The Simons Center for the Social Brain Newsletter

Spring 2023

SIMONS CENTER FOR THE SOCIAL BRAIN

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News & Announcements

Simons Center for the Social Brain Renewed with Five-year Commitment from SFARI to Advance Autism Research

The Simons Center for the Social Brain (SCSB) at MIT, which celebrated its 10th anniversary last year, is pleased to announce its renewal with a $25M commitment from SFARI (the Simons Foundation Autism Research Initiative) for the next five years. SCSB will continue to focus on understanding the neural mechanisms of social cognition and behavior and applying this knowledge to improve the diagnosis and treatment of autism spectrum disorders (ASD). The center plans to continue and expand its programs, including funding for collaborative team projects and postdoctoral fellowships, and hosting events such as a Colloquium Series and a Lunch Talks Series that reach a wide audience.

"A major focus of our effort for the next five years will be to develop mechanism-based therapeutics for autism and neurodevelopmental disorders"' commented Mriganka Sur, SCSB director. "We are crafting innovative targeted projects around teams of investigators, and we look forward to applications from talented postdoctoral applicants for our Simons Fellows program."

Going forward, an important goal of the center is to increase the diversity of its researchers and speakers [https://scsb.mit.edu/our-values/]. "SCSB is committed to bringing researchers together and training young scientists from all backgrounds and perspectives", noted Sur.

MIT research foundational to newly approved Rett syndrome drug

by David Orenstein

Basic research that began almost 20 years ago in the MIT lab of Mriganka Sur had a pivotal role in the March 10 approval by the U.S. Food and Drug Administration of the first treatment for Rett syndrome, a devastating disorder of brain development mainly affecting girls. This treatment is also a first for any neurodevelopmental disorder.

Sur's lab, in a line of research supported early on by the Simons Foundation, sought to understand the molecular machinery that governs neural "plasticity," the ability of the brain to rapidly adapt function to changing experience by changing circuit connections called synapses. In vision experiments using mice, led by then postdoc Daniela Tropea, the lab showed that a protein called IGF-1 prevented plasticity of synapses in the visual cortex, meaning its role was to help synapses mature. They published their results in 2006.

Tropea and other researchers in Sur's lab subsequently showed that in mice that modeled Rett Syndrome, neurons were in a state of "perpetual plasticity". They published a study in 2009 showing that indeed Rett mice had low levels of IGF-1 and pronounced visual cortex plasticity that continued into adulthood. Dosing with an IGF-1 peptide successfully reversed this abnormal plasticity and also treated neurological and other symptoms of the disease.

That study provided the rationale for a pair of companies to test an IGF-1 peptide-based drug in Rett syndrome patients. A series of trials over several years culminated in the March 10 approval of the drug trofinetide. The basis for the idea that IGF-1 could treat Rett syndrome comes directly from the Sur lab's 2006 and 2009 papers, followed up with additional studies in mice as well as human stem cell-derived neurons and organoids ("mini-brains").

"It is the dream of every neuroscientist to have an impact on the world in some way," Sur said. "And this is my dream come true!"

See article in MIT News: https://news.mit.edu/2023/3-questions-mriganka-sur-first-approved-drug-treat-rett-syndrome-0313

Targeted Project Update

Cognitive, neural, and computational foundations of conversation

By members of Fedorenko, Gibson, Kanwisher, Levy, Robertson, Saxe, and Tenenbaum laboratories

The Conversation targeted project aims to investigate human conversational ability—a key ingredient of social interaction—using a synergistic combination of behavioral, neural, and computational approaches with neurotypical adults and children and those with autism. This project is a collaborative effort among seven labs: the Fedorenko, Kanwisher, Gibson, Saxe, Levy, Tanenbaum labs at MIT, and the Robertson lab at Dartmouth.

Talking to others is ubiquitous in everyday life, from a casual exchange at a grocery store, to a job interview, to building friendships and romantic relationships. Conversation is also critical for language learning: children's most critical exposure to linguistic input is through conversation. Finally, conversation is likely a locus of atypical function in autism, one that is abundantly evident in the real-world experience of children and adults with autism, and one that is perhaps at the core of developmental language difficulties in infants and toddlers eventually diagnosed with autism. In spite of the critical role of conversation in our lives, the cognitive and neural bases of conversation remain poorly understood, explicit computational models of conversational ability are lacking, and the precise nature and scope of challenges that arise in communicative disorders, like autism, are still debated. To remedy the situation, we are using a synergistic combination of highly innovative approaches to illuminate the cognitive, neural, and computational bases of human conversational ability.

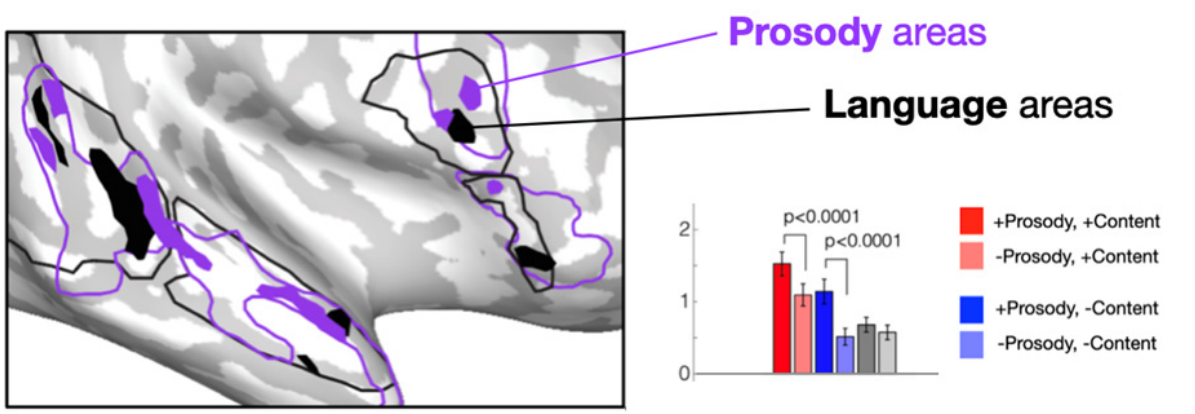


Figure 1. Left: A zoomed in view of the lateral frontal and temporal areas in the right hemisphere of a sample participants. Black outlines show areas within which most individuals show responses during language processing; purple outlines show areas within which most individuals show responses to prosody. Critically, in spite of the general proximity of these areas, at the individual-participant level they are clearly distinct (black vs. purple filled-in areas). **Right:** BOLD signal change in the prosody areas (purple in the left panel) in response to conditions with prosody (dark red, dark blue), conditions without prosody (light red, light blue), and lower-level control conditions (grey).

Ev Fedorenko, Associate Professor of Cognitive Neuroscience, and Nancy Kanwisher, Professor of Cognitive Neuroscience, are probing the organization of the socially-responsive cortex with the goal of discovering key components of the brain's 'conversation network'—a set of brain areas that process and integrate different informational components during conversational exchanges. One current direction targets the processing of intonation or prosody. Intonation, often described as the melody of speech, constitutes a critical ingredient of conversation and is fundamental to language learning. The team is using fMRI in an effort to understand how intonation-sensitive brain areas relate to auditory, language, and social-perception areas on the lateral temporal surface. They started with a broad contrast between snippets of speech from dialogs that are rich in prosodic information and the same content presented with little/no intonation. They also included a similar contrast for materials made up of nonwords, taking content out of the equation, along with lower-level control

conditions. They found that core language areas in the left hemisphere show little sensitivity to the presence of prosody. The right-hemisphere homotopes show some response to prosody, but intriguingly, both right and left-hemisphere language areas have areas in their vicinity that are strongly sensitive to the presence of prosody, in both meaningful materials and those made up of nonwords (Figure 1). These prosody-sensitive areas are distinct from auditory areas sensitive to pitch or speech and from areas that support the processing of facial expressions. The team is now characterizing these candidate prosody-selective areas in greater detail to understand how they fit into the broader functional landscape of language and social cognition.

Edward Gibson, Professor of Language and Cognitive Science, and Caroline Robertson, Assistant Professor of Cognitive Science and Neuroscience, are focusing on core components of conversational ability, including the ability to time conversational turns and to maintain eye contact. In particular, they are investigating how people with autism navigate first-person conversations to achieve conversational alignment. To do so, they are studying how individuals with and without autism (N=40; 20 ASC) coordinate verbal (e.g., semantic, prosodic) and nonverbal (eye-contact) cues during dyadic conversation with a partner, and how these multimodal metrics of conversational proficiency predict autism diagnostic scores. Using a dataset of mobile eye-tracking during semi-structured, naturalistic conversation (ADOS interviews), the team is testing how individuals coordinate turn-taking in a conversation and "track each other" throughout the course of a conversation by exchanging eye contact and converging on shared content within linguistic utterances.

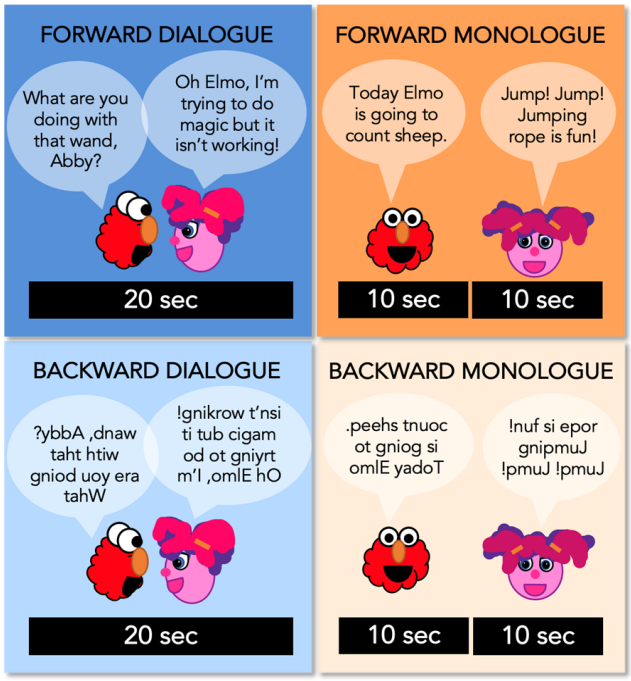


Figure 2: Experiment 1 Task Design. Participants watched 20-second clips of Dialogue (blue) and Monologue (orange) of Sesame Street, in which the audio is played either Forward or Backward.

Rebecca Saxe, Professor of Cognitive Neuroscience, is developing a novel highly engaging fMRI paradigm that would allow probing the brains of children during the time period when much of linguistic and social learning is taking place, and the period when challenges start to arise for children later diagnosed with autism. Language is first heard, learned, and used in informal conversation. By contrast, most research on the neural basis of language comprehension has relied on language from a single source. To understand dialogue, and predict what might come next, listeners must represent the different perspectives of the speakers. Comprehending language in dialogue thus requires additional social processing, compared to comprehending language from a single source. To determine whether canonical left-hemisphere language regions are sensitive to features of dialogue beyond the comprehensibility of the speech stream, the team scanned 20 adults using fMRI on two novel tasks using edited clips of Sesame Street. In the first task, participants watched videos of puppets speaking either to the viewer (monologue) or to a partner (dialogue), while the audio was either comprehensible (forward) or reversed (backward) (Figure 2). Canonical left-hemisphere language regions responded more to forward than backward speech, as expected, but did not respond more to dialogue than monologue (Figure 3). In the second task, two puppets conversed with each other, but only one was comprehensible while the other's speech stream was reversed. Left-hemisphere cortical language regions again responded more to forward than backwards speech, and activity in these regions was only correlated among participants who heard the same characters speaking forward and backward. In contrast, some theory of mind regions and right-hemisphere homotopes of language regions responded more to dialogue than monologue. The next step for this research will be to use these language tasks with young children. These engaging and accessible Sesame Street stimuli may also be useful for other populations that may find classic language tasks hard to tolerate, such as

individuals with developmental or acquired disorders.

Finally, Roger Levy, Professor of Language and Cognitive Science, and Josh Tenenbaum, Professor of Computational Cognitive Science, are working on improving existing models of language processing and conversation. They are targeting several facets of conversational exchanges, including conversations in the context of language learning. Children's early speech is very different from adult speech, yet caregivers are remarkably good at understanding what young children say, which forms a key part of the basis for child–caregiver conversations. What is the computational basis of how caregivers understand children's early speech? In their research on "child-directed listening", the team is using natural language processing and machine learning techniques, together with a large corpus of phonetically transcribed child speech, to investigate this question. They find that their computational models most successfully reproduce adult interpretations of children's speech when two key components are included: (i) strong, context-specific (including child-specific) prior expectations about what meanings children likely intend to convey, and (ii) detailed expectations about how children's speech differs phonetically from adult speech. These results point to a critical role for sophisticated inferential behavior on the part of adult caregivers in supporting conversation between caregivers and young children.

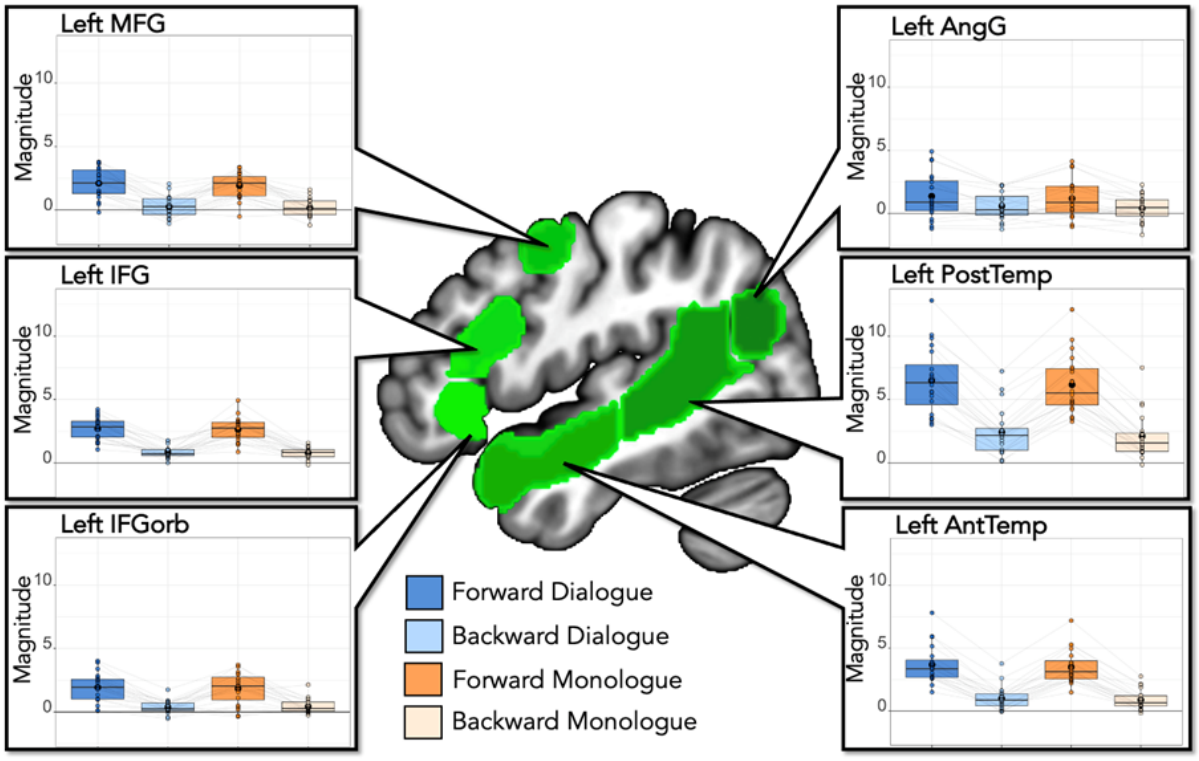


Figure 3: Average BOLD signal response magnitude by condition within language regions. **Center:** Left hemisphere language parcels overlaid on template brain (green; parcels include three areas in the left frontal lobe: IFGorb, IFG, MFG, and three areas in the temporal and parietal cortex: AntTemp, PostTemp, and AngG). These parcels are used to define language areas in each individual. **Panels:** Average response magnitude for each condition (blue: Forward Dialogue; light blue: Backward Dialogue; orange: Forward Monologue; light orange: Backward Monologue). Boxplot with mean in black circle; colored circles show individual participants with light gray lines connecting single participants. There was a main effect of Forward speech compared to Backward speech, but no effect of Dialogue speech compared to Monologue speech within language regions.

Understanding the cognitive and neural foundations of conversational ability would tell us a great deal about what it means to be human and how human social cognition is implemented in the mind and brain. Further, a deeper understanding of the nature, scope, and neural basis of difficulties that arise in autism during conversational exchanges may help develop more effective diagnostics and therapeutics.

Postdoctoral Fellows Profiles

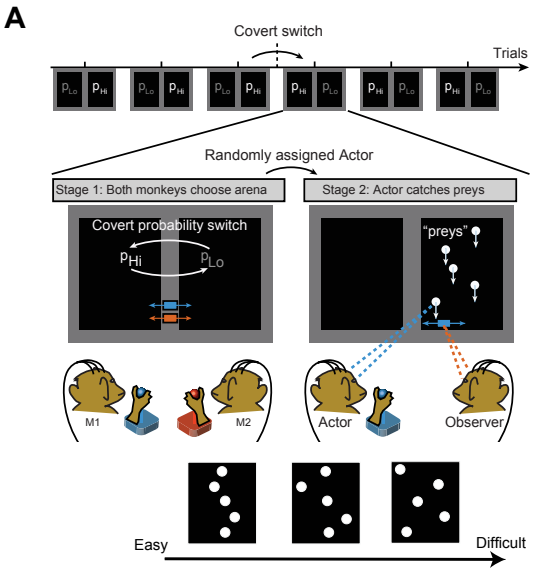
Ruidong Chen, Ph.D. | Jazayeri Lab, MIBR, BCS, MIT

Project Title: Probing the Neural Basis of Observational Learning

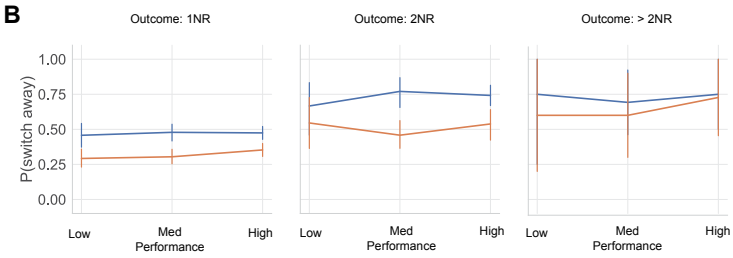
Observational learning is the ability to flexibly infer someone else's intention from observations. An important aspect of our social life, it can be severely compromised in individuals with autism spectrum disorder (ASD). To investigate the neural basis of observational learning, we are conducting two experiments in paired non-human primates (NHPs).

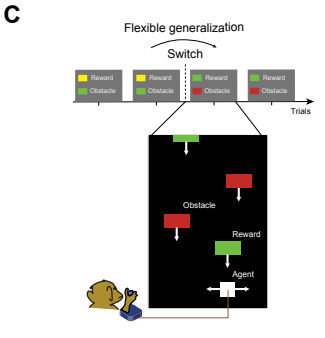
In the first experiment, we have trained two NHPs to perform probabilistic reversal learning in a social context (Figure A). The subjects each choose an arena between left and right, then a randomly assigned actor attempts to capture preys in the chosen arena while the observer watches. The correct arena changes from trial to trial, so subjects need to keep track of the reward outcome for past actions. Since the two subjects share the same environment, they could learn from each other's actions and reward outcomes to make informed choices (Figure B). We are currently recording neural responses in the anterior cingulate cortex while animals learn from each other in this task.

In the second experiment, we are training two NHPs on a one-shot learning task. A subject can either approach or avoid incoming objects and depending on which kind of object, it would be either rewarded or stopped. The identity of both objects changes frequently such that a subject has to learn from a single experience to perform better than chance (Figure C). The first NHP has learned to choose the correct action following a single experience, demonstrating one-shot learning (Figure D). We are planning to train the second subject and test their performance in a paired setting.



These experiments will allow us to probe the neural representations of observational learning and one-shot social inference.





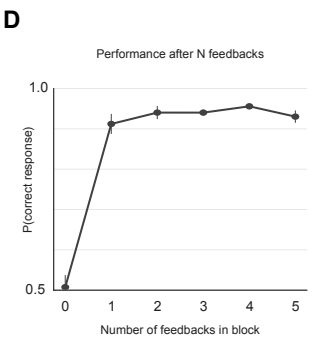


Figure A. The social reversal learning task. In the first stage of each trial, both subjects make independent choices between two arenas using joystick movements. Which one is correct changes covertly. In the second stage, one subject is randomly assigned as the actor and controls a square avatar to capture preys, while the other observes. When the actor's choice in the first stage is correct, the actor gets rewarded on random prey captures.

Figure B. Performance from a pair of monkeys demonstrating observational learning. Probability of switching from a previously chosen arena increases with number of non-rewarded trials (NR: number of previous trials not rewarded). Blue: data showing choice after actor trials. Orange: observer trials. Top and bottom rows: data from two subjects.

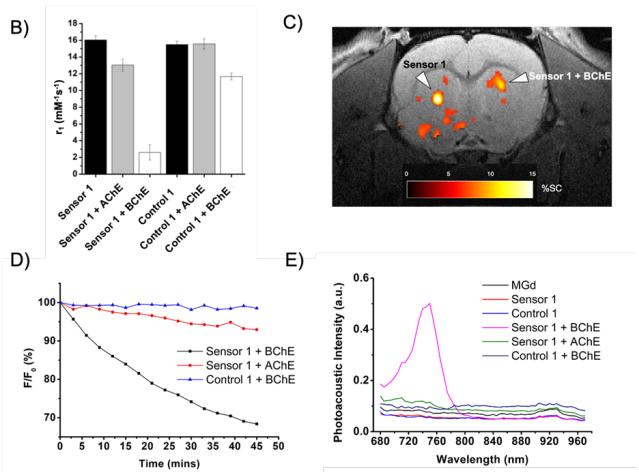
Figure C. The color switch task. Subject uses joystick to move the agent either away from or towards distinct objects with hidden identity. The subject gets juice reward when the agent touches a reward object. When the agent touches an obstacle, the trial is forfeited. On every other trial the appearance of rewards and obstacles both switch to new colors. **Figure D.** Performance of a monkey demonstrating one-shot learning. Probability of acting optimally is at chance when a new block starts, and reaches 90% correct following one feedback (either reward or forfeit).

Sajal Sen, Ph.D. | Jasanoff Lab, Biological Engineering, MIBR, MIT

Project Title: Probing Acetylcholinesterase Activity In Autism Using Novel Multimodal MRI Contrast Agents

Autism spectrum disorders (ASD) are a diverse family of neurodevelopmental conditions that lack any consistent biomarkers to date. Cholinesterase (ChE) enzymes, which lyse choline-based esters at cholinergic synapses, have been emerging as a potential therapeutic target in ASDs, and could serve as synapse-specific biomarkers for these disorders. However, probe technologies to correlate ChE activity and ASD are not yet available. My Simons fellowship proposal, therefore, seeks to design and validate novel ChE-sensitive MRI contrast agents to probe cholinergic phenotypes in ASD models, facilitate therapy development, and ultimately establish a non-invasive diagnostic tool for the clinical evaluation of autistic patients.

Toward this end, we have developed a new family of sensors for multimodal imaging of cholinesterase enzyme activity. Our lead compound, sensor 1, is designed to undergo hydrophilic-to-hydrophobic transitions upon cleavage. This changes their contrast properties and promotes transient accumulation in proportion to local ChE turnover, thereby permitting amplified detection and measurement of ChE activity at cholinergic synapses (Figure A). Control 1, a close analog of sensor 1 but featuring an amide bond instead of the ester bond, was employed as a control molecule as it lacks any esterase-cleavable moiety within the chemical framework. In vitro MRI studies indicate that sensor 1 is responsive to both ChEs, namely, AChE and BChE (Figure B). Next, preliminary in vivo MRI imaging with sensor 1 confirmed enzyme-dependent MRI contrast change (Figure C). Furthermore, sensor 1 benefits from a chemical framework that facilitates probing ChE activity via other multimodal imaging including fluorescence and photoacoustic techniques (Figures D and E). This added feature will permit valuable integration of readouts obtained over a range of spatial scales, both in living subjects and postmortem tissue.



A)

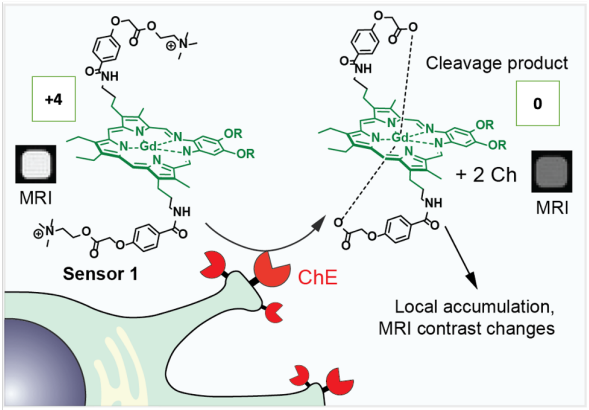


Figure: A. Principle of ChE activity imaging using Tex-based probes. ChE expressed at cholinergic synapses converts sensor 1 into free choline (Ch) plus a less charged/polar cleaved contrast agent, leading to local probe accumulation and changes in MRI contrast. **B.** Change in MRI relaxivity r_1 for sensor 1 or control 1 in the presence of ChE in vitro. **C.** Following intracerebral infusion of sensor 1 (left) and sensor 1 with BChE (right) in a rat brain, we see an increase in the T1-weighted signal. **D.** Change in fluorescence intensity for sensor 1 or control 1 in the presence of ChE in vitro. **E.** Change in photoacoustic signal intensity for sensor 1 or control 1 in the presence of ChE in vitro.

Our continuing work on this project is expected to refine the molecular designs and extend the in vivo applications to examine the ability of the sensors to detect ASD pathologies in mouse models. This work thus establishes a path toward preclinical research, drug development, and possibly clinical utility of our novel imaging tools for evaluating cholinergic function in autism.

Upcoming Events: Spring 2023

Colloquium Series

February

15 - Lauren Orefice, Ph.D.
Harvard Medical School, MGH

March

1 - André Fenton, Ph.D.
New York University

15 - Adele Goldberg, Ph.D.
Princeton University

April

5 - Robert Seyfarth, Ph.D.
University of Pennsylvania

19 - Gail Mandel, Ph.D.
Vollum Institute, OHSU

May

3 - Tobias Grossman, Ph.D.
University of Virginia

10 - Corey Harwell, Ph.D.
University of California, San Francisco

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

Lunch Series

February 10, 2023 – **Shreya Mahajan**
Research Associate, Mriganka Sur Laboratory, MIT

February 24, 2023 – **Stephan Meylan, Ph.D.**
Postdoctoral Associate, MIT Brain and Cognitive Sciences, Computational Psycholinguistics Lab

March 24, 2023 – **Danielle Tomasello, Ph.D.**
Postdoctoral Fellow, Rudolf Jaenisch Laboratory, Whitehead Institute for Biomedical Research

April 28, 2023 – **Halie Olson**
Graduate Student, Rebecca Saxe Laboratory, Department of Brain and Cognitive Sciences, MIT

May 19, 2023 – **Menglong Zeng, Ph.D.**
Guoping Feng Laboratory, McGovern Institute, MIT

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

Simons Postdoctoral Fellowship opportunities

The Simons Center has two rounds of funding annually for postdoctoral fellowships. The Fall 2023 deadline to submit an application is **Friday, September 29, 2023**.

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/.

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