The Simons Center for the Social Brain Newsletter

Spring 2024

Simons Center for the Social Brain

Inside this issue

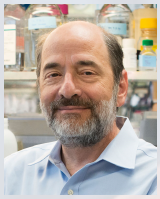
Massachusetts Institute of Technology

Upcoming Events: Spring 2024

Colloquium Series

February 7
Steve Chang, Ph.D.
Yale University

March 6
Amy Lutz, Ph.D.
University of Pennsylvania



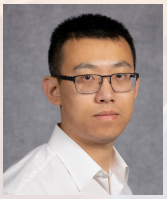
March 20
Michael Greenberg, Ph.D.
Harvard Medical School

April 24
Clifford J. Woolf, MB, BCh, Ph.D.
Boston Children's Hospital/
Harvard Medical School

May 22
Lindsey Powell, Ph.D.
University of California San Diego

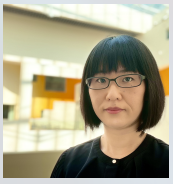
General Info
Time: 4PM–5PM, *reception to follow*
Hybrid Location: Singleton Auditorium, 46-3002 + Zoom Webinar, *registration is not required*

Lunch Series



February 23
Yugang Zhang, Ph.D.
SCSB Postdoctoral Fellow,
Feng Zhang Laboratory

March 15
Thomas Clark
PhD Student,
TedLab and Computational Psycholinguistics Lab



April 5
Tomoe Ishikawa, Ph.D.
SCSB Postdoctoral Fellow,
Gloria Choi Laboratory

May 10
Chhavi Sood, Ph.D.
Simons Postdoctoral Fellow,
Troy Littleton Laboratory

May 24
Winko An, Ph.D.
Postdoctoral Research Fellow,
Boston Children's Hospital/
Harvard Medical School

General Info
Time: 12PM–1PM
Hybrid Location: Simons Center Conference Room, 46-6011 + Zoom Meeting, *registration is not required*

All events are open to public, please visit our website for all upcoming events: scsb.mit.edu/events

New Targeted Project

Meningeal immunity: a novel strategy for treating autism spectrum disorders

by Choi, Heiman, Huh and Sur laboratories

The latest collaborative targeted project of SCSB focuses on leveraging the immune system's impact on the brain to alleviate symptoms of autism spectrum disorders through "immunotherapy" for the brain. This project is centered on harnessing the potential of interleukin-17a (IL-17a), a soluble factor derived from immune cells, which has shown promise in improving social behavior in various neurodevelopmental disorder models. Four laboratories (Choi, Heiman, Huh and Sur) are collaborating to explore different aspects of the gut immune-brain axis and its modulation to increase IL-17a levels within the brain, particularly focusing on the meninges as a key component of this axis.

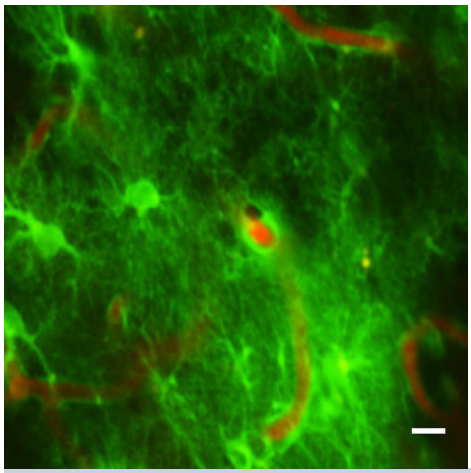


Figure 1. In vivo 2-photon image of astrocytic soma and processes ensheathing blood vessels in the mouse cortex. Astrocytes (green) are labeled with GFAP-GCaMP6f and blood vessels (red) are labeled with dextran-Texas Red. Scale bar = 10um. Image courtesy of Jiho Park, Laboratory of Mriganka Sur.

Their strategy involves investigating immune cell trafficking from the gut to the meninges, controlling cytokine release from meningeal immune cells, understanding astrocytic regulation of glymphatic and vascular systems, and deciphering the gene expression changes in cortical neurons influenced by IL-17a. These studies aim to deepen our understanding of how the neuroimmune axis governs animal behavior, laying the groundwork for developing immunotherapy for neurodevelopmental and autism spectrum disorders.

Jun Huh, Associate Professor of Immunology at Harvard Medical School, will lead efforts to uncover the mechanisms behind immune cell migration from the gut to the brain. He hypothesizes that gut-residing microbes educate immune cells, which then migrate to the meninges to influence brain function. By capitalizing on this mechanism, the Huh lab aims to create an immune cell platform with enhanced migratory potential to the meningeal space, potentially leading to future therapeutics targeting neurodevelopmental disorders.

Gloria Choi, Associate Professor of Neuroscience, will focus on utilizing meningeal immune cells as a source of cytokines. Her research has demonstrated that IL-17a plays a crucial role in rescuing social deficits in mice with autism-like symptoms. By targeting meningeal immune cells, Choi's lab aims to elevate IL-17a levels in the brain, potentially offering a novel therapeutic approach for autism spectrum disorders.

Myriam Heiman, Associate Professor of Neuroscience, will spearhead efforts to create a molecular atlas of the mammalian glymphatic system. This system facilitates convective exchange between cerebrospinal fluid and brain interstitial fluid, regulating the distribution and removal of biomolecules from the central nervous system. By identifying molecular regulators of the glymphatic system, Heiman's lab aims to uncover potential targets for therapeutic modulation.

Mriganka Sur, Professor of Neuroscience, will investigate the role of astrocytes in mediating cytokine availability in the brain. Astrocytes play a key role in regulating vascular and glymphatic dynamics. Sur's lab will employ advanced imaging techniques to understand how changes in vascular and glymphatic flow relate to astrocyte activity, with a particular focus on the intracortical transport of IL-17a and its impact on neuronal responses.

In summary, this collaborative effort aims to advance our understanding of the immune-brain axis and its potential for novel therapeutic intervention in neurodevelopmental and autism spectrum disorders.

Update: Cognitive, neural, and computational foundations of conversation

by Fedorenko, Gibson, Kanwisher, Levy, Robertson, Saxe, and Tenenbaum laboratories

Conversations are ubiquitous in our lives: for most of us, hardly a day goes by without us engaging in or observing conversational exchanges, from interacting with family members, to everyday exchanges in grocery stores, to job interviews and other interactions in work settings. This naturalistic form of communication differs from the kinds of language stimuli that have typically been used in behavioral and neuroscientific research: often, isolated artificial sentences presented in auditory or written form. In this targeted project, seven labs have joined forces to understand both the production and comprehension sides of rich, naturalistic, and multi-modal conversational exchanges, in an effort to then ask what kinds of difficulties may arise in such exchanges in disorders that affect communication, like autism. Summarized below is the progress they have made so far.

Rebeca Saxe, Professor of Cognitive Neuroscience, is using her novel fMRI paradigm, based on edited clips of *Sesame Street*, to probe the brains of toddlers responding to language and conversation. Scientifically, the period of 18-36 months is crucial for understanding the development of the neural basis of social and linguistic processing, it is also the period when challenges start to arise for children later diagnosed with autism. On the other hand, practically, this is also the most difficult age in which to measure brain responses using fMRI (which requires patience, stillness, attention and compliance); indeed, to our knowledge there are no existing fMRI studies in awake toddlers. Although this age group is exceptionally challenging, they are slowly acquiring a unique dataset. Thus far, the team has recruited >70 toddlers to come to MIT for a scanning session. Preliminary group-level results from 16 toddlers (25-36 months) showed higher activation to forward than backward speech in the left anterior temporal region, which is a canonical language region in adults. Language-evoked activation also appears left-lateralized in the toddler sample thus far, with the toddler distribution of lateralization values not differing from the adult distribution. The project is continuing to recruit and scan toddlers to reach its target sample size in this unique age group.

A young child prepares to go inside the MRI scanner so that researchers can study how her developing brain processes language. Image courtesy of Halie Olson, Laboratory of Rebecca Saxe and Kris Brewer, CBMM.

Roger Levy, Professor of Language and Cognitive Science, and **Josh Tenenbaum**, Professor of Computational Cognitive Science, are continuing to work on improving models of language processing and conversation, as well as developing models of early language acquisition that can participate in two-way communication, the precursor to conversation. Following up on work in the Levy lab looking at how adults robustly understand children's speech and scaffold children's early participation in conversation, they have been investigating new ways of modeling child language learning from this conversational lens. Their earlier work suggested that adult inference ensures that children's early non-conventional speech nonetheless has real-world consequences. This leaves the child learner free to revise the imitative and communicative aspects of early communication independently ("does this sound the way other people say it?" vs. "does this transmit the right message to my listener?"). Rather than learning a single target grammar, children are free to learn a "library" of hierarchically structured motor programs that satisfy these imitative and communicative needs (consonant with proposals about symbolic program induction investigated in the Tenenbaum lab). To implement these ideas, the Levy team has been developing a multimodal deep reinforcement learning model of the child learner that learns to produce phrases with a model vocal tract to direct a model adult listener in a common naming task. Representations that emerge in the model learner look like traditional units of linguistic representation (phonemes, morphemes, words, phrases), while the model architecture supports a broader range of "non-linguistic" aspects of speech (e.g., prosody and backchanneling) in the same unified framework.

Caroline Robertson, Assistant Professor of Psychological and Brain Sciences at Dartmouth College, and **Ted Gibson**, Professor of Cognitive Science, have been working on understanding the relationship between what a

person is saying in a conversation (its meaning, roughly) and prosodic features associated with how they say it. Previous research has suggested that more predictable (i.e. less surprising) words are generally reduced in duration. The team is investigating the relationship between surprisal and other prosodic features, as well as listener backchannels (short interjections such as "yeah" or "hmm" that are common in conversation). Using large language models to compute word surprisal, they are investigating a new large corpus of naturalistic conversations (CANDOR). They have found that surprisal robustly predicts duration, pitch, and intensity even when controlling for possible confounds, and is negatively correlated with backchannels. These preliminary results indicate a sensitivity of both speaker and listener behavior to the information content of words in everyday conversation. They are now seeking to see if these prosodic features are produced similarly in participants with autism.

Ev Fedorenko, Associate Professor of Neuroscience and **Nancy Kanwisher**, Professor of Cognitive Neuroscience, have continued to investigate the organization of the social brain, with the goal of discovering key components of the brain's 'conversation network'. One key direction has focused on understanding how our brains perceive intonation or prosody of speech (not WHAT we say but HOW we say it). The postdoctoral fellow leading this work, Tamar Regev, has identified prosody-responsive brain areas that are distinct from the language areas, but overlap with some other areas that process socially-relevant signals. She is writing up her findings and will also present them at a symposium she organized on the brain basis of prosody at the Cognitive Neuroscience Society conference (to take place in Toronto in April). Ongoing work is attempting to use data-driven fMRI voxel decomposition on naturalistic movie viewing data in an effort to identify key neural components of processing social-communicative signals in face-to-face and third-party conversations.

Postdoctoral Fellows

Welcome to new SCSB Fellows!

Christopher Fell, Ph.D.

Project: High resolution mapping of transcription factors during neurodevelopment

Laboratory: Omar Abudayyeh, Ph.D and Jonathan Gootenberg, Ph.D

Ph.D. from: CeMM (Vienna, Austria)

Hobbies: Cooking, football, and running

Lukas Vogelsang, Ph.D.

Project: Examining higher-order temporal processing in autism

Laboratories: Pawan Sinha, Ph.D.

Ph.D. from: École Polytechnique Fédérale de Lausanne (EPFL), Switzerland

Hobbies: Hiking, table tennis, swimming

Gabriel Stine, Ph.D.

Project: Prediction and learning in the cerebello-thalamo-cortical pathway

Laboratories: Mehrdad Jazayeri, Ph.D. and Pawan Sinha, Ph.D.

PhD from: Columbia University

Hobbies: Tennis, snowboarding, and guitar

Simons Postdoctoral Fellows: Profile

Tomoe Ishikawa, Ph.D.
Simons Fellow, Gloria Choi Lab, PILM, BCS, MIT

Project Title: Neural circuits for immune modulation during social contact with sick individuals

Group living increases the risk of exposure to infectious conditions and transmission of pathogens compared to a solitary living lifestyle. Therefore, animals need to change their social engagements based on the health status of interacting conspecifics. We recently found that a subregion of the amygdala, the posteromedial nucleus of the cortical amygdala (COApm), is necessary for suppressing male mating when a female mouse is unhealthy. We also showed that the odor of a sick female is sufficient to activate the COApm and thereby inhibit male mating even with a healthy female. These data suggested that male mice are capable of sensing odorants associated with the 'sickness state' of a potential mate and use that information to adjust the extent of social engagements.

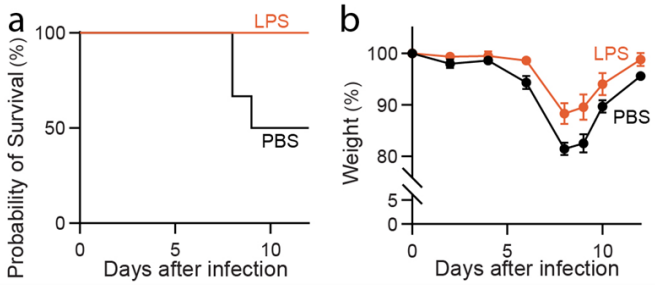


Figure 1. Pre-exposure to sick cagemates improves PR8 mortality rate

My research under the Simons Fellowship seeks to explore whether interacting with sick individuals not only curtails social engagement but also primes the animal's immune system. The objective is to uncover how interactions between the nervous and immune systems, thereby, prepare animals for impending pathogenic threats.

First, I examined whether exposure to sick cagemates mitigates symptoms induced by viral or bacterial infection. In this study, the subject mice were infected with influenza virus (PR8) or gram negative-bacteria (C. *rodentium*) after being exposed to cagemates made sick by being treated with lipopolysaccharide (LPS). I found that animals exposed to LPS-treated sick cagemates exhibited less body weight reduction and a higher survival rate following PR8 infection (Fig. 1). Exposure to LPS-mice also alleviated signs induced by C. *rodentium* infection (Fig. 2). Since LPS-induced sickness is not transmissible to subject mice, this protective effect is likely mediated by neural activity induced by exposure to sick cagemates. Therefore, I subsequently investigated the brain regions activated by interaction with LPS-treated cagemates. The subject animals exposed to sick cagemates exhibited higher expression of cFOS, a marker of neuronal activity in the COApm. Furthermore, chemogenetic activation of COApm was sufficient to lessen the symptoms of PR8 and C. *rodentium* infection. These results suggest that exposure to sick conspecifics indeed primes the animals' immune system to better cope with subsequent pathogenic infection, and this priming is mediated by COApm activation.

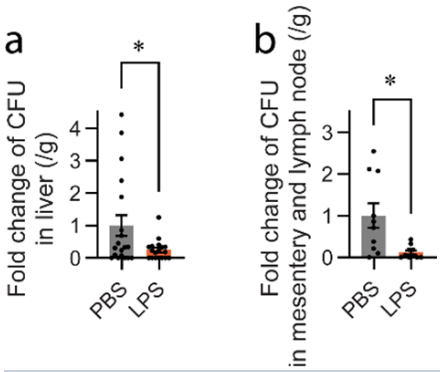


Figure 2. Pre-exposure to sick cagemates alleviates signs induced by C. *rodentium* infection

Chhavi Sood, Ph.D.
Simons Fellow, Troy Littleton Lab, PILM, BCS, MIT

Project Title: Role of FMRP interactions with presynaptic ion channels in Fragile X Syndrome

Active zones (AZs) are specialized subdomains of the presynaptic axon where synaptic vesicle (SV) fusion occurs in response to Ca2+ influx from voltage-gated Ca2+ channels (VGCCs). Multiple conserved proteins cluster SVs and VGCCs at the AZs, where BK channels (Ca2+-activated K+ channels) also cluster to rapidly repolarize the presynaptic membrane to close VGCCs and terminate Ca2+ influx and SV release. How VGCCs and BK channels arrive at AZs and how their abundance and turnover are regulated is poorly understood. Fragile X Syndrome (FXS), a leading genetic cause of autism, causes defective synaptic communication due to silencing of the FMR1 gene by repeat expansion. Two major functions for the FMRP protein include mRNA binding to regulate protein translation and direct interactions with presynaptic Cav2 class of VGCCs and BK channels independent of RNA binding. This latter function is proposed to control surface levels of these channels, though it is unclear how FMRP binding modulates their abundance at AZs. Although biosynthesis, delivery and recycling cooperate to establish AZ protein abundance, experimentally isolating these distinct regulatory processes is difficult.

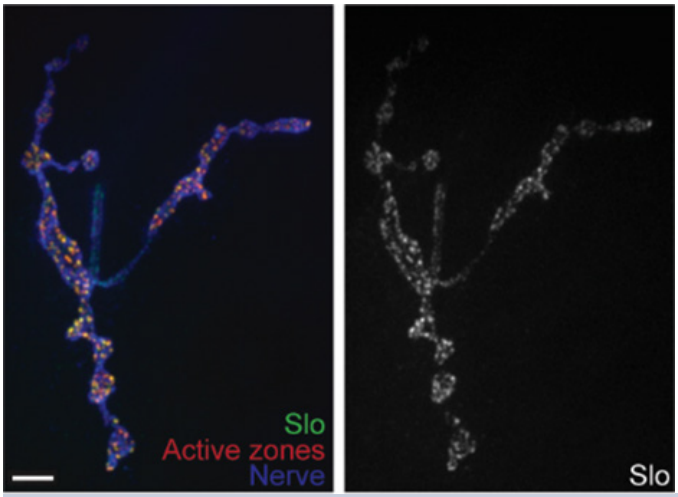


Figure 1. Expression of BK channel, Slo in *Drosophila* NMJ
Representative image of the NMJ, showing the axon (antiHRP; blue), the AZs (anti-BRP; red) and the Slo channels (green). Scale bar = 5µm.

My Simons fellowship is focused on using Drosophila neuromuscular junction as a model to study how FMRP controls VGCC and BK channel synaptic delivery and AZ abundance, and how dysregulation of these interactions contributes to synaptic defects in FXS. To assay AZ abundance of the sole Cav2 VGCC in Drosophila, Cacophony (Cac), I used an existing CRISPR-tagged CacGFP line. I found that Cac AZ abundance was significantly increased in mutants of dFXR compared to control animals. Next, to visualize the sole BK channel in Drosophila, Slowpoke (Slo), I generated a UAS-driven fluorescently-tagged Slo (UAS-Slo-mNeongreen) line.

Using a motorneuron-specific Gal4 (C155Elav-Gal4), I found that Slo colocalized with Bruchpilot (BRP), an AZ scaffold protein (Figure 1). Using this line, I will assay Slo AZ abundance and whether it is altered in mutants of dFXR compared to controls. Further, I will use intravital FRAP and mMaple photoconversion to measure delivery and turnover of these channels at individual AZs over a multi-day period of larval development in controls and mutants of dFXR. In combination with electrophysiology, quantal analysis and presynaptic Ca2+ imaging I aim to determine how loss of FMRP alters synaptic communication, and if these defects are secondary to abnormal Cac and Slo abundance or function at AZs.

News & Announcements

Simons Postdoctoral Fellowship opportunities

The Simons Center has two rounds of funding annually for postdoctoral fellowships.

Fall 2024 deadline: Monday, September 30, 2024
Spring 2025 deadline: Friday, February 28, 2025

Postdoctoral Fellowships are intended for outstanding candidates with recent PhDs (please see eligibility criteria on our website) who wish to conduct autism-related research at MIT under the mentorship of MIT faculty researchers. Applicants currently completing their PhD outside MIT (external candidates), who wish to carry out postdoctoral research at MIT, are strongly encouraged to apply. *We strongly encourage applications from under-represented and under-served backgrounds.*

As part of the Brain & Cognitive Sciences complex at MIT, the Center offers supportive mentorship to postdoctoral researchers, an exceptional environment for scientific inquiry, and a strong commitment to an inclusive, welcoming culture. To learn more about our commitment to Diversity, Equity, Inclusion & Justice (DEIJ), visit here: https://bcs.mit.edu/diversity-equity-and-inclusion-bcs-and-building-46/outreach. To learn more about our postdoctoral resources that support personal, family, and community life here at MIT, visit here: https://postdocs.mit.edu/.

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

Support Our Research

We urge you to support the Simons Center for the Social Brain (SCSB) at MIT. Your gift will fund groundbreaking research into causes, mechanisms and treatments of neurodevelopmental disorders including autism spectrum disorders (ASD). The center supports laboratories that study the brain at multiple levels spanning molecular, circuit and computational mechanisms of brain function and cognition. Our programs include funding for innovative, collaborative team projects and postdoctoral fellowships, as well as events that reach a wide audience.

Please consider making a gift: Simons Center for the Social Brain - **Autism Research Fund 3836050**

Credits:
Editing and Design: Alexandra Sokhina and Mriganka Sur
Cover Art: "Neurons, astrocytes and immune molecules", created with the assistance of Imagine AI Art Generator
Contributing Writers: Targeted Project PIs and their laboratories, Tomoe Ishikawa, Chhavi Sood

SCSB team:
Director: Mriganka Sur | msur@mit.edu
Senior Administrative Manager &
Director of Development: Eleana MacPhail | ericci@mit.edu
Program Coordinator: Alexandra Sokhina | asokhina@mit.edu