THE SIMONS CENTER FOR THE SOCIAL BRAIN (SCSB) NEWSLETTER | Spring 2021

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PUBLICATIONS SPOTLIGHT

Guoping Feng, Frances E. Jensen, Henry T. Greely, Hideyuki Okano, Stefan Treue, Angela C. Roberts, James G. Fox, Sarah Caddick, Mu-ming Poo, William T. Newsome, and John H. Morrison. Opportunities and limitations of genetically modified nonhuman primate models for neuroscience research. Proceedings of the National Academy of Sciences U.S.A. 117(39): 24022-24031, 2020 [https://doi.org/10.1073/pnas.2006515117]

Olessia Jouravlev, Alexander J. E. Kell, Zachary Mineroff, Amanda J. Haskins, Dima Ayyash, Nancy Kanwisher, and **Evelina Fedorenko**. Reduced language lateralization in autism and the broader autism phenotype as assessed with robust individual-subjects analyses. Autism Research 13(10): 1746-1761, 2020 [https://doi.org/10.1002/aur.2393]

Alexander Friedman, Emily Hueske, Sabrina M. Drammis, Sebastian E. Toro Arana, Erik D. Nelson, Cody W. Carter, Sebastien Delcasso, Raimundo X. Rodriguez, Hope Lutwak, Kaden S. DiMarco, Qingyang Zhang, Lara I. Rakocevic, Dan Hu, Joshua K. Xiong, Jiajia Zhao, Leif G. Gibb, Tomoko Yoshida, Cody A. Siciliano, Thomas J. Diefenbach, Charu Ramakrishnan, Karl Deisseroth, and **Ann M. Graybiel**. Striosomes mediate value-based learning vulnerable in age and Huntington's Disease model. Cell 183: 918-934, 2020 [https://doi.org/10.1016/j.cell.2020.09.060]

Sarah Bricault, Ali Barandov, Peter Harvey, Elizabeth DeTienne, Aviad Hai and **Alan Jasanoff**. Image-guided neural activity manipulation with a paramagnetic drug. Nature Communications 11: 136, 2020 [https://doi.org/10.1038/s41467-019-13933-5]

Julie Freschl, David Melcher, Alice Carter, **Zsuzsa Kaldy** and Erik Blaser. Seeing a page of a flipbook: Shorter visual temporal integration windows in 2-year-old toddlers with Autism Spectrum Disorder. Autism Research, 2021 [https://doi.org/10.1002/aur.2430]

Brittany L. Manning, Alexandra Harpole, Emily M. Harriott, Kamila Postolowicz, and **Elizabeth S. Norton**. Taking language samples home: feasibility, reliability, and validity of child language samples conducted remotely with video chat versus in-person. Journal of Speech, Language and Hearing Research 63(12): 3982-3990, 2020 [https://doi:10.1044/2020_JSLHR-20-00202]

Jonathan Cannon, Amanda M. O'Brien, Lindsay Bungert, and **Pawan Sinha**. Prediction in Autism Spectrum Disorder: A systematic review of empirical evidence. Autism Research, 2021 [https://doi.org/10.1002/aur.2482]

POSTDOCTORAL APPLICATIONS: SPRING 2021

We are pleased to announce the 2021 funding opportunities for Simons 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: May 31, 2021.

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

TARGETED PROJECTS: UPDATES

SCSB has two ongoing targeted projects: "Predictive processes in autistic and neuro-typical Individuals. A behavioral, neural and developmental investigation," involving the laboratories of Pawan Sinha, John Gabrieli and Jesse Snedeker; and "Circuit mechanisms of ASD-relevant behaviors in marmosets," involving the laboratories of Robert Desimone, Ann Graybiel, Alan Jasanoff and Mriganka Sur. We present below updates from these two projects.

PREDICTIVE PROCESSING IN AUTISM TARGETED PROJECT

By members of the Sinha, Gabrieli and Snedeker labs

The Predictive Processes targeted project aims to characterize multiple domains of prediction in autism. Uncertainty can pose challenges for individuals with autism. This may have consequences for navigating daily activities that may be unpredictable or rely on rapid updating of changing contingencies. Social interaction in particular, require adapting to rapidly changing perceptual, social, and linguistic demands. Recent theoretical and empirical work suggest that individuals with autism may show differences in prediction, but empirical findings are mixed across paradigms and participant samples. The Sinha, Gabrieli, and Snedeker labs continue to study autism in three domains: temporal auditory prediction, neural adaptation, and language. Each lab has responded differently to COVID-19, and the projects continue to evolve in response to the pandemic's constraints.

Professor **Pawan Sinha** has partnered with the Simons Foundation's SPARK (Simons Foundation Powering Autism Research for Knowledge) initiative, a nationwide database of autistic individuals willing to participate in research studies. SPARK enabled the Sinha lab team to launch several online experiments that participants can complete from home. Auditory detection tasks require participants to detect beeps in background noise, with temporal cues that may aid performance.

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Early results show that non-autistic adults' performance improves with predictable interval- and beat-based cues, relative to randomly presented cues (Figure 1). Contrary to our hypothesis, we observe similar improvement across groups, indicating that the capacity to deploy attention to optimize detection using predictive timing does not appear systematically affected in autism. This team will soon launch new experiments to test linguistic prediction and perception of volatility in probabilistic sequences. The lab is preparing to implement similar experiments using electrophysiologyical tools to probe neural responses to predictable and unpredictable auditory stimuli when they return to MIT's campus. A systematic review recently published by the group in Autism Research, summarizes the literature on prediction in autism across domains and proposes new directions for research.

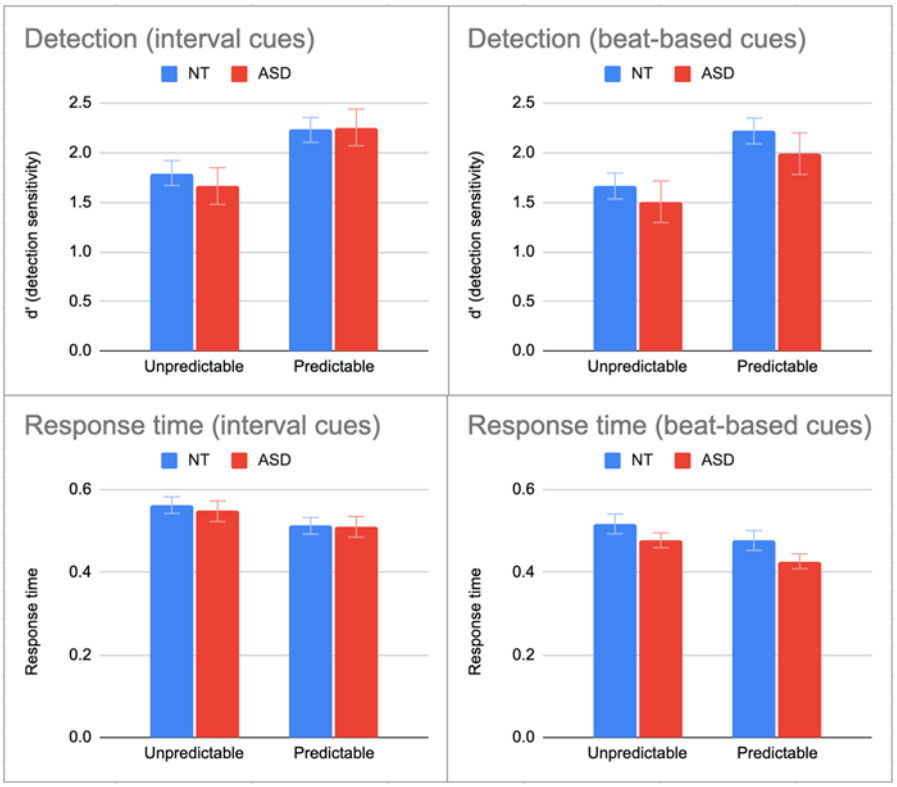


Figure 1. Predictability of auditory target timing due to reliable beat-based and interval-based cueing improves performance relative to unpredictable conditions in both neurotypical (NT) and ASD groups, as measured by detection sensitivity and response time. The ASD group is showing less detection sensitivity and faster responses than the NT group in the beat-based condition, but no significant difference from the NT group in the effect of predictability.

Professor **John Gabrieli** and his team continue to investigate how neural adaptation results in rapid brain plasticity in response to higher-level percepts (faces, speech, objects, and written words). Prior to COVID, his team scanned neurotypical and autistic adults using fMRI. Participants passively viewed blocks of repeating and non-repeating stimuli. Repeating stimuli are quickly recognized and therefore result in reduced brain activation, whereas non-repeating stimuli are actively processed. Neural adaptation is the difference in activation between non-repeating and repeating stimuli. Neural adaptation may support prediction by measuring how well the brain distinguishes repeating from non-repeating events. New analyses of neuroimaging data collected prior to the onset of the pandemic have revealed that individuals with ASD showed reduced neural adaptation to faces, but not to other domains tested. Gabrieli's group plans to continue further neuroimaging to test whether differences in top-down expectations, rather than simple bottom-up brain plasticity, may explain group differences.

Jesse Snedeker, Professor of Psychology at Harvard University, is examining predictions that people make about words as they listen to stories. Prior to COVID-19, her group was pursuing studies using electrophysiological measures to track complex linguistic predictions in children, and adapting some of the Sinha and Gabrieli lab paradigms for younger participants. The Snedeker lab plans to continue EEG testing with children as soon as it becomes safe to do so. Meanwhile, the Snedeker lab has shifted to implementing online behavioral experiments examining linguistic prediction in adults. For example, in one such experiment her group is examining how the ability to predict an upcoming word may affect how it is heard. Participants listen to a story where occasionally parts of certain words are replaced with noise. This can lead to an illusion that the word was correctly pronounced, known as the "phoneme restoration effect." Comparing how often a listener experiences this illusion in predictable and unpredictable words given their context can provide insight into how prediction can affect our perception of speech. Consistent with prior work, early data from typically developing adults suggests that phoneme restoration occurs

more often in words that are predictable. Confirming the expected pattern in typical adults is the final step before beginning studies in the next month with adults from the SPARK database. Additional studies will investigate explicit predictions about upcoming words and when such predictions may affect language comprehension. Finally, by including a non-linguistic prediction task and characterizing participants based on their language ability, the group plans to examine whether linguistic prediction may differ with general predictive ability, language skill, or autism diagnosis.

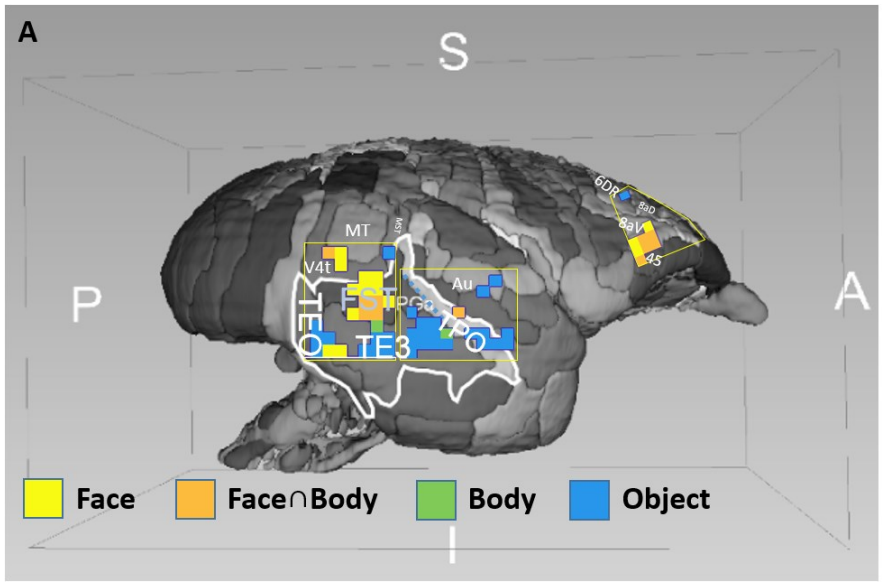
As the results of these studies begin to emerge, we hope they will not only illuminate possible differences in prediction abilities between autistic and typically-developing individuals, but will also inform future versions of neuroimaging experiments in the lab setting when scientists return to campus.

THE MARMOSET TARGETED PROJECT

By members of the Desimone, Graybiel, Sur and Jasanoff labs

The Marmoset targeted project aims to understand autism spectrum disorder (ASD)-relevant behaviors and brain mechanisms in wild-type marmosets, with the goal of subsequently applying this understanding to transgenic marmoset models of ASD. After an initial ramp-down due to Covid, all the labs involved in this project have been able to resume operations.

Professor **Robert Desimone's** lab, in collaboration with the Sur, Feng, and Jasanoff labs, is mapping the brain regions important for social perception through fMRI and electrocorticogram (ECoG) recordings in marmosets. The lab has conducted ECoG recordings in both restrained and unrestrained marmosets. In restrained marmosets trained to watch movies, the lab has recorded ECoG signals from temporal and prefrontal cortex (Figure 1). Their analysis has revealed that several regions in the temporal and prefrontal cortex are responsive to social stimuli such as faces, bodies, and interacting marmosets. The timing and correlations of these signals across regions are currently being further analyzed. Parallel fMRI sessions are being conducted in different marmosets using the same stimuli in to get full-brain coverage. In addition to restrained recordings, the Desimone lab has also performed unrestrained recordings in the home cage while marmosets socially interact. Recordings have been obtained during a range of behaviors such as eating, grooming, sleeping, and mating during the day and night.



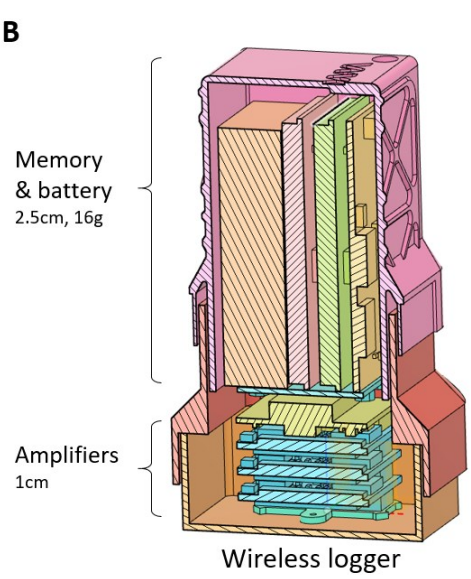


Figure 1. ECoG recordings in temporal and frontal cortex. **A.** Patches of high gamma activity selective for faces, bodies, or objects were localized in temporal and frontal cortex. Yellow outline shows the outline of 3 ECoG arrays. Underlay is a marmoset brain atlas. **B.** A cross-section view of the device used for wireless recording. The miniaturized light-weight wireless logger allows the subject to move and socialize as normal, and provides 8 hours of recordings on a single charge.

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Repetitive or stereotyped behaviors are a cardinal feature of autism spectrum disorder (ASD). Professor **Ann Graybiel's** lab is focused on researching an axis of cortico-striatal and dopaminergic circuitry that correlates with stereotypic behaviors exhibited by rats, mice and squirrel monkeys. The lab has found that in marmosets, the striosomal compartment of the striatum shows greater activation in individuals exhibiting stereotypies (Figure 2). They have also recently established a chemogenetic approach for activating and inhibiting striosomal neurons, a technology the lab plans to combine with striatal compartment-targeting promoters in marmosets. The lab is now directly testing whether inactivation of striosomes in Shank3B KO mice reduces stereotypic behaviors and whether activation of striosomes elevates stereotypic behaviors.

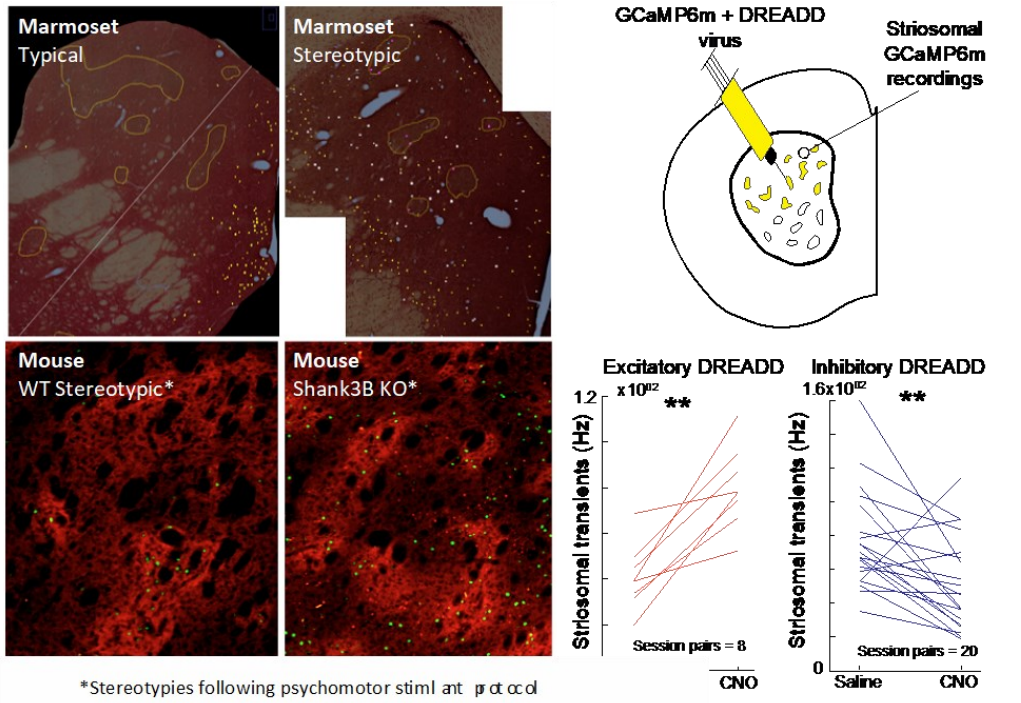
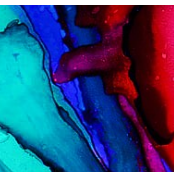


Figure 2. Role of striatal compartments in stereotypic behavior. **A.** Striatal tissue sections from a stereotypic marmoset exhibits higher cfos counts in striosomes than matrix and higher cfos counts overall (ISMP, index of striosomal to matrix predominance, (S-M/S+M)). **B.** DREADD-based chemogenetic approach activates or inhibits calcium transient activity in striosomal neuron populations.

Another proposed cardinal symptom of ASD is the impaired ability to predict events in space and time. Professor **Mriganka Sur's** lab is testing this phenotype in the context of temporal prediction and processing in the marmoset brain. To understand temporal prediction in the face of uncertainty, the lab has used a reaction time behavioral paradigm to show that human and marmoset prediction behavior is similar and undergoes distinct changes with learning, whereby extended task exposure increases the influence of trial context. In the brain, temporal predictions are believed to involve a network that spans multiple cortical regions including visual and parietal areas. To test this, the Sur lab plans to implant ECoG arrays across several brain areas and record activity while animals perform the task. By collaborating with the Desimone lab, the Sur lab has developed and adapted their temporal prediction behavioral paradigm to be integrated with ECoG recordings in awake marmosets. The lab plans to record large scale population activity across visual, parietal and dorsomedial prefrontal cortex to reveal their role in mediating temporal prediction and trial context.

In collaboration with the Desimone and Sur labs, Professor **Alan Jasanoff's** lab has continued building the infrastructure for fMRI recordings in awake marmosets. Some recent developments have included the identification of face-selective responses in regions of the marmoset brain, as well as new experiments designed to probe differences between familiar and unfamiliar faces. In parallel with this work, the lab has made important progress in the development of genetic reporters that they plan to use for dissecting social stimulus processing circuitry in the primate brain. This includes improvements and further validation to their probe technology, as well as initial pilot studies in monkeys.



SIMONS POSTDOCTORAL FELLOWS: AWARDS AND RECOGNITION

Abhishek Banerjee, Ph.D., former Simons Postdoctoral Fellow, Mriganka Sur Laboratory
- Started as Senior Lecturer/Associate Professor and Head, Adaptive Decision-making Lab Biosciences Institute, Newcastle University
- Received INSERM start-up grant

Elizabeth Norton, Ph.D., former Schwinn Postdoctoral Fellow, John Gabrieli Laboratory
- Received the Clarence Simon Award for Outstanding Teaching and Mentoring at Northwestern University

Xuyu Qian, Ph.D., Simons Fellow, Christopher Walsh Laboratory
- Received the UZH-Award for Research in Brain Diseases from The Foundation of University of Zurich
- Received a Postdoctoral Fellowship from the Helen Hay Whitney Foundation

Siyuan Rao, Ph.D., former Simons Postdoctoral Fellow, Polina Anikeeva Laboratory
- Started as Assistant Professor, Department of Biomedical Engineering, University of Massachusetts, Amherst
- Received 2020 BRAIN Initiative Investigators Meeting Trainee Award

Liron Rozenkrantz, Simons Fellow, John Gabrieli Laboratory
- Received MIT McGovern Rising Star Award

Xin Tang, Ph.D., former Simons Postdoctoral Fellow, Rudolf Jaenisch Laboratory
- Started as Assistant Professor, Department of Neurosurgery, Boston Children's Hospital

Jakob Voigts, Ph.D., Simons Fellow, Mark Harnett Laboratory
- Received a K99 award as a result of work as a Simons Fellow
- Starting as a group leader at Janelia Research Campus in summer 2022

Freddy Kamps, Ph.D. | Saxe lab, McGovern Institute, MIT

DEVELOPMENT OF CORTICAL REGIONS FOR SOCIAL PERCEPTION AND COGNITION

Uncovering the neural basis of ASD will ultimately require understanding how neural systems are affected in early stages of development. However, collecting high quality fMRI data from young children is a significant challenge – exacerbated by reliance on relatively unengaging paradigms designed for adults. We addressed this challenge by studying responses to a short, engaging, animated movie depicting natural visual experience, which allowed high-quality data collection from a large sample (N=122) of typically developing children age 3-12 years.

We focused on two face-selective regions hypothesized to be impaired in ASD – the fusiform face area (FFA) and posterior superior temporal sulcus (pSTS) – as well as a set of regions involved in nonsocial perception, including regions selective for scenes/places and objects. Remarkably, adult-like function was already detectable across face, scene, and object regions by just 3 years of age, with children showing peak responses to similar movie events (Figure 1A), and similar patterns of interregional correlations, as adults. Later in development, the magnitude of responses to peak events continued to increase, with individual regions following distinct trajectories. For example, the pSTS showed significantly more protracted developmental change than the FFA (Figure 1B).

Our results provide novel insight into typical development of higher-level visual cortex, and highlight the promise of naturalistic movie data for studying cortical development in childhood, setting the stage for future work in ASD.

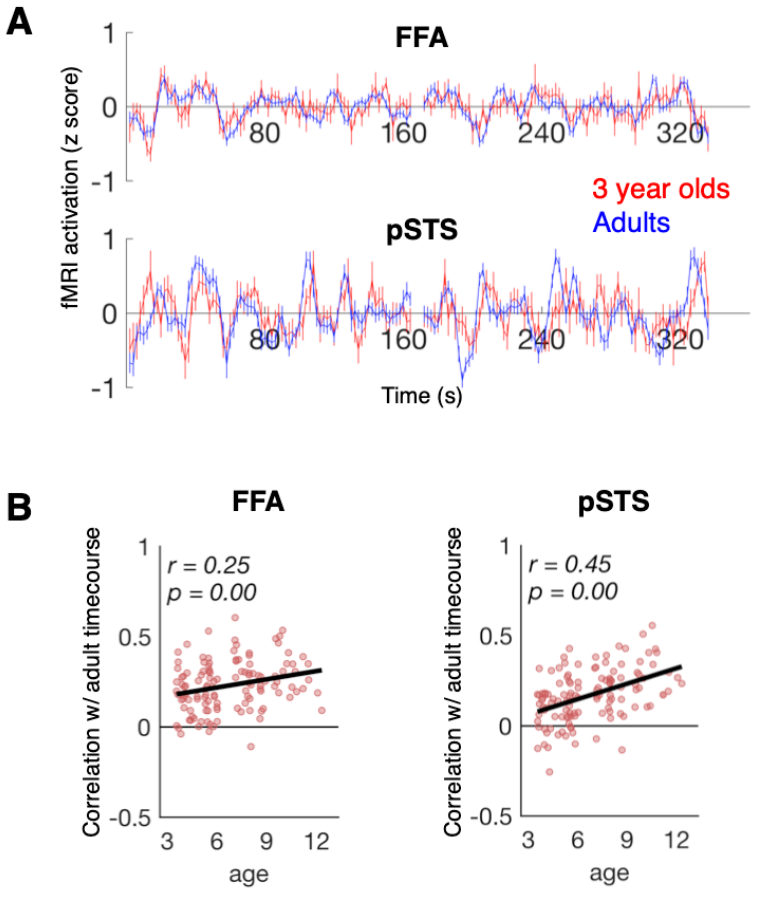
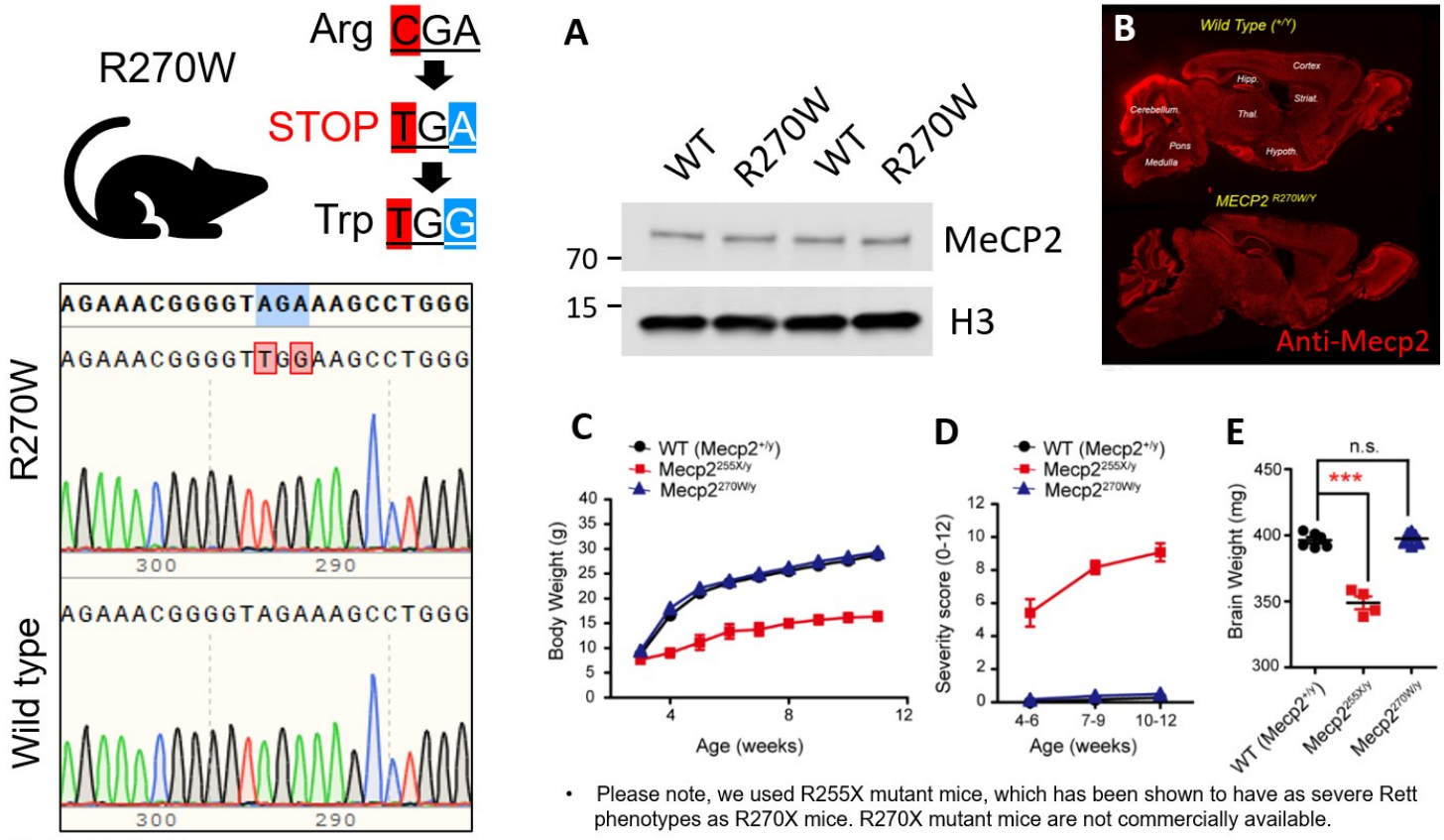


Figure 1. Measuring functional responses to a naturalistic movie in face-selective cortex across development. **A.** Timecourse of fMRI responses to the movie for the FFA (top) and pSTS (bottom). The average timecourse in adults is shown in blue, while that for 3 year olds is shown in red. **B.** The correlation between each child's timecourse and the average adult timecourse (red dots) increases with age in each region, with greater developmental increases in pSTS (right) than FFA (left).

Chenjie Shen, Ph.D. | Feng lab, McGovern Institute, MIT

RNA EDITING AS A GENE THERAPY APPROACH FOR RETT SYNDROME

Genome editing technologies have made unprecedented advances over the past decade. As a result, targeted endonuclease-based approaches to gene therapy now hold realistic promise for treating and curing a large number of human diseases. However, CRISPR/Cas-based genome editing approaches pose the threat of introducing permanent off -target mutations into the genome. To avoid these limitations of DNA nucleases, approaches that instead directly target RNA would be highly desirable, as these would enable tunability, reversibility, and importantly no off-target mutations would be permanent. Additionally, RNA, unlike DNA, can be targeted via simple RNA-nucleic acid hybridization. Thus, RNA base editing via RNA-guided adenosine deaminases of human origin could be an attractive approach for *in vivo* correction of disease-causing point mutations. My Simons Fellowship research is to develop



- Please note, we used R255X mutant mice, which has been shown to have as severe Rett phenotypes as R270X mice. R270X mutant mice are not commercially available.

Figure 1. MECP2 R270W mice (left panel) are indistinguishable from wild type mice. **(A)** Western blot and **(B)** immunostaining show that the Mecp2 protein levels in MeCP2 R270W mice were same as their wild type littermates. **(C-E)** Male MECP2 R270W mice were indistinguishable from wildtype on body weight **(C)**, severity score **(D)**, and brain weight **(E)**. *p < 0.05; **p < 0.01; ***p < 0.001; n.s., not significant. Error bars, SEM.

and test the effectiveness of Cas13-based RNA editing in mice as a means for gene therapy targeting Rett Syndrome.

The most common Rett-associated mutations are C→T mutations which account for >50% of all Mecp2 mutations found in patients to date . All Rett-associated C→T mutations mutate CGA to TGA, changing an arginine residue to a premature stop codon.

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Currently, there are no RNA-editing methods that convert U to C on the resulting mRNA. Taking advantage of the REPAIRv2 system for A→G conversion, I propose to convert UGA to UGG in Mecp2 mRNA, which will turn the premature stop codon to tryptophan (W). It is likely that changing this premature stop codon to tryptophan at the MECP2 R270 location will restore Mecp2 function, at least partially. I used a germline knockin approach in mice to test whether a tryptophan substitution in the R270 location maintains Mecp2 function in mice. We generated MeCP2 R270W mice in our lab and my preliminary data shows that Mecp2 protein levels in these R270W mice are similar to their wild type littermates (Figure 1A, B). More importantly, compared to the Rett syndrome mice, which exhibit severe Rett phenotypes and die at 8 weeks, our R270W trp substitution mice resemble WT mice: the phenotypic features of Trp mice are indistinguishable from WT littermates (Figure 1C-E). Together, these data strongly suggest that converting STOP to Trp could restore Mecp2 function and indicates that RNA editing-based gene therapy holds promise for treating Rett syndrome.

PAST SIMONS POSTDOCTORAL FELLOW: PROFILE

Siyuan Rao, Ph.D. | Anikeeva Lab, Research Laboratory of Electronics, MIT

Current Position: Assistant Professor, Department of Biomedical Engineering at University of Massachusetts, Amherst

ENGINEERING TOOLS TO STUDY SOCIAL BEHAVIORS

I was supported by a Simons Postdoctoral Fellowship from 2016-2018 under the co-supervision of Profs. Polina Anikeeva and Guoping Feng. In my Simons project, we developed a chemomagnetic technique to remotely control chemical release in brain and modulate neural circuits in freely behaving mice (Figure 1; Rao,... Feng, Anikeeva, Nature Nanotechnology 2019). Using this technique, we reshaped mouse depression-like behaviors and social behaviors using wireless magnetic fields and nanoscale magnetic nanoparticles. These remotely-controlled magnetic techniques will provide us with exquisite spatiotemporal precision to probe neural circuits, and improve the accuracy of behavioral observations with tethering-free experimental setups.

Based on my Simons project on chemical modulation, I proposed to expand this magnetic toolkit to genetic manipulation in autism models. This proposal was funded by a NIH K99/R00 award in 2019. During the COVID era, I secured a faculty position as an Assistant Professor in the Department of Biomedical Engineering at UMass Amherst. Recently, I started my faculty position and opened up my Neurobiological Interfaces Laboratory. Together with my young research team, we are continuing our efforts on developing engineering tools to facilitate the study of social behaviors. Our latest work includes inventing hydrophilic polymer-based neural probes to enable long-term optical recording of neural activity combined with simultaneous mouse social behavior tests.

The Simons Postdoctoral Fellowship and the events held by the Simons Center have been indispensable catalysts in my career development. The research project supported by my Simons Fellowship provided me critical training at the intersection of neuroscience and engineering and became the precursor of my career development funding and future research direction. Attending the SCSB Colloquium Series, Lunch Talks, and the discussions among Simons Fellows at SCSB lunches opened up a broad range of opportunities for me to interact with colleagues across different research fields, to acquire research inspiration and to establish new collaborations.

The Simons Center thus brought me to an interdisciplinary research field and spring-boarded me to a new career stage. In future, I hope to continue to combine efforts from multiple disciplines to overcome the challenges of understanding and treating Autism Spectrum Disorder.

Related paper: https://www.nature.com/articles/s41565-019-0521-z
Neurobiological Interfaces Laboratory website: www.syraolab.com

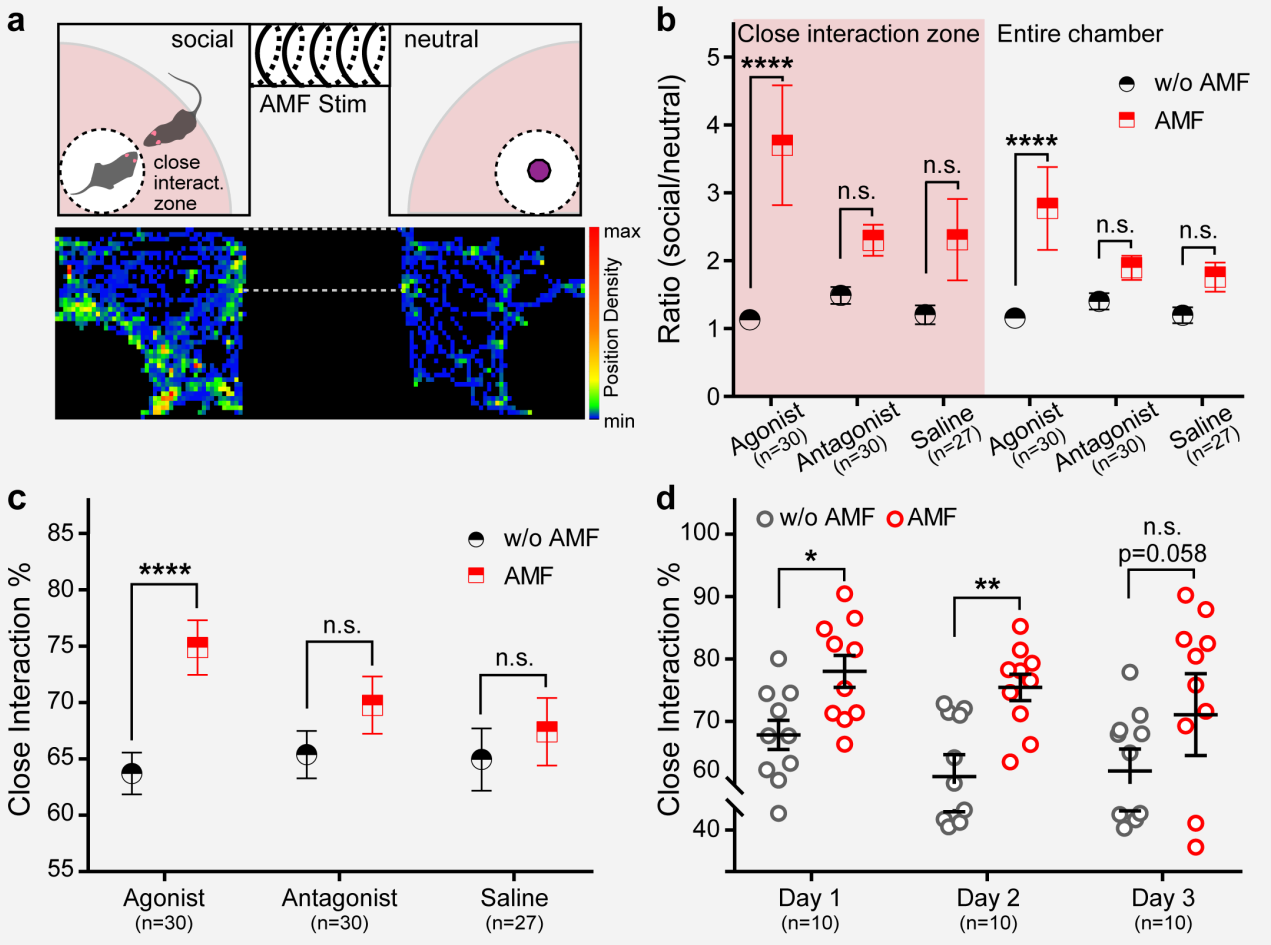

Figure 1. Effects of remote chemomagnetic modulation on mouse social behavior. **a, Top:** The experimental scheme for the mouse social preference test with an alternating magnetic field (AMF) coil encompassing the middle chamber. **b,** The ratio of time spent in the social interaction chamber to the object (neutral) chamber is compared for mice subjected to AMF. The group with agonist-loaded magnetoliposomes exhibits enhanced social preference following exposure to AMF. **c,** The percentage of close interaction in the social chamber. The group injected with agonist-loaded magnetoliposomes spent more time in the close interaction zone. **d,** The group injected with agonist-loaded magnetoliposomes repeatedly showed increased social preference following AMF exposure.

UPCOMING EVENTS: SPRING 2021

COLLOQUIUM SERIES

FEBRUARY

17 - Mina Cikara, Ph.D.
Harvard University

MARCH

17 - David Liu, Ph.D.
Merkin Institute; Broad Institute; HHMI; Harvard University

APRIL

14 - Kafui Dzirasa, M.D., Ph.D.
Duke University

MAY

26 - Claudia Bagni, Ph.D.
University of Lausanne, Switzerland

General Info:
Time: 4PM - 5PM
Location: Zoom Webinar, *registration required*

LUNCH SERIES

February 26, 2021— **Frederik Kamps, Ph.D.**
Simons Postdoctoral Fellow, Rebecca Saxe Laboratory, MIT

March 26, 2021 – **Xuyu Qian, Ph.D.**
Simons Postdoctoral Fellow, Christopher Walsh Laboratory, MIT

April 23, 2021 – **Pawan Sinha, Ph.D.**
Principal Investigator, BCS, MIT

May 14, 2021— **Haoran Xu, Ph.D.**
Research Scientist, Robert Desimone Laboratory, MIT

General Info:
Time: 12PM - 1PM
Location: Zoom Webinar, *registration required*

All events are open to the public, please register for each Webinar via http://scsb.mit.edu/events/

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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