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

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MIT

SIMONS CENTER FOR THE SOCIAL BRAIN

PUBLICATIONS SPOTLIGHT
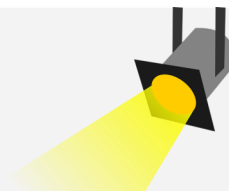
Xin Gong, Diego Mendoza-Halliday, Jonathan T. Ting, Tobias Kaiser, Xuyun Sun, André M. Bastos, Ralf D. Wimmer, Baolin Guo, Qian Chen, **Yang Zhou**, Maxwell Pruner, Carolyn W.-H. Wu, Demian Park, Karl Deisseroth, **Boaz Barak**, **Edward S. Boyden**, Earl K. Miller, **Michael M. Halassa**, Zhanyan Fu, Guoqiang Bi, **Robert Desimone**, **Guoping Feng**. An ultra-sensitive step-function opsin for minimally invasive optogenetic stimulation in mice and macaques. Neuron 107(1): 38-51, 2020 [https://doi.org/10.1016/j.neuron.2020.03.032]

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Moataz Assem, Idan A. Blank, Zachary Mineroff, Ahmet Ademoğlu, **Evelina Fedorenko**. Activity in the fronto-parietal multiple-demand network is robustly associated with individual differences in working memory and fluid intelligence. Cortex 131, 1-16, 2020 [https://doi.org/10.1016/j.cortex.2020.06.013]

Evgeniia Diachek, Idan Blank, Matthew Siegelman, Josef Affourtit, **Evelina Fedorenko**. The domain-general multiple de-mand (MD) network does not support core aspects of language comprehension: a large-scale fMRI investigation. Journal of Neuroscience 40(23): 4536–4550, 2020 [https://doi.org/10.1523/JNEUROSCI.2036-19.2020]

POSTDOCTORAL APPLICATIONS: SPRING 2021

We are pleased to announce the 2021 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: 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 THROUGH THE COVID-19 DOWNTURN

SCSB has two ongoing targeted projects: "Predictive processes in autistic and neuro-typical Individuals. A behavioral, neural and developmental investigation," involving the laboratories of John Gabrieli, Pawan Sinha 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. The last six months have been unusual due to the COVID-19 lab ramp down at MIT. Nonetheless, we have made progress on these projects, as described below.

PREDICTIVE PROCESSING IN AUTISM TARGETED PROJECT

By members of the Sinha, Gabrieli and Snedeker labs

The Predictive Processes targeted project investigates how multiple aspects of prediction may differ in autism. During the first year of the project, the Sinha, Gabrieli, and Snedeker labs joined forces to launch behavioral and neuroimaging studies of autism in children and adults in three domains: temporal auditory prediction, neural adaptation, and linguistic prediction. Since the onset of COVID-19, each lab has responded differently, from re-envisioning lab-based experiments to testing participants online, to delving more deeply into analyses of neuroimaging data collected before nationwide shutdowns began.

The labs plan to partner with the Simons Foundation's SPARK (Simons Powering Autism Research), a nationwide database of autistic adults and children willing to participate in research studies. SPARK will serve as a catalyst to launch online behavioral experiments that participants can complete from the safety of their homes. The results of these experiments 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 can return to campus.

Why prediction? Uncertainty can pose challenges for individuals with autism. This may have consequences for navigating daily activities that may be noisy or unpredictable and rely on rapid updating of changing contingencies. Social interaction and communication, 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 a variety of paradigms and participant samples. Prior studies often examine one paradigm assuming that it reflects a unitary process of prediction. The Predictive Processes targeted project adopts a more integrative approach, implementing a set of interlocking studies at MIT and Harvard.

Pawan Sinha, Professor of Vision and Computational Neuroscience at MIT, whose group proposed the "Magical World" theory of autism as a disorder of prediction, initially designed a series of experiments to probe temporal auditory prediction using electroencephalography (EEG) and behavioral measures. The group was poised to begin data collection during the week that MIT shut down its neuroimaging labs due to COVID-19. Since then, the group has redesigned the experimental tasks to collect data online with autistic adults from the SPARK database, as well as typically-developing peers. The revised online auditory detection tasks require participants to listen for quiet beeps in background noise, with temporal cues that may aid performance. Early results from these tasks show that non-autistic adults' performance improves with predictable interval- and beat-based cues, relative to randomly presented cues (Figure 1). We hypothesize that in autism the performance benefit from temporal cuing will be reduced. This team also designed online experiments that will probe linguistic prediction and perception of volatility in probabilistic sequences.

John Gabrieli, Professor of Cognitive Neuroscience, and his team investigated how neural adaptation results in rapid brain plasticity in response to simple higher-level percepts (faces, speech, objects, and written words) in 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 must be 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 (Figure 2). In Year 2, the Gabrieli group plans to pursue further neuroimaging to test whether differences in top-down expectations, rather than simple rapid bottom-up brain plasticity, may explain group differences.
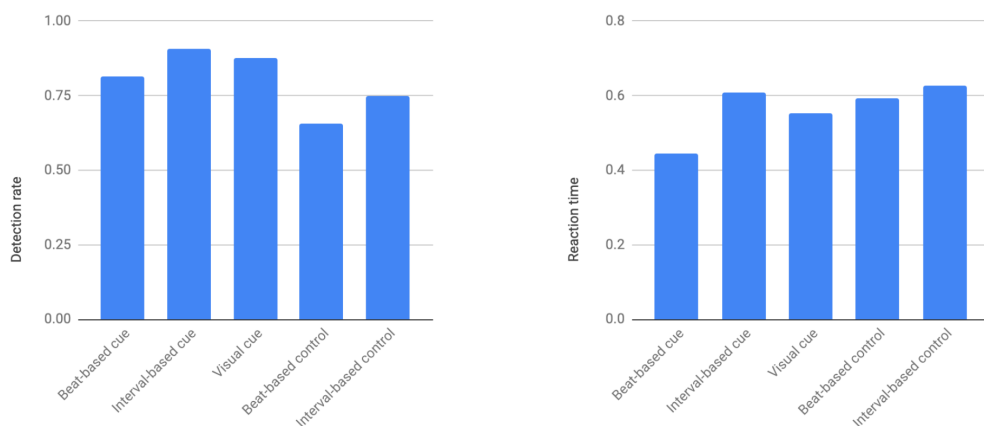

NT example participant

Figure 1. Beat-based, interval-based, and visual cues improve performance as measured by detection rate and reaction time. Beat-based and interval-based control conditions show poorer performance as indicated by lower detection rates and higher reaction times.
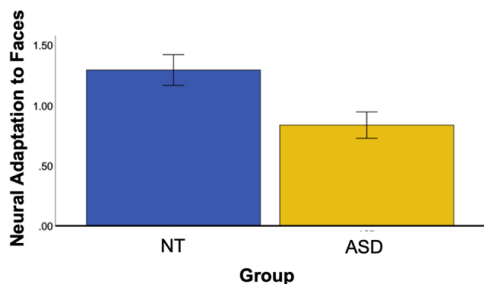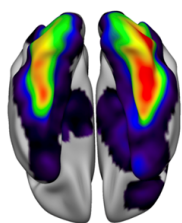
Jesse Snedeker, Professor of Psychology at Harvard University, will examine the predictions that people make about words as they listen to natural stories. Prior to the COVID-19 pandemic, her group planned to pursue studies that use electrophysiological measures to track complex linguistic predictions in children. Her group also planned to adapt a subset of the Sinha and Gabrieli lab paradigms for younger participants.

Due to the hold on human subject testing during the pandemic, the Snedeker lab has now shifted to implement a series of online behavioral experiments examining linguistic prediction in adults. For example, in one such experiment her group will examine how prediction of an upcoming word may affect how it is heard.

Figure 2. (Left) Neural adaptation in fusiform gyri for faces (greater activation for non-repeating than repeating faces) viewed from below with back of brain on top; (Right) Neurotypical individuals (NT) exhibited significantly greater adaptation than ASD individuals.

Participants will listen to a story which will occasionally contain errors – parts of certain words will be replaced with noise. This type of error 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 the incoming speech. In additional studies, they 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. The Snedeker Lab plans to continue with their original research goals to do EEG testing with children as soon as it becomes safe to do so.

While COVID-19 has posed unforeseen challenges, the Predictive Processes team continues its comprehensive, integrated, and rigorous study of predictive skills in autism. By strengthening partnerships across laboratories, delving into datasets collected prior to the crisis, and continuing data collection online, the researchers will characterize prediction in autism through a collaborative approach. A better scientific understanding of the abilities and mechanisms involved in prediction can potentially contribute to improved identification of, and supports for, individuals with autism.

THE MARMOSET TARGETED PROJECT

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

The marmoset targeted project involves a collaboration between four labs – those of Mriganka Sur, Alan Jasanoff, Ann Graybiel and Robert Desimone. Despite the Covid ramp-down, work in all four labs continued apace.

The disruption of the balance of excitatory and inhibitory neurotransmission has been proposed as a key circuit level mechanism of autism spectrum disorder (ASD). It is increasingly recognized that an impaired ability to predict events is congruent with cardinal symptoms of ASD such as repetitive behavior and need for a highly structured environment. **Mriganka Sur**'s lab is testing this hypothesis in the context of temporal processing and prediction. They developed an in-home cage training system in which marmosets are required to predict when an image disappears (**Fig. 1a**).
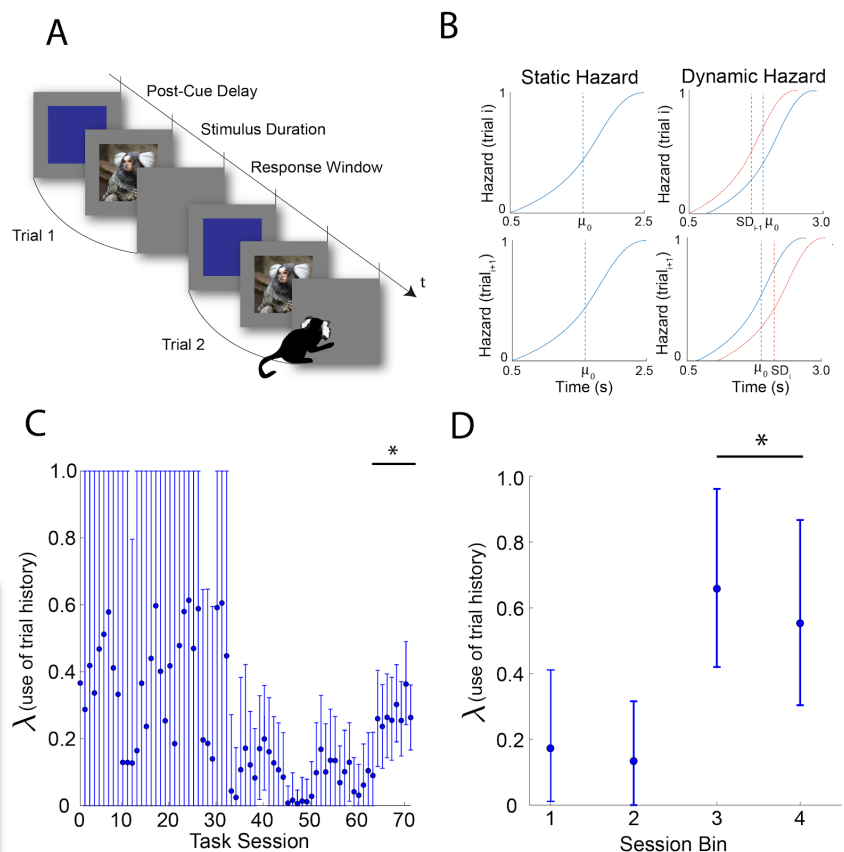
Figure 1. Bayesian model of temporal expectation in marmosets and humans. An analysis of training sessions revealed that in marmosets and humans, trial history begins to influence behavior only following extended task exposure. (A) Temporal prediction task design. (B) Bayesian model predictions. (C) Marmoset behavior. Lambda (λ) values indicate the extent of the influence of trial history on reaction time. (D) Human behavior. Asterisks in all panels represent lambda values significantly different from zero ($p < 0.05$), indicating a prominent influence of trial history on reaction time.

They investigated the influence of temporal prediction on reaction time, and how this effect depends on learning. They found that marmoset behavior undergoes distinct changes with learning whereby extended task exposure increases the influence of trial context, and that this context has a key role in driving reaction time. To model their findings, they developed a Bayesian computational model of temporal expectation where an animal's trial context influences behavior depending on past evidence (**Fig. 1b, c**). These results were successfully replicated in human participants, indicating that marmosets and humans manifest temporal expectation in the same way (**Fig. 1d**). As a next step, the Sur lab plans to use their model to examine whether an impaired ability to predict temporal events is prevalent among ASD subjects.

Alan Jasanoff's lab aims to establish two capabilities that will be used to investigate neural mechanisms of ASD in marmoset models. The first goal is to introduce a tool for facile image-guided neural activity perturbation in marmosets. They addressed this by synthesizing a novel paramagnetic muscimol analog called ParaMus, which can be visualized by magnetic resonance imaging during or after injection. The new compound inhibits stimulus-elicited brain activity in a manner that is predictably dependent on its spread in the brain.
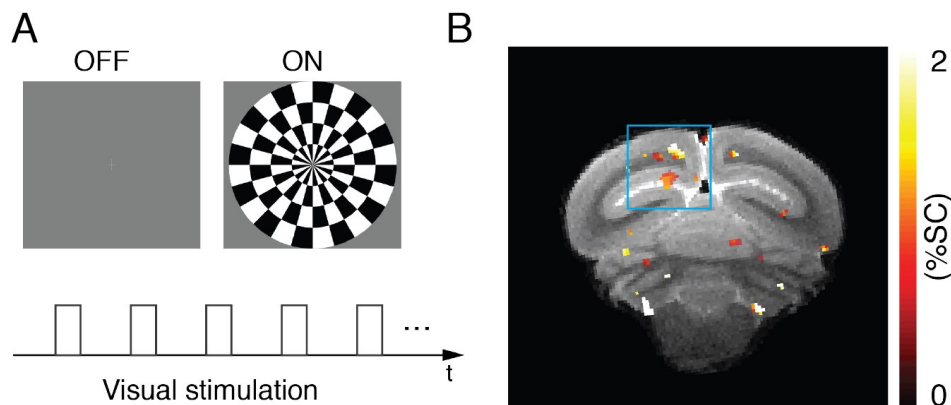

Figure 2. Functional imaging of visual stimulus response in the marmoset brain. BOLD activation found in the primary visual cortex in response to checkerboard pattern visual stimulation. (A) Illustration of the flickering checkerboard paradigm. (B) BOLD activation found in the primary visual cortex in response to visual stimulation.

The second goal is to establish technologies for circuit-specific analysis of social cognition in marmosets. They have created a novel genetically encoded fMRI indicator called NOSTIC, which can be used to investigate input/output relationships involving multiple regions throughout the brain. After initial validation in rodents, the lab is now beginning to evaluate the NOSTIC probe in marmosets. They have collaborated with the Desimone and Sur labs to establish resting-state and visually evoked fMRI paradigms for awake marmosets (**Fig. 2a, b**). This groundwork paves the way for numerous investigations of integrated brain function during social stimuli or tasks.

Ann Graybiel's lab is working to study the involvement of striatal compartments in the development of stereotypic behaviors, a hallmark feature of ASD. Striosomes sit at a crossroads of limbic and cognitively linked structures with inputs from frontal cortical regions known for involvement in features central to ASD, such as behavioral repetitiveness or perseveration and social behaviors, and outputs to dopamine producing regions of the midbrain. The lab has developed the histological protocols in marmoset tissue necessary to assay markers of neural activity (immediate early gene staining) in post-mortem striatal tissue from marmosets exhibiting stereotypic behaviors.

In parallel, the lab has generated mouse lines crossed with the Shank3B knock-out mouse model of ASD in which striosomal regions can be genetically targeted. Viral vectors have been developed to deliver genes to Flp-expressing striosomal populations. Chemogenetic DREADD reagents have been targeted to striosomal populations in Shank3B KO mice and their wild type (WT) counterparts in order to manipulate striosomal neural activity while their behavior is recorded. Analysis is underway to determine if manipulations of striosomal activity impact levels of stereotypic behaviors in the WT or Shank3B KO context.
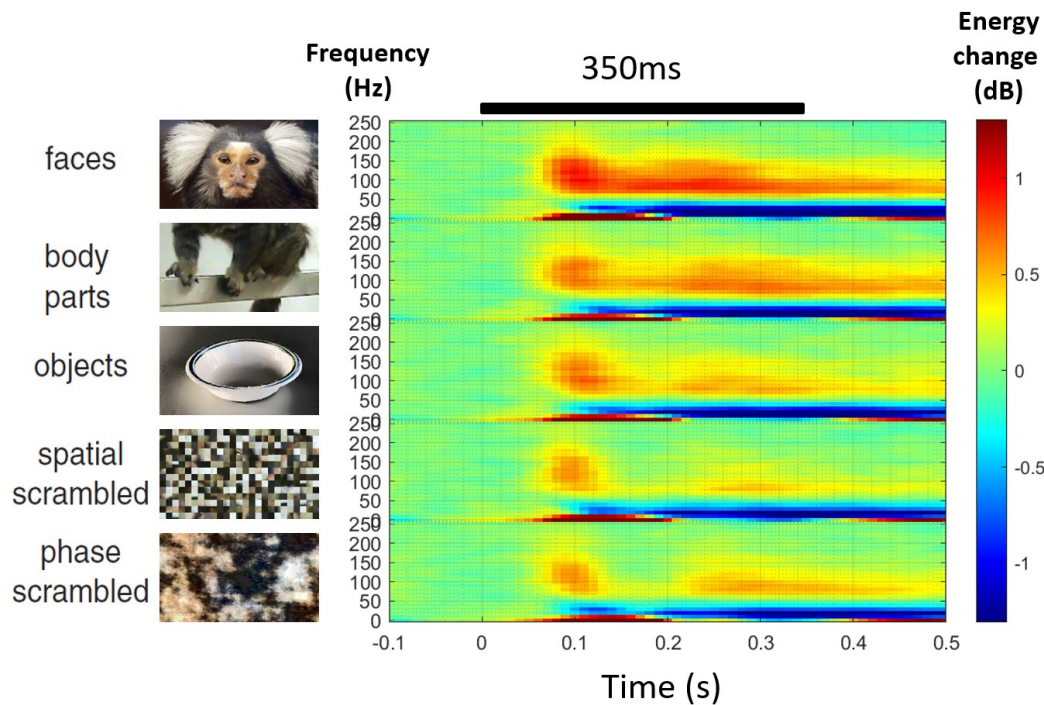

Figure 3. Spectrograms of ECoG data show selectivity to faces. Spectrograms from an example channel in the frontal lobe showed elevated response relative to the baseline in high gamma band (50-150Hz) to face images.

Robert Desimone's lab is mapping the brain regions responsible for social information processing in marmosets, using fMRI and electrocorticogram (ECoG) recordings in awake behaving animals. Dysfunction of some of these regions may contribute to the deficit in social cognition and related behaviors seen in ASD.

The lab successfully implanted 192 channel ECoG arrays in marmosets and recorded neural data while they performed visual tasks. Marmosets were trained to focus on a screen on which images of marmoset faces, body parts, objects and scrambled images as controls were presented while neural signals were recorded simultaneously. They have developed a recording system in conjunction with behavioral assays capable of localizing patches for various distinct features of stimuli. They have been able to map several patches selective for faces among the ECoG electrodes (**Fig. 3**). As next steps, they are now mapping and characterizing channels selective for more complex categories, such as social information.

WELCOME NEW SIMONS POSTDOCTORAL FELLOWS

Sophie Bridgers is a Postdoctoral Fellow in a laboratory of Early Childhood Cognition and of Computation, Cognition, and Development, working on social reasoning, decision-making, and communication across development and neurodiverse populations. In particular, her project combines computational and developmental methods to investigate intuitive goal understanding. She received her PhD from Stanford. She likes to go hiking and camping.

Alex Major is a Postdoctoral Fellow in the Earl Miller lab and is using pharmacology and electrophysiology to test the function of different cortical layers in Predictive Coding, a prominent model of sensory overload in ASD. He received his PhD from University of Western Ontario, Canada. In his free time, Alex enjoys hiking at local parks, biking, and exploring local breweries.

Xuyu Qian is a Postdoctoral Fellow in the laboratory of Dr. Christopher A. Walsh, working on the developmental mechanisms of human brain

evolution. Using human pluripotent stem cell-derived brain organoids as models, he aims to chart the functions of human-specific gene regulatory elements in cortical development and understand their significance in autism pathogenesis. He received his PhD from Johns Hopkins University. He likes to sing in the shower.

Michael Segel is a Postdoctoral Fellow in the laboratory of Professor Feng Zhang. His researches focuses on re-purposing viral-derived elements to enable site-specific repair of the human genome. Michael received his PhD from the University of Cambridge, and in his free time enjoys reading (Brontë novels), running, and whale watching.

Chenjie Shen is a Postdoctoral Fellow in a laboratory of Guoping Feng, working on developing RNA editing-based gene therapy targeting Rett Syndrome. He received his PhD from Zhejiang University in China. He likes to travel and cook.

SIMONS POSTDOCTORAL FELLOW: PROFILE

Liron Rozenkrantz, Ph.D. | John Gabrieli Laboratory, MIT

INVESTIGATING ENHANCED RATIONALITY IN INDIVIDUALS WITH ASD, AND ITS NEURAL CORRELATES

Atypical social cognition in autism spectrum disorder (ASD) is often considered as a deficit, and aligns with practical challenges faced by individuals with ASD. However, such altered social cognition may confer distinctive strengths. A compelling example comes from the study of cognitive biases and irrational reasoning in neurotypical (NT) individuals. Remarkably, multiple studies have found that ASD individuals display *enhanced rationality* relative to NT individuals by exhibiting *more objective and consistent* (and less biased or irrational) evaluation of information.

My Simons Fellowship aims to elucidate the neural mechanisms of enhanced rationality in ASD by probing the *optimism bias* via behavior and neuroimaging (fMRI). In the optimism bias, when presented with information regarding the future, people are found to display a striking behavior: they integrate information that maintains their optimistic future view, yet reject information that contradicts it. In our study, in collaboration with the Affective Brain Lab at UCL, we are recruiting individuals with and without an ASD diagnosis. While participants are lying in the MRI scanner, we ask them to estimate the likelihood of different events, present them with statistics about the actual probability of these events, and ask for their updated estimation, all while simultaneously measuring their neural activations (Fig 1). This way we can investigate how participants' brains respond to information conferring "good news" and "bad news".

While we are still in the data collection phase, preliminary results (N=8 of each group) imply that ASD individuals integrate information in a more objective manner, learning equally well from good and bad news ("learning rates", Fig. 2a).

NT individuals, however, integrate good news more, even though good news and bad news are both equally informative. We also find preliminary evidence that less biased integration of information is correlated with more autistic traits across both ASD and NT individuals (Fig. 2b).
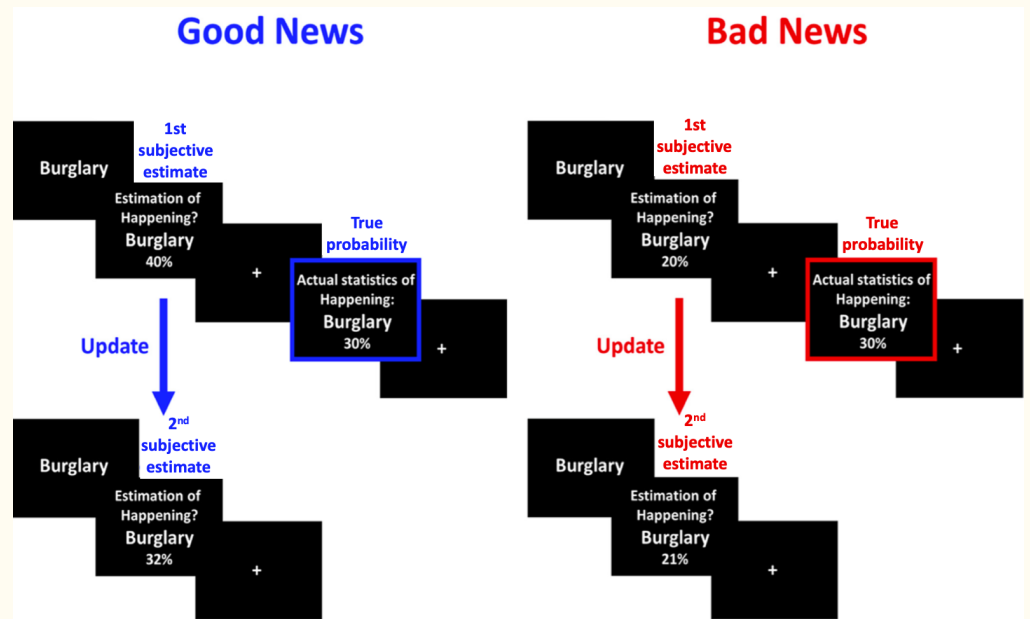

Figure 1 Task design. Participant can either learn that they are less likely to encounter an adverse event than what they initially estimated ("good news" trial, in blue), or more likely to encounter an adverse event than estimated ("bad news" trial, in red). Updates are typically larger when information confers good news.
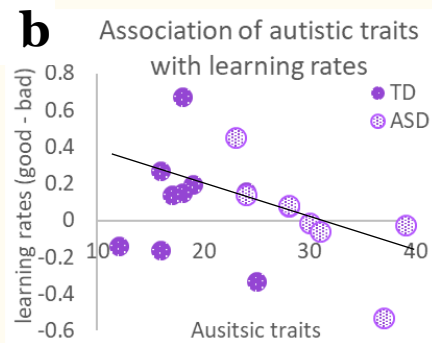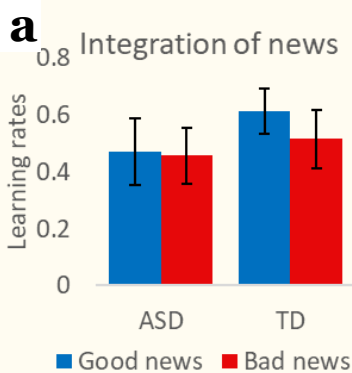

Figure 2 Preliminary results. Learning rates, namely how much one integrates the information one was presented with, were different for good and bad news in the NT group, but similar in the ASD group. This reflects preliminary evidence for a more objective integration of information (a), which was correlated with autistic traits (b). Importantly, these are very small samples and we do not present statistics due to the unrepresentative group sizes.

This study is the first to investigate the neural mechanism of enhanced rationality in ASD, and a step away from a deficit-focused approach and towards understanding strengths and enhanced abilities in ASD.

COLLOQUIUM SERIES

SEPTEMBER

16 - Carlos Portera-Cailliau, M.D., Ph.D.
University of California, Los Angeles

30 - Gordon Fishell, Ph.D.
Harvard Medical School

OCTOBER

14 - Chiara Cirelli, M.D., Ph.D.
University of Wisconsin-Madison

NOVEMBER

4 - Rebecca Lawson, Ph.D.
University of Cambridge

18 - Christopher A. Walsh, M.D., Ph.D.
Harvard Medical School, Children's
Hospital Boston

DECEMBER

9 - Maja J. Matarić, Ph.D.
University of Southern California

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

LUNCH SERIES

September 25, 2020 – **Hiroki Sugihara, Ph.D.**
Research Scientist, Mriganka Sur Laboratory, MIT

October 9, 2020 – **Liron Rozenkrantz, Ph.D.**
Simons Postdoctoral Fellow, John Gabrieli Laboratory, MIT

November 13, 2020 – **Jakob Voigts, Ph.D.**
Postdoctoral Fellow, Mark Harnett 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.

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