UCI Center for Neural Circuit Mapping

2022 CONFERENCE

Linking Brain Function to Cell Types and Circuits

August 15 – 16
8 a.m. - 5 p.m. PT

Beckman Center of the National Academies of Science & Engineering
Irvine, CA

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Welcome to our UC Irvine Center for Neural Circuit Mapping (CNCM) 2022 conference on "Linking Brain function to Cell Types and Circuits" at the Beckman Center of the National Academies of Sciences & Engineering. This meeting follows the success of our first in-person 2021 Center conference "*Relationship Between Transcriptomics and Connectomics*", jointly sponsored by our Center and the Cajal Club. We decide to host an annual CNCM conference in mid or late August each year; each meeting has a different focus to capture the exciting fast-moving field of neuroscience.

The UCI Center for Neural Circuit Mapping is relatively new but has made very good progress. In 2019, our colleagues Drs. Todd Holmes, Bert Semler, Roz Sandri-Goldin, Qing Nie, Zoran Nenadic and Alex Nicolau, and I began to discuss developing our vision for a new Center at UCI to focus on neural circuit mapping and to harness the combined power of neuroscience, virology and engineering in our local communities. The School of Medicine (SOM) Dean Michael Stamos and other SOM leadership approved our Center plan in January 2020 and pledged critical early commitments of funds and space along with the support from the UCI Campus Vice Chancellor's Office of Research. As our Center developed, the scope of our vision grew to include service centers within our planned Center to include viral production resources, optical imaging resources, single cell genomics and advanced statistical and modeling support. The CNCM membership is potentially available to all UCI faculty and faculty at partner institutions. UCI has a long and rich history of accomplishments in the field of neurosciences, and many members of the UCI neuroscience community across multiple units of UCI (SOM, Biological Sciences, Engineering, and Pharmaceutical Sciences) have joined the Center. Soon after, our Center leadership attracted key collaborations with UCSD, UCLA, Salk Institute, University of Washington and the Allen Institute to go after big important questions in the neurosciences that only teams can address. At present, there are 60 faculty who have joined in the Center. We enjoy our recent scientific and team grant successes. Our ambitious goal is to raise the fortunes of not only our own Center members, but to share our progress with the entire field of Neural Circuit Mapping. Our Annual Center conference is an important venue to share our findings, initiate new collaborations and strengthen existing scientific interactions.

The organizers are grateful to the superb group of speakers who have agreed to present their work and insights at our 2022 conference. We also thank the staff of the UCI Center for Neural Circuit Mapping and of the Beckman Center of the National Academies of Sciences and Engineering for their logistic support. Thank you for coming to our Conference and we look forward to a very rewarding two days of interactions and brainstorming.

Sincerely,

Xiangmin Xu, Ph.D.
Professor and Chancellor's Fellow of Anatomy and Neurobiology
Director of the Center for Neural Circuit Mapping
University of California, Irvine

Conference Organizers

Edward Callaway, PhD
Vincent J. Coates Chair in Molecular Neurobiology & Professor,
Salk Institute

Todd Holmes, PhD
Professor & Vice Chair,
Physiology & Biophysics
UCI School of Medicine

Kim Green, PhD
Professor &Vice Chair,
Neurobiology & Behavior
UCI MIND

Doug Nitz, PhD
Professor & Chair, Department of Cognitive Science
UCSD

Bing Ren, PhD
Professor of Cellular and Molecular Medicine
Member, Ludwig Institute for Cancer Research
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Bert Semler, PhD
Distinguished Professor,
Microbiology & Molecular Genetics
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Director, UCI Center for Neural Circuit Mapping
Professor, Department of Anatomy & Neurobiology
UCI School of Medicine

Conference Schedule

Organizing Committee: Edward Callaway, Todd Holmes, Kim Green, Douglas Nitz, Bing Ren, Bert Semler, Xiangmin Xu
External Advisory Board: Edward Callaway, Liqun Luo, Hongkui Zeng

Day 1 Monday, August 15, 2022

7:30 – 8:15 a.m.	Continental Breakfast
8:15 – 8:30 a.m.	Welcome & Introduction : Distinguished Professor & Chair, Anatomy & Neurobiology , Dr. Christine Gall
	Opening remarks by Vice Chancellor of Research Dr. Pramod Khargonekar

Session 1: Cortical cell types and circuit function

8:30 – 9:20 a.m. (50 min)	Keynote speaker, Chair: Dr. Edward Callaway (Salk Institute)
9:20 – 10 a.m. (40 min)	Dr. Ed Lein (Allen Institute)
10:00 – 10:20 a.m.	*Break*
10:20 – 11:00 a.m. (40 min)	Dr. Bernardo Rudy (New York University)
11:00 – 11:40 a.m.	Dr. Lisa Giocomo (Stanford University)
11:40 a.m. – 12 p.m.(20 min)	Short talk: Dr. Wei Xu (UT South Western)
Noon – 1:30 p.m.	*Lunch / Poster Session*

Session 2: Cell-type specific analysis of gene regulatory networks in neural circuits

1:30 – 2:10 p.m. (40 min)	Chair: Dr. Bing Ren (UCSD)
2:10 – 2:50 p.m. (40 min)	Dr. Joe Ecker (Salk Institute)
2:50 – 3:10 p.m.	*Break*
3:10 – 3:50 p.m. (40 min)	Dr. Xin Jin (Scripps Research, California
3:50 – 4:30 p.m. (40 min)	Campus) Dr. Xiang-Dong Fu, (UCSD)
4:30 – 4:50 p.m. (20 min)	Short talk: Dr. Timothy L. Downing (UCI)
5:00 – 6:00 p.m.	*On-Site Reception of All Attendees*
6:15 p.m.	Speaker Dinner, Farmhouse at Roger's Garden

Day 2 Tuesday, August 16, 2022

7:30 – 8:15 a.m.	Continental Breakfast

Session 3: Local and global neural circuits for navigation and learning

8:15 – 8:55 a.m. (40 min)	Chair: Dr. Douglas Nitz (UCSD)
8:55 – 9:35 a.m. (40 min)	Dr. Sung Soo Kim (UCSB)
9:35 – 9:55 a.m.	*Break*
9:55 – 10:35 a.m. (40 min)	Dr. Omar Ahmed (Univ of Michigan)
10:35 – 11:15 a.m.	Dr. Elizabeth Chrastil (UCI)
11:15 – 11:35 p.m.(20 min)	Short talk: Dr. Kei Igarashi (UCI)
11:35 – 12:05 p.m. (30 min)	Special talk (30 min): Dr. Gordon Fishell (Harvard Medical School)
12:05 – 1:30 p.m.	*Lunch / Poster Session*

Session 4: Linking cell types and circuits to disease

1:30 – 2:10 p.m. (40 min)	Chair: Dr. Kim Green (UCI)
2:10 – 2:50 p.m. (40 min)	Dr. Shane Liddelow (New York University)
2:50 – 3:10 p.m.	*Break*
3:10 – 3:50 p.0m (40 min)	Dr. Catherine Kaczorowski (JAX)
3:50 – 4:30 p.m. (40 min)	Dr. Vivek Swarup (UCI)
4:30 – 4:50 p.m. (20 min)	Short talk: Dr. Autumn Ivy (UCI)
4:55 – 5:00 p.m.	Closing remarks: Center director, Dr. Xiangmin Xu

Conference Venue

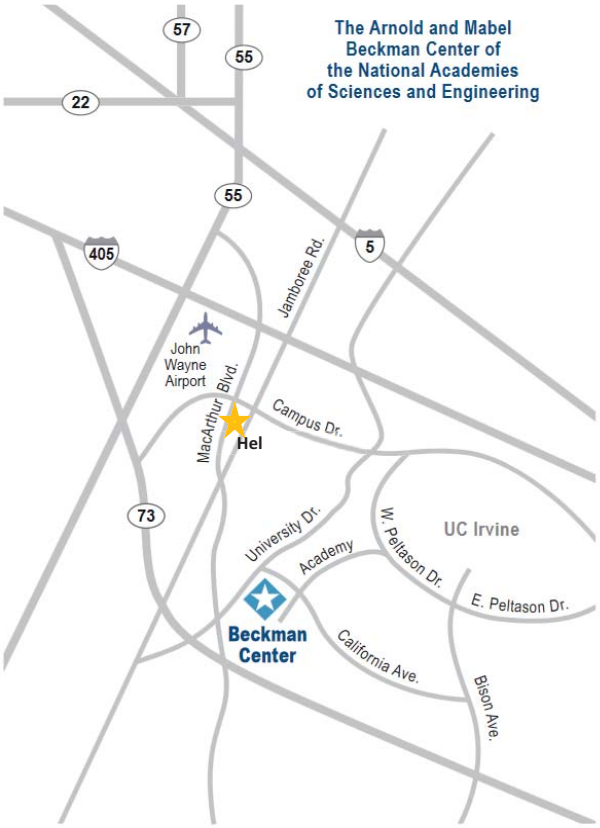
We are honored to hold our conference at the Arnold and Mabel Beckman Center of the National Academics of Sciences and Engineering. Open in 1988, The Beckman Center has brought Dr. Arnold O. Beckman's reality of a West Coast Center where experts could discuss matters of science and technology.

Directions

100 Academy Way, Irvine CA.

Near University Drive, exit from 73.

Adjacent to the University of California, Irvine and less than 3 miles from John Wayne Orange County Airport



Parking

Parking is available on-site at no charge. Electric charging stations are available on-site.

SPEAKER ABSTRACTS

Edward M. Callaway, Ph.D.

The Salk Institute for Biological Studies

Advantages and Limitations of Monosynaptic, Cell Type-Specific Neural Circuit Tracing with G-deleted Rabies Viruses. Application to Cortical Circuit Organization.

Monosynaptic circuit tracing with glycoprotein-deleted rabies virus allows the direct inputs to selected cell types or even single neurons to be revealed across the entire brain. I review methods and reagents used to implement this approach and discuss both advantages and limitations. In particular, I will present evidence that monosynaptic rabies tracing is synapse specific – inputs are only labeled if there are synaptic contacts between pre- and postsynaptic neurons. While there are hundreds of published manuscripts using this approach, there are no examples in which cells have been labeled but are known *not* to be synaptically connected. There are numerous examples of differential labeling of inputs to intermingled cells of different types. There are numerous examples of “newly discovered” connections that have been functionally validated. Some connections are not labeled or are labeled inefficiently, but the mechanisms are understood and predictable. Connections mediated by “volume transmission” (non-synaptic), gap junctions, or axo-axonic contacts are not detected. I will present new data showing that inputs to distal versus proximal dendrites are labeled with nearly equal efficiency.

We have recently applied these methods to study cortico-cortical feedback and cortico-thalamo-cortical circuits. We demonstrate that cortical feedback connections are pathway-specific – that is, cortical feedback neurons preferentially connect to the neurons that provide input to the higher cortical area. We demonstrate that cortico-thalamic driver (layer 5) and modulator (layer 6) neurons connect to thalamic neurons following complementary organizational principles. Layer 5 drivers follow anti-reciprocal rules, avoiding making connections to thalamic neurons projecting back to the same area, while layer 6 modulator connections are reciprocally biased.

Ed Lein, Ph.D.

Allen Institute for Brain Science

Transformative impact of brain cell atlasing

Modern single cell genomics technologies have ushered in a transformative new paradigm for understanding brain cellular complexity. The remarkable scalability and information content of single cell transcriptomics allows comprehensive analysis and classification of cell types defined by their gene expression profiles in any brain region, and this classification creates a robust foundation for defining cellular properties and function. Comparable advances in spatial transcriptomics allows mapping of the spatial organization of molecularly defined cell types in complex brain tissues. These methods work equally well on nuclei from frozen archived tissues, allowing cellular analysis on human brain or other species, and these rich transcriptomic data allow quantitative cell type alignment across species to understand conservation and species specialization of cellular architecture and gene expression. Furthermore, single cell epigenomics extends this classification to understand cell type specific gene regulation and identify short enhancer sequences that are sufficient to drive cell type selective gene expression in adeno-associated viruses in common usage in basic research.

We have established this transcriptomic paradigm in the neocortex with many collaborations in the NIH BRAIN Initiative Cell Census Network, are now extending this approach across the entire brain, across a range of mammalian species, and into studies to understand the cellular and molecular basis of brain disease. Results will be presented describing the use of single cell genomics methods in human cortex to derive a quantitative taxonomy of cell types, and Patch-seq methods to characterize the anatomical and physiological properties of cortical cell types. Applying these methods across cortical areas provides a new approach to understand cytoarchitecture as variation in proportions and properties of specific cell types, while analysis of monkeys, great apes and human allows a characterization of human-specific features. Progress in using the cell atlas data to generate an arsenal of cell type-specific enhancer virus genetic tools will also be presented, along with cross-species validation and testing to identify tools that allow genetic access to conserved cell types across species up to monkey and human. Together these examples illustrate the power of a genomic paradigm for understanding brain complexity and generating a new generation of tools for perturbational neuroscience and even human gene therapy.

Bernardo Rudy, M.D., Ph.D.

Neuroscience Institute, New York University Grossman School of Medicine

Organization and function of enigmatic layer 1

Sensory perception depends on neocortical computations that contextually integrate signals from sensory organs (bottom-up or feed-forward input) with internal information such as expectations, predictions, attention, emotions and memories (top-down proessing). This results in the generation of a percept that is appropriate for the behavioral needs of the animal. Neocortical layer 1 (L1) is the main target of cortical and subcortical inputs that provide “top-down” information for context dependent sensory processing. However, the precise mechanisms that mediate contextual modulation remain unknown. L1 contains no excitatory cells, but it contains the distal, “tuft” dendrites of pyramidal cells located in deeper layers. All the cells present in the layer are GABAergic interneurons (INs). In addition to this resident neuronal population, L1 contains several other sources of inhibition. These include the dendrites of several types of interneurons with somas in L2/3 such as chandelier cells and several subtypes of VIP-expressing INs and the axons of Martinotti cells, a subtype of GABAergic interneuron specialized for dendritic inhibition. Understanding the processing of contextual signals by these GABAergic neurons and the interactions of these cells with the tuft dendrites of pyramidal cells, is crucial to understand sensory perception. However, until recently the neuronal composition of L1 was not known, largely because the GABAergic neurons in this layer are different than those in other layers. I will describe novel findings on the organization and structure of neocortical L1 in the mouse cortex that advance our knowledge of cortical processing.

Lisa Giocomo, Ph.D.

Department of Neurobiology, Stanford University School of Medicine

Multiple maps for navigation and memory

Over the last several decades, the tractable response properties of parahippocampal neurons have provided a new access key to understanding the cognitive process of self-localization: the ability to know where you are currently located in space. Defined by functionally discrete response properties, neurons in the medial entorhinal cortex and hippocampus are proposed to provide the basis for an internal neural map of space, which enables animals to perform path-integration based spatial navigation and supports the formation of spatial memories. My lab focuses on understanding the mechanisms that generate this neural map of space and how this map is used to support behavior. In this talk, I'll discuss how learning and experience shapes our internal neural maps of space to guide behavior.

Wei Xu, Ph.D.

Department of Neuroscience, University of Texas Southwestern Medical Center

Directed stepwise tracing of polysynaptic circuits with transneuronal viral vectors

Brain functions are accomplished by circuits formed by selective wiring of specific neurons distributed across the brain through multiple orders of synapses. Polysynaptic connectivity has been difficult to examine due to the lack of methods to continuously track the pathways in a controlled manner. Here we demonstrate that directed stepwise polysynaptic tracing can be realized by reconstitution of replication-deficient transneuronal viruses – the retrograde pseudorabies virus (PRV) and anterograde YFV-17D. We minimized neurotoxicity of these viruses by temporally restricting viral replication and achieved both tracing and functional control of the circuits. With these tools we delineated the polysynaptic wiring diagrams of the hippocampus-striatum-substantia nigra, and the dentate gyrus-CA3-septum pathways. In the hippocampus-striatum-substantia nigra pathway, we found that neurons in the specific functional domains in the hippocampus project to corresponding domains in the striatum via distinct intermediate regions. In the dentate gyrus-CA3-septum pathway, we found a CA3 subnetwork, characterized by pyramidal neurons selectively projecting to the septum, demonstrating distinct functions in contextual memories. Together, the results indicate that directed stepwise polysynaptic tracing is a powerful technology for functional dissection of brain circuitry.

Bing Ren, Ph.D.

Department of Cellular and Molecular Medicine, University of California, San Diego

Single cell epigenome analysis reveals conserved gene regulatory programs in the human and mouse brains

The state of DNA methylation, chromatin accessibility, combinations of histone modifications and conformation of local chromatin have been referred to as a cell's epigenome. Epigenome is dynamic during development and across the lifespan of an organism, and plays a key role in gene regulation in each cell lineage. Because of the close relationship between epigenome and gene regulation, epigenomic profiling has been used to study gene regulation and interpret noncoding trait- and disease-associated variants. Single-cell epigenomic and multiomic technologies now enable profiling of distinct layers of the epigenome in their native context and are poised to provide new insight into cell type-specific gene regulatory programs and how these programs change during development, in response to environmental cues, and through disease pathogenesis. We have developed and used single-cell epigenomics methods to analyze the epigenome of adult mouse and human brains. These resources have enabled the identification of conserved and species specific gene regulatory elements, infer disease relevant cell types, and interpret the noncoding variants associated with neuropsychiatric diseases.

Joseph R. Ecker, Ph.D.

Howard Hughes Medical Institute, The Salk Institute for Biological Studies

DNA methylome and 3D chromatin landscape of cell types across the mammalian brain

Cytosine DNA methylation is a critical epigenetic regulator involved in brain development that has been implicated in a variety of neurological disease states. Understanding methylation diversity across the whole brain in a 3D context is a fundamental step toward building a complete molecular atlas of brain cell types and understanding their gene regulatory landscapes. We used optimized single-nucleus methylome (snmC-seq3) and multi-omic (snm3C-seq) sequencing technologies to collect 310,605 methylomes and 176,740 chromatin conformation/methylome joint profiles from 117-dissected regions across the adult mouse brain From human brain, we profiled ~ 400,000 snmC-seq methylomes from 45 human brain structures, including basal forebrain, cerebral nuclei, cerebral cortex, hippocampal formation, thalamus, midbrain and hindbrain and 30,000 snm3C-seq cells covering 20 major cerebral cortical cell types. Through iterative clustering, we constructed a DNA methylation-based cell type taxonomy containing ~2,000 distinct mouse brain cell clusters and identified millions of differentially methylated regions between the clusters. Notably, we found massive cellular diversity in the brain stem associated with DNA methylation diversity of specific groups of transcription factors, allowing the prediction of a set of master regulators important for specific brain region structures. We also observed strong cytosine methylation gradients on both genes and regulatory elements in cell types along the anterior-posterior axis within and across brain regions. By integrating cell profiles of DNA methylation and genome architecture data with companion whole-brain chromatin accessibility and gene expression information, we developed an "Activation, Repression in 3D Conformation" (ARC) model, an interpretable machine learning model that weights active (accessibility) and repressive (methylcytosine) epigenetic signals with cell-type-specific 3D chromatin conformation loops to predict gene expression for thousands of cell-types. This model enables the prediction of candidate cell-type-specific enhancers and transcription factors for each gene. Together, our study establishes the first brain-wide, single-cell resolution DNA methylome and 3D multiome atlas, providing an unprecedented resource for understanding cellular-spatial and regulatory genome diversity in the mammalian brain.

Xin Jin, Ph.D.

Department of Neuroscience, Dorris Neuroscience Center, Scripps Research

In vivo Perturb-seq:
scaled investigation of gene functions in the developing brain

The thousands of disease risk genes and loci identified through human genetic studies far outstrip our current capacity to systematically study their functions. I will discuss our attempt to develop a scalable genetic screen approach, in vivo Perturb-seq, and apply this method to the functional evaluation of a panel of autism spectrum disorder (ASD) de novo loss-of-function risk genes. We identified recurrent and cell type-specific gene signatures from both neuronal and glial cell classes that are affected by genetic perturbations and pointed at elements of both convergent and divergent cellular effects across many ASD risk genes. In addition, I will also briefly discuss the research directions in my lab, established in July 2021, in applying spatial transcriptomic approaches to study cell intrinsic and extrinsic effects of these disease risk genes. Our lab will use these systematic approaches, connecting genomic technology development with rigorous dissection of molecular mechanisms, to learn new insight about how complex inputs are integrated into the developing brain.

Xiang-Dong Fu, Ph.D.

Department of Cellular and Molecular Medicine, University of California, San Diego

Leveraging the REST-PTB Axis to Develop a Therapeutic Strategy for Brain Repair

We have been systematically pursuing the function of the RNA binding protein PTB as a key negative regulator of neurogenesis through its functional interplay with the REST complex. Via this regulatory axis, we demonstrate that depletion of PTB activates a large array of lineage-specific microRNAs and transcription factors, many of which have previously been shown to convert non-neuronal cells to functional neurons. This establishes the foundation to generate new neurons from endogenous non-neuronal cells not only in vitro but also in the brain. Indeed, we recently demonstrate the ability of the newly induced neurons to reconstitute the lost nigrostriatal pathway in a Parkinson's disease model, leading to potent reversal of the disease phenotype. Additional preliminary results, coupled with the existing literature information, suggest that the observed therapeutic benefit may result from multiple mechanisms. These findings provide a broad basis for developing a new strategy to treat different forms of neurodegenerative diseases.

Timothy L. Downing, Ph.D.

Departments of Biomedical Engineering and Microbiology & Molecular Genetics,
University of California, Irvine

Elucidating the role of cell-environment interactions in somatic cell acquisition of stemness

Cell reprogramming is an inefficient process. For example, using traditional induced pluripotent stem cell (iPSC) generation techniques, somatic cells transition to pluripotency at a frequency of 1% or less. While genome-wide profiling has suggested the existence of a 'stochastic' bottleneck during the reprogramming process –through which only small fractions of cells are able to transition beyond, the molecular sources of such a bottleneck remain a mystery. Several studies, including some of our own, have demonstrated that cell-adhesive substrate topography, stiffness, and/or cytoskeletal reorganization can facilitate reprogramming, however, how the molecular components used by cells to physically interact and communicate with neighboring cells and/or matrix proteins contribute to the reprogramming process is not known. We performed RNA interference experiments on 103 genes in the integrin and cadherin adhesomes (encoding integrins, cadherins, and associated proteins) that were found to be dynamically regulated across the reprogramming timeline and tested their impact on reprogramming efficiency. Notably, we find that most adhesome gene disruptions enhance the ability of somatic cells to reprogram, suggesting cell adhesion may be a major bottleneck in the acquisition of stemness. Using single-cell RNA sequencing we also identified cell-cell and cell-matrix communication events (using CellChat analysis tool) that are heightened during the late stages of reprogramming and functionally suppress stemness acquisition. We also performed adhesome-disruption in a tumor-derived cell line. Findings from these studies suggests a similar role for cell-environment communications in mediating stemness acquisition in cancer.

Douglas A. Nitz, Ph.D.

Department of Cognitive Science, University of California San Diego

Retrosplenial circuits supporting transformations between spatial and orientational cognition and locomotor actions.

Retrosplenial cortex is positioned anatomically between hippocampal and subicular regions encoding location, anterior thalamic regions encoding head orientation, and secondary motor cortex where neurons robustly encode both planned and current actions. In addition, retrosplenial cortex forms direct links between complementary systems for spatial mapping, in the posterior parietal cortex and the hippocampus. Using projection-specific retrograde tracing with modified rabies viruses, we compare and contrast the sources of input to retrosplenial cortex neurons that project to anterior thalamus, secondary motor cortex, and post-subiculum. Anterior thalamic projecting neurons are strongly innervated by visual cortex and secondary motor cortex inputs while secondary motor cortex projecting neurons are strongly innervated by hippocampal and subicular inputs. In this talk, we will examine the function of these projection-specific sub-populations through DREADD-based manipulation of their activity during tasks that demand the use of location to define actions. We will also examine the spatial directional, and action encoding dynamics of retrosplenial cortex neurons recorded during performance of a complex spatial working memory task. Finally, the talk will consider temporal frameworks for interaction between hippocampal and cortical systems for mapping of actions and locations as well as data pointing to a role for retrosplenial cortex in encoding environmental structure and path integration. Together, our anatomical, behavioral, and neurophysiological findings suggest a division of retrosplenial cortex into distinct circuits subserving functions such as updating of orientation tuning based on landmarks and the transformation of spatial cognition into action.

Sung Soo Kim, Ph.D.

Department of Molecular, Cellular, and Developmental Biology, University of California Santa Barbara

Visual processing for the fruit fly head direction system

Vision provides the richest and the most reliable information for animals to navigate an environment. Your uncertain sense of location and direction in a dark room vanishes as you flick on the light switch and receive visual input from the illuminated scene. Strong visual influence on the navigation system is common across animal species, including the fruit fly, *Drosophila melanogaster*. In flies, E-PG neurons—each innervating one sector of the torus-shaped ellipsoid body—encode the animal's heading. The heading corresponds to an activity peak that, when superimposed on the population activity, resembles a bump: It moves smoothly around the ellipsoid body as the fly turns, and the bump's position relative to the visual landmark is consistent across trials. This suggests visual input is essential for encoding heading, yet the nature of the visual features and how E-PG neurons use them are not well understood. Recently, we used diverse naturalistic visual stimuli to understand how the bump position is determined. We found that E-PG neurons can store a unique bump position relative to the orientation of each naturalistic scene. Interestingly, the more different the two scenes are, the more unpredictable the bump position for a scene is, based on the bump position of the other scene. This suggests that, if two scenes are different, they are decoupled in the memory system, providing an important clue to understanding the mechanisms of scene memory. Since our computational modeling suggests that the number of visual features may dictate memory capacity, we used electron-microscopy data to reconstruct the entire visual pathways from optic lobes to the E-PG neurons with synaptic resolution. Using this connectome data, which includes channels for all visual features, we have predicted and confirmed that light wavelength and visual stimulus shape are encoded in a different way across distinct populations of visual neurons that are presynaptic to E-PG neurons. Overall, this line of work will provide a comprehensive understanding of how visual features are extracted and transformed across multiple stages of processing to provide critical information to compute the fly's head direction.

Omar J. Ahmed, Ph.D.

Departments of Psychology & Biomedical Engineering, Neuroscience Graduate Program, University of Michigan

Spatial Orientation & Head Velocity Circuit Computations in the Retrosplenial Cortex

Successful spatial navigation and orientation are critical for mammalian survival. Lesions to a brain region called the retrosplenial cortex (RSC) dramatically impair spatial orientation abilities, emphasizing the need to decipher the unique aspects of RSC circuit computations supporting its GPS-like functions. Here, using optogenetic circuit mapping, *in vivo* recordings and computational modeling we build towards a comprehensive cellular and circuit understanding of the RSC. We identify a uniquely small and excitable pyramidal neuron and show that it is the primary recipient of spatially-relevant inputs to the RSC. Observed synaptic dynamics enable these small neurons to compute the speed of head rotation, despite receiving head direction inputs that do not explicitly encode speed. We also show that two distinct fast brain rhythms identified in the RSC are the signatures of two very different long-range neuronal synchronization mechanisms, each precisely controlled by the speed of movement. These findings are confirmed across both rats and mice, highlighting key evolutionarily conserved circuit computations performed by the RSC in support of successful spatial navigation.

Elizabeth Chrastil, Ph.D.

Department of Neurobiology and Behavior, University of California, Irvine

Circuits for travel direction and head direction in human navigation

We often assume that travel direction is redundant with head direction, but from first principles these two factors provide differing spatial information. Although head direction has been found to be a fundamental component of human navigation, it is unclear whether travel direction also plays a primary role in navigation. Furthermore, we often consider head direction in terms of allocentric (viewer-independent) coordinate systems, such as cardinal directions. However, an egocentric (viewer-centered) reference frame also provides information about travel trajectory. In this talk, I will discuss several studies from my lab that investigate the relationship between travel direction and head direction. First, we found high-level aftereffects of perceived travel direction by employing a behavioral motion adaptation paradigm from visual neuroscience designed to preclude the contribution of head direction. These findings indicate that travel direction is a fundamental component of human navigation. Interestingly, we discovered a higher frequency of reporting perceived travel toward the adapted direction compared to a no-adapt control – an aftereffect that runs contrary to low-level motion aftereffects. This travel aftereffect was maintained after controlling for possible response biases and approaching effects, and it scaled with adaptation duration. These findings represent the first evidence for a pure travel direction signal in humans, independent of head direction. Next, we used fMRI to investigate the distributed head and travel direction representations in the human brain by testing a large group of people actively navigating in a complex virtual environment. Our model successfully classified both egocentric and allocentric signals for head and travel direction, which evolved during the course of learning. We observed no correlation between classification accuracy and individual navigation performance during the learning phase, suggesting behavior-independent common mechanisms for direction representation when directional signals were emerging in the brain. In contrast, we observed correlations between classification accuracy and navigation performance in the test phase, revealing behavior-dependent variation in direction representation. Notably, good navigators have signals that relate to egocentric movements, suggesting that they have converted this information into actionable trajectories, particularly when considering their previous and upcoming movements. Together, these studies indicate a circuit that not only signals the current head direction information, but that also signals the trajectory of movement in the past, present, and future.

Kei M. Igarashi, Ph.D.

Department of Anatomy and Neurobiology, School of Medicine, University of California, Irvine

Circuit mechanisms of associative memory in health and Alzheimer's disease

Mounting evidence shows that dopamine in the striatum is critically involved in reward-based reinforcement learning. However, it remains unclear how dopamine reward signals influence the entorhinal-hippocampal circuit, another brain network critical for learning and memory. Using in vivo optogenetic and electrophysiological approaches, we recently found that dopamine signals from the ventral tegmental area control encoding of cue-reward association rules in the lateral entorhinal cortex (LEC) (Lee et al., *Nature*, 2021). Our results suggest that LEC represent a cognitive map of abstract task rules, and LEC dopamine facilitates the incorporation of new memories into this map. I will discuss how the systems neuroscience approach can contribute to the understanding of Alzheimer's disease pathogenesis.

Gordon Fishell, Ph.D.

Department of Neurobiology, Harvard Medical School

The intimate dependence and remarkable precision of somatostatin cortical interneuron

Classic work from two decades ago demonstrated that inhibition is mediated through an array of over 50 discrete cortical cell types. Each of these possess unique shapes and properties, suggesting that they have specific roles in the brain. Despite this, our understanding of how these interneurons are assembled into functional cortical circuits is lacking. Somatostatin interneurons, comprise the second largest population of inhibitory cortical cells and are generated in a specialized region of the subcortex, known as the medial ganglionic eminence. Amazingly, this cell type is comprised of at least 10 different types that migrate during development across the brain to form canonical circuits with excitatory cortical cells in a laminar specific fashion. By studying their gene expression during their incorporation into cortical circuitry, we have discovered key regulators of their development, which provided us with the tools to interrogate the different subtypes and witness and perturb their development. These advances provided the tool kit to start tackling two big questions. How do these cells find their right excitatory cell partners in the brain and just how selective are these connections? In this talk, I will focus on the somatostatin populations, which we have recently found selectively connect to different excitatory populations, with one type targeting corticofugal cells and the other targeting intercortical relay neurons. Moreover, it seems these relationships depend on excitatory cells providing signals to the interneurons when they arrive in the cortex. The output and relay excitatory cells, which reside in different layers, appear to provide “instructions” to somatostatin cells as they settle within the cortex, allowing them to literally “learn on the job”. This indicates the existence of a lock and key specificity in connectivity that we are only beginning to understand.

Kim N. Green, Ph.D.

Department of Neurobiology and Behavior, University of California, Irvine

Exploring the roles of microglia in the pathogenesis of Alzheimer's disease

Microglia are firmly implicated in the pathogenesis of late onset Alzheimer's disease (LOAD), both through observational studies in humans and animal models, preclinical studies in animal models, and most importantly, genetic association with AD risk. However, the roles of these cells and their involvement in the underlying mechanisms that contribute to disease pathogenesis remain unclear. A fundamental question has emerged critical to the targeting of these cells and development of future therapeutics: is the microglial response (or response aspects) to plaques beneficial or harmful to the brain? As researchers world-wide contend to develop therapies that promote or inhibit this response, the urgency and importance in addressing this question is evident. This proposal focuses efforts on addressing the problem and dilemma of microglia faced by many in the AD field – microglia can play both a beneficial and detrimental role in disease. Insight into this question will enable the development of more sophisticated methods to target microglia and allow for the much-needed expansion of therapeutic approaches for AD.

Here I will detail a variety of tools that we have developed for exploring the roles of microglia in the pathogenesis of AD and other diseases, including colony-stimulating factor 1 receptor inhibitors that can fully deplete the microglial tissue, and show how this impacts the development of AD-relevant pathologies, and how this changes with disease stage. Furthermore, we have developed a number of novel animal models that recapitulate variants in microglia expressed genes that increase the risk of LOAD in humans, such as $Trem2^{R47H}$ and $Abi3^{S209F}$. Finally, we have also created tool mice that can be used to specifically target and manipulate disease-relevant sub-populations of microglia. Collectively, our data support a causal role for microglia in the initial development of AD, as well multiple functions at different stages of disease pathogenesis, complicating therapeutic options.

Shane A. Liddelow, Ph.D.

Neuroscience Institute, Departments of Neuroscience & Physiology, and of Ophthalmology, Parekh Center for Interdisciplinary Neurology, New York University Grossman School of Medicine

Reactive astrocyte heterogeneity in inflammation and disease

The study of astrocyte reactivity requires careful identification of heterogeneity via transcriptomic profiling, followed by identification using cell based systems to model their functional alterations compared to physiologically 'normal' astrocytes. Further validation by confirmation in rodent models of disease and in human cells and postmortem tissue provides corroboration of biologically important reactive astrocyte sub-states.

We recently completed a large well-powered scRNAseq analysis of astrocyte reactivity profiles following acute systemic inflammation, highlighting several transcriptomically defined sub-states. Further, using integration with other published datasets we find specific disease-associated sub-states in rodent models of Alzheimer's disease, demyelination, and an acute stab wound. Following, we produced in vitro models to further study the functional alterations of these sub-states of reactive astrocytes, and used snRNASeq from human post-mortem Alzheimer's disease patients for cross-specific integration.

In parallel studies, we used animal models of neurodegeneration: the bead occlusion model of glaucoma, and the SOD1G93A model of amyotrophic lateral sclerosis to highlight two key insights. First, we report that neurons must be susceptible to astrocyte-mediated cell death; and second, disease-associated mutations alone may not mediate reactivity states, but instead lower their threshold for 'activation'.

Combined these studies highlight the importance of functional validation of transcriptomic ally defined reactive astrocyte sub-states, and identify a specific set of stop-gaps in the mechanism of reactive astrocyte mediated neurotoxicity.

Catherine Kaczorowski, Ph.D.

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Identification of conserved transcriptional signatures of cognitive resilience to Alzheimer's Disease

It is estimated that a third of the elderly population is not diagnosed with Alzheimer's disease (AD) due to the absence of cognitive impairment despite carrying risk variants of AD or presenting AD pathology post-mortem. This suggests that at-risk individuals may carry protective mechanisms that promote resilience to cognitive impairment, however the underlying molecular processes that promote resilience remain unknown.To determine transcriptional changes associated with resilience, we profiled the transcriptome of hippocampal and prefrontal cortex cell types using single-nuclear sequencing in 7 resilient and 7 susceptible strains from the AD-BXD mouse reference panel[1], a genetically diverse mouse model of AD that better mimics human AD. Here, we used contextual fear memory paradigm to assess memory function in AD-BXDs carrying the 5XFAD mutation. Resilience was defined based on the change in memory function relative to that of the entire AD-BXD population, where strains showing lower than average decline were considered resilient. Using single nucleus RNA-sequencing, we profiled ~220 K nuclei from the hippocampal formation and identified 32 cell clusters representing the major cell types in the hippocampus including glutamatergic neurons, GABAergic neurons, astrocytes, oligodendrocytes and microglia. With the exception of GABAergic neurons, transcriptional changes associated with the 5XFAD mutation were greater in susceptible AD-BXDs. Gene expression changes associated with cognitive resilience were primarily observed in excitatory neurons, specifically in the CA1 and dentate gyrus and were enriched for ribosomal genes and nuclear encoded mitochondrial genes. In attempt to infer potential ligands that regulate resilience-associated transcriptional changes we used a ligand-target interaction analysis and predicted potential ligands regulating resilience programs in excitatory neurons. Conservation of resilience signatures were confirmed using integrated mouse and human snRNAseq data generated from the prefrontal cortex. Our findings demonstrate that the rate of memory decline is concomitant with increased transcriptional changes associated with the 5XFAD mutation across cell types in the hippocampus, as well as prefrontal cortex. We show that molecular programs associated with resilience in excitatory neurons are enriched in protein metabolism, cellular respiration and translation, possibly indicating a response to energy demand and maintenance of cellular homeostasis. Lastly, there was high alignment between the majority of cell types in mouse and human prefrontal cortex from resilient and susceptible individuals, confirming that genetic and phenotypic variation in AD mice are required for modeling complexity of human AD.

1. Neuner SM, Heuer SE, Huentelman MJ, O'Connell KMS, Kaczorowski CC. Harnessing Genetic Complexity to Enhance Translatability of Alzheimer's Disease Mouse Models: A Path toward Precision Medicine. Neuron. 2019.

Vivek Swarup, Ph.D.

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Cell-type specific regulatory architecture in Alzheimer's disease

The human brain changes at the molecular and cellular level with aging, and these molecular changes reflect either healthy or degenerative behavioral and cognitive function. Degeneration at the cognitive level, known as dementia, is seen in a large proportion of the population. Alzheimer's disease (AD) is the most common dementia with a prevalence rate of 16% among individuals older than 65 years of age, which translates to total economic cost of about $290 billion/year. AD is characterized by massive changes in neuronal and glial populations and marked by tangles and plaques, that are pathological hallmarks in AD. Understanding the changes in specific cell-types and uncovering regulatory programs in those cell-types requires a holistic experimental and analytical approach. Our single-cell study uses multi-omics of thousands of nuclei in late-stage Alzheimer's Disease (AD), profiling chromatin accessibility and gene expression in the same biological samples and uncovering vast glial heterogeneity in late-stage AD. We identify cell-type specific, disease-associated candidate cis-regulatory elements and their candidate target genes, including an oligodendrocyte-associated regulatory module containing links to *APOE* and *CLU*. We describe cis-regulatory relationships in specific cell-types at AD risk loci defined by genome wide association studies (GWAS), demonstrating the utility of this multi-omic single-cell framework for uncovering disease and cell-type-specific regulatory mechanisms. Trajectory analysis of glial populations highlighted transcription factors dysregulated in disease-associated glia, and we additionally identify disease-relevant regulatory targets of these transcription factors. Further, we have created scWGCNA, a co-expression network analysis strategy robust to the sparsity of single-cell data, to perform a systems-level meta-analysis of AD transcriptomics.

Autumn Ivy, M.D., Ph.D.

Departments of Pediatrics, Neurology, Anatomy & Neurobiology, Physiology & Biophysics, Neurobiology/Behavior, UC Irvine School of Medicine

An in vivo, neuron-specific approach for pairing translational and epigenetic signatures of early-life exercise.

Aerobic exercise promotes molecular and physiological adaptations in neurons to influence brain function and behavior. The most well studied neurobiological consequences of exercise are those which underlie exercise-induced improvements to hippocampal memory. Epigenetic regulation of genes important for neural plasticity has recently been implicated in exercise mechanisms. In the developing brain, epigenetic modifications resulting from early-life experiences inform long-term function and behavior; however, exercise as an early-life experience has not been fully explored for its effects on brain maturation and neuronal function. In this study we employ a line of transgenic mice expressing the NuTRAP (Nuclear tagging and Translating Ribosome Affinity Purification) cassette in *Emx1* expressing cells, allowing for simultaneous isolation and sequencing of translating mRNA and nuclear chromatin from a hippocampal neuron-enriched cell population. After undergoing early-life exercise (early EX), mouse hippocampi are extracted followed by Isolation of Nuclei TAgged in specific Cell Types (INTACT) and Translating Ribosome Affinity Purification (TRAP). This allows for us to determine neuron-specific epigenetic modifications influencing gene expression programs resulting from early EX. Data from RNA- and CUT&RUN-seq were coupled to evaluate histone modifications influencing the expression of translating mRNA in neurons after early EX. To determine gene expression signatures of early EX and their epigenetic regulation important for facilitating hippocampal memory consolidation after early EX, we introduced a hippocampal learning event and discovered new gene expression – histone modification relationships that are likely critical for enabled memory after early EX. Our data reveal transcriptional and epigenetic signatures of ELE exposure and identify novel candidate gene-histone modification interactions for further investigation. Importantly, our novel approach of combined INTACT/TRAP methods from the same cell suspension allows for simultaneous transcriptomic and epigenomic sequencing in a cell-type specific manner.

POSTER ABSTRACTS

Poster #1 (Z. Yu et al.)

Beyond t test and ANOVA: applications of mixed-effects models for more rigorous statistical analysis in neuroscience research

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In basic neuroscience research, data are often clustered or collected with repeated measures, hence correlated. The most widely used methods such as t test, ANOVA, and their nonparametric versions do not take data dependence into account and thus are often misused. Our data simulations reveal that failure to account for data dependency can lead to over 90% false discoveries, based on the level of dependency observed in our studies. This seriously undermines scientific rigor and reproducibility. In this presentation, I will introduce linear and generalized mixed-effects models that consider data dependence and provide clear instruction on how to recognize when they are needed and how to apply them. The appropriate use of mixed-effects models will help researchers improve their experimental design and will lead to data analyses with greater validity and higher reproducibility of the experimental findings.

Poster #2 (E. Zagha et al.)

Frontal Cortex Gates Distractor Stimulus Encoding in Sensory Cortex

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Frontal cortex suppresses behavioral responses to distractor stimuli. One possible mechanism by which this occurs is by modulating sensory responses in sensory cortex. However, it is currently unknown how frontal cortex modulations of sensory cortex contribute to distractor response suppression. We trained mice to respond to target stimuli in one whisker field and ignore distractor stimuli in the opposite whisker field. During expert task performance, optogenetic inhibition of frontal cortex increased behavioral responses to distractor stimuli. During expert task performance, within sensory cortex we observed expanded propagation of target stimulus responses and contracted propagation of distractor stimulus responses. In contrast to current models of frontal cortex function, frontal cortex did not substantially modulate the response amplitude of preferred stimuli. Rather, frontal cortex specifically suppressed the propagation of distractor stimulus responses, thereby preventing target-preferring neurons from being activated by distractor stimuli. Single unit analyses revealed that wMC decorrelates target and distractor stimulus encoding in target-preferring S1 neurons, which likely improves selective target stimulus detection by downstream readers. Moreover, we observed proactive top-down modulation from frontal to sensory cortex, through the preferential activation of GABAergic neurons. Overall, our study provides important mechanistic details about how frontal cortex gates sensory propagation in sensory cortex to prevent behavioral responses to distractor stimuli.

Poster #3 (N. Nakagawa et al.)

Impaired associative memory encoding in the lateral entorhinal cortexof amyloid precursor protein knock-in mice

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Alzheimer's disease (AD) is the most common cause of dementia. Previous fMRI studies show that the lateral entorhinal cortex (LEC) is the primary site of dysfunction in early-stage AD patients, but circuit mechanisms underlying LEC dysfunction are unknown. We recently found that the LEC neurons in healthy animals are critically involved in associative memory encoding. To test if this LEC activity is affected in AD, we recorded LEC neurons in amyloid precursor protein knock-in (APP-KI) mice engaging in an odor cue-reward task. APP-KI mice showed impaired associative memory performance. LEC neurons in APP-KI mice showed disrupted associative memory encoding. Our results suggest that the disruption of encoding in LEC neurons may lead to associative memory deficit in APP-KI mice.

Poster #4 (M. Telpoukhovskaia et al.)

Conserved cell-type specific signature of resilience to Alzheimer's disease nominates role for excitatory cortical neurons

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Alzheimer's disease (AD), the leading cause of dementia, affects millions of people worldwide. With no disease-modifying medication currently available, the human toll and economic costs are rising rapidly. Under current standards, a patient is diagnosed with AD when both cognitive decline and pathology (amyloid plaques and neurofibrillary tangles) are present. Remarkably, some individuals who have AD pathology remain cognitively normal. Uncovering factors that lead to "cognitive resilience" to AD is a promising path to create new targets for therapies. However, technical challenges discovering novel human resilience factors limit testing, validation, and nomination of novel drugs for AD. In this study, we use single-nuclear transcriptional profiles of postmortem cortex from human individuals with high AD pathology who were either cognitively normal (resilient) or cognitively impaired (susceptible) at time of death, as well as mouse strains that parallel these differences in cognition with high amyloid. Our cross-species discovery approach highlights a novel role for excitatory layer 4/5 cortical neurons in promoting cognitive resilience to AD, and nominates several resilience genes that include *ATP1A1*, *GABRB1*, *PTK2*, and *ROCK2*. Nominated resilience genes were tested for replication in orthogonal data sets and confirmed to be correlated with cognitive resilience. Additionally, we identified several potential mechanisms of resilience, including regulation of membrane potential, axonal and dendritic growth, and general increase of protein cycle, potentially of membrane proteins. Because our discovery of resilience-associated genes in layer 4/5 cortical neurons originates from an integrated human and mouse transcriptomic space from susceptible and resilient individuals, we are positioned to test causality and perform mechanistic, validation, and pre-clinical studies in our human-relevant AD-BXD mouse panel.

Poster #5 (N. Hadad et al.)

Improved stress response in excitatory neurons of the DG, CA1 and Entorhinal cortex is associated with cognitive resilience in Alzheimer's disease.

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Alzheimer's disease is characterized by progressive neurodegeneration accompanied by severe cognitive impairment. However, a subset of the population will present significant AD neuropathology, namely accumulation of Aβ plaques and phosphorylated tau tangles, without exhibiting cognitive decline and are therefore cognitively resilient. The effect of neuropathology on neurons varies by region and neuronal subtypes with specific neuronal subpopulation showing greater degree of vulnerability. We therefore hypothesize that resilience to AD pathology is conferred through reduced vulnerability of selective excitatory neurons subpopulation in the hippocampus. To assess differences in vulnerable cell populations between resilient and susceptible population, we utilized a large single-nucleus RNA-sequencing dataset generated from hippocampal samples from the AD-BXDs, a genetically diverse mouse population carrying familial AD mutations (5XFAD), and their non-transgenic littermates (Ntg-BXD). Data was generated for 14 AD-BXD and Ntg-BXD strains, representing 7 resilient and 7 susceptible strains defined based on their contextual memory acquisition at 6 and 14 months of age. We identified 21 excitatory neurons (Slc17a7 positive nuclei) corresponding to specific anatomical regions of the hippocampus, including each of the Cornu Ammonis subregions (CA1-3) and dentate gyrus (DG), as well as the subiculum and the entorhinal cortex (ENT). At the whole-cluster level, no differences in cell composition were detected between AD-BXDs and Ntg-BXDs or resilient and susceptible AD-BXD strains. Differential expression between resilient and susceptible strains carrying the 5XFAD mutation was observed primarily in the CA1, DG, and ENT. To determine cellular vulnerability across nuclei, we assessed the relationship between summarized score of pathways enriched for resilience-associated differentially expressed genes and resilience status. We found that nuclei with greater proteolysis, improved protein folding response, greater DNA repair and higher ribosomal gene expression are more likely to be resilient. In contrast cells with greater expression of genes involved in lipid metabolisms were more likely to be susceptible. Taken together, our findings suggest that cognitive resilience may be driven by resistance of excitatory neurons to stressors induced by AD neuropathology and offer insights into the molecular events underlying neuronal vulnerability in AD.

Poster #6 (E. Ramirez et al.)

Beyond Reward: The Role of GABAergic Ventral Pallidum Neurons in Aversive Motivation

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The ventral pallidum (VP) is a basal ganglia structure with a key role in motivated behavior and reward. Early work showed an important role for VP in food intake, “liking” of rewarding tastes, conditioned cue responses, and motivated responding for natural and addictive drug rewards. Recent work shows that VP contains at least 2 functionally distinct neuronal subpopulations, GABAergic and glutamatergic. In mice tested in simple behavioral situations, VP^{GABA} neurons seem to mediate reward seeking and approach, while $VP^{Glutamate}$ neurons instead seem to mediate aversion and withdrawal. Our recent work finds that VP^{GABA} neurons in rats also play a key role in appetitive motivation across more complex behavioral situations, including motivated decision-making tasks (Farrell et. al. 2021). However, we also found in this report some tantalizing, but inconclusive evidence for a role for VP^{GABA} neurons in motivated behavior to avoid a punisher, instead of to receive a reward. Here we followed up this finding using complementary behavioral tasks of aversive motivational states, in pursuit of understanding better the exact circumstances in which VP^{GABA} neurons are required for adaptive behavior.

We bilaterally injected a Cre-dependent inhibitory DREADD (hM4Di) vector into the VP of adult male and female GAD:Cre transgenic Long Evans rats, and control rats had no VP DREADDs. We then examined effects of inhibiting VP^{GABA} neurons prior to 1) exposure to a Pavlovian cue which was previously paired with footshock, and which elicits freezing responses, or 2) exposure to a metal probe which previously delivered shock when it was touched, which elicits defensive forepaw treading responses. These behaviors were chosen since they both involve shock punishment and require memory of a previously learned association, but they differ in other characteristics (active versus passive threat response; localizability of the threat, etc) that may help inform the role of VP^{GABA} neurons in these processes, if any.

In a within-subjects design, counterbalanced CNO and vehicle injections preceded tests of the expression of previously-learned fear memories. For Pavlovian fear conditioning, we paired tone cues with one of two different shock intensities (low shock, 0.3 mA or high shock, 0.75 mA), and inhibited VP^{GABA} neurons while the tone was played 24 times in the absence of additional shock (extinction conditions). Fear conditioning and extinction videos were manually scored for measures of freezing, locomotion, sniffing, grooming, rearing, and escape attempts. For the defensive burying task, responses to unelectrified probes that previously delivered 1.5mA shock were measured, with manual scoring of probe investigations and defensive treading/digging of bedding material, as well as bedding pile dimensions. Results presented in this poster will bring insight to the less-understood role of VP^{GABA} neurons in response to different types of fear-eliciting stimuli.

Poster #7 (B. Noarbe et al.)

Diffusion Tensor Tractography Reveals Changes Along the Caingulum Following Early Life Adversity

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The cingulum bundle is a multi-segmented large white matter tract that connects a wide variety of limbic regions. Diffusion magnetic resonance imaging (dMRI) has reported decreased fractional anisotropy (FA) and increased mean diffusivity (MD) within the cingulum of individuals exhibiting a variety of pyschopathologies (schizophrenia, depression, post-traumatic stress disorder, etc). In adult male and female mice exposed to early life adversity, we examined if the cingulum bundle is altered using non-invasive MRI derived metrics (volumes, T2-relaxation, dMRI) and whether differences can be associated with behavioral changes. C57BL/6J mice were either assigned limited bedding and nesting (LBN) or normal bedding conditions from postnatal day (PND) 2-9 (n = 13/21 control/LBN males [5 litters], n = 10/7 control/LBN females [3 litters]). In young adulthood (PND 94-161), the mice underwent *ex vivo* MRI (9.4T) volumetric and high-resolution dMRI (5 b0, 30 directions, b=3000mm^2/sec). Regional tissue features were extracted from FA, MD, axial diffusivity (AxD), and radial diffusivity (RD) parametric maps. Tractography within the cingulum was performed based on the Australian Mouse Brain Mapping Consortium (AMBMC) atlas. T2 relaxation times and regional volumes were extracted from anatomical T2-weighted images (repetition time=4000ms, echo time=10ms). Social behavior was quantified using the 3-chambered social interaction test. The cingulum in LBN males (but not females) reported decreased FA relative to controls. Additional DTI metrics were assessed to probe microstructural integrity of the cingulum bundle. We observed a robust correlation between FA and RD, FA and MD, but not for AxD. Reconstruction of tracts within the cingulum revealed elevated FA and AxD in control males compared to LBN males. In the 3-chambered social interaction test, LBN males spent significantly less time with the peer and the object. The amount of time spent with peer and object was positively correlated with AxD within the cingulum. In conclusion, the cingulum exhibited male-specific changes in volume following early life adversity. Male LBN mice had decreased FA in the cingulum compared to controls. Our negative correlations between FA and RD/MD (but not AxD) and tractography analysis reveal that a larger cingulum fiber bundle would have no overt change in fiber number. These modifications to the cingulum bundle in the brain of LBN mice following early life adversity may have significant effects on social behavior in adulthood.

Poster #8 (A. Davidson et al.)

Arginine-Vasopressin Expressing Neurons in the Murine Suprachiasmatic Nucleus Exhibit a Circadian Rhythm in Network Coherence *In Vivo*

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The Suprachiasmatic Nucleus (SCN) is composed of functionally distinct sub-populations of GABAergic neurons which form a neural network responsible for synchronizing most physiological and behavioral circadian rhythms in mammals. To date, little is known regarding which aspects of SCN rhythmicity are generated by individual SCN neurons, and which aspects result from neuronal interaction within a network. Here, we utilize *in vivo* miniaturized microscopy to measure fluorescent GCaMP-reported calcium dynamics in AVP-expressing neurons in the intact SCN of awake, behaving mice. We report that SCN AVP neurons exhibit periodic, slow calcium waves which we demonstrate, using *in vivo* electrical recordings, likely reflect burst-firing. Further, we observe substantial heterogeneity of function in that AVP neurons exhibit unstable rhythms, and relatively weak rhythmicity at the population level. Network analysis reveals that correlated cellular behavior, or coherence, among neuron pairs also exhibited stochastic rhythms with about 25% of pairs rhythmic at any time. Unlike single-cell variables, coherence exhibited a strong rhythm at the population level with time of maximal coherence among AVP neuronal pairs at CT/ZT 6 and 9, coinciding with the timing of maximal neuronal activity for the SCN as a whole. These results demonstrate robust circadian variation in the coordination between stochastically rhythmic neurons and that interactions between AVP neurons in the SCN may be more influential than single-cell activity in the regulation of circadian rhythms. Furthermore, they demonstrate that cells in this circuit, like those in many other circuits imaged *in vivo*, exhibit profound heterogenicity of function over time and space.

Poster #9 (L. Weiss et al.)

Comparison of AAVmyo and MyoAAV as promising vectors to deliver gene therapy in the VCP ^{R155H} KI mouse model

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Background and Objective

Pathogenic variants in Valosin Containing Protein (*VCP*) gene cause a unique autosomal dominant disease characterized by inclusion body myopathy, Paget disease of bone and frontotemporal dementia (also known as multisystem proteinopathy (MSP). *VCP* pathogenic variants lead to hyperactive enzymatic activity, suggesting a gain-of-function. Concomitantly, overexpression of *VCP* pathogenic variants in cells dominantly interfere with autophagy and endolysosomal sorting. To ameliorate the gain-of-toxicity of VCP mutant proteins, an ideal approach is to silence the mutant gene in an allele-specific manner and to leave the wildtype allele intact. We therefore propose to silence VCP with strategies such as microRNA, antisense oligonucleotides and CRISPR technology. A limitation, however, is obtaining sufficient expression in muscle to target the VCP mutant allele. Recently AAVmyo and MyoAAV have emerged as promising vectors to deliver gene targeting strategies to muscle tissue. We have performed studies in the VCP KI mouse model to study the efficacy and immunological response to these vectors as a means to deliver gene modifying strategies in muscle.

Methods

To determine the tropism of the viral vectors through systemic injection, we used C57BL/6 WT and VCP R155H/+ mice at age 6–8-week-old to deliver a single dose of 1×10^{12} and 4×10^{12} vector genomes (vg) of either AAVmyo-CAG-EGFP, MyoAAV4A-pAM-CAG-TdTomato, or AAV9-CAG-EGFP by retro-orbital injection. After 3 weeks of regular monitoring for viability and signs of toxicity, the mice were sacrificed. All muscle groups in addition to multiple organs were harvested and analyzed to detect GFP expression to determine muscle tropism. Serum was collected to examine markers of liver, renal and muscle toxicity. A recall antigen assay using splenocytes was performed to assess the development of AAV immunity in mice immunized with 1×10^{12} vg of MyoAAV4A-pAM-CAG-TdTomato.

Results

GFP expression was significantly higher in both doses of AAVmyo and MyoAAV compared to AAV9 in various muscle groups. Further, we observed the induction of MyoAAV4A-specific T cells that produced IFN-gamma and upregulated CD44 in WT and R155H/+ VCP mice. However, there was no remarkable signs of inflammation of myofibers in H&E staining. Our preliminary studies indicated better muscle tropism and less tropism for the liver with MyoAAV deeming it safer and muscle specific. We plan to combine our gene modifying strategies with MyoAAV for future studies in the mutant mice to study the effect on muscle pathology and function.

Discussion

Preliminary results show that using MyoAAV is a promising approach to deliver gene therapy to muscle tissue -a most challenging tissue to target. Caution should be exercised as AAV in this setting is immunogenic. Therefore, transient immunosuppression may be required to prevent immune-mediated toxicity. This leads to an exciting next step of targeting the mutant VCP allele and if needed replacing with WT VCP in the mouse model. If successful, this strategy has great translational potential in correcting disease pathology in VCP and other autosomal dominant disorders.

Poster #10 (Q. Ye et al.)

Hippocampal neural circuit connectivity alterations in an Alzheimer's disease mouse model revealed by monosynaptic rabies virus tracing

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder with growing major health impacts, particularly in countries with aging populations. The examination of neural circuit mechanisms in AD mouse models is a recent focus for identifying new AD treatment strategies. We hypothesize that age-progressive changes of both long-range and local hippocampal neural circuit connectivity occur in AD. Recent advancements in viral-genetic technologies provide new opportunities for semi-quantitative mapping of cell-type-specific neural circuit connections in AD mouse models. We applied a recently developed monosynaptic rabies tracing method to hippocampal neural circuit mapping studies in AD model mice to determine how local and global circuit connectivity to hippocampal CA1 excitatory neurons may be altered in the single *APP* knock-in (APP-KI) AD mouse model. To determine age-related AD progression, we measured circuit connectivity in age-matched littermate control and AD model mice at two different ages (3–4 vs. 10–11 months old). We quantitatively mapped the connectivity strengths of neural circuit inputs to hippocampal CA1 excitatory neurons from brain regions including hippocampal subregions, medial septum, subiculum and entorhinal cortex, comparing different age groups and genotypes. We focused on hippocampal CA1 because of its clear relationship with learning and memory and that the hippocampal formation shows clear neuropathological changes in human AD. Our results reveal alterations in circuit connectivity of hippocampal CA1 in AD model mice. Overall, we find weaker extrinsic CA1 input connectivity strengths in AD model mice compared with control mice, including sex differences of reduced subiculum to CA1 inputs in aged female AD mice compared with aged male AD mice. Unexpectedly, we find a connectivity pattern shift with an increased proportion of inputs from the CA3 region to CA1 excitatory neurons when comparing young and old AD model mice, as well as old wild-type mice and old AD model mice. These unexpected shifts in CA3-CA1 input proportions in this AD mouse model suggest the possibility that compensatory circuit increases may occur in response to connectivity losses in other parts of the hippocampal circuits. We expect that this work provides new insights into the neural circuit mechanisms of AD pathogenesis.

Poster #11 (P. Gao et al.)

Immunolabeling-compatible PEGASOS tissue clearing for high-resolution whole mouse brain imaging

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Due to the inherent 3D structure of molecules, cells and tissues, improving high-throughput approaches for visualizing the intact biological samples is critical. Tissue clearing, by reducing the refractive index (RI) difference between different components of the tissue, enables opaque tissue to appear transparent. Combined with volumetric imaging by a Light-sheet microscope, new tissue technologies help to fully capture the spatial distribution and anatomical features of neural circuits in the intact samples. The Polyethylene glycol-associated solvent system (PEGASOS) described in 2018 is an organic solvent-based clearing method and renders superior transparency in nearly all types of tissue rapidly (Jing et al., 2021). Here, we report a whole-mount immunostaining compatible version of PEGASOS (iPEGASOS), which can restore and enhance endogenous fluorescent signals being quenched during clearing or immunolabeling processes. Our applications of iPEGASOS are extended from whole adult mouse brains with transgenic reporter expression, viral labels and Alzheimer's disease pathologies to large monkey brain samples with immunostaining. We further show large brain-wide neural circuit mapping can be achieved in the 3D, intact samples. We foresee that our new techniques have broad applications in large-scale neural circuit mapping.

Jing, D., Men, Y., & Zhao, H. (2021). Tissue Clearing and 3-D Visualization of Vasculature with the PEGASOS Method. In *Methods in Molecular Biology* (Vol. 2319, pp. 1–13). Humana Press Inc. https://doi.org/10.1007/978-1-0716-1480-8_1

Poster #12 (K Krishnan et al.)

Age- and cell-type specific compensatory expression of epigenetic regulator MECP2 is associated with regression phenotype in female mouse model for Rett syndrome

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Rett syndrome is diagnosed as a neurodevelopmental disorder, characterized by an early period of typical development and then, regression of learned motor and speech skills in girls. Due to lack of well-characterized model systems to phenocopy regression, the underlying mechanisms from normalcy to regression are unclear. The prevailing ideas are that functional MECP2 protein is not essential before regression period, and that loss of MECP2 expression is the major driver for Rett syndrome phenotypes. Due to random X-chromosome inactivation, female patients of Rett syndrome, and female mouse models of Rett syndrome (*Mecp2*^{Heterozygous}, Het) express a functional copy of wild-type MECP2 protein in half of all mature cells in brain and body. As much work in the field has focused on the MECP2-deficiency component, we focused our attention on the wild type expression of MECP2 in the female Het pre-symptomatically at 6 weeks of age, and post-symptomatically, at 12 weeks of age. We use whole brain registration and image analysis for cellular characterization, frame-by-frame DataVyu analysis for whisker sensory perception and DeepLabCut for pose estimation during pup retrieval. Intriguingly, we found a compensatory increase in wild-type MECP2 expression in non-Parvalbumin+ GABAergic neurons of the primary somatosensory cortex in 6-week-old Het, which was not maintained in the 12-week-old Het. This MECP2 expression phenotype is concomitant with typical synaptic plasticity (as measured by perineuronal nets, extracellular matrix structures), mild simple tactile sensory perception and efficient complex pup retrieval behavior. Comparatively, 12-week-old adult Het mice display overt tactile sensory perception and inefficient pup retrieval phenotypes. Thus, we have identified a period of normalcy and regression in the apt female mouse model for Rett syndrome. We hypothesize that compensatory increases in wild-type MECP2 expression in Het allows for normal functioning at an early age, while the inability to maintain this increased expression level changes leads to observed stereotypic Rett syndrome phenotypes. We speculate such compensatory mechanisms at the protein level to play crucial roles in other X-linked disorders. Ongoing work involves incorporating novel tools to identify relevant circuits and protein regulation mechanisms across ages, with cell type-specificity.

Poster #13 (X. Lin et al.)

Projection-Specific Retrosplenial Cortex Circuits and The Transformation of Spatial Cognition to Action

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Retrosplenial cortex (RSC) plays a key role in the neural coding of location and orientation relative to environment boundaries as well as left/right tunning actions within path networks. RSC is anatomically interconnected with multiple cortical and subcortical brain regions, including sensory cortices, the hippocampal/parahippocampal formation, and the anterior thalamus. Prior work has suggested that the encoded spatial information from the hippocampal formation integrates with RSC and then is transformed into the action-related secondary motor cortex. However, neural circuit mechanisms for the transformation of spatial information into planned action through pathway-specific circuitry remain largely undefined. To address this, we used Cre-dependent retrograde monosynaptic rabies virus and adenovirus mapped and compared circuit input connections of layer-specific RSC excitatory neurons, M2-projecting, anterior thalamus-projecting, and postsubiculum-projecting RSC neurons in micebrains. We find that there are significantly stronger inputs from the subiculum, visual cortex, somatosensory cortex, auditory cortex, and thalamus to M2-projecting RSG neurons while AD-projecting RSC neurons receive stronger inputs from the cingulate cortex, motor cortex, and media septal nucleus.Based on this study, result/As a result, we developed a spatial place-based cross-maze task that required mice to make left/right choices depending on where they were located in the room. We find that genetic inactivation of the projection of RSG to M2 impairs the accuracy of space-based L/R turn decision-making. These results provide an anatomical circuit basis to understand RSG neurophysiological function and its role in the transformation of spatial cognition to action planning.

Poster #14 (M. Garduño et al.)

Cognitively Impaired Aged Octodon degus Recapitulate Major Neuropathological Features of Sporadic Alzheimer's Disease

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The long-lived Chilean rodent (*Octodon degus*) has been reported to show spontaneous age-dependent neuropathology and cognitive impairments similar to those observed in human AD. However, the handful of published papers on degus of differing genetic backgrounds yield inconsistent findings about sporadic AD-like pathological features, with notably differing results between lab in-bred degus versus wild caught degus. This motivates more extensive characterization of spontaneously occurring AD-like pathology and behavior in degus. In the present study, we show higher levels of AD-like neuropathological markers in the form of amyloid deposits and tau abnormalities in a cognitively impaired subset of aged wild caught degus. Compared to the aged degus that show normal burrowing behavior, the age-matched degus with burrowing behavior deficits correlatively exhibit more detectable human AD-like Aβ deposits and tau neuropathology, along with neuroinflammatory markers that include enhanced microglial activation and higher numbers of reactive astrocytes in the brain. This subset of cognitively impaired aged degus also exhibit cerebral amyloid angiopathy and tauopathy. We find robust neurodegenerative features in behaviorally deficient aged degus, including hippocampal neuronal loss, altered parvalbumin and perineuronal net staining in the cortex, and increased c-Fos neuronal activation in the cortex that is consistent with the neural circuit hyperactivity reported in human AD patients. By focusing on the subset of aged degus that show AD-like behavioral deficits and correlative neuropathology, our findings establish wild caught degus as a natural model of sporadic AD and demonstrate the potential importance of wild-type outbred genetic backgrounds for AD pathogenesis.

Poster #15 (Y. Sun et al.)

Neural circuit dynamics of drug-context associative learning in the hippocampus

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The environmental context associated with previous drug consumption is a potent trigger for drug relapse. However, the mechanism by which neural representations of context are modified to incorporate information associated with drugs of abuse remains unknown. Using longitudinal calcium imaging in freely behaving mice, we find that unlike the associative learning of natural reward, drug-context associations for psychostimulants and opioids are encoded in a specific subset of hippocampal neurons. After drug conditioning, these neurons weakened their spatial coding for the non-drug paired context, resulting in an orthogonal representation for the drug versus non-drug context that was predictive of drug-seeking behavior. Furthermore, these neurons were selected based on drug-spatial experience and were exclusively tuned to animals' allocentric position. Together, this work reveals how drugs of abuse alter the hippocampal circuit to encode drug-context associations and points to the possibility of targeting drug-associated memory in the hippocampus.

Poster #16 (L. Chen et al.)

Hippocampal neural ensemble representations of spatial mapping in freely behaving mice

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An emerging theory about neuronal organization of hippocampus CA1 area is that CA1 pyramidal neurons may formulate parallel cell assemblies that simultaneously processing different types of memories (Soltesz & Losonczy, 2018). However, studies about the functional and anatomical profiles of these potential organization scheme are still inconclusive. In the present study, we address spatiotemporal ensemble representations in hippocampal CA1 during behavior tasks through in vivo Ca++ imaging using head-mounted miniature microscopes and divide the neural activity into specific activation groups that share similar calcium event patterns in the temporal domain. Interestingly, when correlating the identity of these “temporal clusters” to the anatomical location of neurons, neurons in the same "temporal cluster" are locally concentrated and form anatomical clusters to a degree well beyond chance. At the same time, these temporal clusters are dynamic across time and between different environments. Between different periods of a single trial, the neuron composition of temporal clusters evolves somewhat with time. Across days and environments, temporal and anatomical clustering is more dynamic, but with significant overlap for the same shaped environments. We believe that this representational topography in hippocampal sub-region CA1 reveals a previously less discussed in temporal and spatial dynamics according to neuron groupings in anatomical space

Soltesz, I., & Losonczy, A. (2018). CA1 pyramidal cell diversity enabling parallel information processing in the hippocampus. *Nature Neuroscience, 21*(4), 484-493. doi:10.1038/s41593-018-0118-0

Poster #17 (H. Zhang et al.)

Degenerate Mapping of Environmenatal Location Presages Deficits in Object-Location Encoding and Memory in the 5xFAD Mouse Model for Alzheimer's Disease

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In Alzheimer's disease (AD) patients, neuropathology appears to precede measurable cognitive impairments by years or even decades, thus a key challenge in developing diagnosis and treatments for AD is to detect disease at as early a stage as possible. Recent studies indicate abnormal neural circuit activity underlies the pathophysiology of AD, suggesting measurement of circuit activity could be useful in early detecting of AD. To provide evidence of the temporal relationship between pathology, abnormal circuit activity and memory deficits, it is important to longitudinally assess how these abnormal functions develop in AD model. Briefly, we expressed calcium indicator GCaMP6 in the CA1 pyramidal neurons in wild type and 5XFAD mice model to monitor neuronal activity when mice performing spatial navigation and spatial memory tasks, including object location memory, open field and linear track. We examined amyloid pathology, object location memory, and spatial representation of CA1 place cells in the spatial environments across 4-14 months of age. We find that pathology and abnormal circuit activity appear at very early stages by 4-month-old in 5xFAD mice, including accumulation of amyloid plaques, suppressed hippocampal CA1 neuron calcium activity especially during immobile stages of open field exploring, and unreliable hippocampal neuron spatial tuning to environmental location. This is followed by progressive degradation in spatial representation and impaired encoding of object locations. By 8 months of age, such progressive degeneration is accompanied by memory deficits in 5xFAD mice, indicating abnormal circuit activity detected at early stages before the emergence of memory deficits. In conclusion, our results indicate that measurement of spatial representation and baseline firing rates in hippocampal neurons represent key opportunities to detect AD related abnormalities at very early stages before measurable memory deficits. Our findings also highlight the close connection between hippocampal tuning to object locations and memory deficits. This suggests that functional imaging of neural circuit deficits in human AD may eventually allow for early detection and intervention.

Poster #18 (A. Bouin et al.)

A comprehensive array of novel rabies virus vectors for multi-scale neural circuit mapping

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New viral genetic tools are critical for improving anatomical mapping and functional studies of cell-type-specific and circuit-specific neural networks in the intact brain. The goal of our work is to develop new and improved viral tools that can be used for a broad range of applications and to make them widely available to the neuroscience field. Using the genome of the rabies vaccine strain, SAD B19, we developed multiple recombinant rabies viruses (RABV) that encode bright fluorescent proteins along with subcellular localization signals that replace the viral glycoprotein (G) as well as RABV vectors expressing ferritin light chain to extend the imaging range further to electron microscopy micro-imaging and to MRI macro-imaging. These engineered viruses cannot spread from initially infected cells, as they do not encode the rabies glycoprotein and thus can be safely used under BSL2 conditions. To propagate these modified viruses, they are cultured in cell lines stably expressing the viral glycoprotein.

We have generated a series of novel spectrally distinguishable recombinant RABV that express blue (EBFP), teal (mTFP1), turquoise (mTurquoise2), green (mNeonGreen), red (tdTomato), and far-red (smURFP) reporters. Among the fluorescent reporters, mNeonGreen and tdTomato are brighter, longer-lasting than others previously described, and they do not quench as easily compared to traditional GFP and RFP (DsRed and mCherry). We also engineered a range of reporters that localize to different sub-cellular compartments, including the cytoplasm, nucleus, cellular membranes, mitochondria, somatodendritic, and pre- and post-synaptic locations.

We used *in vitro* cell culture assays to assess the fluorescence and localization of the reporters in B7GG cells and produced viral stocks. To determine if our modified recombinant rabies viruses perform as they were designed, C57BL/6J mice were injected with recombinant RABV intracranially. At eight days post-injection, mice were perfused and brains were collected and prepared for imaging. A bright and localization-specific fluorescent signal was detected in infected neurons, allowing for sensitive and precise monosynaptic tracing.

Recombinant RABV expressing eGFP and ferritin were injected in mice. Fluorescent signal was readily observable using fluorescent microscopy. Using a correlated light, X-ray, and electron microscopy workflow (CLXEM), we were able to detect ferritin aggregates scattered within axons and synaptic termini, as well as higher density near mitochondria of presynaptic boutons. In each case, electron-dense ferritin particles are easily distinguishable, and axons with ferritin label are readily identified as distinct from the other non-infected axons as well. Our rabies viral vectors encoding ferritin and EGFP also produce strong and unambiguous MRI signals at and around viral expression sites. This was clearly demonstrated in MRI images taken from the horizontal, sagittal and coronal planes as MRI.

In summary, our newly developed recombinant RABVs offer a range of sub-cellular targeted reporters that facilitate a wide repertoire of cell-type specific and circuit specific mapping studies that are amenable to automated computer analysis. The recombinant RABV expressing ferritin allow a detection from micro- to macro-imaging using electron microscopy as well as MRI. Ongoing studies are aimed at attenuating viral toxicity *in vivo*.

Poster #19 (K. Johnson et al.)

scGradient: a Neural Network Model for Detection of Transcriptional Gradients in Neurons

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Recent studies investigating the effects of transcriptome on the electrophysiological and morphological properties of neurons indicate that subtle variations in gene expression can induce significant variations in signaling properties within an individual cell type. Many neuron cell types exhibit continuous variation of gene expression along spatial and transcriptomic gradients. While previously, cell type clustering has been used to identify neuronal subtypes, this causes information loss, as the continuous nature of the cell type is lost. Here, we introduce scGradient, a machine learning method for identification of transcriptional gradients within and between cell types. We demonstrate that scGradient detects known gene expression gradients in the cortex, and then demonstrate the method's usefulness in detection of novel transcriptional gradients in interneurons and other neuronal cell types. We demonstrate that these transcriptional gradients induce electrophysiological variations within cell types, and suggest a method for viewing neurons on a continuum identified by scGradient. This enables visualization of the primary expression axes for each celltype, improving interpretability over alternative methods, and demonstrating the variation between cell types without requiring hard clustering methods.

Poster #20 (O. Koyuncu et al.)

Adeno associated virus mediated neuronal expression of Herpes simplex virus type-1 VP16 protein induces Pseudorabies virus escape from silencing and reactivation by activating Jun

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Alpha herpesvirus (α-HV) particles enter their hosts from mucosal surfaces and efficiently maintain fast transport in peripheral nervous system (PNS) axons to establish infections in the peripheral ganglia. We have established a well-controlled, reproducible and reactivateable latency system using Pseudorabies virus (PRV) in compartmented rodent neurons by infecting isolated axons with a small number of viral particles. This system not only recapitulates the physiological infection route, but also facilitates treatment of isolated cell bodies or axons separately and enables study of not only the stimuli that promote reactivation, but also the factors that regulate the initial switch from latent to productive infection. We have previously showed that activation of protein kinase A or presence of tegument proteins in neuronal cell bodies induce escape from silencing on axonally entering PRV genomes via distinct mechanisms. Here, we tested whether expression of Herpes simplex virus-1 (HSV-1) or PRV encoded trans-activator tegument protein, VP16 is sufficient to induce such escape on PRV genomes. Interestingly, adeno associated virus (AAV)-mediated expression of HSV-VP16 alone in neuronal cell bodies enabled incoming PRV genomes escape from silencing. Furthermore, HSV-VP16 expression was able to reactivate latent PRV infection in this system. Surprisingly, expression of PRV-VP16 protein supported neither PRV escape from silencing nor reactivation. We compared transactivation profile of both viral proteins in primary neurons by RNA sequencing and found that while both proteins induced cAMP-responsive element modulator (CREM) expression, HSV-VP16 specifically induced expression of proto-oncogenes including Jun, Pim2 and Rras. We further showed that HSV-VP16 induces phosphorylation of Jun in neurons, and when this activity is inhibited, escape of PRV silencing is dramatically reduced.

Poster #21 (S. Grieco et al.)

Parvalbumin-cholecystokinin co-expressing interneurons and their implications in neuropsychiatric disorders

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Inhibitory interneurons are crucial to brain function; their dysfunction results in psychiatric disorders such as schizophrenia. Emerging evidence indicates that cholecystokinin (CCK)-expressing interneurons (CCK+) are highly heterogenous. We find that a large subset of parvalbumin-expressing (PV+) interneurons express CCK strongly; nearly 50% of PV+ interneurons express CCK in mouse hippocampal CA1. Monkey hippocampal interneurons also exhibit substantial PV+/CCK+ co-expression. Mouse PV+/CCK+ and PV+/CCK- cells show distinguishable electrophysiological and transcriptomic features. Of note, the overall action potential hyperpolarization of PV+/CCK- cells is significantly larger than that of PV+/CCK+ cells. Transcriptomic analyses show that PV+/CCK+ are a subset of PV+ cells, not of synuclein gamma positive (SNCG) cells. We also find both at the transcriptomic and protein level that cytochrome c oxidase subunit 6A2 (COX6A2, a mitochondrial complex IV gene implicated in a subset of schizophrenia with mitochondrial dysfunction and known to be expressed in PV+ interneurons), is strongly expressed by PV+/CCK+, but not PV+/CCK- cells. Selective functional inactivation of mouse PV+/CCK+ interneurons in CA1 impairs memory performance for both the object-location memory task and the fear memory renewal paradigm. These data reveal a novel class of interneurons co-expressing PV and CCK and reveal their functional implications in psychiatric diseases including schizophrenia and anxiety disorders.

Poster #22 (A. Keiser et al.)

Exercise parameters that open a 'molecular memory window' for cognitive enhancement shine light on key memory mechanism in the adult, aging, and Alzheimer's Disease brain

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The ability to learn, consolidate and retrieve information is critical for everyday survival and this ability begins to decline with normal aging and is severely exacerbated by Alzheimer's Disease (AD). Basic research and clinical trials have universally demonstrated the benefits of exercise for cognitive function including enhancements in long-term memory formation and synaptic plasticity in addition to alleviating cognitive impairments associated with normal aging and AD, however, the mechanism by which exercise leads to cognitive enhancement is unclear. Here, we apply exercise as an approach to unlock a novel understanding of the molecular mechanisms that drive memory consolidation by utilizing specific exercise parameters that enhance cognitive benefits. Employing an intermittent exercise protocol, we demonstrate that 14 days of voluntary wheel-running facilitates hippocampus-dependent memory and synaptic plasticity in adult mice, effects which can be maintained and re-engaged with brief 2-day re-introduction to exercise following a sedentary delay. To identify novel mechanisms that drive memory consolidation, we utilized an unbiased RNA-sequencing approach to uncover genes in the dorsal hippocampus that are differentially expressed under conditions where exercise benefits are maintained throughout sedentary delay periods and enable the formation of long-term memory and synaptic plasticity. We identify a gene coding for a type 1 receptor for the TGF-β family of signaling molecules, *Acvr1c* as one of few genes (including *Bdnf*) showing up-regulation in the hippocampus under exercise conditions that enable the formation of long-term memory and synaptic plasticity. Utilizing viral manipulations in the adult hippocampus to disrupt and over-express *Acvr1c*, we identify *Acvr1c* as a key bi-directional regulator of hippocampus-dependent long-term memory and synaptic plasticity. We find *Acvr1c* levels decrease in the hippocampus with age in C57Bl/6J and 5xFAD female and male mice and demonstrate that *Acvr1c* over-expression ameliorates age and AD-associated impairments in memory and synaptic plasticity. These data suggest that promoting ACVR1C through exercise or pharmacological intervention may protect against age and AD-associated cognitive impairment, providing a potentially powerful and novel disease modifying treatment strategy for AD.

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Acknowledgments

The UCI Center for Neural Circuit Mapping would like to give many thanks to all the people who have made this conference a reality. The Center itself has seen a tremendous amount of growth this year through new collaborations.

I wanted to thank our cooperate sponsors, AaaverGene and Vizgen, who's financial contribution made this conference possible.

I would like to thank the UCI School of Medicine, especially Dean Stamos and the Dean's Office for their support for our Center.

We would like to acknowledge the special administrative support from Rachel Pearlman at the Dean's Office. We would also like to express much gratitude to UCI School of Medicine marketing team, especially Jessica Banfield for creating all the beautiful programing items our cover image and Anne Warde for her guidance.

We would also like to thank the Anatomy and Neurobiology Department, especially Lesley Dowd and Laura Ng.

We also would like to give a huge thank-you to The Beckman Center, especially Katrina Vera De Castro for her critical assistance.

Lastly, we would like to recognize the staff behind the scenes especially the newly departed Nicole Ha (good luck in Grad school), Michele Wu, and Ginny Wu for their countless hours of hard work.

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