THE SIMONS CENTER FOR THE SOCIAL BRAIN (SCSB) NEWSLETTER | Fall 2018

The Simons Center for the Social Brain has 3 major programs:

- Our **Targeted Projects program** supports innovative, collaborative projects undertaken by multiple laboratories.
- Our **Simons Postdoctoral Fellows program** supports the training of young researchers in collaborating labs.
- We build the autism research community through **events** that reach a wide audience, including a **Colloquium Series** and a **Lunch Talks Series**.

INSIDE THIS ISSUE

Our Targeted Projects, which extend for 2-3 years, are structured to require collaboration among researchers in order to address pressing questions in autism research. Here is a timeline of past and current projects:

16p11.2

- NANCY KANWISHER + ANGELA MORGAN
- MARK DALY
- MARK BEAR
- MRIGANKA SUR

THALAMIC RETICULAR NUCLEUS

- MATTHEW WILSON
- GUOPING FENG
- DARA MANOACH
- MICHAEL HALASSA

2013 — 2014 — 2015 — 2016 — 2017 — 2018 — 2019 — 2020

SHANK3

- TROY LITTLETON
- GUOPING FENG
- RUDOLF JAENISCH

LANGUAGE PRAGMATICS

- EV FEDORENKO + REBECCA SAXE
- EDWARD GIBSON
- LAURA SCHULZ + JOSH TENENBAUM

MARMOSET

- MRIGANKA SUR
- ROBERT DESIMONE
- ALAN JASANOFF
- ANN GRAYBIEL

PUBLICATION SPOTLIGHT

- Dorit Kliemann, Hilary Richardson, **Stefano Anzellotti,** Dima Ayyash, Amanda J. Haskins, **John D.E. Gabrieli**, and **Rebecca R. Saxe**. Cortical responses to dynamic emotional facial expressions generalize across stimuli, and are sensitive to task-relevance, in adults with and without Autism. Cortex 103:24-43 [https://doi.org/10.1016/j.cortex.2018.02.006], February 2018.

- Anjali Sadhwani, **Neville E. Sanjana**, Jennifer M. Willen, Stephen N. Calculator, Emily D. Black, Lora J. H. Bean, Hong Li, Wen-Hann Tan. Two Angelman families with unusually advanced neurodevelopment carry a start codon variant in the most highly expressed UBE3A isoform. American Journal of Medical Genetics Part A [https://doi.org/10.1002/ajmg.a.38831], April 2018.

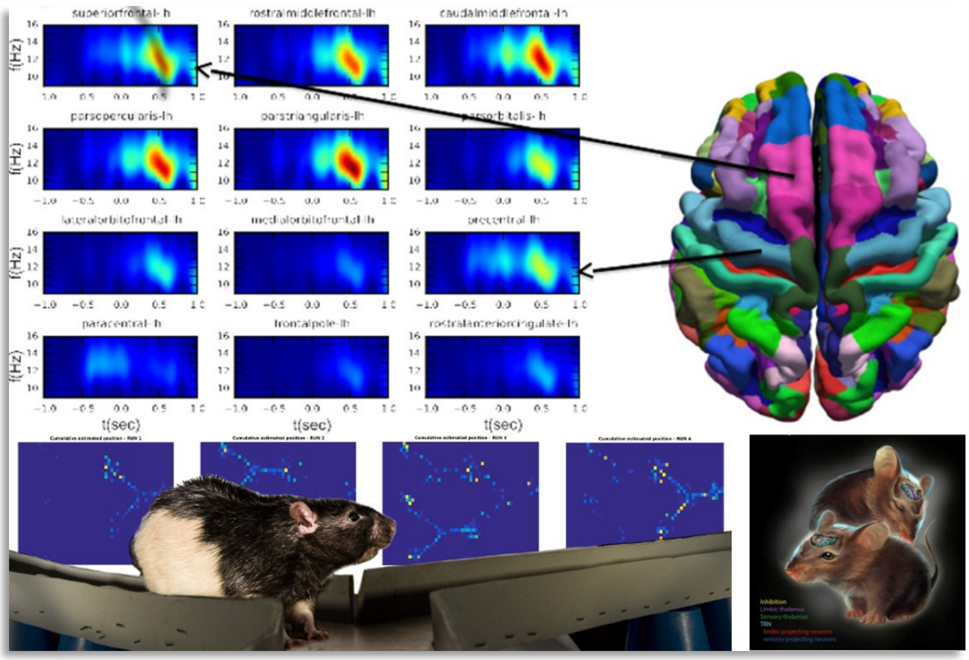
- Jacque P.K. Ip, **Ikue Nagakura**, Jeremy Petravicz, Keji Li, Erik A.C. Wiemer, and **Mriganka Sur**. Major Vault Protein, a Candidate Gene in 16p11.2 Microdeletion Syndrome, Is Required for the Homeostatic Regulation of Visual Cortical Plasticity. The Journal of Neuroscience 38:3890-3900 [https://doi.org/10.1523/JNEUROSCI.2034-17.2018], April 2018.

- Antje Kilias, Andres Canales, **Ulrich P. Froriep**, Seongjun Park, Ulrich Egert, and **Polina Anikeeva**.Optogenetic entrainment of neural oscillations with hybrid fiber probes. Journal of Neural Engineering 15:5 [https://doi.org/10.1088/1741-2552/aacdb9], July 2018.

TARGETED PROJECT UPDATES:

THALAMIC INVOLVEMENT IN ASD, FROM SENSORY AND COGNITIVE PROCESSING TO SLEEP

The thalamus of the brain is the main gateway by which information from the senses reaches the cortex, and the reticular nucleus of the thalamus (TRN) is the guardian of that gateway. Risk genes for autism spectrum disorders (ASD) affect TRN function and may alter communication between the thalamus and the cortex and contribute to the manifestations of ASD. This project brings together a team of four investigators using mouse genetic models of ASD combined with human and rodent electrophysiological approaches to study thalamic involvement in cognition, memory, and sleep. The primary objectives are to validate scalable biomarkers of TRN function that could be used for screening and tracking of disorder progression, and to identify electrophysiological signatures and molecular targets that may relate to brain mechanisms underlying core symptoms.



Top: Using simultaneous EEG and MEG allows localization of cortical activity that is associated with sleep-dependent enhancement of motor memory in both typically developing individuals and those with autism.
Bottom: Neuronal recordings in rodents allow decoding cognitive processing during behavior, rest and sleep. RNA sequencing allows the identification of different neuronal subpopulations within the rodent TRN.

Dara Manoach at Harvard/MGH is using simultaneous magnetoencephalography and EEG in humans to examine sleep spindles -- rhythmic events that are generated by the TRN during sleep and are propagated to the cortex via thalamocortical circuitry. Sleep spindles play important roles in learning and memory and several studies suggest that they are abnormal in ASD. Findings that manipulating spindles improves memory consolidation in typically developing individuals raise the possibility that treating spindle deficits by targeting underlying TRN circuit dysfunction may improve cognition and symptoms in ASD.

Matthew Wilson at MIT has been using simultaneous recording of populations of individual neurons in the TRN, thalamus, and cortex of freely behaving rodents to study the role of sleep rhythms in cognition and memory and how they may be altered in mouse models of ASD.

Michael Halassa at MIT is specifically interrogating TRN subnetworks that project to the cognitive mediodorsal thalamus (MD), testing the hypothesis that MD-projecting TRN neurons play a role in regulating cognitive flexibility and that this function is disrupted in a mouse model of ASD.

Work in the laboratory of Guoping Feng at MIT using cellular and molecular approaches has unveiled the complex heterogeneity of TRN neurons and built a comprehensive atlas of TRN cell types by applying integrated single-cell analysis. Most importantly, this work has established correspondence between molecular, morphological, connectional, electrophysiological and functional features of TRN neuronal types, which will facilitate our understanding of how TRN influences thalamo-cortical pathways in attentional control, sensory processing and sleep rhythms.

CIRCUIT MECHANISMS OF ASD-RELEVANT BEHAVIORS IN MARMOSETS

The marmoset targeted project proposes to develop marmosets as a model system for studying complex behaviors and their neural circuit substrates. Considerable evidence supports the notion that there is a significant overlap in both perceptual and motor domains between humans and marmosets. Similarities in temporal dynamics, as well as interactions between primary cortical and higher order brain areas make marmosets highly effective experimental models.

Utilizing marmosets as a model organism for researching social behavior is rapidly becoming popular.

Four collaborative projects between the **Desimone**, **Graybiel**, **Sur**, and **Jasanoff** labs will implement marmoset research to furthering our understanding of neural circuit mechanisms of ASD-relevant behaviors.

Robert Desimone, Director of the McGovern Institute, will define circuits of social gaze and reward using fMRI, and neuronal recordings of behaving marmosets.

Ann Graybiel, Institute Professor in the Department of Brain and Cognitive Sciences, will examine circuits implicated in repetitive, stereotypic behaviors, focusing on anatomical characterization of striosome-based circuits.

Mriganka Sur, Director of the Simons Center for the Social Brain, will examine circuit mechanisms of ASD-relevant behavioral persistence in visual cortex, utilizing fMRI and wide-field and multi-photon imaging of neuronal activity.

Alan Jasanoff, Professor of Biological Engineering and Brain and Cognitive Sciences, will carry out image-guided activity manipulation and functional connectivity mapping in marmosets to reveal circuits of social cognition.

We envision that these studies will be important for not only describing crucial circuits for ASD, but potentially also for developing translatable mechanism-based biomarkers.

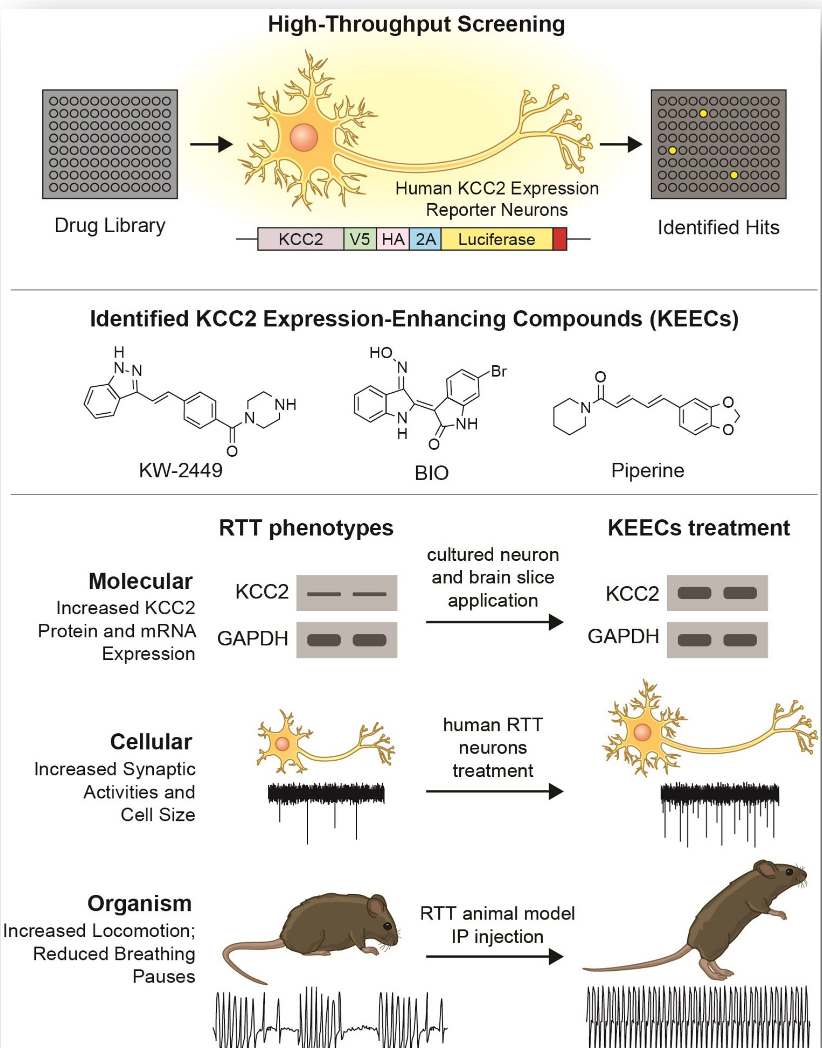
For additional information on Targeted Projects, please visit: http://scsb.mit.edu/research/targeted-projects/

SIMONS POSTDOCTORAL FELLOWS:

Xin Tang, Ph.D. [Rudolf Jaenisch Laboratory, Whitehead Institute, MIT]

IDENTIFYING KCC2 ENHANCERS TO TREAT RETT SYNDROME

K+/Cl- cotransporter-2 (KCC2) is an essential gene that maintains excitatory/inhibitory balance in the brain. Rett syndrome (RTT) is a neurodevelopmental disorder that is characterized by severe deficits in neuronal function and neural circuit development. My previous work has demonstrated that restoration of decreased KCC2 expression levels in RTT neurons through molecular means leads to the recovery of impaired neuronal function. In my Simons Fellowship project, I have developed a novel screening platform that utilizes a gene-targeted KCC2 reporter to identify compounds that increase the expression of KCC2 in human neurons. We have further demonstrated the effectiveness of candidate KCC2 enhancer compounds in rescuing morphological and electrophysiological phenotypes in stem cell-derived human RTT neurons, and in alleviating behavioral symptoms including apnea and lethargy in an animal model of RTT. The results from this study will potentially lead to novel therapeutic strategies that target KCC2 to halt or even reverse the progression of RTT. Furthermore, it is possible that the KCC2 enhancer compounds identified in our screen may be applicable for treating other types of autism spectrum disorders.



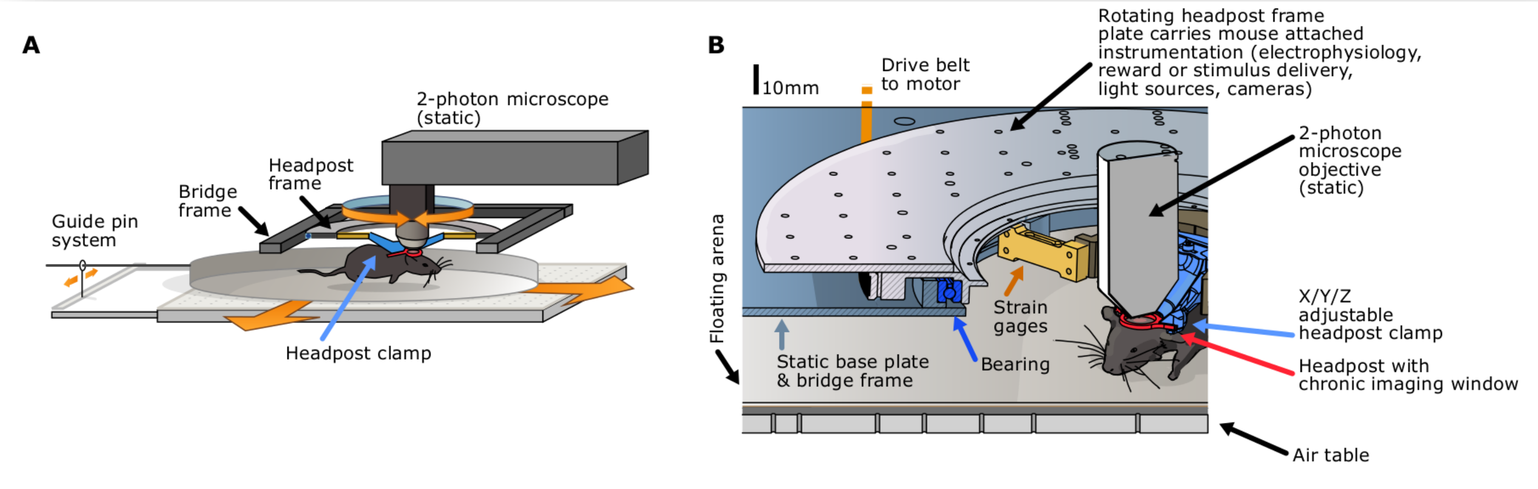
High-throughput drug screening powered by a newly-developed KCC2-luciferase reporter platform led to the discovery of the first group of KCC2 expression-enhancing compounds (KEECs). Treatment of cellular and animal models of Rett syndrome with KEECs rescues disease phenotypes at the molecular, cellular and organism levels.

Jakob Voigts, Ph.D. [Mark Harnett Laboratory, MIT]

DENDRITIC MECHANISMS OF CONTEXT DEPENDENT CORTICAL COMPUTATIONS

One central roadblock in the study of cortical computations is that it is hard to use current tools such as microscopy or high-throughput electrophysiology during the naturalistic and complex behaviors that most engage neocortex. Instead, many current studies have to use head-fixed animals and repeated stereotyped behaviors that rely on memorization and lack the complexity of natural behaviors, such as foraging, predator avoidance, or social interactions.

In my Simons Fellowship project, I have taken steps towards removing this barrier by developing a method that allows mice to feel as if they move freely in a 2-D environment, but allows full use of 'classical' head-fixed methods. An actively controlled motorized bearing allows head-fixed mice to freely rotate their heads around the vertical axis, with negligible inertia and friction, while locomoting in a real or virtual environment.
This additional degree of freedom over existing virtual-reality systems, and the vestibular cues that come with it, lead to a non- incremental improvement in animal comfort and behavior: mice explore arenas within seconds of being head-fixed for the first time, behave naturally, and remain comfortable for long sessions. In the future, this method will enable new classes of complex, naturalistic tasks that closely mimic the behaviors that rodents naturally engage in, without having to compromise the use of cutting-edge tools which require head-fixation.



A: Schematic of the system. The animal-actuated rotating headpost holder fits under a conventional 2-photon microscope. The mouse can walk on a translating, but not rotating arena.
B: Close-up of the rotating headpost holder. Small forces exerted by the mouse on the headpost are measured by strain gauges, and drive a motor system that rotates the holder, making it appear virtually weightless. https://biorxiv.altmetric.com/details/33829308/twitter

UPCOMING EVENTS: FALL 2018

LUNCH SERIES

- September 14, 2018 – **Laurel Gabard-Durnam, Ph.D.**
  Autism Science Foundation Postdoctoral Fellow, Labs of Cognitive Neuroscience, Boston Children's Hospital, Harvard Medical School
- October 5, 2018 – **Yang Zhou, Ph.D.**
  Principal Investigator, Montreal Neurological Institute and Hospital; Assistant Professor, Department of Neurology and Neurosurgery Faculty of Medicine, McGill University, Canada
- October 19, 2018 – **Jakob Voigts, Ph.D.**
  Simons Postdoctoral Fellow, Mark Harnett Lab, MIT
- November 2, 2018 – **Guoping Feng, Ph.D.**
  Poitras Chair Professor of Neuroscience, Department of Brain and Cognitive Sciences, McGovern Institute, MIT
- November 16, 2018 – **Rogier Landman, Ph.D.**
  Research Scientist, Robert Desimone Lab, McGovern Institute, MIT

General Info:
Time: 12PM - 1PM
Location: SCSB Conference room, Building 46, Room 6011
43 Vassar Street, Cambridge, MA 02139

All events are open to the public, registration is not required

COLLOQUIUM SERIES

SEPTEMBER

12 - Jaideep Bains, Ph.D.
Hotchkiss Brain Institute, University of Calgary

26 - Alika Maunakea, Ph.D.
University of Hawai'i

OCTOBER

10 - John Huguenard, Ph.D.
Stanford University, School of Medicine

24 - Elizabeth Redcay, Ph.D.
University of Maryland

NOVEMBER

14 - Elise Robinson, Ph.D.
Harvard Chan School of Public Health, Broad Institute, MIT & Harvard

28 - Ilana Witten, Ph.D.
Princeton University

DECEMBER

5 - Nathalie van Bockstaele, Ph.D.

General Info:
Time: 4PM - 5PM, reception to follow
Location: Singleton Auditorium, Building 46, Room 3002
43 Vassar Street, Cambridge, MA 02139

POSTDOCTORAL APPLICATIONS: FALL 2018

We are pleased to announce the 2018 Round 2 funding opportunities for Postdoctoral Fellowships.

Postdoctoral Fellowships are intended for outstanding candidates with very recent PhDs who wish to conduct autism-related research at MIT under the mentorship of MIT faculty researchers. Applicants currently completing their PhD outside MIT, who wish to carry out postdoctoral research at MIT, are strongly encouraged to apply.

Deadline: Friday, September 28, 2018

For information on how to apply and eligibility, please visit our website at: http://scsb.mit.edu/funding/postdoctoral-fellowship-funding/

Supporting Autism Research at MIT

Gift of alumni/ae and friends to be used for supporting collaborative research on Autism and Neurodevelopmental Disorders at MIT:

Please visit https://giving.mit.edu/ to make a gift.

Simons Center for the Social Brain – Autism Research Fund 3836050