the phase space), which allowed us to analyze the fine temporal structure of phase-locking in a realistic network model and match it with the experimental data. The experimentally observed intermittent synchrony can be generated just by moderately increased coupling strength in the basal ganglia circuits due to the lack of dopamine. Comparison of the experimental and modeling data suggest that brain activity in Parkinson's disease resides in the large boundary region between synchronized and nonsynchronized dynamics. Such a situation may be beneficial in the healthy state, as it may allow for easy formation and dissociation of transient patterns of synchronous activity which are required for normal motor behavior. Dopaminergic degeneration in Parkinson's disease may shift the brain networks closer to this boundary, which would still permit some motor behavior while accounting for the associated motor deficits.

One particularly interesting aspect of this observed synchrony is the potential for desynchronizing deep brain stimulation. Recently, a lot of interest has been devoted to desynchronizing delayed feedback deep brain stimulation. This type of synchrony control was shown to destabilize synchronized state in networks of simple model oscillators as well as networks of coupled model neurons. However, the dynamics of the neural activity in Parkinson's disease exhibits complex intermittent synchronous patterns, far from the idealized synchronous dynamics used to study the delayed feedback stimulation. When model parameters are such that the synchrony is unphysiologically strong, the feedback exerts desynchronizing action. However, when the network is tuned to reproduce the highly variable temporal patterns observed experimentally, the same kind of delayed feedback may *increase* the synchrony. As network parameters are changed from the range which produces complete synchrony to those favoring less synchronous dynamics, desynchronizing delayed feedback may gradually turn into synchronizing stimulation. This suggests that delayed feedback DBS in Parkinson's disease may boost rather than suppresses synchronization and is therefore unlikely to be clinically successful. This also indicates that in general, desynchronizing stimulation may not necessarily exhibit a desynchronization effect, when acting on a physiologically realistic partially synchronous dynamics.

10:30 - 11:00 (B5) Contributions of the thalamus and basal ganglia to neocortical beta oscillation: A novel computational hypothesis
Stephanie Jones (Brown University), and Christopher Moore

For over 80 years, researchers have observed rhythmic electrical activity in the neocortex, the outer shell of neurons covering the mammalian brain. Despite the prevalence of these oscillations, their meaning for computation—if and how they help us move, perceive and/or think—is a topic of intense debate. 'Beta' oscillations, rhythmic activity at 15-°©-29 Hz, are prominent in neocortex. Over-°©- expression of Beta is a hallmark of Parkinson's disease (PD). Treatments that relieve motor symptoms in PD also diminish beta. Similarly, beta oscillations predict a failure by human subjects to perceive sensory stimuli. These findings directly implicate beta as important for information processing and healthy brain function.
Understanding the detailed origins of beta is crucial to knowing its role
And to potentially guiding targeted therapies.

The present study will test a recently developed hypothesis that explains the natural expression patterns of beta in the human brain. This hypothesis emerged from a detailed biophysically accurate and multi-°©-area computational neural model. To test this hypothesis, the proposed research uses detailed simulations of multiple brain areas to guide experimental recordings and brain stimulation. These data are in turn used to advance and constrain the model. The model includes interconnected elements from the basal ganglia, thalamus and neocortex.

These same areas are targeted for neural recording, to understand how their activity correlates with neocortical beta in anesthetized and behaving preparations processing sensory information. Causal testing of model predictions will be achieved by leveraging recent innovations in 'optogenetics,' the application of light pulses to turn 'off' and 'on' neurons with millisecond precision and cell-°©-type specificity. Optogenetics will be used to enhance and decrease activity, testing the sufficiency and necessity of the activity patterns predicted by the model to lead to expression of this potentially important brain rhythm.

11:00 - 11:30 (B6) Strategy-Dependent Encoding of Planned Arm Movements in Dorsal Premotor Cortex
Dan Moran (Washington University)

11:30 - 12:00 (B7) Mathematical modeling and imaging cardiac electrophysiology
Yoram Rudy (Washington University)