THE SIMONS CENTER FOR THE SOCIAL BRAIN (SCSB) NEWSLETTER | Spring 2020

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PUBLICATIONS SPOTLIGHT

Siyuan Rao, **Ritchie Chen**, Ava A. LaRocca, Michael G. Christiansen, Alexander W. Senko, Cindy H. Shi, Po-Han Chiang, Georgios Varnavides, Jian Xue, **Yang Zhou**, Seongjun Park, Ruihua Ding, Junsang Moon, **Guoping Feng**, and **Polina Anikeeva**. Remotely controlled chemomagnetic modulation of targeted neural circuits. Nature Nanotechnology 14: 967-973, 2019 [https://doi.org/10.1038/s41565-019-0521-z]

Cory Shain, Idan A. Blank, Marten van Schijndel, William Schuler, and **Evelina Fedorenko**. fMRI reveals language-specific predictive coding during naturalistic sentence comprehension. Neuropsychologia 138: 107307, 2020 [https://doi.org/10.1016/j.neuropsychologia.2019.107307]

Julia Uddén, Annika Hultén, Katarina Bendtz, Zachary Mineroff, Katerina S. Kucera, Arianna Vino, **Evelina Fedorenko**, Peter Hagoort, and Simon E. Fisher. Towards robust functional neuroimaging genetics of cognition. Journal of Neuroscience 39: 8778-8787, 2019 [https://doi.org/10.1523/JNEUROSCI.0888-19.2019]

Miho Nakajima, L. Ian Schmitt, **Guoping Feng**, and **Michael Halassa**. Combinatorial targeting of distributed forebrain networks reversed noise hypesensitivity of an ASD model. Neuron 104: 488–500, 2019 [https://doi.org/10.1016/j.neuron.2019.09.040]

Satoko Amemori, Ken-ichi Amemori, Tomoko Yoshida, Georgios K. Papageorgiou, Rui Xu, Hideki Shimazu, **Robert Desimone**, and **Ann M. Graybiel**. Microstimulation of primate neocortex targeting striosomes induces negative decision-making. European Journal of Neuroscience 2019 [https://doi.org/10.1111/ejn.14555]

Michael D. Reed, **Yeong Shin Yim**, Ralf D. Wimmer, Hyunju Kim, Changhyeon Ryu, Gwyneth M. Welch, Matias Andina, Hunter O. King, Ari Waisman, **Michael M. Halassa**, Jun R. Huh, and **Gloria B. Choi**. IL-17a promotes sociability in mouse models of neurodevelopmental disorders. Nature 577: 249-253, 2020 [https://doi.org/10.1038/s41586-019-1843-6]

Just Announced...

ELEANA MACPHAIL, Administrative Manager of SCSB, has been awarded a MIT Excellence Award for 2020. This is one of the highest awards that MIT presents to staff members, to acknowledge extraordinary dedication to MIT's goals, values and mission, and recognize colleagues who excel in service to all.

POSTDOCTORAL APPLICATIONS: SPRING 2020

We are pleased to announce the 2020 Round 1 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 of MIT, who wish to carry out postdoctoral research at MIT, are strongly encouraged to apply.

Deadline: Friday, February 28, 2020.

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

TARGETED PROJECTS :

SCSB has two ongoing targeted projects: “Circuit mechanisms of ASD-relevant behaviors in marmosets,” involving the laboratories of Drs. Robert Desimone, Ann Graybiel, Alan Jasanoff and Mriganka Sur; and “Predictive processes in autistic and neuro-typical Individuals. A behavioral, neural and developmental investigation,” involving the laboratories of Drs. Pawan Sinha, John Gabrieli and Jesse Snedeker. We present below the findings from one of the Marmoset projects, and a brief overview of progress on the Predictive Processes project.

A NOVEL VIEW OF TEMPORAL EXPECTATION IN MARMOSETS

Tudor Dragoi, Hiroki Sugihara, Ming Hu, Jitendra Sharma, Mriganka Sur

Exposure to statistical regularities helps humans and non-human primates build internal models that govern behavior and enable adaptation to uncertain environments. In natural environments, visual stimuli rarely occur in isolation, but rather are presented in specific contexts that help predict the identity of a stimulus. The rise of expectations following exposure to repeated patterns of visual inputs may contribute to reducing the computational burden of the brain and help guide behavior.

In an effort to model temporal expectation, Bayesian models of stimulus probability have been implemented to understand how recent events affect future behavior. Previous studies have not focused on whether an animal’s dependence on the history of task-related events is innate, or rather is acquired as an animal is exposed to the temporal structure of a task. Additionally, what strategies predominate through different stages of task performance, and at what point, if any, does trial history begin to bias responses, is unknown. Such evidence is necessary to better understand how the brain builds internal models of temporal expectation.

We implemented a simple timing task in which freely behaving marmosets were required to make a timed response prompted by a visual stimulus change **(Fig. 1A).** The durations of all visual stimuli were randomly sampled from a uniform distribution, with an equal probability from 500 ms to 2500 ms **(Fig. 1B)**.

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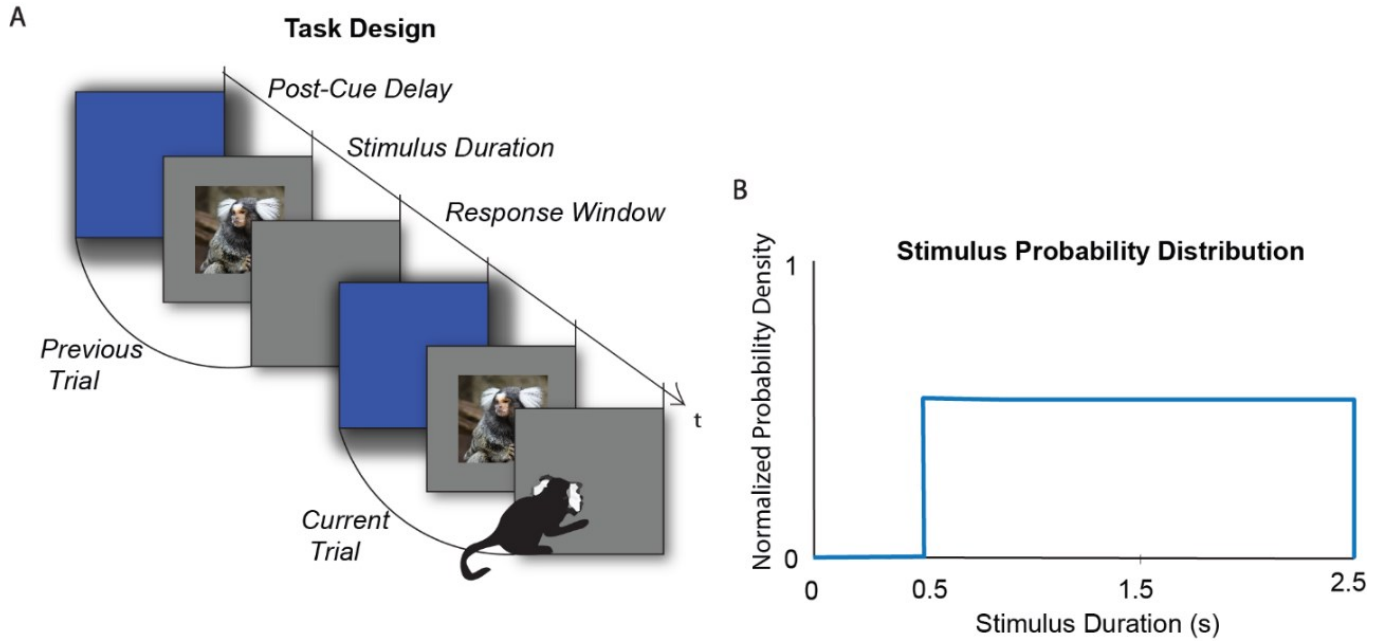

Fig. 1 | Temporal prediction task. A) Animals were trained to report stimulus offset in response to a range of different stimulus latencies. B) Stimulus durations were sampled from a uniform probability density function, with an equal stimulus duration probability from 500 ms to 2500 ms.

As is known from previous studies in humans and macaque monkeys, the reaction time of marmosets decreased as the stimulus duration increased, roughly as a function of the 'hazard rate' of stimulus disappearance. However, as task sessions progressed and marmosets became more proficient in the task, we found a surprising result: the reaction time diverged systematically from the hazard rate prediction (**Fig. 2A,B**). Indeed, the mean error between the predicted hazard rate fit and experimental data systematically increased with task exposure (**Fig 2C**).

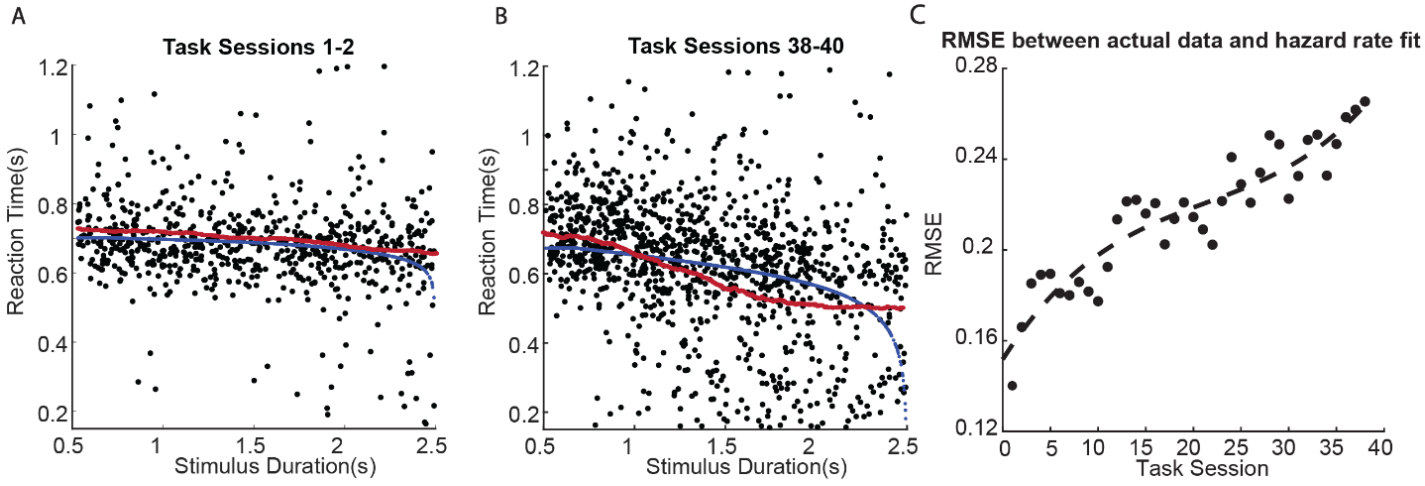

Fig. 2 | The hazard rate model fit to the data loses accuracy with task exposure. A) Reaction time (red) and hazard rate fit (blue) for the first two task sessions. B) Reaction time (red) and hazard rate fit (blue) for the last two task sessions. C) Root mean squared error between the hazard rate fit and experimental points (bin size, 2).

Randomly occurring stimulus patterns may only begin to be noticed after enough exposure to the task, at which point they begin to influence temporal expectation. Our results suggest that as a pattern detector, the brain constantly scans its environment for discernable temporal structure, even when behavioral consequences are not optimal. Ongoing experiments are investigating whether humans exhibit behavior similar to marmosets in counterintuitively expressing a history bias only after repeated exposure to unpredictably occurring patterns of time. Previous studies implicate frontal-parietal circuits as playing a key role in generating temporal expectation. We plan to optogenetically manipulate these circuits by disrupting the balance of excitation-inhibition and thereby modulate behavior in this and similar temporal expectation tasks. Atypical temporal prediction has been implicated in autism; thus, our research has the potential to uncover whether disruptions in the E-I ratio in circuits can account for cardinal symptoms of ASD.

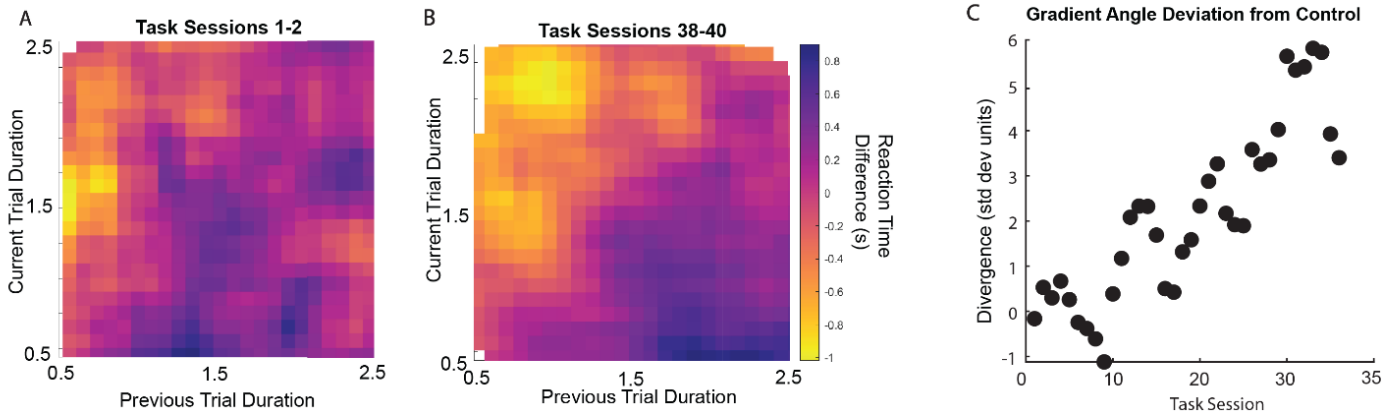

Fig. 3 | The reaction time difference between consecutive trials depends on stimulus history as task sessions progress. A) Trial history matrix for the first two task sessions. For each trial history matrix, the previous trial duration was plotted on the x-axis, the current trial duration on the y-axis, and the reaction time difference between both trials on the z-axis. The color gradient is designed such that magenta represents reaction time getting slower, and yellow represents reaction time getting faster. B) Trial history matrix for the last two task sessions. C) Gradient angle deviation as task exposure progresses. The divergence (number of standard deviations between the gradient angle and the mean of the shuffled control) is plotted on the y-axis.

PREDICTIVE PROCESSES IN AUTISTIC AND NEURO-TYPICAL INDIVIDUALS: A BEHAVIORAL, NEURAL AND DEVELOPMENTAL INVESTIGATION

Jon Cannon, Annie Cardinaux, Anila D'Mello, John Gabrieli, Tanya Levari, Pawan Sinha, Jesse Snedeker

The Predictive Processes Targeted Project represents a collaboration between three laboratories with the goal of exploring different facets of predictive processing in autism. The project is now underway, with each lab actively collecting pilot data, conducting initial analyses, refining experiments, and launching into full-scale data collection.

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The three groups meet regularly to coordinate strategies and share findings across the two different age groups and multiple experimental tasks being conducted as part of the three-pronged study.

Pawan Sinha's lab at MIT is using simple auditory stimuli with well-defined temporal structure and probabilistic contingencies to probe the formulation and deployment of temporal predictions by autistic and non-autistic individuals. Such stimuli allow for a characterization of predictive processes while side-stepping the complexities associated with social cues. Hence, studies with these stimuli can help reveal whether basic computations underlying temporal prediction are affected in autism. The lab's pilot recordings using electro-encephalography (EEG) and precise finger-tap recordings have led them to design a set of experiments to more precisely address the following question: Does autism impair the extraction of temporal regularities in a sensory stream, or the usage of learned knowledge about the regularities for the purpose of temporal prediction, or both? In their new task design, performance and reaction time during an auditory detection task with and without temporal cuing will supplement EEG as measures of temporal prediction. They are currently piloting their new tasks in a population of typically developing adults.

John Gabrieli's lab at MIT is using functional magnetic resonance imaging (fMRI) to assess neural adaptation in individuals with and without autism. The brain responds to repeated events in the environment by reducing neuronal firing – a process called neural adaptation. FMRI can identify adaptation in the human brain, and localize adaptation to specific regions of the brain. Neural adaptation may support predictive processing by helping individuals to distinguish repeating events from novel events. Recent findings from Gabrieli's group suggest that individuals with ASD have reduced neural adaptation to faces, but not to other types of stimuli (such as written words, spoken words, and objects). In addition, they find correlations between the degree of neural adaptation to faces and the severity of ASD-relevant social communication symptoms. Individuals with greater social communication challenges show less neural adaptation. This suggests that neural adaptation deficits may be specific to domains relevant to social cognition, and may be associated with social communication behaviors. Gabrieli's lab is now examining how modulating expectations of repetition is associated with ASD traits. Previous research has shown that neural adaptation may be influenced by top-down cognitive expectations and that these may be disrupted in ASD.

Jesse Snedeker, Professor of Psychology at Harvard University, is developing a comprehensive examination of predictive processing in typically developing children and children on the autism spectrum. Their earlier work focused primarily on predictive processing during language comprehension using a naturalistic listening task.

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Children hear an age-appropriate story while EEG is recorded. The event-related-potentials recorded at each word can be analyzed to determine how prediction and bottom-up processes interact during language comprehension (**Fig. 1**).

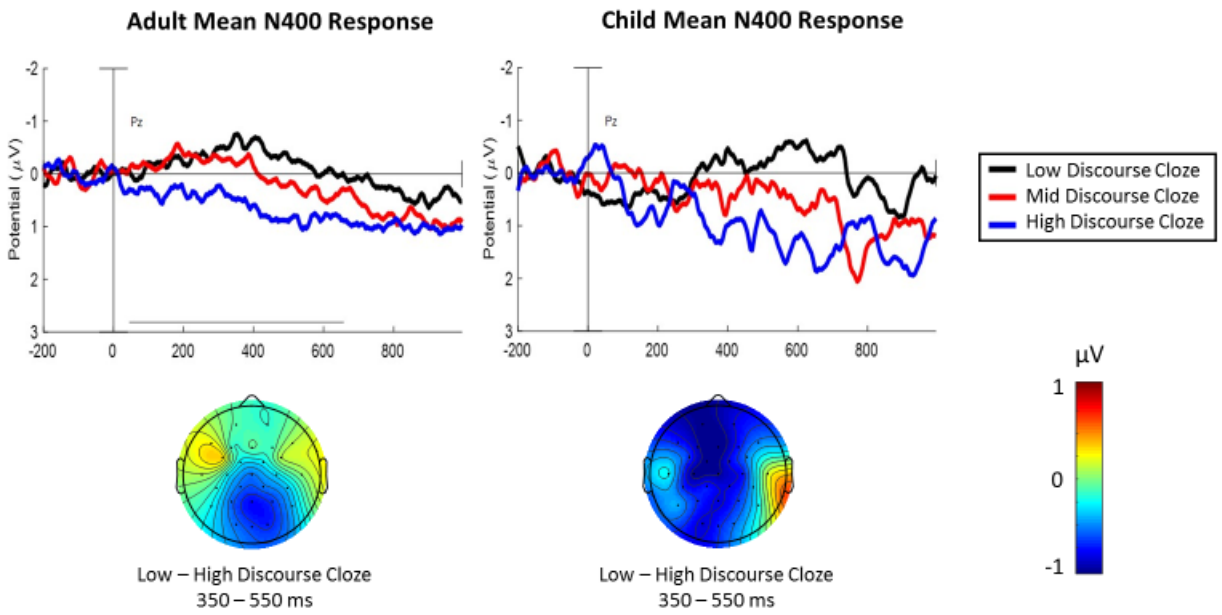

Figure 1: Grand average waveforms to low, middle, and high predictability words, as measured by discourse cloze probability, at electrode Pz in adults (right) and children (left) and voltage maps of the difference between low and high predictability words in the time window of the N400 response (350 – 550 ms).

The researchers find that typically developing children make predictions about upcoming words based on their understanding of the story up to that point. In the current project, they are expanding this paradigm to look at language related predictions in children with ASD.

The collaborative nature of the project enables each group to conduct versions of their experiments in both adults and children. In addition to the language paradigms described above, Professor Snedeker's group is evaluating a broad range of predictive skills across the same group of child participants, using both behavioral and electroencephalographic measures. Specifically, the Snedeker lab has adapted tasks from the Sinha lab to evaluate adaptation to metronomic auditory sequences and tasks from the Gabrieli lab to explore habituation to both social and non-social visual stimuli. The Sinha lab will also conduct the Snedeker group's naturalistic story paradigm in adults with and without autism, allowing the groups to compare performance on the task across a broad age range. The three projects provide a holistic look at predictive processing in different age groups and across a range of both social and non-social domains, helping to better define challenges associated with autism spectrum disorder.

SIMONS POSTDOCTORAL FELLOWS: NEWS SPOTLIGHT

Some recent awards received by current and past Simons Fellows:

SIYUAN RAO, Postdoctoral Fellow (2016-18), Laboratory of Polina Anikeeva, received a K99 award from National Institute of Mental Health, National Institutes of Health

ANILA D'MELLO, Postdoctoral Fellow (2018-19), Laboratory of John Gabrieli, received the Ruth L. Kirschstein National Research Service Award (F32) from the National Institute of Mental Health, National Institutes of Health

YANG ZHOU, Postdoctoral Fellow (2012-13), Laboratory of Guoping Feng, currently Assistant Professor, Department of Neurology and Neurosurgery, McGill University, Canada, received the CAD Canada Research Chair award for research in Neurobiology of Developmental Brain Disorders

DANIELLE TOMASELLO, Postdoctoral Fellow (2018-20), Laboratory of Hazel Sive, received a Trainee Award for Oral Presentation, and Axion Biosystems Travel Award, Human Genome Meeting, Seoul, South Korea

SIMONS POSTDOCTORAL FELLOW: PROFILE

Menglong Zeng, Ph.D. | Guoping Feng Laboratory, MIT

CHARACTERIZATION OF THE FUNCTIONAL IMPACT OF SHANK3-CAMKIIα INTERACTION

Shank family proteins are multi-domain scaffold proteins in the postsynaptic density (PSD) of excitatory synapses. It includes three family members, Shank1/2/3, encoded by three different genes. Mutations or disruptions of the *SHANK* family genes represent highly penetrant risk factors for autism spectrum disorder (ASD) and several other neurodevelopmental disorders. But the underlying molecular mechanisms remain to be ascertained. All Shank family proteins share a high degree of homolog in domain organization and structure. Interestingly, human genetic data suggest ASD patients with *SHANK3* mutations show more severe intellectual disability (ID) (with an average IQ ~30) when compared to ASD patients with *SHANK1* or *SHANK2* mutations (with an average IQ ~95 and ~62, respectively).

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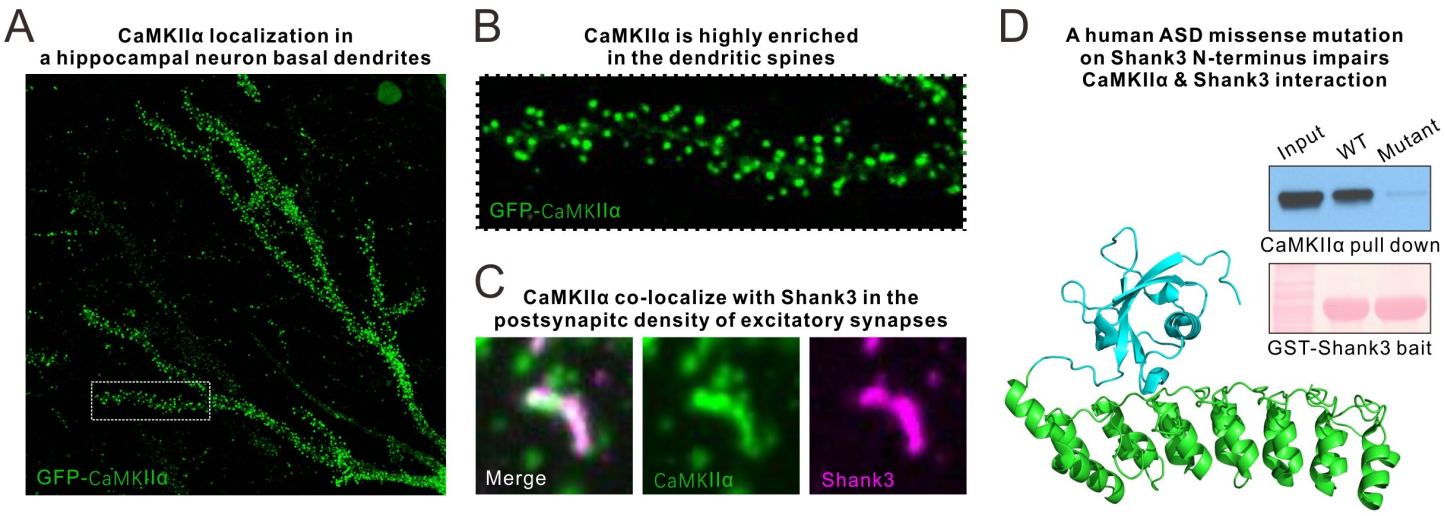

A. By sparsely knock-in a GFP tag into the N-terminus of endogenous CaMKIIα, we are able to observe the precise localizations of endogenous CaMKIIα proteins in different brain regions. Panel A shows the localization of CaMKIIα in the basal dendrites of a hippocampal neuron. Dashed box is zoom-in in panel B.

B. Zoom-in analysis showing CaMKIIα is highly enriched in the dendritic spines, where the majority of excitatory synapses dwell on in the brain.

C. Expansion microscopy-based super-resolution imaging showing co-localization of endogenous CaMKIIα and Shank3 in the postsynaptic density of excitatory synapses.

D. Pull down assay comparing the interaction between CaMKIIα and wild type or mutated Shank3. A missense mutation found in a human ASD patient with severe ID impairs this interaction.

Mutations of *SHANK3* are present in 2-3% of ASD patients with moderate to severe ID. What makes Shank3 unique in the Shank family that renders its high penetrance in ASD patients with profound cognitive impairment is currently unclear.

My Simons Fellowship research program aims to investigate a Shank3-specific molecular mechanism in synaptic plasticity. Synaptic plasticity is the ability of a neuron to modify its synaptic strength in response to various stimulations, which is believed to be the cornerstone of a human's capacity to learn and to adapt to the environment. In my current study, I first found Shank3 has a specific molecular interaction to a major synaptic plasticity regulator named CaMKIIα. A *SHANK3* missense mutation found in a human ASD patient with severe ID impairs this interaction. I then generated a *SHANK3* knock-in mouse carrying this missense mutation. Now I am using multidisciplinary approaches to characterize the potential defects of this mutant mice, from molecular and cellular levels to circuitry and behavioral levels. I am interested to see whether the mutant mice will show cognitive impairment that is commonly observed in *SHANK3* mutated human ASD patients.

Knowledge gained from this study will help to illustrate a Shank3-specfic molecular mechanism underlying PSD organization and synaptic plasticity. It will provide us a better understanding of gene-specific etiology in ASD and other developmental disorders.

COLLOQUIUM SERIES

FEBRUARY

12 - Charles Nelson, Ph.D.
Boston Children's Hospital

26 - Kevin Bender, Ph.D.
University of California, San Francisco

MARCH

11 - Josh Hartshorne, Ph.D.
Boston College

APRIL

15 - Mark Zylka, Ph.D.
The University of North Carolina at Chapel Hill

29 - Paul Sternberg, Ph.D.
California Institute of Technology

MAY

27- Uri Hasson, Ph.D.
Princeton University

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

LUNCH SERIES

- February 21, 2020 – **Jesse Snedeker, Ph.D.**
  Professor, Department of Psychology, Harvard University
- March 20, 2020 – **Jakob Voigts, Ph.D.**
  Simons Postdoctoral Fellow, Mark Harnett Laboratory, MIT
- April 3, 2020 – **Menglong Zeng, Ph.D.**
  Simons Postdoctoral Fellow, Guoping Feng Laboratory, MIT
- April 24, 2020 – **William Menegas, Ph.D.**
  Simons Postdoctoral Fellow, Robert Desimone Laboratory, MIT
- May 8, 2020 – **Hiroki Sugihara, Ph.D.**
  Research Scientist, Mriganka Sur Laboratory, 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

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). Our 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.

Our account information: Simons Center for the Social Brain - **Autism Research Fund 3836050**

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