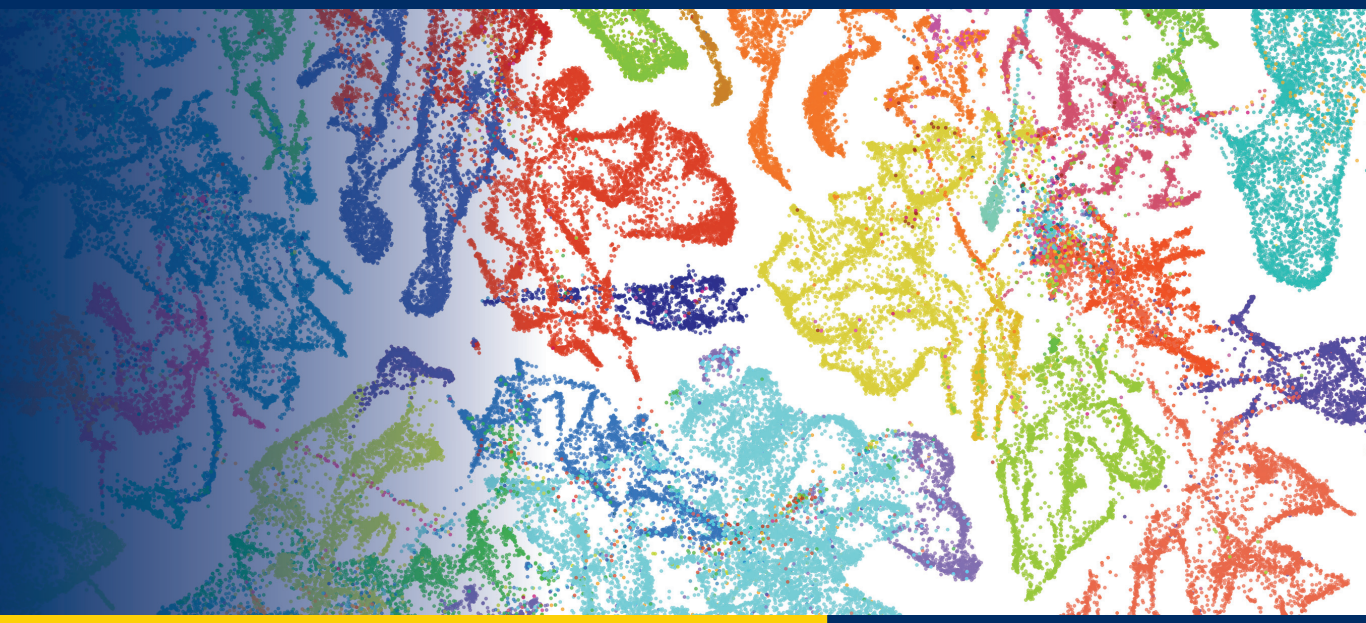
UCI Center for Neural Circuit Mapping | Cajal Club | ALLEN INSTITUTE for BRAIN SCIENCE



2023 CONFERENCE

Structure, Function and Development of Neural Circuits

August 21 – 23

7:30 a.m. - 5:00 p.m. PT

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

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On behalf of the Organizing Committee, I welcome you all to the CNCM 2023 Conference on "Structure, Function and Development of Neural Circuits". This is the third conference hosted by the Center for Neural Circuit Mapping (CNCM) at UC Irvine under the direction of Dr. Xiangmin Xu, following the success of the first two conferences held in 2021 and 2022. This year's conference is co-sponsored by CNCM, the Cajal Club, and the Allen Institute for Brain Science.

The first CNCM neural circuit conference was held in August 2021, with a hugely successful first in-person meeting, "Relationship Between Transcriptomics and Connectomics", jointly sponsored by the Center and the Cajal Club. For most of the conference attendees, that was their first in person scientific meeting that they attended after the start of the COVID pandemic. Taking advantage of a relative lull in the pandemic, the CNCM staff meticulously implemented a carefully designed, strict COVID prevention process that ensured an interactive and safe meeting environment. The second conference, "Linking Brain function to Cell Types and Circuits", held in August 2022, continued the theme of multilevel investigation of brain function from genes to cell types and circuits, and to behaviors and diseases. This year, we are extremely excited to host another front-of-the-field conference with many thought leaders who will bring unique perspectives to the theme of integrating the different facets of neural circuits – structure, function, development and disease.

I'm thrilled to work alongside my fellow Cajal Club Board members, Drs. Leah Krubitzer (current President of the Cajal Club) and John Rubenstein in co-organizing this conference and to continue the Cajal Club's legacy of pushing the frontier of neuroanatomy. I also acknowledge the inimitable Dr. Charles Ribak (Cajal Club's Secretary-Treasurer) for facilitating the meeting.

The organizers are deeply grateful to the superb group of speakers who have agreed to present their work and insights at our 2023 conference. We are especially excited about the joining of multiple international speakers, elevating our conference to the international level. Finally, we are greatly honored to announce this year's P. J. Harman Lecturer of the Cajal Club, Dr. Tirin Moore from Stanford University.

We thank the staff of CNCM and of the Beckman Center of the National Academies of Sciences and Engineering for their attention to detail and logistic support. Thank you all for coming to our Conference and we look forward to stimulating interactions and brainstorming throughout the course of the meeting.

Sincerely,

Hongkui Zeng, Ph.D.

Executive Vice President and Director, Allen Institute for Brain Science

Conference Organizers

Hongkui Zeng, PhD
Executive Vice President,
Director of the Allen Institute
for Brain Science

Leah Krubitzer, PhD
Distinguished Professor,
Psychology,
Center for Neuroscience,
University of California, Davis

John Rubenstein, MD, PhD
Professor, Psychiatry,
School of Medicine
Weill Institute for Neurosciences,
University of California,
San Francisco

Xiangmin Xu, PhD
Director, UCI Center for Neural Circuit Mapping
Professor, Department of Anatomy & Neurobiology
School of Medicine, University of California, Irvine

2023 Conference Schedule

Co-sponsors:
The Cajal Club, the Allen Institute for Brain Science, and
the UCI Center for Neural Circuit Mapping
Conference Venue:
The Beckman Center of the National Academies of Sciences & Engineering near the UCI campus
Organizing Committee:
Hongkui Zeng (Allen Institute), Leah Krubitzer (UC Davis),
John Rubenstein (UC San Francisco), Xiangmin Xu (UCI)
External Advisory Board:
Edward Callaway (Salk), Liqun Luo (HHMI/Stanford U.),
Hongkui Zeng (Allen Institute), Bing Ren (UC San Diego)

Day 1 - Monday, August 21

7:30 - 8:15 a.m.	Continental Breakfast
8:15 - 8:30 a.m.	Welcome & Introduction

Session 1: Cell Types and Circuits (Chair, Hongkui Zeng, PhD)

8:30 - 9:20 a.m.	Keynote speaker, Hongkui Zeng, PhD (Allen Institute)
9:20 - 9:55 a.m.	Maria Antonietta Tosches, PhD (Columbia University)
9:55 - 10:30 a.m.	Yuki Oka, PhD (California Institute of Technology)
10:30 - 10:50 a.m.	Break
10:50 - 11:25 a.m.	Silvia Arber, PhD (Biozentrum and Friedrich Miescher Institute Basel, Switzerland)
11:25 - 12:00 p.m.	Fan Wang, PhD (Massachusetts Institute of Technology)
12:10 - 1:30 p.m.	Lunch / Poster Session

Session 2: Circuit Development (Chair, Liqun Luo, PhD)

1:30 - 2:05 p.m.	Denis Jabaudon, MD, PhD (University of Geneva, Switzerland)
2:05 - 2:40 p.m.	Hollis T. Cline, PhD (The Scripps Research Institute)
2:40 - 3:15 p.m.	Corey Harwell, PhD (UC San Francisco)
3:15 - 3:35 p.m.	Break
3:35 - 4:10 p.m.	Nenad Sestan, MD, PhD (Yale University)
4:10 - 4:45 p.m.	Sergiu Pasca, MD (Stanford University)
5:00 - 6:30 p.m.	On-site reception for all attendees
6:30 p.m.	Speaker Dinner (location to be determined)

Day 2 - Tuesday, August 22

7:30 - 8:30 a.m.	Continental Breakfast

Session 3: Systems and Function (Chair, Leah Krubitzer, PhD)

8:30 - 9:30 a.m.	PJ Harman Lecture, Cajal Club: Tirin Moore, PhD (Stanford University)
9:30 - 10:05 a.m.	Cory Miller, PhD (UC San Diego)
10:05 - 10:40 a.m.	Cris Niell, PhD (University of Oregon)
10:40 - 11:00 a.m.	Break
11:00 - 11:35 a.m.	Karen Sears, PhD (UC Los Angles)
11:35 - 12:10 p.m.	Leah Krubitzer, PhD (UC Davis)
12:10 - 1:30 p.m.	Lunch / Poster Session

Session 4: Developmental Disorders of Connectivity (Chair, John Rubenstein, PhD)

1:30 - 2:15 p.m.	Thomas Südhof, MD (Stanford University) Distinguished Nobel Laureate Presentation
2:15 - 2:50 p.m.	Anna Victoria Molofsky, MD, PhD (UC San Francisco)
2:50 - 3:15 p.m.	Break
3:15 - 3:50 p.m.	Linda Richards, PhD (Washington University in St. Louis)
3:50 - 4:25 p.m.	John Rubenstein, MD, PhD (UC San Francisco)
4:25 - 5:00 p.m.	John Ngai, PhD (BRAIN Initiative, NIH)

Day 3 - Wednesday, August 23

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

Session 5: Special & Selected Presentations (Chair, Edward Callaway, PhD)

8:15 - 9:35 a.m.	Special talks from the Cajal Institute (Madrid, Spain) and other Spanish institutions Ruth Benavides-Piccione, PhD Carlos Vicario, PhD Sandra Jurado, PhD Juan M. Encinas, PhD
9:35 - 10:15 a.m.	Selected talks: Laszlo Zaborszky, MD, PhD (Rutgers University) Don B. Arnold, PhD (University of Southern California)
10:15 - 10:40 a.m.	Break
10:40 - 12:00 p.m.	Selected talks: Xiaoxiao Lin, PhD (UC Irvine) Shen-Ju Chou, PhD (Academia Sinica) Alec J. Davidson, PhD (Morehouse School of Medicine) Michel Baudry, PhD (Western University of Health Sciences)
12:00 - 1:30 p.m.	Lunch

Session 6: Conference Workshops

1:30 - 5:00 p.m.	(1) Spatial Transcriptomics (90+ minutes) presented by Vizgen (2) Miniscope imaging (90+ minutes) by UCLA Miniscope
5:00 p.m.	Main conference end

Additional Events - Thursday, August 24

4D Nucleome Consortium & Vizgen Co-hosted Bootcamps
[Interdisciplinary Science and Engineering Building (ISEB), UCI]

8:30 - 3:30 p.m.	MERSCOPE Bootcamp (selected applicants only, live stream available)
8:30 - 2:00 p.m.	Statistics Bootcamp for Neuroscience & Single Cell Omics Data Analysis

Conference Venue

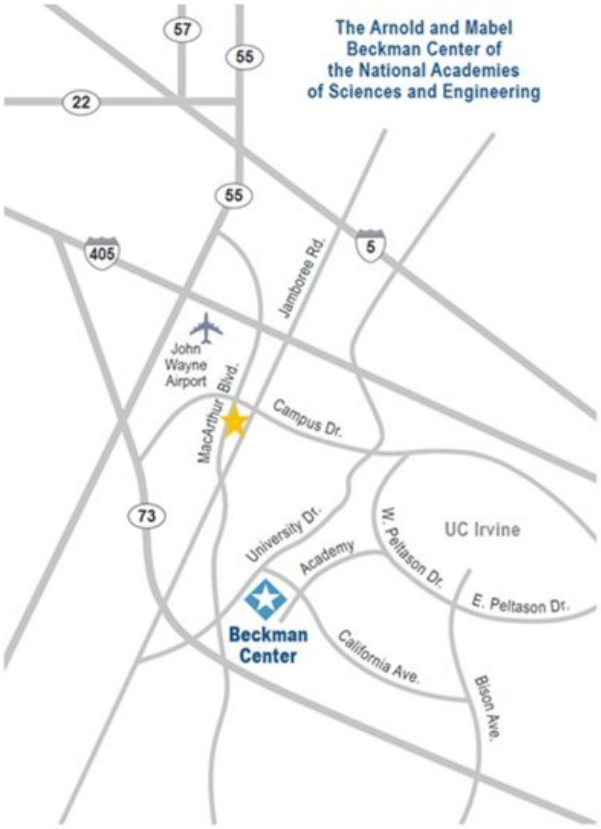
We are pleased to hold our conference at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering. Open in 1988, The Beckman Center has brought Dr. Arnold O. Beckman's reality of a West Coast Center where experts could discuss matters of science and technology.

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

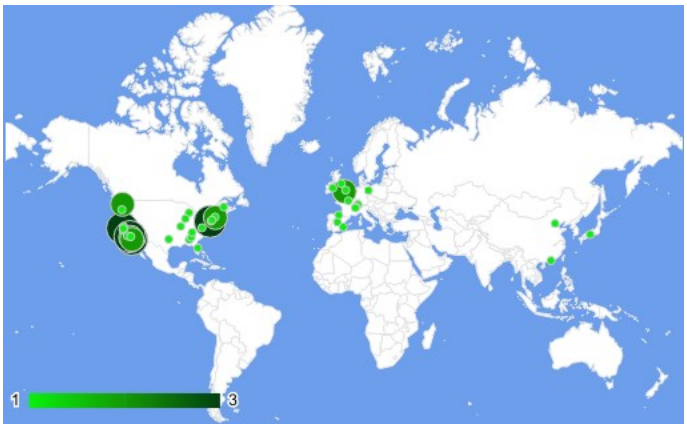
Parking is available on-site at no charge.

Electric charging stations are available on-site.

No overnight parking.

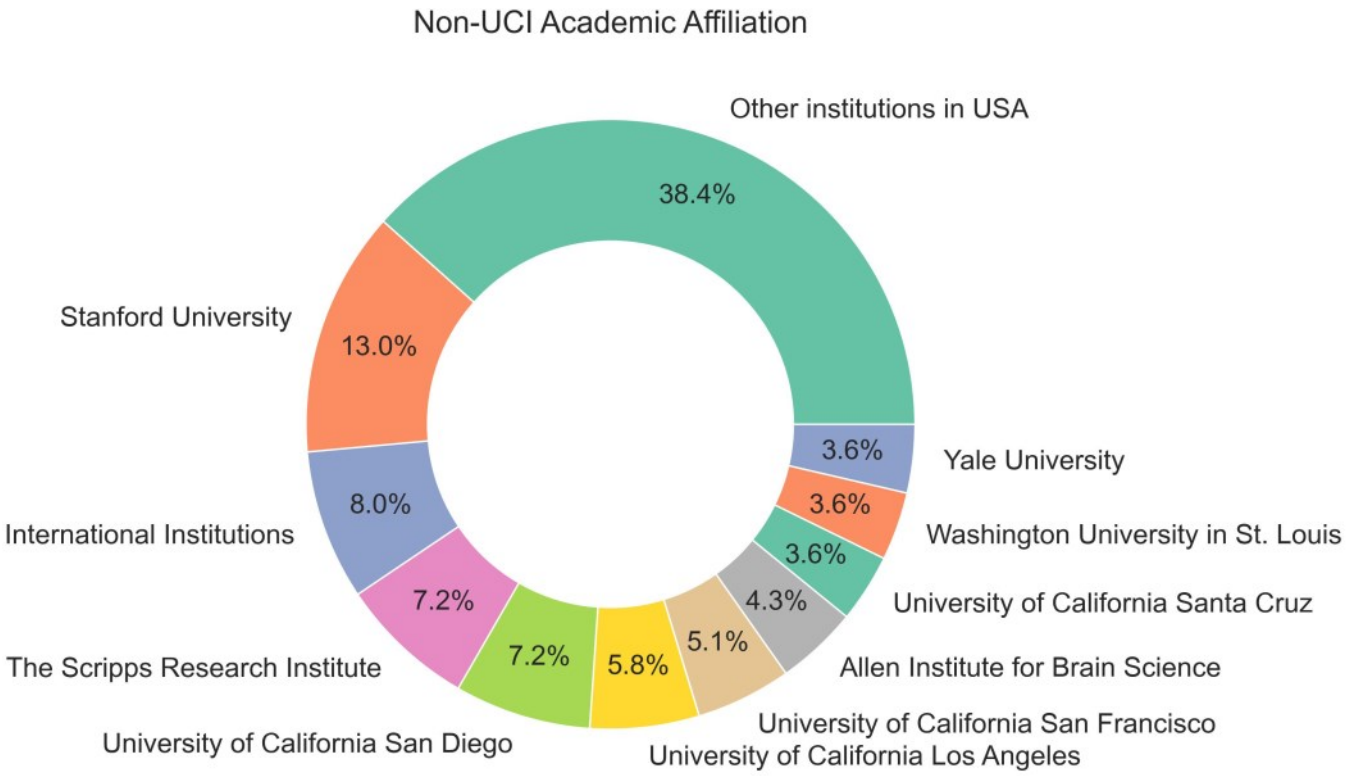
Geographic Locations of Conference Attendees

Locations in the globe



Locations in the USA

Non-UCI: 164 (65% of all registrants, 18 international)
UCI: 87 (35% of all registrants)



DAY 1—INVITED PRESENTATIONS

Hongkui Zeng

Allen Institute for Brain Science, Seattle, Washington, USA

Cell Type Organization Across the Mouse Brain

To understand the function of the brain and how its dysfunction leads to brain diseases, it is essential to uncover the cell type composition of the brain, how the cell types are connected with each other and what their roles are in circuit function. At the Allen Institute, we have built multiple technology platforms, including single-cell transcriptomics, spatial transcriptomics, single and multi-patching electrophysiology, 3D reconstruction of neuronal morphology, and brain-wide connectivity mapping, to characterize the molecular, anatomical, physiological, and connectional properties of brain cell types in a systematic manner, towards the creation of multi-modal cell atlases for the mouse and human brains.

We have now generated a comprehensive and high-resolution transcriptomic and spatial cell type atlas for the whole adult mouse brain, based on the combination of two single-cell-level, whole-brain-scale datasets by scRNA-seq and MERFISH. The atlas is hierarchically organized into five nested levels of classification: 7 divisions, 32 classes, ~300 subclasses, ~1,000 supertypes and ~5,200 clusters. We systematically analyzed the neuronal, non-neuronal, and immature neuronal cell types across the brain and identified a high degree of correspondence between transcriptomic identity and spatial specificity for each cell type. The study uncovered tremendous heterogeneity in neurotransmitter and neuropeptide expression and co-expression patterns in different cell types, suggesting they mediate myriad modes of intercellular communications. We also found that transcription factors are major determinants of cell type classification in the adult mouse brain and identified a combinatorial transcription factor code that defines cell types across all parts of the brain. This study reveals extraordinary cellular diversity and underlying rules of brain organization. It establishes a benchmark reference atlas and a foundational resource for deep and integrative investigations of cell type and circuit function, development, and evolution of the mammalian brain.

Maria Antonietta Toches

Department of Biological Sciences, Columbia University,
New York, New York, USA

The Evolution of Cortical Cell Types and Circuits

The cerebral cortex is arguably the brain area that underwent the most profound transformations in vertebrate brain evolution. The expansion of the cerebral cortex in mammals was accompanied by an explosion of neuronal diversity. To discover general principles underlying the evolution of neuron types and circuits, we study the simple cerebral cortices of non-mammalian vertebrates.

Our work on amphibians and reptiles indicates that the cerebral cortex of ancestral tetrapods was layered, with two main classes of neurons with distinct laminar positions, molecular identities, and long-range projections (intra-telencephalic vs extra-telencephalic). In salamanders, these two layers are generated sequentially from multipotent progenitors in an outside-in sequence. We propose that in mammals new types of pyramidal neurons evolved from these two ancestral classes by diversification, through the emergence of novel gene regulatory interactions in post-mitotic neurons.

Yuki Oka

Departments of Biology and Biological Engineering, California Institute of Technology, Pasadena, California, USA

Cell-Type-Specific Representation of Body Fluid Balance in the Mammalian Brain

Maintaining water-salt balance is crucial for all animal species, and the brain is responsible for achieving this function through constant monitoring of the body fluid status and inducing appropriate ingestive behaviors. However, the central mechanisms for sensing internal fluid balance remain poorly understood. Recently, we demonstrated, through transcriptomic and genetic methods, that fore- and hindbrain interoceptive circuits are involved in detecting water and salt deficits and has causal roles in water/salt appetites. These findings provide a unique opportunity to investigate internal-state-sensing with cell-type-specific resolution. In this talk, I will show the combinatorial neural coding of distinct fluid need states. I will also discuss how individual neuron types mediate the behavioral responses toward water and salt.

Silvia Arber

Biozentrum, University of Basel; Friedrich Miescher Institute, Basel, Switzerland

Cell Types and Circuits for Body Movements: Focus on the Brainstem

Movement is the behavioral output of the nervous system. Recent work has begun to dissect the cell types and circuits involved in the regulation of diverse forms of body movement. The brainstem is an important switchboard between motor system planning centers and the circuit elements engaged in movement execution in the spinal cord. Using circuit tracing approaches intersectionally with mouse genetics and a variety of technologies to record from identified neurons in combination with tracking behavior, we have identified brainstem centers dedicated to the generation of full body movements including locomotion and posture, as well as regions involved in the construction of complex forelimb movements. Strikingly, dedicated circuit modules defined by cell types are at the core of generating these diverse forms of movement with high specificity. The regulation of these specific cell types by synaptic inputs from higher motor centers including cortex and basal ganglia as well as intra-brainstem processing of information are important ingredients in the process of generating behavioral specificity as well as flexibility.

Fan Wang

Department of Brain & Cognitive Sciences;
McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

Brainstem Cells and Circuits for Generating Rhythmic Vocalization and Licking Behaviors

Healthy humans can talk, drink, and eat with ease using coordinated activity of distinct but overlapping sets of orofacial muscles. The basic modular circuits that control these fundamental orofacial behaviors reside in the brainstem although the details remain largely vague. Using modern viral-genetic tools, we have been able to identify specific premotor neurons for different muscles and their associated circuits controlling different orofacial actions. Here I will describe two such studies. The first focuses on the circuits controlling patterned vocalization and vocal-respiratory coupling, and the second examines the mechanisms separately controlling tongue licking rhythm and licking amplitude. These studies also reveal interesting interactions between neural circuits and physiology.

Denis Jabaudon

Department of Basic Neurosciences, University of Geneva, Geneva, Switzerland

Temporal Controls Over Neuronal Diversity in the Developing Brain

The developing brain exhibits a remarkable diversity of neuronal cell types, each with specialized functions that contribute to the proper function of the mature brain. The mechanisms underlying the generation and specification of neuronal diversity during development are complex and incompletely understood. Here, we investigate temporal controls over this process by analyzing the developmental diversity of neuronal progenitors across multiple brain regions and developmental timepoints. Our results demonstrate that distinct spatial and temporal transcriptional programs control the timing and pattern of neuronal differentiation and specification during brain development. Our findings provide new insights into the mechanisms underlying neuronal diversity in the developing brain and suggest novel strategies for manipulating these processes to direct neuronal identity and connectivity.

Hollis T. Cline

Department of Neuroscience, The Dorris Neuroscience Center,
The Scripps Research Institute, La Jolla, California, USA

Visual Neurons Recognize Complex Image Transformations

Natural visual scenes are dominated by sequences of transforming images. Spatial visual information is thought to be processed by detection of elemental stimulus features which are recomposed into scenes. How image information is integrated over time is unclear. We explored visual information encoding in the optic tectum. Unbiased stimulus presentation shows that the majority of tectal neurons recognize image sequences. This is achieved by temporally dynamic response properties, which encode complex image transitions over several hundred milliseconds. Calcium imaging reveals that neurons that encode spatiotemporal image sequences fire in spike sequences that predict a logical diagram of spatiotemporal information processing. Furthermore, the temporal scale of visual information is tuned by experience. This study indicates how neurons recognize dynamic visual scenes that transform over time.

Corey Harwell

Department of Neurology; Eli and Edythe Broad Center of Regeneration Medicine, University of California San Francisco, San Francisco, USA

Development and Neural Diversity of Septal Nuclei

Septal nuclei in the basal forebrain have critical roles in regulating motivational and emotional states including fear, anxiety, and aggression. Dysfunction of septal neurons believed to contribute to the pathophysiology of various psychiatric disorders including schizophrenia, bipolar disorder and depression. The septum can be classified into two regions: the medial septum and the lateral septum. The medial septum is composed of cholinergic, GABAergic and glutamatergic neurons that primarily project to the hippocampus. While the lateral septum is made up of a diverse array of GABAergic projection neurons that have reciprocal connections with several brain regions known to regulate emotional and motivational states. It is currently unclear how septal neuronal diversity and circuit wiring are specified during development. We have employed molecular genetic approaches and single-cell/nuclei RNA-seq to systematically assess the extent of septal cell diversity and the developmental logic for the production and wiring of these diverse neural cell types. We will discuss our recent progress in understanding the anatomical organization and functional specialization of neuronal cell types in the lateral septal nuclei.

Nenad Sestan

Department of Neuroscience, Yale School of Medicine, New Haven, Connecticut, USA

Development and Evolution of the Prefrontal Cortex

In my presentation I will discuss the importance of the prefrontal cortex (PFC) in cognitive control, and the role of retinoic acid signaling in the development and evolution of the PFC. Our transcriptomic studies of the developing human and macaque monkey brain have identified several genes involved in retinoic acid signaling or regulated by retinoic acid that are upregulated in the early-fetal and mid-fetal prospective PFC and motor cortex. Follow-up studies discovered an anterior (frontal) to posterior (temporal), PFC-enriched gradient of retinoic acid, a signaling molecule that regulates neural development and function. We identified several potential sources of retinoic acid, including the species-specific expression and cortical expansion of retinoic-acid-synthesizing enzymes specifically in primates as compared to mice. Furthermore, retinoic acid signaling is largely confined to the prospective PFC by CYP26B1, a retinoic-acid-catabolizing enzyme, which is upregulated in the prospective motor cortex. Studies conducted on genetically edited mice, human primary neurons, and organoids have revealed that retinoic acid signaling through RXRG and RARB receptors, along with CYP26B1-dependent catabolism, plays a crucial role in controlling gene expression in the developing PFC. This signaling pathway contributes to proper molecular patterning of the prefrontal and motor areas, development of PFC-mediodorsal thalamus connectivity, intra-PFC dendritic spinogenesis, and the expression of the layer 4 marker RORB. These findings collectively demonstrate the crucial role of retinoic acid signaling in the development of the prefrontal cortex (PFC) and potentially its evolutionary expansion.

Sergiu Pasca

Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA

From Stem Cells to Organoids to Assembloids and Toward Buildings Human Circuits in Living Systems

The construction of the human nervous system involves a series of complex and largely inaccessible processes. In my talk, I will describe efforts in my lab towards understanding the rules that govern the molecular and cellular steps underlying the assembly of the human brain and the mechanisms that lead to disease. Towards this, we have been developing approaches to generate and assemble, from multi-cellular components, human neural circuits in vitro and in living systems. We initially introduced instructive signals to derive, from pluripotent stem cells, self-organizing 3D tissue structures called regionalized brain organoids that resemble domains of the developing central nervous system. We have shown that these cultures recapitulate many features of neural development, can be derived with high reliability across dozens of cell lines and experiments, and can be maintained for years in vitro to recapitulate an intrinsic program of maturation that progresses into postnatal stages. To model complex cell-cell interactions, we developed assembloids and demonstrated their use in modeling cell migration, formation of neural circuits and disease processes. To advance maturation and circuit integration of organoids, we developed a transplantation paradigm and demonstrated that engrafted human neurons can respond to sensory stimulation in the animal and can drive reward-seeking behavior therefore enabling behavioral readouts from patient-derived cells. Lastly, I will illustrate how these methods can be combined with modern neuroscience tools to study the cellular and molecular consequences of mutations and copy number variants associated with neuropsychiatric disorders.

DAY 2—INVITED PRESENTATIONS

Tirin Moore

Howard Hughes Medical Institute; Department of Neurobiology,
Stanford University, Stanford, California, USA

Pinckney J. Harman Memorial Lecture of the Cajal Club: **Large-scale, High-Density Recordings in the Primate Brain**

Recent advances in recording technology have facilitated the development of large-scale, high-density micro-electrode arrays resulting in a substantial increment (>10x) in the number of neurons that can be studied simultaneously within a localized area of neural tissue. A prime example is the recent development of the Neuropixels probe (IMEC, Inc.), which consists of a high-channel count Si shank with continuous, dense, programmable recording sites (~1000/cm). Neuropixels probes are transforming neurophysiological studies in rodent models by enabling recording from large populations of neurons anywhere in the rodent brain. However, their utility in other model systems, particularly nonhuman primates (NHP), which more closely model human brain function, has been limited. I will first talk about the recently developed NHP Neuropixels probes, which were designed to enable flexible and configurable recordings from large populations of neurons throughout the entire macaque brain with single-neuron resolution. Next, I will describe a couple of specific scientific questions we recently addressed using large-scale, high-density recordings in NHPs.

Cory Miller

Department of Psychology, University of California San Diego,
La Jolla, California, USA

Representing Social Space in the Marmoset Hippocampus

Social space reflects the intersection between where individuals are in the environment and their identities and is foundational to the decision-making strategies at the core of the primate social cognitive faculty. Here I will present work on how identity and spatial representations are evident in the hippocampus of marmosets. Specifically, I will describe recent neurophysiology experiments showing cross-modal representations of identity are evident at the single neuron and population level, as well as complementary studies investigating the nature of spatial representations in freely-moving marmosets in this substrate.

Cris Niell

Department of Biology, University of Oregon, Eugene, Oregon, USA

Neural Circuits for Active Vision and Natural Behavior

In the natural world, animals use vision to analyze complex scenes and enable a wide range of visually-driven behaviors, many of which require movement through the environment. However, in practice most studies of vision are performed in stationary subjects performing artificial tasks in response to simple stimuli. In order to bridge this disconnect between how vision is actually used and how it is studied in the lab, we are investigating the neural circuits mediating ethological behaviors that mice perform. We have developed two behavioral paradigms, prey capture and gap crossing, that have provided insight into behavioral strategies and cell type-specific neural circuits for detection of relevant stimulus features within a complex and dynamic sensory environment. We have also implemented novel experimental approaches to measure neural coding of the visual scene as animals freely move through their environment, which has revealed the impact of movement-related signals and active sampling on visual processing.

Karen Sears

Department of Ecology and Evolutionary Biology,
University of California Los Angeles, Los Angeles, USA

Developmental Origin and Evolution of Bat Wings

Bats (Order Chiroptera) are the only mammalian group that has achieved powered flight. This achievement proceeded the massive adaptive radiation of bats into diverse ecological niches. As a result, today's bats exhibit diverse flight styles, the broadest range of dietary and sensory adaptations of any mammalian group, and comprise 20% of mammalian species. As stated in Popular Science, "Bats are like Darwin's finches, only weirder." My lab takes advantage of the incredible diversity of bats to study questions of relevance to evolution and human health. In this talk, I will present some of our research on the developmental mechanisms through which bats arose and then diversified, focusing on the structure that enables the group's powered flight - the wing. The bat wing is formed from a mix of homologous elements including the long bones of the fingers and arms, and novel structures including the membrane which connects the 5th finger to the body and hind limb. Our work suggests that the homologous long bones of the bat wing have diversified through tweaks in existing limb developmental programs. In contrast, the novel membranes arose through de novo outgrowths of the body flank that subsequently adhere and fuse to the limbs.

Leah Krubitzer

Department of Psychology, University of California Davis,
Davis, California, USA

Combinatorial Creatures: Cortical Plasticity Within and Across Lifetimes

The neocortex is one of the most distinctive structures of the mammalian brain, yet also one of the most varied in terms of both size and organization. Multiple processes have contributed to this variability including evolutionary mechanisms (i.e., changes in gene sequence) that alter the size, organization and connections of the neocortex, and activity dependent mechanisms that can also modify these same features over shorter time scales. Because the neocortex does not develop or evolve in a vacuum, when considering how different cortical phenotypes emerge within a species and across species over time, it is also important to consider alterations to the body, to behavior, and the environment in which an individual develops. Thus, changes to the neocortex can arise via different mechanisms, and over multiple time scales. Brains can change across large, evolutionary time scales of thousands to millions of years; across shorter time scales such as generations; and across the life of an individual – day-by-day, within hours, minutes and even on a time scale of a second. The combination of genetic and activity dependent mechanisms that create a given cortical phenotype allows the mammalian neocortex to rapidly and flexibly adjust to different body and environmental contexts, and in humans permits culture to impact brain construction during development.

Thomas Südhof

Howard Hughes Medical Institute; Departments of Molecular and Cellular Physiology, and Neurosurgery, Stanford University School of Medicine, Stanford, California, USA

Distinguished Nobel Laureate Presentation:

Trans-Synaptic Adhesion Complexes Controlling the Molecular Logic of Synapse Formation

The brain processes information via signals that are processed in a vast number of neural circuits that operate in a parallel, interleaved, or sequential fashion. In each neural circuit, information transmitted from one neuron to the next at synapses that computationally process the information as it is being transmitted, translating a presynaptic spike code into distinct postsynaptic signals depending on the properties of the synapses. Information processing by neural circuits critically depend on the number and location of synapses between their constituent neurons and equally on the computational properties of these synapses that vary greatly. We posit that the synaptic architecture of neural circuits is based on a molecular logic that governs the establishment and functional specification of synapses. Moreover, we posit that this molecular logic is controlled by transsynaptic adhesion complexes formed between pre- and postsynaptic recognition and signaling molecules. Multiple cell-surface and signaling molecules contributing to the molecular logic of neural circuits have been characterized. Two types of complexes mediating trans-synaptic interactions that control the architecture of synapses stand out: Presynaptic neurexin adhesion molecules and their multifarious postsynaptic signaling partners, including neuroligins and cerebellins, and postsynaptic latrophilins and Bai's that act as adhesion-GPCRs and interact with presynaptic ligands, including teneurins and RTN4Rs, in synapse formation. In my lecture, I will describe recent progress in understanding how selected trans-synaptic interactions guide and shape the formation of synapses and thereby control the molecular logic of neural circuits.

Anna Victoria Molofsky

Department of Psychiatry; Weill Institute for Neurosciences,
University of California San Francisco, San Francisco, USA

Defining the Brain-immune Circuits that Regulate Synapse Remodeling

Synaptic remodeling occurs during development and throughout life. However, remodeling is not unique to brain synapses. Across organs, tissue remodeling is coordinated by the innate immune system, whose ground crew are tissue-resident macrophages analogous to microglia in the brain. Similarly, all tissues contain stromal cells and extracellular matrix (ECM) that provide structural and trophic support, just as the stroma (astrocytes) and ECM of the brain shape and stabilize synaptic connections. Thus, while neuron-autonomous mechanisms of synaptic remodeling are critical, there is also an ecosystem of cell type outside of neurons, whose functional principles are highly conserved throughout the body but poorly defined in the brain. A central goal of my group is to define the immune circuits that regulate synaptic remodeling "one cytokine at a time". For example, my group discovered that the cytokine Interleukin-33 promotes microglial engulfment of the extracellular matrix to remodel excitatory synapses. We aim to define the mechanisms of microglial ECM remodeling and conversely, to understand the composition and function of the brain ECM at the level of individual synapses. We have also discovered other cytokines that regulate neural circuit development, including cytokines that target microglia to eliminate whole neurons, and others that directly signal to neurons to promote inhibitory synapse formation. These findings reveal an unexpected precision in how immune circuits that are conserved throughout the body guide distinct features of neural circuit formation in the brain.

Guoping Feng

Yang-Tan Collective and McGovern Institute for Brain Research, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard; Cambridge, Massachusetts, USA

Dissecting Neurobiological Mechanisms of Autism Spectrum Disorders: From Genes to Circuits

Recent genetic studies have identified a large number of candidate genes for autism spectrum disorder (ASD), many of which encode synaptic proteins, suggesting that synaptic dysfunction might be a key pathology in ASD. Using a variety of animal models, we have identified distinct synaptic and circuitry mechanisms related to repetitive behaviors, social interaction deficits, sensory abnormalities, attention deficit and sleep disruption. Combining single cell transcriptomic analysis and cell type-specific functional manipulation, we have begun to reveal circuit-specific targets for developing potential treatment for some of the debilitating symptoms. In additions, new genome editing technologies allow us to develop non-human primate models and explore gene therapy as an effective treatment for monogenic ASD.

Linda Richards

Department of Neuroscience; McDonnell Center for Cellular & Molecular Neurobiology, Washington University in St Louis,
St. Louis, Missouri, USA

Developmental Mechanisms Shaping Cortical Interhemispheric Connectivity and Function

The corpus callosum connects the cerebral hemispheres and is the largest fiber tract in the brain of placental mammals. Congenital corpus callosum dysgenesis (CCD) is evident by 20 weeks of fetal life and can occur in isolation or as part of a syndrome with other brain or organ system abnormalities. People with CCD often have difficulties in processing complex, novel information and generally have slower cognitive processing, which impacts their decision making and social interactions. The development of the corpus callosum is mediated by more than 400 genes. These regulate specific pathways controlling the formation of callosal neurons, remodeling of the brain's midline tissue to form a substrate for callosal axon growth, and the guidance of callosal axons into the contralateral hemisphere. Structural MRI and tract tracing have demonstrated that CCD not only affects interhemispheric connections, but also significantly alters long-range ipsilateral projections. These findings suggest that the brain's long-range projections are highly plastic during development and may vary considerably between individuals and in conditions such as CCD. Our long-term goal is to understand the relationship between specific circuits and cognitive function and how similar brain functions can be derived from circuits organized in dramatically different ways in both humans and animals with CCD compared to neurotypical brains. To discover the mechanistic drivers of long-range axonal plasticity, and how circuits underpin function, we are also investigating the development of cortical wiring and the emergence of activity patterns in the early brain of the marsupial fat-tailed dunnart, which develops largely outside the womb and lacks a corpus callosum. This work is uncovering how activity-dependent and molecular mechanisms regulate the development of functional cortical circuits in neurotypical brains and compensatory networks in the context of CCD.

John Rubenstein

Department of Psychiatry, University of California San Francisco
San Francisco, USA

ASD gene TBR1 Dependent WNT-signaling Promotes Synaptogenesis of Cortical Excitatory Neuron - Rescue with WNT Agonists and LiCl

ASD gene TBR1 is nearly exclusively expressed by postmitotic cortical excitatory neurons from the time that they are generated through adult stages. Its early prenatal functions include specifying layer 6 identity - in its absence, or with reduced dosage, layer 6 takes on layer 5 properties. Then early postnatally Tbr1 is required for promoting the formation of excitatory and inhibitory synapses. Tbr1 mutants (homozygotes and heterozygotes) have reduced synaptic density; these defects persist into adulthood. The cellular basis of reduced synaptic density is a failure of synaptic spine maturation. Tbr1 drives expression of Wnt7b. Synaptic spine maturation and synapse formation is induced within 24 hours of treating young and mature Tbr1 mutants with LiCl, a medicine that has known WNT agonist properties.

John Ngai

BRAIN Initiative, National Institutes of Health, USA

Accelerating Discovery Toward Cures

The NIH Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative is an ambitious program whose mission is to develop and apply new technologies to answer fundamental questions about the brain and to find new treatments for human brain disorders. Launched in 2013, the NIH BRAIN Initiative supports research on understanding neural circuit function by developing novel tools and applying innovate techniques to map brain circuits. Organized as a highly collaborative initiative encompassing ten NIH Institutes and Centers, the Initiative is uniquely situated for cross-cutting and accelerated discovery in neuroscience by tapping into synergies across multiple fields to address the personal and societal challenges imposed by human brain disorders.

Continuing investments by the Initiative have yielded exciting new tools for monitoring and modulating neural circuits across diverse experimental models and probing neural circuit function in humans; translational projects that shift technology from bench to clinic; and a growing ecosystem for managing and integrating the Initiative's burgeoning informatics and data resources. In addition, the Initiative recently launched three bold "transformative projects" that promise to transform neuroscience research: the BRAIN Initiative Cell Atlas Network (BICAN), which will create a comprehensive atlas of the human brain; the Armamentarium for Precision Brain Cell Access, which will provide new tools for cell access in diverse species to a broad and diverse cross-section of researchers; and the BRAIN Initiative Connectivity across Scales (BRAIN CONNECTS) Project, designed to develop and validate tools for creating whole brain connectivity maps.

Based on a foundation of new tools supported by the BRAIN Initiative, the potential to change the future of treating neurologic and neuropsychiatric diseases is fast coming into focus: within a decade of its inception, the initiative is already having an impact in the clinic while also developing foundational knowledge to enable a new generation of cures and treatments. This knowledge will play a key role in understanding the mechanistic basis of these diseases and arm scientists with tools for early diagnosis, prevention, and treatments. The Initiative's early deliverables to date portend significant and broader impact of the BRAIN Initiative transformative projects through the discovery of additional brain cell types and circuits specifically affected in human brain disorders and the ability to intervene with precision cell- and gene-based therapies.

DAY 3—SPECIAL & SELECTED PRESENTATIONS

Ruth Benavides-Piccione

Cajal Institute, Madrid, Spain

The Structure of Human Pyramidal Cells

Understanding the biological sources of human capacities is of great interest to basic and applied neuroscience. However, most of our present knowledge of brain structure and behavior has been obtained from experimental animals. It has been shown that the human cerebral cortex, presents some unique molecular, physiological and anatomical features, which emphasize the importance of directly studying human brain. The basic building block of the cerebral cortex, the pyramidal cell, has been shown to be characterized by markedly different structure among species. In terms of function, differences in the structure of the dendrites and axons of these neurons appear to be crucial in determining how they integrate information. In the human cortex, pyramidal cell structure show distinctive attributes, that contribute to distinct information processing characteristic of the human brain. I will discuss to what extent human pyramidal neurons in different cortical regions and species have parallel morphologies. In particular, intracellularly injected and 3D-reconstructed dendritic and axonal morphologies show that there are some morphological parameters of the pyramidal cells that are conserved, whereas others are species-specific.

Carlos Vicario

Cajal Institute, Madrid, Spain

Generation of functional neurons from human iPSCs: The impact of Parkinson´s and Alzheimer´s risk factors

Studying the processes and the mechanisms of human cell differentiation and neurodegeneration has been difficult due to the scarcity of human cellular models. Human induced pluripotent stem cells (iPSCs), first reported by S. Yamanaka and colleagues (Takahashi et al., 2007), are very useful neuronal sources for investigating the process of neurodegeneration in diseases such as Parkinson´s disease (PD) and Alzheimer´s disease (AD). They are also instrumental to test the activity of new molecules with the potential capacity to restore the healthy phenotypes in neurons and glia derived from PD and AD patients. In particular, we are studying the impact of mutations in the GBA1 gene on iPSC-dopaminergic neurons from PD patients (Rodríguez-Traver et al., 2019). Similarly, we are investigating the effect of APOE polymorphism and of a PSEN1 mutation on iPSC-hippocampal neurons from AD patients (Díaz-Guerra et al., 2019). I will present a summary of the results obtained and discuss that iPSC and cerebral organoid technologies, combined with transplantation, could help us shed light on how dysfunction and neurodegeneration occur in PD and AD.

Sandra Jurado

Institute of Neuroscience, CSIC-UMH, San Juan Alicante, Alicante, Spain

Specification and Function of the Hypothalamic Oxytocinergic System

The oxytocinergic system plays a crucial role in regulating both vital homeostatic functions and complex behaviors such as social interaction, and its deregulation has been associated with several psychiatric and neurodevelopmental disorders, including autism spectrum disorder. Despite its importance, many details regarding the formation and function of oxytocinergic modulation in the central nervous system remain unknown. In this talk, I will present our latest research on the neurodevelopmental specification of the oxytocinergic system and its plastic properties in the adult brain.

Using iDISCO+ and light-sheet ultra-resolution microscopy, we have reconstructed the formation of the oxytocinergic circuit in 3D during mouse brain development. Our results indicate a profound remodeling of the oxytocinergic system during early postnatal stages, suggesting a critical period for neurotransmitter plasticity in the first two postnatal weeks. In addition to developmental adaptations, oxytocinergic neurons in the paraventricular nucleus (PVN) of the hypothalamus undergo plastic changes to modulate their connections in response to environmental variations.

To explore the plastic properties of this circuit in the adult brain, we have performed visually-guided electrophysiological recordings to assess the outcomes of different stimulation protocols which are known to induce distinctive forms of plasticity in other brain areas such as the hippocampus. Our findings indicate that long-term depression is the most prevalent form of plasticity in PVN oxytocinergic neurons, and that OXT-dependent signaling plays a major role in sustaining synaptic transmission in the PVN crucial for the maintenance of various homeostatic and complex functions.

Juan M Encinas

Achucarro Basque Center for Neuroscience, Leioa, Bizkaia, Spain

Induction of Reactive Neural Stem Cells and Aberrant Neurogenesis by Neuronal Hyperexcitation

Postnatal and adult neurogenesis, the generation of newborn neurons, takes place in the hippocampus in the vast majority of mammals due to the persistence of a population of neural stem cells (NSCs). Hippocampal NSCs give rise to progenitors that proliferate first and then undergo neuronal differentiation, finally integrating into the granule cell of the dentate gyrus. The properties of NSCs as well as the process of neurogenesis are tightly regulated by neuronal activity. Different levels of neuronal hyperexcitation induce divergent responses from NSCs and newborn neurons. Higher levels of neuronal hyperexcitation, such as those found in models of mesial temporal lobe epilepsy with hippocampal sclerosis, trigger a reactive pro-neuroinflammatory program in NSCs at the expense of abolishing neurogenesis. On the other hand, milder seizures or epileptiform activity trigger an excess of newborn neurons although with abnormal migration, dendritic arborization and dendritic spine density, namely aberrant neurogenesis. In search of mechanism driving these alterations, we have identified ATP signaling as a main actor linking neuronal hyperexcitation and the induction of reactive neural stem cells and aberrant neurogenesis.

Laszlo Zaborszky

Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, New Jersey, USA

The Functional Architecture of the Forebrain Cholinergic System: Database and Analysis

In order to understand the organizational features of the basal forebrain (BF) cholinergic projection system we developed a pipeline for spatial registration of vectorial and image data from 73 rat brains that received pairwise conventional retrograde (FB and FG) or virus tracer injections in neocortical areas, (n=106), many of the regions electrophysiologically defined, and cholinergic projection neurons in the BF were mapped in 200 µm series. Cholinergic neurons in this virtual environment were assessed for spatial correlation in respect to density and to their cortical targets. We found high density spaces that showed systematic correlation of cholinergic projection neurons to pairwise targets that deviated from random distributions, such as between various body parts of the somatosensory and motor cortex; V1/prelimbic, auditory/postrhinal, retrosplenial/entorhinal cortex. It is assumed that these spaces represent architectural features that may enable the cholinergic system to participate in spatially selective signaling, including parallel modulation of multiple groupings of functionally interconnected cortical areas.

Supported by NIH/NINDS R01NS023945 and RF123945-28.

Don B. Arnold

Department of Biological Sciences, University of Southern California, Los Angeles, California, USA

ATLAs, a Rationally Designed Monosynaptic Anterograde Transsynaptic Tracer from Genetically Determined Neurons

ATLAs (Anterograde Transsynaptic Labeling using Antibody-like probes) is a monosynaptic strictly anterograde transsynaptic tracer for efficient tracing of neuronal circuits. ATLAs is based on the AMPA.FingR (AF), an antibody-like protein that binds with high affinity and specificity to the extracellular N-terminal domain of the GluA1 AMPA receptor. To trace transsynaptically, we engineered AF-Cre to be released from presynaptic terminals and confirmed this property with direct visualization. At the postsynaptic side, AF-Cre binds specifically to GluA1 receptors undergoing endocytosis at perisynaptic sites. Following endocytosis, AF-Cre collects in endosomes and then translocates to the nucleus, providing genetic access to the postsynaptic cell. Thus, ATLAs is the only tracer that has been confirmed to be truly transsynaptic. Using floxxed versions of ATLAs containing AF-FLPo, we have traced anterograde connections from Cre lines. Furthermore, it has no retrograde component and is non-toxic. Currently, we have traced circuits that included cells in the thalamus, cortex, inferior colliculus, superior colliculus, retina, cerebellum, hippocampus, and brainstem.

Xiaoxiao Lin

Department Anatomy & Neurobiology, University of California, Irvine, Irvine, CA, USA

Two Distinct Pathways within Retrosplenial Cortex Granular Layer Facilitate Mice Action during Navigation

The retrosplenial cortex (RSC) contributes to complex cognitive functions in primates and rodents, including spatial navigation, mnemonic processing, and planning. RSC has reciprocal connections with many cortical and subcortical brain regions. It has been suggested that the corticocortical connections between the RSC and secondary motor cortex (M2), as wel as corticothalamic connections between the RSC and anterodorsal thalamus (AD), function as semi-independent, but parallel pathways that regulate spatial information in distinct ways during navigation. To examine distinctions in connectivity and function among different projection-specific populations of RSC neurons, we used retrograde and anterograde viral tracers alongside a monosynaptic retrograde rabies virus to quantitively characterize and compare the afferent and efferent distributions of projection-defined RSC neuron sub-groups. We find that M2-projecting RSC neurons obtain more extensive afferent input from the dorsal subiculum, lateral dorsal and lateral posterior thalamus, and sensory cortices compared to AD -projecting neurons. AD-projecting RSC neurons obtain greater afferent input from the anterior cingulate cortex and the medial septum. While AD-projecting and M2-projecting RSC neurons overlap in their projections to other brain regions, they do not project to M2 and AD, respectively. To test the functional role of these projection-specific RSC populations, we performed chemogenetic inhibition of M2- and AD-projecting RSC neurons and examined its impact on object-location memory, object-recognition, open-field exploration, and place-action association. Our findings indicate that inhibition of M2-projecting RSC neurons impairs object location memory as well as place-action association, while the RSC to AD pathway impacts only object-location memory. Our study demonstrates that RSC connectivity and function is organized as a set of semi-independent circuits that integrate information from distinct sets of RSC afferents. The findings highlight the importance of investigating the roles of association cortices such as RSC in cognitive processes through the characterization and manipulation of its specific input/output circuitries.

Shen-Ju Chou

Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan

Specifying Neuronal Regional Properties by Expression Gradients of Patterning Transcription Factors

The mammalian cerebral cortex is a remarkably complex organ responsible for the perception of sensory stimuli, the execution of motor actions, learning, cognition, and consciousness. To perform such complicated functions, it is compartmentalized into multiple functional units called cortical regions, including the newly evolved neocortex and evolutionarily older paleocortex and archicortex. Each cortical region has unique cytoarchitectures, patterns of gene expression, and distinct sets of input and output projections to perform specific functions. We study how a specific cortical region arises at a specific location and acquires its specific properties during development. Previously, patterning transcription factors were shown to regulate area patterning in the neocortex. For example, COUP-TFI, an orphan receptor expressed in a high-caudal-lateral-to-low-rostral-medial gradient in cortical progenitors, determines the size and position of primary sensory areas in the neocortex. Recently, we found COUP-TFI expression gradient further determines neuronal fate outside of the neocortex. Altering the expression level of COUP-TFI affects the relative position of neocortex and medial entorhinal cortex, two abutting cortical regions generated from the same progenitor lineage. Further, the COUP-TFI expression gradient induces differential cell affinity, which establishes sharp boundaries between cortical regions. Additionally, within the hippocampus, the expression gradient of COUP-TFI regulates the relative size of the dorsal and ventral hippocampus. Thus, we demonstrated that the determination of different cortical regions and sub-regions relies on expression gradients of patterning transcription factors. As many neurological disorders assault specific types of neurons in specific brain regions, uncovering the mechanisms controlling cortical regional specification will contribute to the understanding of cortical dysfunction in disease states.

Alec J. Davidson

Neuroscience Institute, Morehouse School of Medicine,
Atlanta, Georgia, USA

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

The suprachiasmatic nucleus (SCN) is composed of functionally distinct subpopulations 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 arginine vasopressin (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 33% 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, exhibit profound heterogenicity of function over time and space.

Michel Baudry

Western University of Health Sciences, Pomona, California, USA

Neuroscience Research at Western University: Past, Present and Future

Western University of Health Sciences (WesternU) was started in 1977 as the College of Osteopathic Medicine of the Pacific (COMP). It grew from 36 students in 1978 to over 400 in 1986. A Master of Science in Health Professions Education was started in 1986, which led to the creation of the College of Allied Health Professions, which became the College of Health Sciences in 2018. In 1996, a College of Pharmacy was added, resulting in changing the name of the institution to Western University of Health Sciences. In 2008, a College of Graduate Nursing and a College of Veterinary Medicine were added. The following year, 4 more Colleges were added, Dental Medicine, Optometry, Podiatric Medicine and a Graduate College of Biomedical Sciences (GCBS). As the university grew, so did research activities, as many colleges recruited faculty with research programs. I moved from USC to WesternU in 2012 as the Dean of the GCBS with the mission to start a PhD program, since WesternU only had master programs. WesternU had significant research programs in 4 broad areas: neuroscience, infectious diseases, metabolic disorders and cancer. I recruited several faculty members in the GCBS with a strong background in neurosciences, which has now become the strongest research area at WesternU. WesternU just recruited a new Sr VP Research, Dr. Andrea Giuffrida, who was VP Strategic Ventures, Technology and Innovation at UT San Antonio, and who has a strong background in neuroscience. I will present our plans to start an Institute for Brain Disorders, an integrated platform across all the Colleges of WesternU to perform basic, clinical and translational research on the mechanisms underlying brain and eye disorders, in order to identify novel approaches to diagnose, prevent and/or treat these disorders.

DAY 3—WORKSHOP LECTURES

Spatial Transcriptomics Workshop

The Vizgen Team will instruct this workshop hosted by the UCI Center for Neural Circuit Mapping (CNCM), which currently houses two Vizgen MERSCOPE Platforms. The MERSCOPE® Platform leverages MERFISH (multiplexed error-robust fluorescence in situ hybridization) technology, developed by Xiaowei Zhuang's group (Harvard). MERFISH expands on the capabilities of single molecule FISH (smFISH) by using combinatorial labeling, sequential imaging, and error-robust barcoding to detect 100s-1000s of RNA species with single cell and subcellular resolution.

This workshop will provide an overview of the technology and an introduction to MERSCOPE, the end to end single-cell spatial genomics platform. Vizgen will also demonstrate the application of MERSCOPE imaging across a variety of case studies, including user cases presented by Dr. Xiangmin Xu's team on their research in Alzheimer's disease and muscular dystrophy leveraging the MERSCOPE Platform.

Agenda:

45 Minutes: Vizgen introduction led by Dr. George Emanuel,
Sr. Director of Scientific Affairs, Vizgen, Inc.

30 Minutes: Customer Case Studies, Dr. Xiangmin Xu and team,
UCI Center for Neural Circuit Mapping

15 Minutes: Group discussion

Miniscope Imaging Workshop

Open-source miniaturized microscopes have revolutionized systems neuroscience allowing large-scale and long-term recordings of large identified neuronal populations in freely behaving animals. Dr. Peyman Golshani in collaboration with Dr. Daniel Aharoni, Dr. Matt Shtrahman, Dr. Pingping Zhao, Dr. Blake Madruga will organize the workshop lecture; they will review new developments in epifluorescent miniaturized microscopes and introduce our large -field-view miniaturized two-photon microscopes for higher resolution and deeper imaging of neuronal activity.

Agenda:

15 minutes: Introduction by Dr. Peyman Golshani

25 minutes: New miniscope updates by Dr. Daniel Aharoni

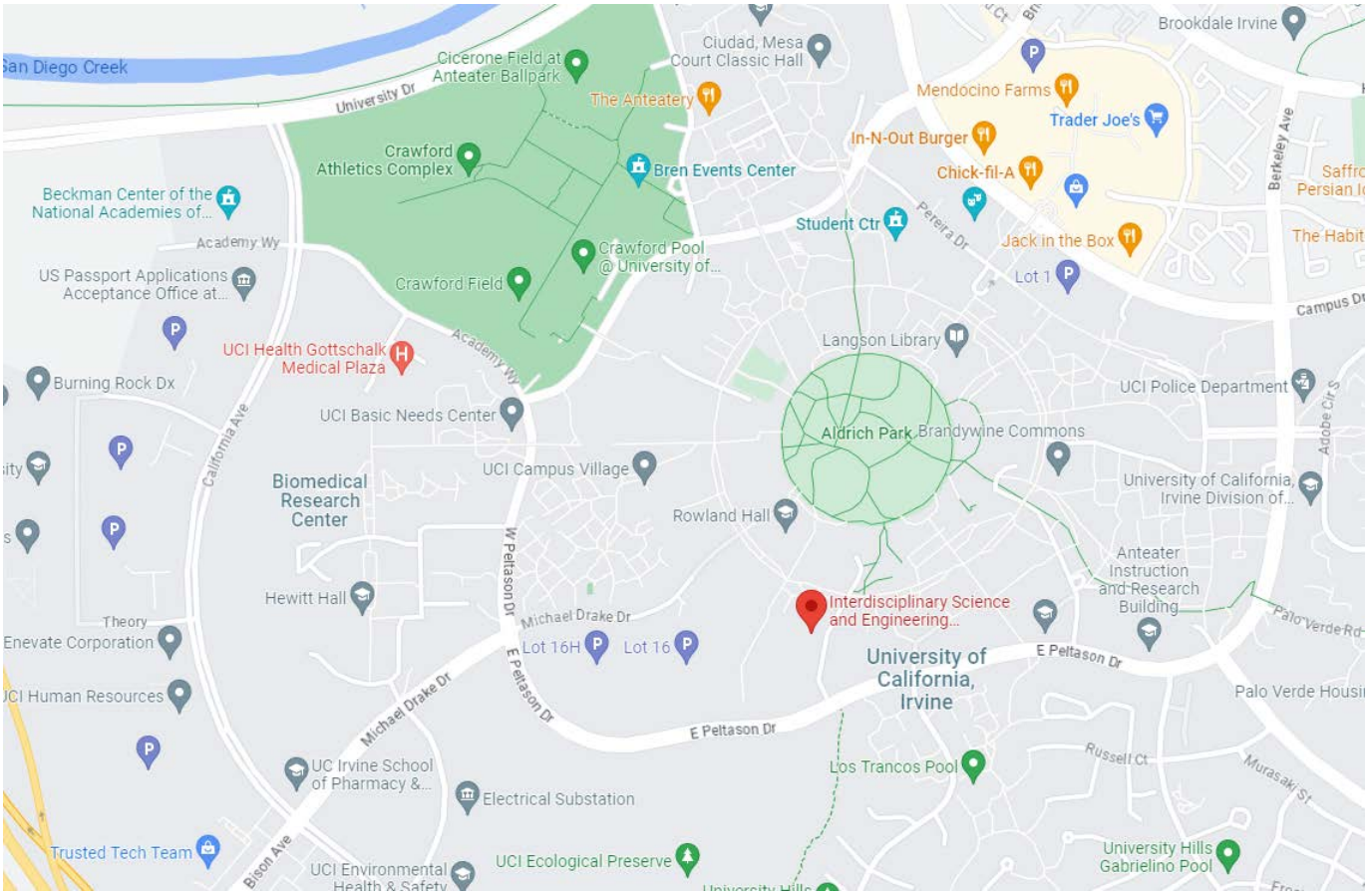
30 minutes: Miniaturized two-photon microscopes by Drs. Blake Madruga & Matt Shtrahman

20 minutes: Miniscope surgery and case studies by Dr. Pingping Zhao

Day 4： Additional Events

(Location: Interdisciplinary Science and Engineering Building (ISEB), UCI)

419 Physical Sciences Quad, Irvine, CA 92697



Statistics Bootcamp for Neuroscience and Single-Cell Omics Data Analysis

This bootcamp will be free and open to all conference registrants. Professor Zhaoxia Yu and Professor Wei Li will be the instructors for this bootcamp, which includes engaging lectures and hands-on components (data visualization, processing and statistical testing using statistical packages). Dr. Yu's research is focused on developing statistical methods to address the challenges confronting scientists when analyzing multivariate and high dimensional data. Dr. Yu has recently published a well-cited article in Neuron (Yu et al. 2022). During the bootcamp, she will guide participants through the practical application of the methods described in her paper, as well as other relevant methods. She will also provide statistical consulting through the UCI CNCM.

Dr. Li is an Endowed Chair and Professor of Bioinformatics in the Department of Biological Chemistry at UCI School of Medicine. He has developed a series of widely used bioinformatics algorithms to harness the full power of population-scale genomics and epigenomics data. He will present two recent projects that leverage bioinformatics and all-in-human large-scale data analysis to facilitate scientific discoveries. He will also discuss the importance of statistical rigor in data analysis, and the solution to deal with the exaggerated false positives by popular differential expression methods when analyzing human population samples.

Statistics Bootcamp for Neuroscience and Single-Cell Omics Data Analysis (continued)

Agenda:

8:30 am – 9:50 am: Analyzing Clustered / Dependent Data in Neuroscience Research

8:30 am – 9:00 am: A review of linear models and their limitations

9:00 am – 9:50 am: Introduction to mixed-effects models

9:50 am – 10:10 am: coffee break

10:10 am – 11:30 am:

10:10 am – 10:30 am: exaggerated false positives in popular differential expression methods

10:30 am – 11:00 am: epigenetic liquid biopsy for caner and brain disorders

11:00 am – 11:30 am: RNA therapy targeting Alternative Polyadenylation

11:30 am – 1:00 pm: Lunch break

1:00 pm – 3:30 pm: hands-on demos (a laptop is required)

1:00pm – 1:30pm: Install R and R Studio

1:30pm – 3:30pm: Use R to visualize and model clustered data

References:

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4. Li L, Huang KL, Gao Y, Cui Y, Elrod ND, Wang G, Ji P, Peng F, Russell WK, Wanger EJ, Li W: An atlas of alternative polyadenylation quantitative trait loci contributing to complex trait and disease heritability. ***Nature Genetics*** 53 (2021) 994
5. Xu J, Shi J, Cui X, Cui Y, Li JJ, Goel A, Chen X, Issa JP, Su J, Li W: Cellular Heterogeneity-Adjusted cLonal Methylation (CHALM) improves prediction of gene expression. ***Nature Communications*** 12 (2021) 400. Kandimalla R^, Xu J^, Link A, Matsuyama T, Yamamura K, Parker MI, Uetake H, Balaguer F, Borazanci E, Tsai S, Evans D, Meltzer SJ, Baba H, Brand R, Von Hoff D, Li W*, Goel A*: EpiPanGI Dx: A cell-free DNA methylation fingerprint for the early detection of gastrointestinal cancers. ***Clinical Cancer Research*** 27 (2021) 6135-6144.

MERSCOPE Bootcamp (Selected applicants only)

The MERSCOPE bootcamp will provide an immersive training experience to work with Vizgen's MERSCOPE platform, and learn how to use this powerful single-cell, spatially resolved transcriptomic imaging platform to gather deeper insights in different biological systems. Working with mouse brain samples , attendees will learn and get hands-on experience in sample preparation, instrument operation and data visualization and analysis.

Agenda:

8:30-9:00am: MERSCOPE workflow overview

A short presentation to explain the general workflow of sample preparation for MERSCOPE

9:00-12:30pm: MERSCOPE sample preparation demonstration

Hands on sample preparation training with fresh frozen mouse brain samples, covering key steps of MERSCOPE's sample preparation workflow, including:

- Probe hybridization (0.5 hours)
- Gel embedding (2 hours)
- Clearing (0.5 hours)

12:30-1:30pm: Lunch break

1:30-2:30pm: MERSCOPE instrument demo

A live demo walk-through of instrument loading for MERSCOPE imaging

2:30-3:30pm: MERSCOPE data visualization

A live demo of how to visualize MERSCOPE data using MERSCOPE Visualizer

POSTER ABSTRACTS

Poster # 1 (A Bhandiwad et al.)

Curvilinear coordinate systems for visualizing adult and developmental neuroanatomical structures

Ashwin A Bhandiwad[1], Lydia Ng[1]

[1]Allen Institute for Brain Science, Seattle, WA, USA

The complex three-dimensional geometry of neuronal cell type organization and connectivity, particularly through development, poses challenges in understanding brain structure. Understanding how brain regions' shape and connectivity change throughout an animal's lifespan allows extraction of topographic and organizational features for studying structural organization and patterns of development. To understand these features, a nonlinear coordinate system is essential. This system would transform data from Cartesian (x,y,z) coordinates into a flatmap, a visualization that preserves nearest-neighbor relationships while unfolding brain regions into a rectangular prism. Previously, Laplace's equation was used to find the shortest distance across the columnar axis of the mouse cortex to generate curvilinear coordinates. Here we apply Laplace's equation to develop a generalized workflow for generating curvilinear coordinates for multiple brain structures. We provide specific examples from the adult mouse hippocampus and in developmental prosomeric model parcellations. The resulting flatmaps convert Cartesian axes to anterior-posterior, roof plate-floor plate, and radial axes. Using parcellations and anterograde connectivity data, we show that the resulting shortest distance paths preserve local topography and nearest-neighbor geodesic distances. We show how curvilinear flatmaps reveal regional compartmentalization within the hippocampal dentate gyrus and Ammon's horn. Finally, we show how flatmaps from hindbrain rhombomeres in early development can be aligned with the goal of connecting regional flatmaps into a comprehensive geodesic map of the adult and developmental mouse brain.

Poster # 2 (A Deryckere et al.)

Developmental programs underlying the expansion of neuron types in the vertebrate forebrain

Astrid Deryckere[1], Saket Choudhary[2], Elias Gumnit[1], Jamie Woych[1], Rahul Satija[2,3], Maria Antonietta Tosches[1]

[1] Department of Biological Sciences, Columbia University, New York, NY , USA
[2] New York Genome Center, 101 Avenue of the Americas, New York, NY, USA
[3] Center for Genomics and Systems Biology, New York University, NY, USA

The central nervous system is one of the most complex organs, allowing organisms to execute daily tasks with astonishing accuracy. During vertebrate evolution, new neuron types have evolved in the brain, contributing to a general expansion of nervous system complexity, and ultimately behaviors. This expansion of neuron types originates from changes in the developmental program, where progenitor cells sequentially generate distinct neuron types. In the insect nervous system, new neuron types generally evolve by expanding the neurogenic phase of a progenitor cell. By adding extra cell cycles and diversifying the progenitors' temporal gene expression programs, new neuron types are added to the lineage of progenitor cells. Whether a similar mechanism underlies the expansion of neuronal diversity in vertebrate brains remains unclear.

To generate new insights on the evolution of neuron types in the vertebrate brain, we study the development of neuronal diversity in the pallium (dorsal telencephalon) of tetrapods. By studying the salamander Pleurodeles waltl, we discovered that pyramidal neuron types are organized in at least two sublayers across the pallium, indicating that layering of neuron types is ancestral in tetrapods. Additionally, birthdating experiments indicate that these layers are generated sequentially in the salamander brain, similar to what has been described in reptilian and mammalian cortices. To investigate whether the diversity of salamander and mammalian pallia correlates with differences of radial glia progenitors, we profiled the developing telencephalon of salamanders using single-cell RNA sequencing. We found that the diversity of salamander and mammalian radial glia progenitors over developmental time could be described by gradual changes in the expression of similar gene sets, including the same temporal transcription factors. This indicates that an insect-like model for the developmental expansion of neuronal diversity does not apply to the vertebrate cerebral cortex. Our data suggest that the expansion of neuronal diversity in vertebrate brains might have arisen through changes of neuronal specification programs in post-mitotic neurons rather than in progenitors.

Poster # 3 (A Halley et al.)

Movement representations in the primary somatosensory cortex (S1) of the greater galago Otolemur garnetti

Andrew C. Halley[1], Iwona Stepniewska2, Qimeng Wang[2], Jamie L. Reed[2], Hui-Xin Qi[2], Jon H. Kaas[2], Leah Krubitzer[1,3]

[1]Center for Neuroscience, University of California, Davis
[2] Department of Psychology, Vanderbilt University
[3]Department of Psychology, University of California, Davis

What role does primary somatosensory cortex (S1) play in generating movements that are unique to primates? S1's role in movement has been shown by the application of long-train intracortical microstimulation (LT-ICMS) in a wide range of mammals, including primates, rodents, bats, and marsupials. It has also been shown that stimulation of S1, primary motor cortex (M1), premotor cortex (PMC) and posterior parietal cortex (PPC) results in distinct movement types (e.g. forelimb extension vs. retraction). In New and Old World monkeys, S1 plays a central role in motor control, but no study has yet applied these methods to a species of prosimian primate – the lineage of living primates thought to most closely resemble the earliest primate ancestors. In this study, we used LT-ICMS in order to characterize movement representations in the primary somatosensory cortex (S1/3b), frontal motor (e.g. M1, PMC) and posterior parietal (PPC) cortex of the greater galago (Otolemur garnetti). We found that S1 contains motor representations of the hindlimb, torso, forelimb, jaw, lips, tongue, ears, and eyelids. Stimulation of M1, PMC, S1, and PPC elicited distinct movement types of the forelimb, hindlimb, and tongue. Each region included a large representation of the forelimb. In comparison to other primates, the representation of forelimb digits was relatively smal in the cortical areas that we examined. We also observed a large region of tongue representation across cortical fields. This research shows that in galagos, as in other primate lineages, S1 plays a central role in motor control of forelimb and other parts of the body. Given its similar role in other mammalian lineages, it is likely that S1 has played a part in neocortical control of movement since the earliest ancestors of living mammals.

Poster # 4 (A Mabou Tagne et al.)

Frequent Δ9-THC exposure during adolescence impairs sociability in adult mice exposed to an aversive painful stimulus

Alex Mabou Tagne[1], Yannick Fotio[1], Zachary Alan Springs[1], Shiqi Su[1], Daniele Piomelli[1,2,3]

[1]Department of Anatomy and Neurobiology, School of Medicine, University of California, Irvine, CA, United States
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Early-life exposure to Δ9-tetrahydrocannabinol (Δ9-THC), the intoxicating constituent of cannabis, has been found to potentially induce enduring neurochemical changes in brain structures involved in the regulation of sociality. However, the precise impact of these changes on social behavior later in life remains unclear. In this study, we exposed male mice to moderate daily doses of Δ9-THC (5 mg/kg, intraperitoneal) during adolescence (postnatal day, PND, 30 to 43) and, when animals reached adulthood (PND70), we assessed their performance in the three-chamber social interaction task before and three weeks after injection of the chemical irritant formalin (1 % vol, intraplantar), which produces both immediate and persistent pain-related behaviors in mice. The results of our study revealed that prior Δ9-THC treatment did not alter social interaction in control adult mice. By contrast, it disrupted social behavior in animals that developed lasting sensory abnormalities following formalin injection. These findings suggest that frequent exposure to Δ9-THC during adolescence causes in male mice a dormant dysfunction in social behavior which can be unmasked in adulthood when the animals experience a painful aversive state. Further research is needed to elucidate the underlying neurobiological mechanisms and to determine whether these effects are specific to male mice or extend to other populations. Understanding the impact of early-life cannabis exposure on social behavior is crucial for informing public health policies and interventions related to cannabis use, particularly among teenagers.

Poster # 5 (A Malci et al.)

Anatomical and functional connectivity between the visual cortex and the anterior cingulate cortex in a mouse model of Angelman Syndrome

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The anterior cingulate cortex (ACC) is a prefrontal area involved in multiple functions including cognitive control, emotion regulation and pain perception in mice. Also, ACC is visually responsive and receives direct input from the visual cortex (VIS). Our previous work demonstrated that patterned visual experience drives plasticity in mouse ACC. Here, we seek to understand the circuits underlying visual encoding and experience-dependent plasticity in mouse ACC. We investigate anatomical connectivity of ACC and VIS by using viral tracing tools and immunohistochemistry. To investigate the functional role of VIS-ACC projections in visual information processing, we manipulate VIS-ACC projections by using chemogenetic tools and combine this approach with in vivo visualy evoked local field potential (VEP) recordings in awake mice. We show that ACC receives monosynaptic inputs from both primary visual cortex (V1) and medial secondary visual cortex (V2M), with a stronger input coming from V2M. We confirm that presentation of visual sequences across four days drives experience-dependent plasticity in ACC and V1. In addition, chemogenetic inhibition of V1 during stimulus presentation seems to affect experience-dependent plasticity in ACC.

Sensory processing deficits are common in individuals with neurodevelopmental disorders, such as Angelman syndrome (AS) which results from functional loss of the maternal copy of the UBE3A gene. According to studies in AS mouse models, impaired circuit development may lead to functional deficits, particularly in visual processing. Therefore, we study anatomical and functional circuitry to ACC in a mouse model AS. Our aim is to characterize long-range anatomical projections from VIS to ACC in wild-type mice and test the hypothesis that differences in VIS-ACC connectivity may lead to abnormal VIS and ACC function in AS.

With ongoing in vivo studies, we plan to better understand how VIS-ACC projections are valuable for encoding visual input. Anatomical and functional characterization of VIS-ACC circuitry wil prepare a strong basis for the future AS studies focusing on visual processing dysfunction.

Poster # 6 (A Ozgur et al.)

Neuronal population dynamics for learning in the posterior parietal cortex

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Decision-making is a critical component of behavior. Learning to make a correct decision often implies that an association becomes predictable, leading to stabilized action selection in order to maximize reward. Neuronal ensembles are theorized to underpin these associations through distinct networks of neurons that correspond to specific outputs such as memories, decisions, and ultimately behaviors. Yet, little is understood about how these ensembles form and evolve throughout learning. We have developed a freely moving, two-alternative forced choice behavioral paradigm to assess the ensemble dynamics in mice learning a decision-making task. Our data indicates that this task is dependent on the posterior parietal cortex, and we take advantage of genetically encoded calcium indicators to follow neuronal dynamics in this region via head-mounted miniature microscopes. Using a generalized linear model, we can decode behavioral accuracy based on neuronal activity in expert, but not in naive mice. By following the dynamics of neuronal populations, we gain insight into the changes in characteristic clusters that occur across learning. Our data indicates a clear distinction between neuronal activity encoding navigation and decision-making

Poster # 7 (A Soronow et al.)

Bell Jar: A Semi-Automated Registration and Cell Counting Tool for Mouse Neurohistology Analysis

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To investigate the anatomical organization of neural circuits across the whole brain, it is essential to accurately register the experimental brain tissue sections to a reference atlas. This procedure is also a prerequisite to quantify the locations and numbers of cells of interest in specific regions. However, it remains challenging to do registration on experimental tissue due to the intrinsic variation among the specimens, tissue deformation introduced by histological processing, and the potential inconsistency of the experimenter during manual annotation. Here, we introduce Bel Jar, a multi-platform analysis tool with semi-automated affine warping of atlas maps onto microscopic images of brain sections, and machine learning-based cell detection. Bell Jar's graphical user interface (GUI) and dependency management enable users to obtain accurate results without programming expertise. To compare Bell Jar with previously published methods, we fluorescently labeled neurons in the mouse visual cortex with either an engineered rabies virus or an adeno-associated virus (AAV) for neural circuit tracing and quantified Bell Jar's performance at each step of the pipeline for image alignment, segmentation, and cell counting. We demonstrated that Bell Jar's output is as reliable as manual counting by an expert; it is more accurate than currently available techniques, even with noisy data, and takes less time with fewer user interventions. Bel Jar provides a semi-automated analysis workflow to facilitate the precise mapping of histological images of the mouse brain to the reference atlas, and the quantification of cellular signals users train it to recognize.

Poster # 8 (C Davis et al.)

A neural circuit for male sexual behavior and reward

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Male sexual behavior is innate and rewarding. Despite its centrality to reproduction, a molecularly-specified neural circuit governing innate male sexual behavior and reward remains to be characterized. We have discovered a neural circuit necessary and sufficient for innate male mating. This circuit connects chemosensory input to BNSTprTac1 neurons, which innervate POATacr1 neurons that project to centers regulating motor output and reward. Epistasis studies demonstrate that BNSTprTac1 neurons are upstream of POATacr1 neurons, and BNSTprTac1-released Substance P following mate recognition potentiates activation of POATacr1 neurons through Tacr1 to initiate mating. Experimental activation of POATacr1 neurons triggers mating, including in sexually-satiated males and is rewarding such that it elicits dopamine release and self-stimulation of these cells. Together, we have uncovered a neural circuit that governs the key aspects of innate male sexual behavior: motor displays, drive, and reward.

Poster # 9 (C Driskill et al.)

Vagus nerve stimulation (VNS) alters activity in networks that regulate drug-seeking

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Substance use disorder is a chronic relapsing condition often marked by the inability to cease drug use despite negative outcomes. Environmental stimuli presented during drug taking become hyper-salient reward indicators or cues and can make abstaining from drugs difficult. Extinction is a learning process that can reduce the power of these cues by creating a neutral association with a previously drug paired cue. Unfortunately, extinction-based therapies have had limited success in long term prevention of relapse. Our lab has previously shown that vagus nerve stimulation during extinction training from drug-seeking behavior reduces drug seeking during cue-induced reinstatement. Additionally, we found changes between rats given VNS versus Sham stimulation in the expression of immediate early genes in regions associated with reinstatement. The medial pre-frontal cortex (mPFC) is implicated in the regulation of drug seeking behavior, but little is known about the networks that drive mPFC activity during cue-induced reinstatement. Here we tested how pairing extinction learning with VNS alters expression of the immediate early gene cFos during reinstatement in networks that converge on the mPFC.

We infused a GFP expressing retrograde AAV into either the infralimbic cortex (IL) or prelimbic cortex (PL) to label cells that project to the mPFC. Rats self-administered cocaine for 15 days and then underwent 10 days of extinction training with VNS or sham stimulation, followed by cue-induced reinstatement. Rats were sacrificed after reinstatement and tissue from regions associated with reinstatement were stained for cFos as a marker of neuronal activity. We then quantified how VNS altered the total number of cFos-positive cells, as well as the co-localization of cFos+ cells that project to the mPFC. We hypothesize that these changes in neuronal activity in mPFC-projecting neurons contribute to the VNS-induced suppression of drug seeking during cued reinstatement. These results help us gain a better understanding of the mechanisms of how VNS facilitates extinction learning from drug seeking behavior.

Poster # 10 (C Escoubas et al.)

Type I interferon responsive microglia shape cortical development and behavior

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#These authors contributed equally

Microglia are brain resident phagocytes that can engulf synaptic components and extracellular matrix as well as whole neurons. However, whether there are unique molecular mechanisms that regulate these distinct phagocytic states is unknown. Here we define a molecularly distinct microglial subset whose function is to engulf neurons in the developing brain. We transcriptomically identified a cluster of Type I interferon (IFN-I) responsive microglia that expanded 20-fold in the postnatal day 5 somatosensory cortex after partial whisker deprivation, a stressor that accelerates neural circuit remodeling. In situ, IFN-I responsive microglia were highly phagocytic and extended across multiple cell diameters to actively engulf whole neurons. Conditional deletion of IFN-I signaling (Ifnar1fl/fl) in microglia but not neurons resulted in dysmorphic 'bubble' microglia with staled phagocytosis and an accumulation of neurons with double strand DNA breaks, a marker of cell stress and hyperexcitability. Conversely, exogenous IFN-I was sufficient to drive neuronal engulfment by microglia and restrict the accumulation of neurons with dsDNA breaks. Juvenile IFN-I deficient mice had excess excitatory neurons in the developing somatosensory cortex and displayed tactile hypersensitivity to whisker stimulation suggesting altered sensory processing. These data define a molecular mechanism through which microglia engulf neurons during a critical window of brain development. More broadly, they reveal key homeostatic roles of a canonical antiviral signaling pathway in brain development.

Poster # 11 (C Kuan et al.)

A Cell-Fate Protomap of Neuroglial Progenitors in the Murine Cerebral Cortex?

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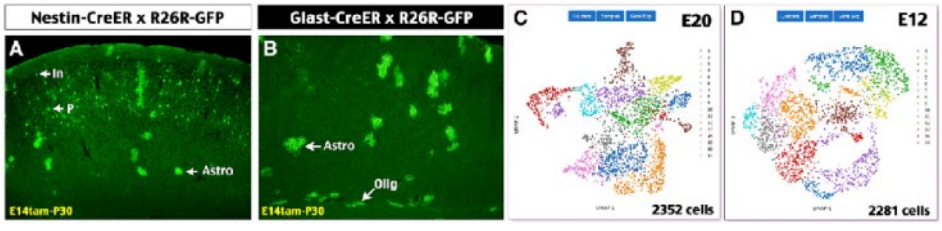
The mammalian brain comprises heterogeneous neuroglial cell-types that expand at distinct times in development. These diverse cell-types may derive from omni-potential stem cell/radial glia (RG) following a sequential order. Alternatively, the neuroglial progenitors in the mammalian brain may be specified early, but expand in a temporal order, i.e. a protomap of cell-fate diversification.

To distinguish between these two possibilities, we performed lineage tracing in Nestin-CreER and Glast-CreER (the RG driver) mice crossed with R26R-EGFP mice, respectively, using tamoxifen-dosing at embryonic day 14 and analyzing the progeny at postnatal day 30 (E14tam-P30 chase). The lineage tracing in Nestin-CreER mice detected cortical pyramidal neurons (P), interneurons (In), astrocytes (Astro) and oligodendrocytes (Olig), as anticipated for neuroglial progenitors (Fig 1A). In contrast, lineage-tracing in Glast-CreER mice only detected astrocytes, oligodendrocytes, and postnatal neurons in the subventricular and the hippocampal sub-granular zones, suggesting a restricted cell-fate potential in RG (Fig 1B). Next, we used FACS to isolate neuroglial progenitors in E12, E14, E16, E18, E20/P0, and P3 Nestin-EGFP embryos/mice for scRNA-Seq analysis with the SPLiT-Seq method. When one of 6 SPLiT-Seq sub-libraries was sequenced, we captured the transcriptome of >1,000 Nestin-EGFP+ progenitors and found distinct cell-clusters in al examined ages. For example, 2,352 progenitors form 17 distinct clusters in E20 Nestin-EGFP embryos (Fig 1C), while 2,281 progenitors in E12 Nestin-EGFP embryos are also parcelled into 15 clusters (Fig 1D), suggesting early diversification of neuroglial progenitors in the murine cerebral cortex. This scenario is reinforced by the absence of a predominant cluster in scRNA-Seq from E12 to P3.

We are sequencing additional sub-libraries captured with the SPLiT-Seq platform to increase the scale of scRNA-Seq analysis, and will use trajectory analysis to assess the ontogeny relationships among cell clusters of Nestin-EGFP+ neuroglial progenitors in development. These results wil be discussed at the meeting.



Poster # 12 (C Nguyen et al.)

Characterizing the Impact of Thalamocortical Afferents on Cortical Fate Specification

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The thalamus has largely been thought of as a relay center for sensory information destined for the cortex. However, the thalamus also plays a vital developmental role. It grows in paralel with the cortex and together these areas form early reciprocal thalamocortical afferents (TCAs). According to the protocortex hypothesis, extrinsic thalamic signaling is necessary for refining cortical areas and cell types. However, the specific contribution of thalamic input and TCA-derived cues remain unknown. Organoids, 3D structures generated from stem cells, provide a tractable system to answer these types of questions as they recapitulate aspects of early human development. Thus, they can be used to assess the factors required to transition pluripotent cells into differentiated cell types. Furthermore, organoids allow us to visualize cortical development in isolation or with extrinsic inputs by fusing cortical and thalamic organoids. In this study, we generate cortical and thalamic organoids to investigate thalamic signaling and TCA-derived molecular cues involved in cortical patterning. In our thalamic organoids, we induce discrete morphogenetic gradients to enrich for neuronal populations of interest. Furthermore, we validate a protocol to fuse organoids resembling early developing human cortex and thalamus into thalamocortical assembloids. Using single-cell RNA sequencing and immunohistochemistry techniques, we reveal the ability of reciprocal TCAs to induce arealization of human cortex and thalamus. Revealing the contributions of early thalamic signaling can enhance our knowledge of neurodevelopmental disorders characterized by thalamocortical dysregulation, including schizophrenia and autism. Elucidating the mechanisms underlying this developmental divergence may help inform future therapeutics.

Poster # 13 (C Pineda et al.)

Pharmacological deactivation of the cortex reveals how the cortical reorganization that results from the early loss of vision in the short-tailed opossum (Monodelphis domestica) is associated with behavioral and kinematic adaptations in sensory-guided ethologically relevant tasks

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Early sensory input dramatically impacts neocortical organization and behavior. In humans, congenitally blind adults adopt new strategies to navigate and acquire new means of written communication, such as Braille reading. These behaviors are supported by the spared senses, which blind adults use in new ways to generate adaptive behavior. It has been shown that the occipital cortex of blind humans is active during braille reading tasks. However, despite the importance of these compensatory behaviors to the lives of congenitally blind humans, it is not known how the reorganized occipital cortex contributes to such behavioral compensation. Studies in our laboratory in short-tailed opossums (Monodelphis domestica) that are bilaterally enucleated at post-natal day 4 (EB), before the formation of retinogeniculate and thalamocortical pathways, reveal drastic changes to the behavior and cortical organization of EB opossums. For example, EB opossums have lower texture discrimination thresholds than sighted controls (SC) and lower error rates in complex navigation tasks, which are accompanied by postural differences when compared to SC opossums (Englund et al., 2020; Rammamurthy et al., 2021). These differences in behavior co-occur with the functional reorganization of the visual occipital cortex (rV1) of EB opossums. Studies show that the cortical area usually devoted to vision in SC opossums is reorganized and represents somatosensory and auditory stimuli in EB opossums (Kahn & Krubitzer, 2002). To examine how EB opossums compensate for blindness in an ethologically relevant context, we trained EB and SC opossums in a skilled reaching task. Animals were recorded with 3 video cameras positioned in stereo, which allowed us to extract pose kinematics in three dimensions using DeepLabCut, a deep learning algorithm (Mathis et al., 2018). Results show from tests that EB opossums compensate for the lack of vision under light and dark conditions, and both EB and SC rely heavily on tactile and olfactory information. Kinematic differences accompany the compensation in performance accuracy. To examine what compensatory function the reorganized occipital cortex imparts to the performance of EB opossums, the occipital and somatosensory cortex of EB and SC opossums was pharmacologically deactivated during reaching and grasping, and ladder-rung walking tasks. Characterizing the effects of the deactivation of both S1 and rV1 alowed us to determine how the behavioral contributions of rV1 compare to that of S1 in both ethologicaly relevant behavioral tasks. These data contribute to the growing body of knowledge about the impact of cortical reorganization on the behavioral compensations of congenitally blind individuals.

Poster # 14 (C Zhang et al.)

Local Connectivity of Mouse Primary Visual Cortex

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In the mammalian neocortex, local interactions among excitatory and inhibitory neurons play essential roles in processing and integrating thalamocortical and corticocortical inputs. While tremendous diversity in the molecular, morphological, and functional properties of cortical neurons have been discovered, it remains largely unknown how different cell types are wired into function-specific pathways. Large-volume serial section electron microscopy (ssEM) provides unprecedented opportunities to uncover the anatomical underpinnings of complex cortical circuits. From a previously acquired milimeter-scale ssEM image volume of mouse primary visual cortex (VISp), we reconstructed and analyzed synaptic connectivity of intratelencephalic neurons (ITs) in layers 2/3 (L2/3) and 5 (L5). We focused on the local intralaminar connections among these ITs and their networks with nearby inhibitory neurons. VISp L2/3 ITs exhibited heterogeneous axonal morphology and output connectivity patterns, which well correlates with our earlier findings of multiple dendritic morphological groups of L2 and L3 ITs. L2 ITs avoided synapsing with L4 neurons, whereas L3 ITs made a significant number of synapses across layers. Both L2 and L3 ITs heavily invested in inner-group inhibitory networks (i.e., L2-specific and L3-specific), instead of intralaminar inhibition. Compared to L2 ITs, L3 ITs made more synapses with L5 ITs. VISp L5 ITs also showed different axonal output patterns. The majority of L5 ITs had long axons extending laterally and exceeded the edges of the image volume, whereas a small group of L5 ITs stood out with vertically ascending axons that heavily branched within L2/3. As a result, these L2/3-dense L5 ITs had significantly more output synapses onto L2/3 neurons compared to other L5 ITs. Furthermore, this L2/3-dense population could be divided into two subgroups based on their distinct morphologies as well as synaptic connectivity. Subgroup 1 preferentially drove inhibition onto L3 ITs, whereas subgroup 2 provided more excitation to L2 than L3 ITs. While both subgroups largely targeted L2/3, subgroup 2 had more innervation with L5 neurons than subgroup 1. Overall, this study demonstrates how the morphological heterogeneity of cortical neurons is reflected in the local connectivity of VISp. Moreover, our findings provide anatomical evidence on cell type-specific local interconnections between VISp L2/3 and L5, which would shed light on mapping specific pathways previously proposed by molecular and functional studies to be involved in the cortical microcircuits involved in predictive coding.

Poster # 15 (D Gallardo et al.)

Selective genetic labeling to track neurodegeneration in 5xFAD mice: Preliminary evidence that mTOR activation via PTEN deletion delays neurodegeneration

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Although there are known factors that contribute to the development and progression of Alzheimer's disease (AD), mechanisms of neurodegeneration are not firmly established. Because of this, methods for tracking neuronal death in transgenic mouse models of AD may be useful for identifying a potential therapeutic target to prevent, delay or halt neurodegeneration. In the 5xFAD model of AD, there is extensive age-related death of neurons in the cortex and hippocampus. Layer V neurons are a subset of those that degenerate. Here, we describe a novel method for genetically labeling layer V pyramidal neurons using a new transgenic line created by crossing 5XFAD mice withRosatdTomato reporter mice, which allows tracking of neurodegeneration. When mice were 4-5 months old, layer V neurons were retrogradely transduced by injecting AAVrg/Cre into the spinal cord, which permanently turns on tdT expression in these neurons. Cre-dependent activation of tdT expression provides a robust, selective and permanent marker for layer V neuron cell bodies, dendrites and axons. To track neurodegeneration, mice were perfused at 7-15 months of age. Neurodegeneration was evidenced by loss of tdT-positive neurons and progressive appearance of large axonal swellings, fragmentation, nuclear condensation and dendritic dystrophy. Along with this, there were large (20+µm in diameter), extracellular and irregularly shaped TdT-positive profiles in cortical laminae V and below. These tdT-positive profiles may be degeneration debris from layer V neurons that have died. In contrast, control RosatdTomato mice without 5XFAD, retrogradely-transduced layer V neurons expressing tdT exhibited normal morphology up to 26 months of age. The ability to track timing morphological changes in layer V neurons in 5XFAD mice provides a unique platform to test potential therapeutic interventions that reduce, delay or prevent neurodegeneration in this murine model of AD. We used this model to assess whether PTEN deletion had a protective effect against neurodegeneration by creating a triple transgenic 5xFAD mouse with PTENflox/flox and RosatdTomato. As described above, AAVrg/Cre was introduced into the spinal cord in order to transduce layer V neurons, delete PTEN and simultaneously turn on tdT expression. These mice were injected at 4 months of age and perfused at 8-15 months. Preliminary results suggest that PTEN deletion results in greater survival of layer V neurons when compared to control mice (5xFAD; PTENWT/WT; tdT injected with AAVrg/Cre). These results highlight the potential of our tracking method to assess therapeutic interventions aimed at reducing, delaying, or preventing neurodegeneration in AD mouse models.

Poster # 16 (D Huilgol et al.)

Orderly production and deployment of cortical glutamatergic projection neuron types through intermediate progenitors

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The mammalian neocortex is thought to be assembled through an orderly generation of glutamatergic projection neurons (PyN) in an inside-out sequence through direct neurogenesis (dNG) mediated by radial glia (RG), and indirect neurogenesis through intermediate progenitors (IP). Our lab recently established that while dNG generates al PyN classes, iNG differentially amplifies and diversifies PyNs within each class. iNG, therefore, contributes to the vast majority and diversity of PyNs, yet the mechanism and logic of IPs in generating PyN classes remains poorly understood. IP-targeted genetic fate mapping with a Tbr2-CreER driver, birth-dating, PyN typing based on laminar position and viral labeling of projection patterns revealed that PyNs are generated according to their projection targets and laminar position instead of a simple inside-out rule. Using MADM (Mosaic Analysis with Double Marker), we found that individual IPs generate “twin” PyNs with near-identical position and morphology. iNG first produced intrahemispheric (associational) PyNs, followed by calosal and corticofugal PyNs, ending with corticostriatal PyNs (CSPN). During E16-E18, CSPNs were generated for L3 with a calosal branch followed by L2 with an associational branch. The last cohort was deployed back to L5. However, corticothalamic PyNs were relatively sparsely generated. Furthermore distinct PyN types within the same layer were produced at different embryonic time points. Together, these results suggest an overarching logic of corticogenesis based on projection targets, which reflect the sequential assembly of PyNs mediating intracortical circuits and cortical output channels.

Poster # 17 (D Oettler et al.)

Exogenous detection of 13C-glucose metabolism in tumor and diet-induced obesity models

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Metabolic rewiring is a hallmark feature prevalent in cancer cells as well as insulin resistance (IR) associated with diet-induced obesity (DIO). For instance, tumor metabolism shifts towards an enhanced glycolytic state even under aerobic conditions. In contrast, DIO triggers lipid-induced IR by impairing insulin signaling and reducing insulin-stimulated glucose uptake. Based on physiological differences in systemic metabolism, we used a breath analysis approach to discriminate between different pathological states using glucose oxidation as a readout. We assessed glucose utilization in lung cancer-induced cachexia and DIO mouse models using a U-13C glucose tracer and stable isotope sensors integrated into an indirect calorimetry system. Our data showed increased 13CO2 expired by tumor-bearing (TB) mice and a reduction in exhaled 13CO2 in the DIO model. Taken together, our findings illustrate high glucose uptake and consumption in TB animals and decreased glucose uptake and oxidation in obese mice with an IR phenotype. Our work has important translational implications for the utility of stable isotopes in breath-based detection of glucose homeostasis in models of lung cancer progression and DIO.

Poster # 18 (E Ghanbarian et al.)

Enriched experience in adult mice results in long-lasting changes in hippocampal cell dynamics

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Cognitive reserve is known as the main protective factor against age-related cognitive decline. To study cognitive reserve in animals, we developed a new model of environmental enrichment that has shown superior and longer-lasting effects on several cortical and hippocampal memory tests compared to the standard home cage enrichment. The aim of this study is to examine whether this enrichment method, when performed in adult mice, can change hippocampal dependent spatial coding, and how long it lasts. One group of adult male mice (6-8 months, n=5) were trained to run on the enrichment track, which was a square track, loaded with several complex objects made with different textures and materials. The control group (n=5) were trained to run on the control track, which was similar to the enrichment track but loaded with simple, repetitive ramp-shaped objects. We trained the mice on the enrichment/control tracks for one hour per day for three months. When the subjects were middle-aged (13-15 mo) and old (22-24 mo) we imaged CA1 neural activity using head-mounted one-photon miniscopes during free exploration of a familiar and a novel environment. We found that fraction of active cells and firing rate (calcium event rate) of cells in the enriched mice were lower in both familiar and novel environments until old ages. We also tested their memory performance with an object memory retention task, in which they had to explore familiar or novel objects to reach a reward zone. The results showed that the enriched group finished the task faster than the control group both with familiar objects (4.28 ± 1.92 vs 14.12 ± 2.2 min, respectively; $p<0.001$) and novel ones (41.84 ± 10.60 vs. 75.11 ± 8.65 min, respectively; $p= 0.03$). These findings indicate that our enrichment model, when started in adult mice, develops a memory for objects (schemas) that lasts into older ages.

Poster # 19 (E Gingrich et al.)

Repeated use of Teneurin-3 and Latrophilin-2 in circuit-wide topographic target selection of the extended hippocampal network

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Precise circuit assembly is critical for nervous system function and is accomplished, in part, through cell-surface proteins (CSPs) that mediate cell-cell interaction during target selection. Contact-dependent attraction and repulsion are two mechanisms mediated by these CSPs that can be used to select synaptic partners, but the relatively low number of CSPs compared to the vast number of synapses that must be specified presents a biological chalenge to developing axons. A possible strategy to overcome this chalenge is repeated use of the same receptor-ligand pair to specify multiple connections across a network. One such receptor-ligand pair, Teneurin-3 (Ten3) and Latrophilin-2 (Lphn2), has complementary expression across multiple interconnected regions of the extended hippocampal network: Ten3 is expressed only in the medial sub-network (MHN) and Lphn2 only in the lateral sub-network (LHN), following a “Ten3 to Ten3 and Lphn2 to Lphn2” connectivity rule. Within one of these projections, CA1 to subiculum (Sub), Ten3-expressing CA1 axons from MHN are attracted to subicullar Ten3 and repelled by subicullar Lphn2 while Lphn2-expressing CA1 axons from LHN are repeled by subicullar Ten3 (Berns et al., Nature 554:328-333.2018; Pederick et al., Science 372:1068–1073, 2021). The stereotyped, topographical connections and the circuit-wide complementary expression of Ten3 and Lphn2 make this system ideal to test whether the same mechanisms of Ten3/Lphn2-mediated repulsion and homophilic Ten3/Ten3-mediated attraction are re-used at each anatomical node of the circuit. Using a conditional knockout approach in mice, we have found that Ten3 is required in entorhinal cortex (EC) axons to correctly target proximal CA1 and distal Sub. Furthermore, EC axons mistarget when Ten3 and Lphn2 are conditionally deleted from Sub, suggesting these mechanisms generalize to other local connections. To our knowledge, this study is the first to examine if a single receptor-ligand pair can instruct wiring specificity across multiple nodes of a functional network using a conditional knockout approach.

Poster # 20 (E Meamari et al.)

Recruitment of neuronal ensembles linked to compulsive ethanol seeking in rats with a history of negative reinforcement by ethanol

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Fos protein can be utilized to visualize activated neurons that mediate stimulus information and learned associations underlying drug seeking behavior. Here, we sought to examine whether the activation patterns of stimulus-reactive neurons are distinct in rats having learned to associate environmental stimuli with (1) positive reinforcement by ethanol in the nondependent state vs. (2) negative reinforcement (alleviation of withdrawal) by ethanol in rats with a dependence history. The experience of negative reinforcement or withdrawal-related learning (WDL) separates the learning taking place during casual alcohol use from the learning that occurs when alcohol is consumed during withdrawal. WDL-associated stimuli produce significant craving as reflected by several experimental measures of compulsive ethanol seeking compared to stimuli conditioned to ethanol in the non-dependent state. The WDL model is, therefore, ideal to investigate the neurobiological control specifically of compulsive ethanol seeking, and to identify how learned associations between ethanol and the environment are established in the brain. To accomplish this, we have developed a semi-automated brain-wide profiling method for imaging data to count Fos-expressing cells. We identified recruitment of neuronal ensembles that mediate ethanol seeking linked to WDL in seven out of eight brain regions analyzed, including the amygdala and paraventricular nucleus of the thalamus. Moreover, the findings revealed an overall highly differential pattern of neurocircuitry activation by ethanol-associated stimuli linked to negative (WDL) vs. positive reinforcement and suggest the formation of distinct engrams as a consequence of learning that occurs during repeated consumption of ethanol during withdrawal in the presence of contextual stimuli.

Poster # 21 (E Ramirez et al.)

Using intersectional virus targeting of GABAergic neurons in a rat subcortical reward pathway

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The use of rat models is imperative for modeling behaviors that mimic human complexity and find translatable outcomes. However, the ease of making transgenic lines and knockouts in mice has not extended to the rat, limiting the behavioral neuroscience questions that can be answered. The use of intersectional viral targeting utilizing 1 or more recombinases packaged into adeno-associated virus (AAV) vectors has the potential to overcome these limitations, and allow for experimenters to target cell-type specific pathways in many species. While the use of this method in rats has recently been used in cortical regions, protocols for use in deeper brain structures is are stil in need of optimization.

The ventral pallidum (VP) is a structure in the mesocorticolimbic reward pathway involved in cue-motivated reward seeking behaviors and embedded within wider brain reward and aversion circuits. The VP sends major efferents to the reward-related ventral tegmental area (VTA), and the aversion-linked lateral habenula (LHb), suggesting VP importantly regulates both positive and negative motivational states. Both VP GABA and glutamate populations project strongly to both target regions, but the behavioral functions of these pathways, especially during more complex behaviors or mixed motivational states, is poorly understood.

Here we target GABAergic neuronal projections from the VP to the VTA using two different viral strategies in GADiCre transgenic rats: 1) combining Cre-dependent Flp (AAV2-pEF1a-DIO-FLPo) and Flp-dependent DREADDs (rgAAV-hSyn-fDIO-hM3DGq) and 2) using the CreON-FlpON double dependent recombinase engineered by the Diesseroth lab to target the same pathway (VP: AAV8-hSyn-Con/Fon-EYFP;VTA: AAVrg-EF1a-Flpo). Each method wil be evaluated for specificity of cell bodies localized in the VP and axonal projections in the VTA, furthermore, the LHb will also be examined for determining specificity of the targeting. Results presented in this poster will provide insight into choosing the ideal viral targeting strategy when manipulating cell-type specific pathways in deeper subcortical rat reward pathways.

Poster # 22 (Y Ding et al.)

Large-scale Whole Mouse Brain Image Data Processing Using Collaborative Data Workflows on Texera

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Within the realm of neuroscience, gaining a comprehensive understanding of the intricate 3D structure of the brain has become imperative. Traditional histological techniques involve the process of manual sectioning, mounting, and scanning to reconstruct 3D tissue representations, and they have exhibited labor intensity and susceptibility to errors. TissueCyte, an automated serial two-photon tomography imaging system, enables the visualization and reconstruction of complete brain tissues with remarkable robustness. However, the seamless acquisition facilitated by TissueCyte brings in a subsequent demanding post-imaging processing. To solve the problem, we have developed a data analysis pipeline in Python to process the tile images from TissueCyte, generating a single high-resolution image of a brain section. The pipeline is executed in three steps: deformation correction, brightness calibration, and stitching. For modeling deformation, we use bezier surfaces. For brightness calibration, we calculate an average intensity profile. For stitching, we design algorithms for efficient overlap estimation and image blending. Each step represents a unique problem that requires careful analysis and collaboration between researchers for efficient algorithm design. Another challenge is that the participants of brain image processing have various backgrounds. The people include computer scientists who have strong programming skills and neuroscientists who have domain knowledge but limited IT experience. The Python solution does not support efficient collaboration between these researchers. To address this challenge, we also developed a method using Texera, an open source system that supports collaborative data analysis using GUI-based workflows. Deployed as a cloud service, the system allows users to develop and deploy workflows to conduct image-processing analysis. In addition to its user-friendly interface, Texera was able to reduce the total running time from 6 hours to 2.5 hours, thanks to its built-in capabilities to support parallel data processing.

Poster # 23 (F Gomez et al.)

The impact of the environment on the development of the motor cortex: How can a dynamic environment influence the structure and function of the primary motor cortex?

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The developing neocortex is highly malleable. Early experience tunes neural systems to match an organism's environmental context, allowing the organism to generate adaptive behavior necessary for survival, growth, and reproduction in a changing environment. Environmental enrichment (EE) studies have long emphasized the importance of the early environment in which an organism is raised regarding brain development and behavioral outcomes. EE has shown the potential to illuminate how early-life experiences impact adult behavior by influencing the structure and function of the brain. However, some limitations of these studies are their highly controlled and static nature. Furthermore, few studies examine how differences in motor opportunities (affordances), particularly those available in large three-dimensional spaces, impact the motor system. Thus, the current research aims to measure the influence of a more dynamic environment with numerous affordances on the organization of the primary motor cortex (M1) and motor behavior. Specifically, we are interested in determining whether rearing in a semi-naturalistic environment with more diverse movement opportunities can lead to quicker motor development, increased coordination of the limbs, and a more extensive and synergistic (multilimb) body representation in M1. We do this by rearing Norwegian brown rats (Rattus norvegicus) in a dynamic semi-natural environment 3000 times the size of standard laboratory cages and quantifying changes in the functional organization of M1 and subsequent behavior at different developmental milestones. We employ a battery of behavioral tasks designed to uncover differences in limb coordination, gross motor activity, latency in learning, and the ability to adapt to a novel challenge. To assess differences in M1 organization, we generated movement maps of the body representation in M1 with long-train intracortical microstimulation (LT-ICMS) at critical developmental time points (Post Natal Day 28, 40, and ≥ 60) and compare cortical real estate devoted to the representation of particular movements, multilimb representations (synergies), the emergence of these representations, and stimulation thresholds. Results from this study wil allow us to appreciate the extent to which early experience impacts the development of the motor system and the time course over which this natural plasticity occurs.

Poster # 24 (F Zampa et al.)

Ribo-STAMP - A New Method for Measuring Translation in Neurons

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A detailed census of the identity and function of the cell types of the brain is necessary to understanding the complex biology of cognition and behavior. Gene expression programs determine cell-type specification, differentiation, migration, connectivity and ultimately the mature function of brain cell types. RNA sequencing (RNA-seq) is currently used to map brain transcriptomes as proxies of developmental and functional states and advances in single-cell technologies have greatly increased the resolution of cell classifications. However, transcript profiles do not capture the numerous post-transcriptional mechanisms that regulate gene expression, a concern for neuronal cells which heavily rely on translational controls to regulate synaptic plasticity and transmission. Available methods to infer the translatome rely on purification of ribosome-associated mRNA from cell populations (e.g. BAC-TRAP/RiboTAG) or from single cells (e.g. scRibo -seq), suffering from transcript biases, limited coverage or scalability. Moreover, unbiased single-cell proteomics lags next-generation sequencing depth.

To overcome these limitations, we have developed a novel technology called Ribosome Surveying Targets by Antibody-free Mutation Profiling (Ribo-STAMP) (Brannan et al, Nature Methods, 2021), which allows for simultaneous measurement of both the transcriptome and the translatome. In Ribo-STAMP, a fusion of the cytidine deaminase APOBEC1 with a ribosomal protein is expressed in cells, resulting in cytosine into uracil (C -to-U) edits that permanently mark translated mRNAs and that are identified by standard RNA-seq analyses using mutation-aware transcript mapping algorithms.

Here, we establish the utility of Ribo-STAMP for neuroscience research. Using Ribo-STAMP, we analyzed the neuronal translatome at baseline and in response to neuronal stimulation, obtaining a comprehensive perspective of activity-dependent gene expression by concurrently profiling transcriptome and translatome dynamics. We characterized transcriptionaly-independent, translational upregulation of synaptic genes upon stimulation. We integrated Ribo-STAMP and single-cell RNA-seq to obtain the translatome of al cells from the mouse hippocampus. We identified genes uniformly expressed across hippocampal cells but selectively translated in CA1 pyramidal neurons.

Results from this study indicate that Ribo-STAMP can be used for broad neuroscience applications such as cell-type identity mapping throughout the brain as wel as measuring neuronal stimulation-induced translation. Understanding the translational profiles of different neuronal subtypes at baseline and after synaptic changes wil provide insights into how the brain functions in a healthy state and how it may go awry during disease.

Poster # 25 (G Hubbard et al.)

CD40 Modulates Neural Oscillation

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In vivo local field potentials (LFP) provide a valuable perspective on neuronal activity and function. Previous research has elucidated the reflective nature of aberrant neural network function and subsequent field perturbation. However, the cellular basis and electrophysiology of such deviations is incompletely understood. The CD40 receptor protein was recently identified as a contributory modulator of neurite organization and seizure mediation. Alteration of the CD40 molecular signals suggest a role on neuronal activity and subsequent neuronal network organization. Our study aims to better characterize CD40 on neural oscillations.

Multielectrodes assembled within silicon probes were implanted across the cortex-hippocampal axis in adult male CD40 knockout mice (CD40KO) and wild type mice (WT). Spontaneous chronic (LFP) was recorded in freely moving mice. Signal morphology and frequency analysis was then conducted using signal analysis software. The preliminary data demonstrates that CD40 deficiency directly implicates neural activity. The neural oscillations of CD40 knockout mice are predominated by greater proportions of low frequency bands in comparison to WT mice. On average, CD40KO mice have considerably smaller θ/δ ratios during normal activity.

The persistence of intensified low frequency bands in CD40KO mice demonstrates the contributory facets of CD40 on neural activity. Further investigation of this relationship may improve our understanding of neural circuits and network function.

Poster # 26 (G Lippi et al.)

Universal and cell type-specific roles for microRNAs in developing Purkinje cells

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Mammals and soft-bodied cephalopods, two evolutionarily distant bilaterians with remarkable cognitive functions, quickly expanded their miRNA repertoire during evolution. These novel miRNAs are enriched in neural tissues and during development, suggesting that they may play critical roles in the assembly of complex brains composed of many cell types. However, there is a lack of mechanistic studies that support this fascinating hypothesis. Two limitations have prevented progress: inadequate tools to induce miRNA loss-of-function in postmitotic neurons and the limited access to cell type-specific miRNA-target networks.

Here, we overcame these bottlenecks by re-engineering the toolbox to study miRNAs. We applied this toolbox to Purkinje Cell (PC) development, a process where miRNAs were thought to be dispensable. Using a peptide - T6B - that rapidly blocks miRNA function, we found that miRNAs are necessary for PC postnatal differentiation processes. These include dendritic and somatic growth, miRNA functions that are universal to other neuronal subtypes, but also the formation of climbing fiber synapses (CF), that is unique to PCs. We developed an inducible and reversible T6B peptide and showed that we can decouple cell death form developmental phenotypes, and more importantly, that PCs have distinct critical miRNA windows for regulating differentiation processes. To understand the underlying mechanisms, we generated a conditional by inversion knock-in Ago2 mouse line (cSpy3-Ago2). Ago2 is the effector of miRNA function, hence this mouse line allows us to robustly map MTIs in PCs, which represent a rare population of cells in the cerebellum. We identified a PC-specific miRNA-target network, suggesting that miRNAs might contribute to cell type-specific features. Indeed, we showed that expression of the PC-specific miR-206 in pyramidal neurons (PNs) induced PC-like features such as an exuberant dendritic arbor. Conversely, loss-of-function of miR-206 reduces dendritic complexity in PCs and regulates CF innervation during PC development. These miRNAs and other PC-enriched miRNAs maintain their expression patterns into adulthood suggesting they might play important roles for mature PC function.

Our findings show that miRNAs have a universal role in regulating fundamental developmental processes of neurons whilst also providing a layer of gene regulation that gives rise to neuronal subtype-specific features. The tools we developed have enabled us to dissect miRNA-target networks in developing neurons at unprecedented temporal resolution and will be instrumental in uncovering fundamental miRNA mechanisms instructing the assembly of the mammalian brain.

Poster # 27 (G Lur et al.)

Cell type-specific, nonlinear interactions of feedforward and feedback synaptic inputs to posterior parietal cortex

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The integration of feedforward (sensory or bottom-up) and feedback (top-down) neuronal signals is a principal function of the neocortex. Yet, we have limited insight into how these information streams are combined by individual neurons. Using a dual color optogenetic strategy, we found that layer 5 pyramidal neurons in the posterior parietal cortex receive monosynaptic dual innervation, combining sensory inputs (from auditory or visual cortices) with top-down signals (from the anterior cingulate cortex). Subclasses of layer 5 pyramidal neurons integrated these synapses with distinct temporal dynamics. Specifically, regular spiking cells (that are typically considered to be intertelencephalic projection neurons) exhibited supralinear enhancement of delayed, but not coincident inputs. In contrast, intrinsic burst firing neurons (that typically project extratelencephalic afferents) selectively boosted coincident synaptic events. These subthreshold integration characteristics translated to nonlinear summation of action potential firing. Complementing electrophysiology with computational modeling, we found that distinct integration profiles arose from a distinct interaction of Ca2+, Na+ and NMDA conductances and cell-type specific feedforward inhibition. There is growing evidence that subclasses of layer 5 cells form independent microcircuits, carry cell-type specific information, and control distinct aspects of behavior. Our data indicates that underlying these functional differences are distinct cellular properties guiding the integration of sensory information with top-down signals at markedly different time scales.

Poster # 28 (H Nedelescu et al.)

3D brain-wide profiling of neuronal ensembles reactive to relapse-promoting vs. relapse-suppressing cues in rats

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Drug addiction is a chronically relapsing brain disease. We found that while environmental stimuli that signal drug availability (S+) promote relapse, those that signal drug omission (S-) can suppress relapse in rats. This bidirectional modulation of relapse is regulated by two functionally distinct neuronal ensembles (engram cells) of infralimbic cortex (IL) neurons, with each ensemble selectively reactive to S+ or S- (as visualized by Fos protein). The neuroanatomical source of afferents that activate these neurons, however, remains unknown. Furthermore, procedures for automated brain-wide profiling are available for mice, but not rats, which is the preferred animal model for studying more complex models of drug addiction. To address both issues, in rats trained to self-administer cocaine/alcohol, we conducted a brain-wide analysis to identify neuronal ensembles that send axonal projections (visualized by AAV2retro-GFP) to the IL. We developed an automated brain-wide 3D profiling procedure for rats, where image data and cell counts were registered using NeuroInfo to the Waxholm rat atlas (ref: https://www.nitrc.org/projects/whs-sd-atlas). Briefly, [1] whole slide images of serial brain sections (60 µm) were captured by a ZEISS Axioscan slide scanner microscope, [2] these 2D images were aligned and registered using NeuroInfo to the Waxholm rat atlas coordinate system, [3] Fos- and GFP-positive IL-projecting neurons were detected with single cell resolution in NeuroInfo using deep learning methods with anatomic specificity conferred by matching image data to the atlas coordinate space. This method provides superior cellular tagging (staining) and image resolution – especially for the larger rat brains – than similar methods using brain clearing and light-sheet microscopes. Our new NeuroInfo tool can be used to identify brain-wide neuronal networks reactive to relapse-promoting vs. relapse-suppressing stimuli. In short, this study provides a new tool for automated 3D brain-wide profiling of rats and expands our knowledge of brain circuitry mediating environmental modulation of drug relapse.

Poster # 29 (J Chien et al.)

Inter-individual variability in human brain cell type transcriptomes and DNA methylome

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Diversity and individual variability are essential to human cognitive function. Identifying the conserved and variable transcriptomic and epigenomic signatures of the brain's cellular components is critical for understanding the neurobiological basis of individual variation in brain function. We applied single nucleus methylome and transcriptome sequencing (snmCT-seq) to neurons from the frontal cortex (Broadmann Area BA46) of 11 adult human donors spanning a range of ages from 23 to 74, including males and females.

We clustered cells into brain cell types based on methylation features and identified two excitatory neuron types that are most affected by aging. Taking advantage of the multimodal measurements in single cells, we found that changes in mRNA expression between young and old adults correlated with corresponding differences in DNA methylation. We used a mixed-effects model to assess the inter-individual variance within each cell type. Our analysis revealed that compared with other neuron types, upper layer excitatory neurons have higher inter-individual variance in the transcriptome and DNA methylome.

Our multiomic single cell epigenome and transcriptome data from donors with sex and age diversity provide new insight into the diversity of brain cell molecular identity across individuals.

Poster # 30 (J Lim et al.)

Nuclear factor one transcription factors regulate neuronal differentiation during cortical development

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Cortical development involves the differentiation of both neurons and glia in a timely manner. This process is driven by both transcriptional and epigenetic mechanisms that regulate gene expression in precise spatiotemporal patterns. The nuclear factor one (NFI) transcription factors are expressed in almost al cell types during development and in the adult brain. They are also disrupted in human disease, including a variety of developmental disorders and brain cancer. Not only are there multiple NFI genes (NFIA, B, C and X) but there are also multiple isoforms of each gene, making their biological function quite complex and potentially redundant across family members. It is therefore crucial to understand what core aspects of development are essentially controlled by the NFI gene family as a whole, but this has been challenging to study in single gene mutants. To address this, we generated an Emx1-Cre-driven conditional mouse model to delete Nfia, Nfib and Nfix in cortical progenitors and their progeny (note Nfic is expressed at only low levels in brain). Histological analyses of these mice indicated broad defects in brain development and alterations in both neuronal and glial differentiation. To further investigate NFI function in different cell types, we utilised a single-cell multiomics approach to identify changes in chromatin accessibility and gene expression in the developing cortex at embryonic day 14.5 and postnatal day 0. We are currently analysing this large dataset to provide a set of core regulatory functions of the NFI gene family.

Poster # 31 (J Liu et al.)

RWD in vivo stimulation and recording tools for neuron circuits study in disease mouse model and dynamic behavior

Ya-dong Li[1], Yanni Yang[2], Xiaoxuan Yu[2], Zheng Zhou[2], Jing Yang[2], Siqi Wang[2], Linlin Wu[2], Huan He[2], Juan Song[1], **Justin Liu[2]**

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Adult hippocampal neurogenesis plays a critical role in memory, cognition, and emotion processing, and this process is dynamically regulated by neural circuit activity. Here we report that chronic patterned optogenetic stimulation of supra mammillary nucleus (SuM) neurons in the mouse hypothalamus robustly promotes neurogenesis at multiple stages, leading to increased production of neural stem cells and behaviorally relevant adult-born neurons (ABNs) with enhanced maturity. Diverse optogenetics can enhance hippocampal neurogenesis in the disease mouse brain, increase microglia phagocytosis of plague in Alzheimer's disease, result in activation of SuM-enhanced adult-born neurons (ABNs) rescue memory and emotion deficits, promote hippocampal plasticity and activity in Alzheimer's disease (AD). Functionally, selective manipulation of the activity of these SuM-promoted ABNs modulates memory retrieval and anxiety-like behaviors. Our study also discovered that SuM neurons are highly responsive to environmental novelty (EN) and are required for EN-induced enhancement of neurogenesis. Moreover, SuM is required for ABN activity-dependent behavioral modulation under a novel environment. Additionally, this study identifies a critical hypothalamic circuit that couples novelty signals to the production and maturation of ABNs and highlights the activity-dependent contribution of circuit-modified ABNs in behavioral regulation.

Poster # 32 (J Wang et al.)

Deorphanization, Structural and Functional Characterizations of BAI Adhesion-GPCRs

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Brain-specific angiogenesis inhibitors (BAIs, BAI1-3) are crucial in nervous system development and have been implicated in various neurological diseases including schizophrenia. However, little is known about their ligands and functions in the brain. Using proteomic screening, we identified RTN4 receptors (RTN4Rs) as high-affinity ligands for BAI adhesion-GPCRs (aGPCRs). In the high-resolution BAI1/RTN4R complex structure, BAI1 engages RTN4R via a unique glycan-mediated interface, including C-mannosylaton and O-fucosylation. By deleting RTN4Rs in human neurons, we found that RTN4Rs inhibit dendritic and axonal growth, but promote synapse formation by differential binding to glial versus neuronal BAIs, thereby controlling neural network activity.

We further studied the physiological functions and molecular mechanisms of BAIs using transgenic knockout (KO) mice. Indeed, BAI1 and BAI3 promote excitatory synapse formation while restricting dendritic and axonal growth, recapitulating the RTN4R KO phenotypes in human neurons. Moreover, we found that BAI3-dependent regulation of synapse formation requires extracellular binding to RTN4R and C1qls, intact GPCR autoproteolysis-inducing (GAIN) domain, alternative splicing and G protein coupling. Its regulation of axonal and dendritic arborization requires RTN4R binding, alterative splicing, G protein coupling and intracellular ELMO binding. Interestingly, unlike other aGPCRs, autoproteolysis of the GAIN domain and Stachel peptide integrity are dispensable for BAI function. In addition, BAI3 inhibits Gi-mediated signaling while having no effect on other G protein subtypes. Overall, BAI aGPCRs differentially regulate multi-facets of neuronal development via distinct mechanisms.

Poster # 33 (J Yi et al.)

Subcortical activity during the process of coma recovery can be partitioned into distinct network states associated with arousal

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Cardiac arrest (CA) is a major cause of debilitating neurological injury leading to loss of consciousness and eventually coma, resulting from global ischemia and reperfusion injury. A unified picture of how cortical as well as subcortical brain activity, particularly in the brainstem arousal centers and their ascending projections, facilitates the emergence from post-CA coma remains unclear. Male Wistar rats (N = 27) were exposed to 8 minutes of CA by asphyxiation and then resuscitated & monitored by electrocorticography (ECoG) throughout recovery. At 2 hrs (N = 6), 4 hrs (N = 7), 24 hrs (N = 8), and 72 hrs (N = 6) post-CA, rats were sacrificed for c-Fos immunofluorescence and compared against control animals that either did not undergo CA (N = 4) or received sham CA with (N = 3) and without (N = 4) a two-hour anesthesia-free period. Surprisingly, during the deepest coma at 2-4 hours (as characterized by profound ECoG burst-suppression), c-Fos expression peaked in key arousal-promoting reticular activating system (RAS) nuclei (locus coeruleus [LC], periaqueductal gray [PAG], parabrachial nucleus [PBN], mesencephalic reticular thalamus [mRt], all $p < 0.001$, Tukey test unless otherwise stated). Interestingly, c-Fos also peaked at 2-4 hours in regions not previously thought to be critical for coma arousal such as the hippocampal (CA1 $p < 0.01$, CA3 $p < 0.001$, & dentate gyrus $p < 0.001$), tectal (superior & inferior colliculi, all $p < 0.001$), limbic (central nucleus of amygdala, $p < 0.001$), and basal ganglia (caudoputamen, $p < 0.001$) nuclei. Then, c-Fos expression returned slowly to baseline over 72 hours post-CA in all regions. A mathematical model built from the population-level c-Fos expression & ECoG dynamics predicted the early surge of c-Fos activity at 2-8 hours, particularly from the LC, correlates with cortical arousal as measured by decreasing ECoG burst-suppression ratio to baseline levels. After 8 hours, the model predicted that LC c-Fos expression becomes decoupled from ECoG changes. This suggests that recovery from anoxic coma can be partitioned into at least two states: (1) immediate (2-8 hours) elevated RAS activity with paradoxical cortical hypo-arousal, followed by (2) a decay of subcortical activity to baseline levels within 8-72 hours, during which the cortex displays self-sustained non-bursting activity. These findings may inform future methods for monitoring and prognosis of coma recovery in animals and humans by revealing how brainstem activity sets the stage for re-emergence of consciousness. In turn, this may also enable treatment of coma to help promote improved arousal and regain of consciousness after cardiac arrest and other catastrophic conditions.

Poster # 34 (K Krishnan et al.)

Behavioral regression and underlying cellular plasticity in X-linked neurodevelopmental disorders using female mouse models

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Regression is a key feature of neurodevelopmental disorders such as Autism Spectrum Disorder, Fragile X Syndrome and Rett syndrome. In humans and in preclinical models, it is clear that syndromic phenotypes are dynamic over time but phenotyping regression of acquired skills over time has remained elusive. This phenotypic delineation is critical to determine the underlying dynamic changes in cellular and molecular plasticity over disease progression. Using emerging computational neuroethology tools such as DeepLabCut and MoSeq, we have now identified distinct regression phenotypes in a heterogeneous population of a female mouse model for Rett syndrome, an X-linked neurodevelopmental disorder. Particularly, I will present evidence that shows regression is dependent on individuals, age, and behavioral context.

At the cellular level, it has been difficult to make progress on etiology of Rett syndrome in the female brain, due to the inherent mosaicism and X-linked heterogeneity in individual brains. Using quantitative whole brain microscopy analysis such as ABBA and CellPose, we have now identified specific time points, brain regions and cell types that are particularly vulnerable to the mosaic expression of MECP2, the epigenetic master regulator that is dysregulated in Rett syndrome. Most of the field has focused on the hypothesis that cells without MECP2 cause Rett syndrome phenotypes. From these new tools and results, we propose a novel hypothesis that in the mosaic brain, wild-type MECP2 expression levels at particular time points and cell types are critical for Rett syndrome disease progression.

I will share our ongoing technical and conceptual progress in understanding X-linked neurodevelopmental disorders in females.

Poster # 35 (L Chen et al.)

Conditional deletion of Neurexin-2 alters neuronal network activity in hippocampal circuitries and leads to spontaneous seizures.

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Neurexins (Nrxns) have been extensively studied for their role in synapse organization and have been linked to many neuropsychiatric disorders, including autism spectrum disorder (ASD), and epilepsy. However, no studies have provided direct evidence that Nrxns may be the key regulator in the shared pathogenesis of these conditions largely due to complexities among Nrxns and their non-canonical functions in different synapses. Recent studies identified NRXN2 mutations in ASD and epilepsy, but little is known about Nrxn2's role in a circuit-specific manner. Here, we report that conditional deletion of Nrxn2 from the hippocampus and cortex (Nrxn2 cKO) results in behavioral abnormalities, including reduced social preference and increased nestlet shredding behavior. Electrophysiological recordings identified an overall increase in hippocampal CA3→CA1 network activity in Nrxn2 cKO mice. Using intracranial electroencephalogram recordings, we observed unprovoked spontaneous reoccurring electrographic and behavioral seizures in Nrxn2 cKO mice. This study provides the first evidence that conditional deletion of Nrxn2 induces increased network activity that manifests into spontaneous recurrent seizures and behavioral impairments.

Poster # 36 (M Bensafi et al.)

Expertise in olfaction modulates odor perception and functional connectivity in olfactory and associative areas

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Olfaction is a chemosensory modality that plays a major role in our emotional life and well-being. If we know that odors influence our behaviors, we still do not know according to which principles and mechanisms olfactory perception is so variable from one individual to another. Several factors of variation have been identified such as age, sex, or cultural background. Another factor that can explain individual differences in olfaction is expertise. Although it is known that experts not only acquire systematic knowledge of odorant chemistry, but also learn to describe the olfactory qualities of odorants and odor sources in a common language, it is not known whether these semantic and cognitive skills are associated with better detection (lower thresholds) of odorant molecules. Furthermore, very little is known about the anatomical and functional plasticity associated with this perceptual modulation. In the present study, we set out to examine these two questions by comparing a group of experts in olfaction with a control group. The study involved 36 participants, 18 non-experts and 18 experts (mean age: 22.9±3.5 years, 12 women in each group). Participants were asked to perform a threshold test to phenyl ethanol (smelling like rose). Afterwards, they were invited to participate in an anatomical MRI session, followed by a functional MRI session (3 Tesla Prisma Siemens MR-scanner; TR=2,500 ms, TE=30 ms, FA=90, voxel size: 2.70x2.70x2.70 mm, FOV: 270) during which they were asked to smell a series of 7 odorants diffused using an air-dilution olfactometer. Replicating previous studies, we observed that experts provided significantly richer olfactory descriptions than non-expert controls. Second, threshold analysis revealed that experts had a lower olfactory detection threshold than controls (p=0.004). Third, analysis of fMRI data showed that regardless of group, odors induced activations in olfactory and associative regions including the olfactory cortex, amygdala, orbitofrontal cortex, and insula (p-values all corrected for multiple comparisons). Functional connectivity analysis revealed greater connectivity between the olfactory cortex and the right orbitofrontal cortex in experts compared to controls (p-FDR=0.022). Taken together, these results suggest an influence of expertise on odor detection and verbalization abilities on the one hand, and on the neural processing of odor information on the other. The olfactory cortex is involved in both sensory and perceptual processing of olfactory information, whereas the orbitofrontal cortex is involved in associative processing (emotions, semantics). Experts are regularly exposed to olfactory stimuli that they associate with specific terminologies and/or contexts. This increased exposure could strengthen the connections between the olfactory and orbitofrontal cortexes, thus facilitating the processing and integration of olfactory information.

Poster # 37 (K Malyavantham)

Validation of a fully automated lab developed test (LDT) for plasma phosphor-tau 181 levels for Alzheimer's disease diagnosis

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The potential usefulness of plasma phosphorylated tau (pTau) measurements for identifying individuals likely to be on the Alzheimer's disease (AD) continuum is evident from recent literature (1). Here we report the validation of a lab developed test (LDT) for measurement of p-Tau 181 in human plasma that will aid in the evaluation of Alzheimer's pathology in cases presenting with mild cognitive impairment. This novel, noninvasive, blood plasma based Simoa® (Single Molecule Array) immunoassay was validated as a LDT following CLSI guidelines on the fully automated Quanterix HD-X platform for detection of tau protein phosphorylated at the threonine 181 site (p-Tau 181) and aiding in the diagnostic evaluation of Alzheimer's Disease (AD)

Poster # 38 (M Garduño et al.)

Perineuronal nets and microglia in Octodon degus across the lifespan

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Specialized extracellular matrix (ECM) structures known as perineuronal nets (PNNs) have been proposed as key regulators of synaptic plasticity in the mammalian brain. Emergence of these neuron-enwrapping ECM condensates coincides with critical period closure, and PNN disruption in adult rodents has been shown to revert neural plasticity back to critical period-like states. Complementary to PNNs, microglia, the resident immune cells in the brain, play a crucial role in synapse remodeling during development and are thought to be able to regulate the ECM itself. In the present study, we investigate these intersecting mediators of plasticity in the Octodon degus (degu), a precocial Chilean rodent that may be an opportune model for investigating developmental learning and age-related neuropathology. Via immunofluorescent staining, we assessed PNN and microglia expression patterns in 9 anatomical brain regions from 32 degus ranging from 1 month to 40 months of age. Across brain regions, juvenile degus (1-3 months old) exhibited low-PNN but high levels of microglia, while full adults (12-40 months old) showed high-PNN and low levels of microglia, following expected patterns of developmental plasticity. Adolescent (5-8 month old) degus exhibit adult-like PNN levels but, intriguingly, intermediate levels of microglia. We also discover that degus exhibit patterns of PNN expression that differ from those seen in human, mouse, and rat. Degu primary somatosensory cortex shows laminar variation, with deep layers showing the greatest levels of PNN density. The dorsal hippocampus exhibits intense PNN signal in CA3a, less intense yet still robust signal in subiculum, CA3b, CA3c, dentate gyrus, and no detectable PNN signal in hippocampal CA1. These results provide a broad and important glimpse into neuroplasticity across the degu lifespan and help build a foundation for a broader comparative understanding of neural and cognitive development.

Poster # 39 (M Phillips et al.)

Ten color identification within miniscope acquired functional imaging reveals mPFC coding of social identity

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Current capabilities of state-of-the-art in vivo imaging during freely moving behavior can record two, spectrally distinct, fluorophores. This severely limits the number of cell types identifiable in a functional imaging experiment. Here we present a pipeline that enables the distinction of nine neuronal subtypes from regions defined by behaviorally relevant cells during in vivo GCaMP imaging. These subtypes are identified utilizing unique fluorophores that are co-expressed with GCaMP, unmixed by multispectral lambda imaging on a confocal, and spectral fingerprints co-registered with functional data obtained on miniaturized microscopes. Using this method, we recorded pyramidal neurons in the medial prefrontal cortex categorized by projection region during a freely moving social memory task. As neural activity in each category was concurrently imaged, we can determine which projection neurons most preferentially encode identity versus novelty/familiarity and what types of social behaviors are most important for this distinction. This method wil not only increase efficiency for calcium imaging experiments by enabling nine neuronal populations to be investigated simultaneously but also enhances the statistical power of the results by utilizing within subject comparisons.

Poster # 40 (M Rue et al.)

Modular cell type organization of cortical areas revealed by in situ sequencing

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The cortex is composed of neuronal types with diverse gene expression that are organized into specialized cortical areas. These areas, each with characteristic cytoarchitecture, connectivity, and neuronal activity, are wired into modular networks. However, it remains unclear whether cortical areas can be similarly defined by their transcriptomic signatures and how any molecular organization of the cortex is developed. Here, we applied BARseq-based in situ sequencing to interrogate the expression of 104 cortical excitatory cell type markers in 10.3 million cells from nine mouse forebrain hemispheres at cellular resolution. De novo clustering of gene expression in single neurons revealed transcriptomic types that were consistent across animals and recapitulated cell types found in reference single-cell RNAseq datasets. We found that the spatial patterns of fine-grained transcriptomic types of neurons followed the contours of cortical areas. Although individual transcriptomic types were shared across many cortical areas, the compositional profiles of al transcriptomic types were highly predictive of cortical area identity. Grouping cortical areas by similarities in their compositional profiles of transcriptomic types revealed cortical modules that matched cortical subnetworks that are highly interconnected, suggesting that cortical areas that are similar in cell types are also wired together.

As a first step in understanding the developmental control of the characteristic compositional profiles of cortical areas, we removed thalamocortical inputs to the visual cortex by performing binocular enucleation at P1 in four of the nine animals. Enucleation broadly affected cell types across many cortical areas, including a strong effect on excitatory neuron types across al layers in the primary visual cortex (VISp). Surprisingly, although the overall change in cell type composition diminished compositional signatures that were characteristic of primary sensory areas, the compositional profile of VISp remained highly distinct from other cortical areas, including higher visual areas, suggesting a refinement role of thalamocortical inputs in defining area identity. Because BARseq is high-throughput and low-cost, it is uniquely suited for examining differences in cell types across the whole brain in multiple individuals following developmental perturbation, and thus can establish causal relationships between developmental mechanisms and brain-wide cellular organizations.

Poster # 41 (M Tetzlaff et al.)

Spatial transcriptomic characterization of the paraventricular thalamus: A node coding enduring emotional memories

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Rationale: The paraventricular thalamus (PVT) is an emerging node of motivational regulation implicated in reward-seeking, arousal, and fear-learning. Specifically, our previous work has implicated the PVT in encoding early life adversity (ELA). ELA results in a variety of long-term, sex-dependent cognitive and affective alterations to motivated behaviors, but the neural mechanisms of these changes remain unclear. Using a limited bedding and nesting (LBN) model of ELA results in increased reward-seeking behavior in LBN-reared adult female mice and anhedonic behavior in LBN-reared adult male mice. Importantly, fosTRAP methods have shown a robust and specific increased activation of PVT cells in pups during the LBN period. However, the role of transcriptomic changes in select populations of the heterogenous, spatially organized PVT in mediating the effects of ELA on adult motivated behaviors remains unknown.

Methods and Results: This ongoing study employs spatial transcriptomics in adult mice after ELA and in humans with ELA-related depression as compared to healthy controls. We aim to examine the potential changes in transcriptomics in specific peptidergic and other cell populations located throughout the PVT. Initial analyses demonstrates robust activation of genes of interest, holding promise that this approach will allow us to identify mechanisms that encode enduring emotional memory and underlie ELA-induced changes to PVT-related networks and uncover potential therapeutic targets.

Poster # 42 (N Shvedov et al.)

In vivo Imaging in Transgenic Songbirds Reveals Superdiffusive Neuron Migration in the Postnatal Brain

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Songbirds generate newborn neurons that disperse widely throughout their brains throughout life. How these newborn neurons migrate through adult brain tissue is unclear. Here, we leverage transgenic, GFP-expressing zebra finches to systematically characterize migratory dynamics of cell populations in vivo. We demonstrate that previously created transgenic songbirds exhibit GFP in the neurogenic lineage and that expression is strong and sparse enough for cellular resolution imaging through optical implants. Using time lapse two-photon imaging, we followed hundreds of migrating cells in awake, adult animals for up to 12 hours. Migratory neurons were randomly distributed and dispersed in al directions while making frequent course changes, a pattern observed across males and females, juveniles and adults. Cells did not appear to follow known migratory scaffolds, such as blood vessels and radial glia, exclusively. Furthermore, cells appeared to move independently, and were largely uncorrelated in their speed, position, and direction. Importantly, we found that migration dynamics across ages and brain regions were well fit by a super diffusive model. Finally, using a computer simulation, we show that these migratory dynamics are sufficient to quickly disperse throughout the song nucleus HVC. Together, our observations that the cells independently disperse and are super diffusive in their migration allow us to propose a new model of collective cell migration in which cells migrate via a strategy that may maximize dispersal. These behaviors may reflect a specialized form of migration that enables neurons to flexibly navigate through the dense, functional circuitry of the postnatal brain.

Poster # 43 (P Gao et al.)

Mapping the Afferents of GABAergic Interneurons in the Distal Dorsal Subiculum: Unveiling Novel Circuitry in the Hippocampal Formation

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The hippocampal formation, comprising the dentate gyrus (DG), hippocampus proper (hippocampus), and subiculum (SUB), plays a crucial role in episodic memory and spatial navigation. The DG and hippocampus receive and process episodic or spatial-related inputs from layer II/III of the entorhinal cortex, distributing this information to downstream cortical and subcortical regions. While traditionally considered a relay station between CA1 and downstream regions, emerging evidence indicates that the subiculum possesses unique features distinct from CA1, including inputs that are not solely dependent on the hippocampus, specific cellular composition, and distinct spatial/non-spatial representation. These findings suggest that the subiculum may have complemental or even unique roles in information processing. Despite its postulated importance, the subiculum has received considerably less attention compared to the hippocampus, with minimal focus on subicullar GABAergic interneurons. Therefore, the objective of this project is to address this research gap by investigating the anatomical connections of interneurons in the subiculum, specifically focusing on the afferents to the distal part of the dorsal subiculum. The investigation will utilize engineered rabies virus to target overal GABAergic cells, with a specific focus on two major subtypes, Parvalbumin and Somatostatin, in the distal part of the dorsal subiculum.

Poster # 44 (M Hiramoto et al.)

Recognition of transforming image dynamics by chains of sequential firing in the midbrain

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Natural visual scenes are dominated by multifactorial image sequences, but the circuits that integrate complex temporal dynamics of visual inputs are not understood. We explored visual information encoding in the optic tectum, an area which is known to process temporally dynamic sensory information. We found that the majority of optic tectal neurons recognize complex image sequences that transform over time, such as rotations. This is achieved by temporally dynamic response properties, which encode specific trajectories of image transitions over several hundred milliseconds. Furthermore, the scale of the temporal response is plastic in response to training. Calcium imaging reveals that neurons in the circuit respond in a reproducible sequence and the temporal sequence of activity predicts a logical diagram of information processing. This study reveals principles of circuit organization that encode complex the temporal sequence of sensory stimuli.

Poster # 45 (Q Ye et al.)

Monosynaptic Rabies Viral Tracing Reveals Subiculum Circuit Connectivity Alterations in Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly and causes progressive memory and behavioral impairment. Examining the changes in neural circuitry using AD model mice is an emerging strategy for a better understanding of AD neural mechanisms toward discovering new therapeutic targets. Our recent work indicates the disruption of long-range and local neural circuit connections in the hippocampus using an AD mouse model. The subiculum is the major output structure of the hippocampus and is among the earliest AD-impacted brain regions. We hypothesize that age-progressive alterations also occur in the neural circuit organization of the subiculum in the 5xFAD mouse model. To comprehensively map cell-type-specific circuit inputs, we utilized the novel viral-genetic tool of monosynaptic rabies tracing. We quantitatively assessed and compared the circuit connectivity of subiculum excitatory neurons in age-matched C57BL6 control and 5xFAD model mice at young and middle ages (3-4 months vs 8-9 months) in both sexes. The major subiculum input brain regions mapped by rabies tracing include hippocampal subregions, medial septum and diagonal band (MS-DB), subiculum (SUB), post subiculum (post SUB), visual (VIS) cortex, auditory (AUD) cortex, entorhinal cortex (EC), thalamus, and temporal association cortex (TeA). Our results reveal significant alterations in local and long-range circuit connections to the subiculum in AD model mice. The overall brain-wide connectivity strengths of subiculum inputs in aged AD model mice are weaker than in wild type mice. There are significant age and sex differences in the connectivity strengths of multiple input regions, including the hippocampal CA1, CA2, MS-DB, thalamus, RSC, VIS, AUD, and TeA. Our work provides new insights into subiculum-directed neural circuit mechanisms during AD progression and supports neural circuit disruptions as a prominent feature of AD.

Poster # 46 (R Guajardo et al.)

Neuronal extracellular matrix production promotes hippocampal learning

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The brain extracellular matrix (ECM) is a latticework of proteoglycans and associated molecules that both stabilizes synapses and restricts synaptic plasticity. Chondroitin sulfate proteoglycans (CSPGs), most notably aggrecan (gene: Acan), close cortical periods of plasticity through the formation of perineuronal nets, structures thought to stabilize synaptic connections. Furthermore, enzymatic digestion of hippocampal ECM results in contextual learning deficits, suggesting that ECM may stabilize learning-related synaptic changes. The dentate gyrus (DG) is a key region of the hippocampal tri-synaptic circuit, playing an obligatory role in contextual memory encoding. We found that granule cells (GCs), the principal excitatory cells of the DG, heterogeneously express aggrecan-based perineuronal nets. Moreover, GCs produce Acan mRNA in an activity-dependent manner following learning. GC-specific Acan loss during development led to deficits in contextual fear learning in adulthood. These findings demonstrate a role for neuronal ECM production in hippocampal memory. Ongoing studies aim to define the pattern of aggrecan deposition at synapses and the impact of aggrecan on synaptic function.

Poster # 47 (S Ma et al.)

Insulo-frontal Projection Conveys Prior Outcome to Guide Set-shifting

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Cognitive flexibility is the ability to adapt behavioral choices to changes in a complex environment. The brain integrates information about current sensory cues and bodily states with prior decision outcomes to shift attentional sets and make correct decisions. The anterior insular cortex (aIC) processes interoceptive information and directly innervates the medial prefrontal cortex (mPFC), a region indispensable for cognitive flexibility. However, it remains unknown how aIC communicates with mPFC and impacts attentional set-shifting, a type of cognitive flexibility. Here we show that in mice performing attentional set-shifting tasks (AST), the activity of mPFC-projecting aIC neurons decreases with correct decisions and increases after incorrect, unrewarded outcomes. Optogenetically increasing aIC→mPFC projection impairs the shift. Then we use miniscopic calcium imaging to record mPFC excitatory neuron activity and find that in control animals, mPFC neuronal ensembles carry information relevant to decision-making and gradualy stabilize over trials. Optogenetic activation of aIC→mPFC projection disrupts mPFC decoding of prior trial outcomes, ensemble stabilization over trials, and acquisition of set-shifting behavior. Furthermore, activating aIC→mPFC projection exerts a predominantly inhibitory effect on mPFC and pharmacogenetic inhibition of parvalbumin-expressing inhibitory interneurons (PV+ INs) in mPFC prevents the behavioral impairment caused by optogenetic activation of aIC→mPFC projection. In summary, our study suggests that aIC plays a key role in flexible decision-making by conveying prior outcomes to mPFC through feedforward inhibition mediated by PV+ INs.

Poster # 48 (S Wang et al.)

Activity-Dependent Alternative Splicing of Adhesion-GPCR Latrophilin-3 Controls Synapse Formation

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How synapses are assembled and specified in brain is incompletely understood. Latrophilin-3, a postsynaptic adhesion-GPCR, mediates Schaffer-collateral synapse formation in the hippocampus but the mechanisms involved remained unclear. Here we show that Latrophilin-3 organizes synapses by a convergent dual-pathway mechanism by which Latrophilin-3 simultaneously activates GαS/cAMP-signaling and recruits phase-separated postsynaptic protein scaffolds. We found that cell type-specific alternative splicing of Latrophilin-3 controls its G protein coupling mode, resulting in Latrophilin-3 variants that predominantly signal via Gαs and cAMP or via Gα12/13. A CRISPR-mediated genetic switch of Latrophilin-3 alternative splicing from a GαS- to a Gα12/13-coupled mode impaired synaptic connectivity similar to the overall deletion of Latrophilin-3, suggesting that GαS/cAMP-signaling by Latrophilin-3 splice variants mediates synapse formation. Moreover, GαS- but not Gα12/13-coupled splice variants of Latrophilin-3 recruit phase-transitioned postsynaptic protein scaffolds that are clustered by binding of presynaptic Latrophilin-3 ligands. Strikingly, neuronal activity promotes alternative splicing of the synaptogenic variant of Latrophilin-3, thereby enhancing synaptic connectivity. Together, these data suggest that activity-dependent alternative splicing of a key synaptic adhesion molecule controls synapse formation by parallel activation of two convergent pathways, GαS/cAMP signaling and the phase separation of postsynaptic protein scaffolds.

Poster # 49 (S Yau et al.)

Chronic activation of the vHipp-mPFC pathway reduces depression-like behavior but impairs spatial memory

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The hippocampus and medial prefrontal cortex (mPFC) have been implicated in depression pathology and antidepressant response. Brain imaging studies suggest that a dysfunctional connection between these two structures underlies depression symptomatology. Previous studies demonstrated that the ventral hippocampus (vHipp) sends specific excitatory projections to the mPFC (the vHipp-mPFC pathway), which have been implicated in several psychiatric disorders. Here, we investigated whether chronic activation of the vHippo-mPFC pathway using chemogenetic approach elicits antidepressant effects and enhances hippocampal function. Retrograde adenovirus (AAV) driving the expression of Cre recombinase was injected in the mPFC (prelimbic and infralimbic regions) of adult C57BL/6J mice, whereas AAV driving the expression of the human muscarinic Gq-coupled receptor 3 (hM3Dq) under the human synapsin gene promoter (hSyn) was injected in the vHipp. Animals were treated with clozapine N-oxide (CNO, 0.3 mg/kg, i.p.) to selectively activated the targeted vHippo-mPFC pathway for 14 consecutive days, followed by a battery of behavioral tests to assess depressive phenotypes and immunohistochemical analysis for neuronal activation using antibodies against c-Fos. Our preliminary data showed a significant reduction in depression-like behavior in forced swim test, but impaired hippocampal-dependent spatial memory in Y maze test. This memory impairment is in association with reduced number of proliferating progenitor cells and immature neurons (Ki-67 and DCX positive cells, respectively) in the hippocampal dentate gyrus and reduced neuronal activation in the mPFC. The results may suggest that a vHippo-mPFC pathway is involved in reducing depression-like behavior, however, chronic activation of this pathway can lead to impairment in spatial memory.

Poster # 50 (S Park et al.)

Exposure to repeated multimodal stress alters visual processing in adult posterior parietal cortex.

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Our recent data indicate that adolescent exposure to repeated multimodal stress (RMS) disrupts the anatomy and function of the posterior parietal cortex (PPC), with implications to higher order sensory processing. How similar stresses affect the adult parietal circuit is currently unknown. To address this question, we first quantified markers for postsynaptic differentiation. We found that in contrast to adolescents, RMS in adult male C57BL/6J mice does not affect the density of inhibitory or excitatory synapses. To test the effect of adult RMS exposure on more subtle, functional properties of the PPC, we assessed sensory representation using in-vivo two-photon calcium imaging in awake, head-fixed mice. Using a longitudinal experimental design, we measured visual responses of the same PPC neurons before and after a ten-day RMS or home cage (time control) exposure. We found a significant, stress-induced increase in the turnover of visually responsive cells which corresponded to higher mouse-to-mouse variance in the number of visually responsive cells than what we observed in the control group. Additionally, RMS reduced visually evoked response magnitudes and arrested the development of correlational structure in the PPC neuronal population. To determine whether the above changes were specific to sensory circuits, we tested the same parameters during locomotion onsets. Overall, our results suggest that while the effects of stress in adult mice are more subtle than in adolescents, RMS will specifically alter sensory information processing in the PPC.

Poster # 51 (W Cao et al.)

A recently developed "microglia-targeting" AAV capsid enables specific genetic access to hippocampal and neocortical excitatory neurons

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Genetically modified adeno-associated viruses (AAV) using enhancer elements and capsid variants have been used for cell-type specific targeting in the central nervous system. It has been recently reported that adeno-associated virus (AAV) capsid variants (AAV-MG1.1 and AAV-MG1.2) produced by directed evolution capsid engineering (Lin et al., 2022), can mediate efficient in vitro and in vivo microglial transduction, capable of delivering various genetic payloads into microglia with high efficiency. In this study we report that AAV-MG1.2 actualy enables specific genetic access to hippocampal and neocortical excitatory neurons in vivo, but does not infect non-neuronal cells including microglia in vivo. We packaged CAG-EGFP and CAG-tdTomato into the AAV capsid MG1.2, respectively, and stereotaxicaly injected the virus into hippocampal CA1, subiculum and visual cortical regions of adult wild type mice. Through quantification of CaMKIIa+ and GABA- immunostaining, we identified almost 100% of EGFP- or tdTomato-expressing cells to be excitatory cells in hippocampal CA1 / subiculum, and identified 90 % of EGFP- or tdTomato-expressing cells to be excitatory cells in visual cortex. Thus the MG1.2 capsid primarily labeled excitatory principal neurons in hippocampal CA1/ subiculum and visual cortex. In addition, we found that the MG1.2 capsid specificaly labeled the deep layer of the CA1 pyramidal layer in a titer-dependent manner. Lower virus titers (5.15x1012 GC/ml compared to 5.15x1013 GC/ml for MG1.2-CAG-eGFP) resulted in more precise labeling specificaly within the deep layer. This specificity for the deep layer was more pronounced in the ventral CA1. Given the cell type heterogeneity among CA1 pyramidal cells exists along the superficial-deep axis, AAV-MG1.2 can be used to genetically target the deep sublayer of CA1 stratum pyramidale for structural and functional analysis. Taken together our new discovery regarding the AAV capsid MG1.2 expands our genetic toolset to target overal and specific excitatory cell types in the brain.

Poster # 52 (X Zheng et al.)

An AAV-based system for scalable in vivo genetic screens

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Human genetics have identified a long list of risk genes associated with neurodevelopmental disorders and diseases, such as autism spectrum disorder (ASD). However, the detailed mechanisms underlying many of these risk genes remain elusive. To understand the diverse mechanisms of ASD, there is an emerging need for large-scale, high throughput methods to dissect the mechanism of risk genes to reveal their effect with high-resolution, cell-type specific readouts. We developed an adeno-associated virus (AAV) vector-based genetic screening approach to dissect the mechanism of many risk genes at scale with cell type specificity in vivo. We performed an AAV serotype screen and identified a new AAV serotype that can efficiently transduce neural progenitors and newly born neurons in the developing brain. This technology can be applied to dissect the cellular consequences of genetic mutations in different brain regions, and at different time points of neurodevelopment. This high-resolution phenotyping approach would be helpful to understand the onset of diseases, giving insights into the critical window and target cell type and brain region for future therapy designs.

Poster # 53 (Y Ng et al.)

Investigating the Role of Top-Down Cortical Control in Feeding Behavior and Energy Homeostasis

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Obesity is a health epidemic impacting many developed countries, due to the shift towards a sedentary lifestyle and an increased availability of high fat and highly processed foods. The comorbidities of obesity include increased cardiovascular risk, hypertension, stroke, diabetes, al of which negatively affect our population health and longevity. The economic burden imposed on our healthcare system raises an urgent need to address this epidemic and understand the neurobiology of feeding associated with excessive energy intake. Previous studies have shown that the hypothalamus and its various nuclei function as feeding regulators to control energy homeostasis, especially the hypothalamic arcuate nucleus in need-driven feeding behavior. Convergent findings also suggest the presence of other circuits driving compensatory and hedonic feeding behavior. While studies have highlighted the role of reward pathway and homeostatic pathway in energy dysregulation, little attention has been paid to higher order brain regions responsible for cognition and executive function and the role they have in food intake decision-making. The prefrontal cortex (PFC) is responsible for higher order cognitive decision-making and executive functions, and it is implicated eating disorders such as binge-eating disorder. Our preliminary studies have identified a novel neural circuit where cells from the prefrontal cortex (PFC) projects to and innervate the lateral hypothalamic area (LHA). When this circuit was attenuated, mice exhibited a weight increase due to increased food intake. Using circuit tracing and immunohistochemistry, we have identified these the cells of interest in the PFC and their molecular identities and characteristics. Further studies would illustrate the role of these cells play in regulating this feeding pathway and the possibilities of regulating this pathway to treat obesity.

Poster # 54 (Y Senzai et al.)

The superior colliculus is critical for virtual head turns and eye movements during REM sleep

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Since the discovery of REM sleep, the nature of the rapid eye movements that characterize this sleep phase has remained elusive. Do they reveal gaze shifts in the virtual world of dreams or simply reflect random brainstem activity? In a previous study, we harnessed the head direction (HD) system of the mouse thalamus, a neuronal population whose activity reports, in awake mice, their actual HD as they explore their environment and, in sleeping mice, their virtual HD. We discovered that the direction and amplitude of rapid eye movements during REM sleep reveal the direction and amplitude of the ongoing changes in virtual HD, i.e. virtual head turns.
What coordinates the direction of rapid eye movements with that of virtual head turns during REM sleep? We have tested the role of the superior coliculus (SC) because, in awake animals, the SC coordinates eye and head movements to generate gaze shifts. We have discovered that the SC activity can predict the direction of rapid eye movements and virtual head turns during REM sleep. Furthermore, we have also discovered that silencing the SC has a major impact on virtual head turns during REM sleep. These discoveries suggest that the SC, by orchestrating sensorimotor representation in the sleeping brain, may mediate gaze shifts in the virtual world of REM sleep.

Poster # 55 (Y Xie et al.)

Cell-type specific proteomic analysis reveals an activity-induced protein synthesis inhibitor that regulates neuronal plasticity

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Activity-induced protein dynamics is the underlying player of neuronal plasticity. A direct interrogation of the activity-dependent proteome is a crucial step towards understanding the protein components and their individual functions in neuronal plasticity. Here we employed the cell-type specific metabolic labeling and bio-orthogonal non-canonical amino acid tagging (BONCAT), to sample and detect cell type specific nascent proteome upon visual experience in the mouse visual cortex. We detected 2092 proteins on average in excitatory and inhibitory neurons, P28 and P56. We quantified 364, 278, 253, 231 significantly regulated proteins in EX-P56, EX-P28, IN-P56 and IN-P28 respectively, with both unique and shared candidates amongst the tested conditions. Correlation analysis of our proteomic datasets with RNAseq and Riboseq under similar conditions only showed alignment to a limited extend, which indicates the involvement of unique regulatory elements for different proteins at different levels. Pathway analysis revealed protein clusters for synaptogenesis, cytoskeleton remodeling and synaptic transmission. To further understand the functions of these significantly regulated proteins, we designed a secondary functional screening for 11 candidates in vitro, particularly examining their effect on synaptic density and calcium signaling. While al candidates showed significance in different aspects, an inner nucleus membrane protein showed unexpected effect in suppressing global protein synthesis rate. RNAi suppression reverses the effect of protein synthesis suppression. Moreover, different stimulants, both in vitro and in vivo, can al increase its level. The effect size is proportional to the intensity and duration of stimulation. During development, eye opening induces a surge in its expression, which then persists throughout critical period and returns to low level by the closing of the critical period. These data suggest that it might either work as a general activity-inducible homeostatic regulator or participates in activity-dependent plasticity. With stimulation, the newly synthesized protein puncta visualized through FUNCAT-PLA were observed in the nucleus, ER, and neuronal processes, based on which we speculate that this protein regulates protein synthesis both transcriptionaly and post-transcriptionaly, both globaly and localy. With knockdown (KD) and overexpression (OE) experiments in vitro, we found that KD increases excitatory synapse density, but decreases neuronal spontaneous firing frequency. Moreover, the affected neurons fire in a more diverse range of frequency, compare to scramble shRNA control, OE and OE-control neurons, indicating that the culture synchrony is lost. Conversely, OE decreases excitatory synapse density, increases inhibitory density and slightly increases the synchronous network firing frequency. Therefore, we hypothesize that this protein candidate responses to activity by suppressing the synthesis of a selective group of protein, and as a result, unwanted synapses are eliminated to shape a mature network. We are currently gathering data to test our hypothesis. In summary, we conducted a comprehensive interrogation of the activity-induced protein dynamics in the brain, generated an informative proteomic resource to understand activity-dependent plasticity, which leads to the discovery of a potential activity-dependent protein synthesis inhibitor with a function on refining neuronal network.

Poster # 56 (Y Zhang et al.)

Embryonic temporal–spatial delineation of excitatory spinal interneuron diversity

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Neural circuits in the spinal cord that execute movement are comprised of multiple cardinal classes of neurons that emerge from distinct progenitor lineages during embryonic development. While each cardinal class contains multiple neuronal subtypes characterized by distinct molecular, anatomical and physiological characteristics, how these cellular distinctions are acquired and to what extent they translate into functional differences between spinal interneuron subtypes remains unclear. Through a focus on the excitatory V3 interneuron class, here we demonstrate that interneuron subtype diversity is delineated through a combination of neurogenesis timing and final laminar settling position. Birthdating and lineage-tracing of embryonic V3 interneuron development revealed early-born or late-born temporal classes, each of which further diversifies into subclasses with spatially and molecularly discrete identities. Interestingly, while neurogenesis timing accounted for V3 morphological diversification and corresponding membrane properties, laminar settling position accounted for unique electrophysiological profiles distinguishing V3 subtypes within the same temporal classes. Furthermore, temporally and molecularly distinct V3 IN subtypes displayed independent behavioural recruitment patterns demonstrating a functional modularity underlying V3 interneuron diversity. These studies provide a framework for how early embryonic temporal and spatial mechanisms combine to delineate interneuron classes into molecularly, anatomically, and functionally relevant subtypes in adults.

Poster # 57 (Z Dobler et al.)

Adapting and facilitating responses of excitatory neuron populations in mouse somatosensory cortex are dynamic and shaped by experience across days.

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To construct a stable and coherent experience of the external world, sensory circuits must adapt their activity to the statistics of the surrounding environment and filter out irrelevant stimuli. This is achieved in part via stimulus-evoked sensory adaptation (SA), whereby neuronal activity is repeatedly adjusted in response to repetitive sensory stimuli. While SA has been extensively studied at the level of individual neurons on timescales of tens of miliseconds to a few seconds, little is known about SA at the population level and whether SA dynamics are stable across hours or days. Here, we investigate population-level SA in the barrel field of the mouse somatosensory cortex (S1BF), which processes whisker inputs, using in vivo 2-photon calcium imaging of layer (L) 2/3 excitatory neurons in awake adult Slc17-Cre x Ai162 mice (GCaMP6s). In addition to previously described adapting neurons that decreased their firing with repetitive stimulation, we found facilitating neurons that increased their activity, and stil others that were neither adapting nor facilitating. Within each of these populations, individual responses to different whisker deflections were strikingly heterogeneous and stochastic. Replication of these experiments using Scnn1a-Cre x Ai162 mice showed that the response profiles of excitatory neurons in L4 of S1BF were similarly heterogeneous. We also discovered that adaptation to one stimulus does not generalize to different stimuli; when we delivered mice 10 whisker stimuli at one frequency folowed by a second bout at an alternate frequency, we found that adapting L2/3 neurons (but not facilitating neurons) exhibited increased response peak amplitudes after switching to a higher frequency. We also investigated the stability of population SA dynamics by longitudinaly imaging the same L2/3 neurons over several days. Strikingly, most stimulus-responsive neurons did not maintain their SA response profiles (adapting, facilitating, etc.) and the population progressively shifted toward more facilitation and less adaptation across days. These results indicate that 1) Population-level SA is encoded heterogeneously in S1BF and does not universaly generalize; 2) Adapting neurons are most sensitive to shifts in stimulus parameters; and 3) The balance between adaptation and facilitation at the population level is experience-dependent.

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Acknowledgments

This year, over 250 attendees from around the globe are joining our UCI Center for Neural Circuit Mapping (CNCM) conference at the Beckman Center of the National Academies of Sciences & Engineering near the UC Irvine campus. This conference is jointly sponsored by the Cajal Club and the Allen Institute for Brain Sciences. The UCI CNCM would like to express our sin-cere gratitude to individuals and organizations who have contributed to the success of this conference.

We would like to acknowledge the unwavering support of the UCI School of Medicine, especially Dean Michael Stamos, Vice Dean Geoffrey Abbott and the Dean's Office staff. Rachel Pearlman's administrative proficiency has been invaluable in streamlining crucial operations. Jessica Banfield at the marketing team of UCI School of Medicine, has infused energy and vibrancy into communications and promotion materials of this conference. The Anatomy and Neurobiology Department administration, particularly Lesley Dowd, has played a pivotal role in augmenting the scientific reach of our event. Katrina Vera De Castro and The Beckman Center's contributions have helped ensure the logistical success of this event.

Furthermore, we want to thank our 2023 supporters: Vizgen, RWD, Frontiers Media, SFARI (Simons Foundation Autism Research Initiative), Western University of Health Sciences, 4D Nucleome, and CHOC Neuroscience Institute for their financial contributions, and for helping to provide educational and technical training opportunities to our attendees through workshops and bootcamps. Their commitment to fostering the synergy between academia and industry is truly inspiring.

We want to express our sincere gratitude to the CNCM center staff including Lin Lin, Michele Wu, Ginny Wu and Samson Lautzenheiser, who have dedicated countless efforts to make this conference possible.

LinLin

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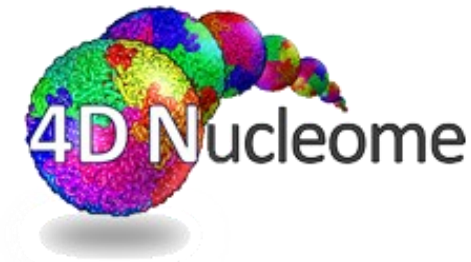

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