PRINCETON
Neuroscience
INSTITUTE

Faculty Candidate Symposium

Tuesday, March 13th
2:00pm – 4:30pm
A32 Princeton Neuroscience Institute

Rishidev Chaudhuri, University of Texas at Austin
Low- and high-dimensional computations in neural circuits

Qili Liu, Johns Hopkins University
Neural plasticity and motivational drive: How hunger and sleepiness persist in time

Catherine Jensen Peña, Icahn School of Medicine at Mount Sinai
Early life stress increases lifelong risk for depression via transcriptional and epigenetic alterations in reward circuitry

Rishidev Chaudhuri, PhD University of Texas at Austin, Ila Fiete Lab

Low- and high-dimensional computations in neural circuits

I will discuss two approaches to understanding collective computation in neural populations. First, I will introduce a method to decode unknown variables encoded in neural population activity by parameterizing low-dimensional manifold structure in data. In the rodent head direction system, the method reveals a nonlinear ring manifold and recovers the animal's internal directional estimate. When applied to sleep, it provides mechanistic insight into the underlying circuit organization and, during non-REM sleep, reveals a new dynamical regime possibly linked to memory consolidation. I will then briefly address the problem of understanding genuinely high-dimensional computations in the brain, where low-dimensional structure does not exist. Modern work studying distributed algorithms on large sparse networks may provide a compelling approach to neural computation, and I will use insights from such recent work to construct a novel architecture for high-capacity neural memory. Unlike previous models, which yield either sub-optimal increases in capacity with network size or exhibit poor robustness to noise, this network stores a number of states exponential in network size while preserving noise robustness, thus resolving a long-standing theoretical question. These results demonstrate new approaches for analyzing neural representations and computation across a variety of scales, both when low-dimensional structure is present and when computations are high-dimensional.

Qili Liu, PhD Johns Hopkins University, Mark Wu Lab

Neural plasticity and motivational drive: How hunger and sleepiness persist in time

Motivation, defined as the energizing of behavior in pursuit of a goal, is shared by all animals to fulfill basic needs for survival, including food, water, and sleep. Where is motivational drive generated? How does it persist to ensure that the need is satisfied? These fundamental to our understanding of motivation remain poorly understood. During my postdoctoral research in Dr. Mark Wu's lab at Johns Hopkins University, I dissected and characterized key circuit mechanisms underlying two different motivated behaviors: sleep and protein feeding. Our studies uncovered a previously unrecognized, but critical strategy for homeostatic regulation of motivated behaviors: synaptic plasticity of a relevant neural circuit encodes the persistence of motivational drive.

Catherine Jensen Peña, PhD Icahn School of Medicine at Mount Sinai, Eric Nestler Lab

Early life stress increases lifelong risk for depression via transcriptional and epigenetic alterations in reward circuitry

The broad goal of my research is to understand mechanistically how early life experiences are encoded and maintained into adulthood to have long-lasting impact on behavior. In particular, I have sought to understand how environmental experiences in early sensitive periods impact behavior via enduring transcriptional and epigenetic mechanisms. My current research is translationally motivated by the robust clinical finding that child maltreatment increases the lifetime risk of depression and other mood, anxiety, and drug disorders by 2-4 -fold. Studies in humans and animals suggest that early life stress sensitizes individuals to stress later in life, leading to a first appearance or synergistic worsening of

depression-like symptoms only after additional stress. To study the molecular correlates of lifelong stress vulnerability, I established a “two-hit” stress paradigm in mice in which early life stress in a sensitive window increases susceptibility for depression-like behavior, but only after experience of an additional stressor in adulthood (*Science*, 2017). Using genome-wide RNA-seq approaches across brain reward regions which are implicated in depression-like behavior, I discovered several broad and long-lasting transcriptional patterns associated with early life stress and vulnerability to depression-like behavior. Within the VTA, the dopaminergic hub of the brain’s reward circuitry, I identified a novel role for the transcription factor orthodenticle homeobox 2 (OTX2) as an upstream regulator of these transcriptional effects. My work also demonstrated a causal and temporal relationship between VTA *Otx2* levels and stress susceptibility in mice, showing that there is a postnatal sensitive window for down-regulation of *Otx2* to cause enduring stress sensitivity. My work is now investigating the epigenetic consequences of early life stress that mediate such long-lasting transcriptional changes and behavioral vulnerability to stress.