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

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PUBLICATIONS SPOTLIGHT

Amemori S., **Graybiel A.M.**, and Amemori K.-I. (2021) Causal evidence for induction of pessimistic decision-making in primates by the network of frontal cortex and striosomes. Frontiers in Neuroscience, 15: 649167. [https://doi.org/10.3389/fnins.2021.649167]

Gandhi T.K., Tsourides K., Singhal N., Cardinaux A., Jamal W., Pantazis D., Kjelgaard M., **Sinha P.** (2020) Autonomic and Electrophysiological Evidence for Reduced Auditory Habituation in Autism. Journal of Autism and Developmental Disorders, 51: 2218-2228. [https://doi.org/10.1007/s10803-020-04636-8]

Segel M., Lash B., Song J., Ladha A., Liu C. C., Jin X., Mekhedov S. L., Macrae R. K., Koonin E. V., Zhang F. (2021) Mammalian retrovirus-like protein PEG10 packages its own mRNA and can be pseudotyped for mRNA delivery. Science, 373: 882–889. [https://doi.org/10.1126/science.abg6155]

Rozenkrantz L., D'Mello A.M., **Gabrieli J.D.E.** (2021) Enhanced Rationality in Autism Spectrum Disorders. Trends in Cognitive Sciences, 25: 685-696. [https://doi.org/10.1016/j.tics.2021.05.004]

Tang X, **Jaenisch R**, **Sur M**. (2021) The role of GABAergic signalling in neurodevelopmental disorders. Nature Reviews Neuroscience, 22: 290-307. [https://doi.org/10.1038/s41583-021-00443-x]

Wehbe L., Blank I., Shain C., Futrell R., Levy R., Malsburg T., Smith N., **Gibson E., Fedorenko E.** (2021) Incremental language comprehension difficulty predicts activity in the language network but not the multiple demand network. Cerebral Cortex, 31: 4006-4023. [https://doi.org/10.1093/cercor/bhab065]

TARGETED PROJECTS: UPDATES

PREDICTIVE PROCESSING IN AUTISM TARGETED PROJECT

By members of the Sinha, Gabrieli and Snedeker labs

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. In the Predictive Processing Targeted Project, the Sinha, Gabrieli, and Snedeker labs collaboratively investigate autism in three domains: temporal auditory prediction, neural adaptation, and language.

Early in the pandemic, Pawan Sinha and his team pivoted to conduct online studies. They have now collected full datasets from neurotypical and autistic cohorts for three different experiments. A cued auditory detection experiment showed only small differences between groups in the effect of temporally predictive cueing on auditory detection sensitivity, but a significantly larger effect of rhythmic cues on response bias in the autistic population. In addition, this experiment revealed noteworthy interactions between sex, diagnosis, and target timing predictability on target detection sensitivity. The language prediction experiments showed similar group-level effects of prediction on language perception across the autistic and neurotypical groups, with an enhanced use of bottom-up cues in the ASD group (Figure 1). Individual differences related to vocabulary size and history of speech-language intervention are currently being explored. The final experiment on motor skill learning showed that ASD individuals may not make prediction-related errors early in learning. Each of these studies is currently being prepared for publication.

Since all three experiments were performed with the same participants, the group is in the early stages of exploring the relationships between the results of the three experiments on a participant-by-participant basis. They are also preparing to launch a fourth online experiment looking at audio-motor entrainment in ASD using newly released software that makes possible precise online recording of the relative timing of pacing cues and entrained finger taps.

Finally, the results of their online experiments have informed a redesign of the postponed EEG experiments, which will be ready to deploy in the fall.

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. 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.

Reductions in neural adaptation were associated with greater social communication challenges in adults with ASD. This fall semester, as faculty, students, and staff return to campus, 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, examines predictions that people make about words in natural stories. Over the course of the pandemic, the Snedeker lab implemented a series of online experiments examining linguistic prediction in adults with and without ASD. For example, one such experiment looks at participants' ability to use context to make explicit predictions about upcoming words in a story. Although data collection is currently ongoing, preliminary results suggest that both Typically Developing (TD) and ASD participants can use information from both the local sentence and the broader narrative to make such predictions. Additional studies investigate how prediction may affect perception of incoming speech.

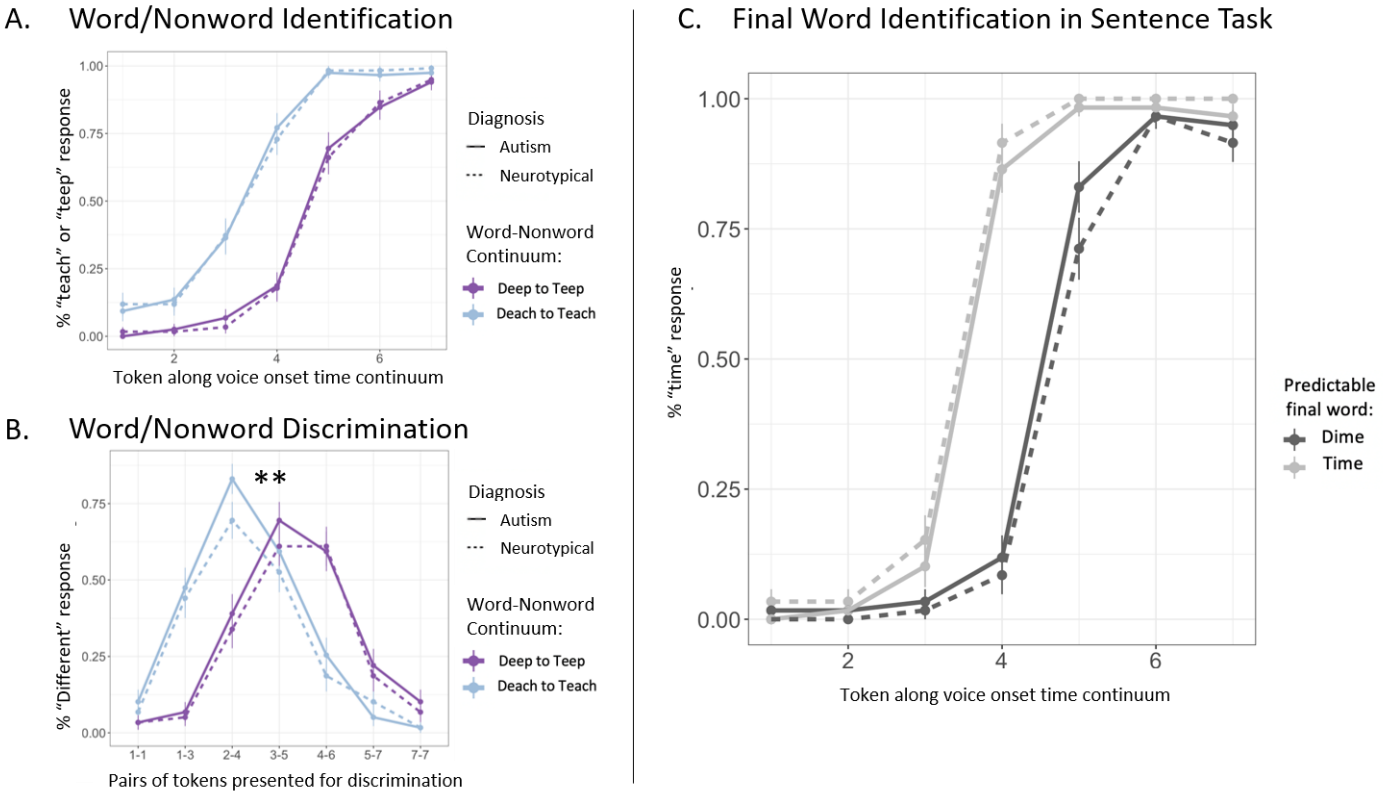


Figure 1. Perception of real predictable words with varying initial voice onset times. **A.** Participants were presented with word tokens that varied along a voice onset time (VOT) continuum from a real word to a nonword (e.g., "deep" to "teep") and from a nonword to a real word ("deach" to teach"). Participants were asked to report what word they heard. We expected to see a shift in perception toward the real word ("deep" is reported longer than "deach"). The ASD (n = 59) and NT (n = 59) groups both show similar shifts in perception toward the real words, suggesting similar influence of prior word knowledge. **B.** Participants were then presented with pairs of the word and nonword tokens and asked if they were the same or different. The ASD group showed enhanced discrimination between word tokens, suggesting increased use of bottom-up cues during speech processing. **C.** Participants were presented with predictable sentences that were biased to end with a word on one end of the VOT continuum (i.e., dime or time), and asked to report the final word that they heard in the sentence. We expected to see a shift in perception toward the predictable word. ASD and NT groups show similar shift toward perception of predictable words. Individual differences related to vocabulary size and speech intervention history are being explored.

By including a non-linguistic prediction task, vocabulary test, and report of symptoms (the AQ), the group can assess whether variation in linguistic prediction may differ with general predictive ability, language skill, and/or autistic diagnosis. With the resumption of in-person testing, the group is designing a series of behavioral and electrophysiological studies to track complex linguistic predictions in children. They have also adapted a subset of the Sinha and Gabrieli lab paradigms for younger participants, assessing response to simple auditory sequences and neural adaptation to faces and objects.

The results of these recent studies are beginning to reveal both similarities and differences in prediction abilities between autistic and typically-developing individuals. When the research teams transition back to campus, they will apply new results to refine planned in-person neuroimaging and behavioral experiments. Each lab is actively planning and developing protocols for a much-anticipated return to in-person data collection this fall.

THE MARMOSET TARGETED PROJECT

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

The 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.

The Desimone lab has conducted ECoG recordings in both restrained and unrestrained marmosets. They showed that marmosets will readily watch movies on a screen, which demonstrates that marmosets could be a useful model for studies of cognitive functions. In line with previous findings, they identified four face patches corresponding to PD, PV, MD and a45 in fMRI studies (Figure 1). Going beyond fMRI studies, they found a sub-second temporal progression of signals through the face patches.

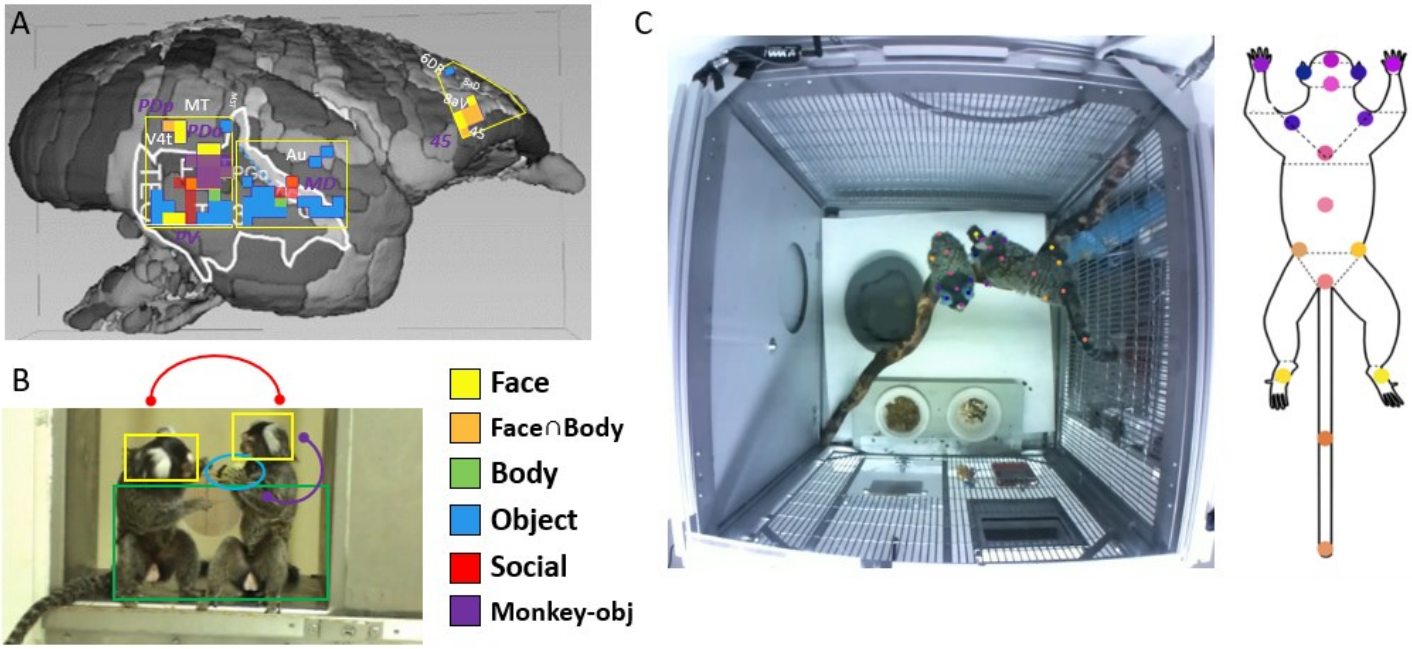


Figure 1. Social and monkey-object patches found with ECoG high gamma signal. **A.** Patches of high gamma activity selective for social patches were localized in temporal lobe – one in TE3 between face patches PD and PV; one in TPO next to face patch MD. Yellow outline shows the outline of 3 ECoG arrays. Underlay is a marmoset brain atlas. Monkey-object patch was found next to face patch PD and an adjacent body patch. **B.** Diagram showing a hypothetical schematic of how these networks work in social scene processing. Face, body and object patches first recognize the agent and non-agent, then social and monkey-object patches analyze relationships. **C.** Wireless recording and automatic tracking of freely moving marmosets. Left is a top-down view into the cage, estimated tracking dots overlaid on a pair of marmosets. On the right is an illustration of tracking dots on a marmoset cartoon picture.

The dynamic analysis indicates feedforward excitation followed by feedback excitation of face patches after presentation of a face image. They further identified social and monkey-object patches in the temporal lobe.

From patch activity, they can decode both social vs other categories, and sub-categories of social interactions, indicating these patches process detailed social content. With unstrained freely moving wireless recordings, they are obtaining automatic behavior tracking and are now asking if the social and face patches respond similarly as during restrained movie watching.

The Graybiel lab has previously demonstrated in rodents and primates that repetitive behaviors, a hallmark feature of ASD, correlate with the degree of hyperactivation of striosomes, a striatal region that connects the medial prefrontal cortex and the midbrain dopamine system. They are finding the same pattern in marmosets. In order to test more directly the role of striosomes in repetitive behaviors, they have developed the targeting of chemogenetic tools to this striatal compartment and are finding that tamping down striosomal activity impacts the degree of repetitive behaviors in an autism model mouse, the Shank3B knockout mouse. In order to gain chemogenetic control of striosomal circuits in the marmoset, they have now turned to capitalizing on their recent snRNA-seq work to hunt for promoters likely to target striosomal neurons in the marmoset. In collaboration with the laboratory of Guoping Feng and other leaders in the field of genomics and transcriptomics, this work will provide the field with new tools for wider study of striatal circuits in ASD and in an emerging primate model.

In partnership with collaborators on the project, the Jasanoff lab has used fMRI to reveal social stimulus-evoked responses across an array of brain areas as in awake marmosets. Results correspond well to literature reports and form a basis for analyzing the effects of genetic and physiological perturbations on processing of social stimuli in primates. In addition to expanding the current dataset, ongoing efforts focus on probing mechanistically specific contributions to face-specific responses in the visual system. As part of this work, the team showed that expression of a circuit-specific fMRI sensor could be achieved following viral infection in the marmoset visual cortex. This establishes a route for circuit-level dissection of inputs to social stimulus-responsive centers in the brain.

The Sur lab studies temporal prediction and its processing in the marmoset brain. The predictive coding hypothesis posits a progressively increasing frontoparietal influence on sensory areas as an animal utilizes an internal model of prediction. To test whether neural responses in marmosets follow predictive coding models, the lab designed a simple timing task: freely behaving marmosets were required to make a timed response prompted by a visual stimulus change, with varied stimulus duration. As animals learned the task, their reaction times were modulated by the stimulus duration; faster reaction time accompanied longer stimulus durations. The lab implanted a wireless EEG recording system in one marmoset to simultaneously record from occipital, parietal, and frontal cortices. They found that low frequency oscillations increased in power across cortical regions, but especially in occipital cortex, and high frequency oscillations broadly decreased in power for sessions when the marmoset had learned the task. These findings are consistent with a model in which low frequency oscillations carry top-down predictions which inhibit high frequency oscillations in sensory areas. The lab plans to use electro-corticogram, or ECoG, recording next, with the help of Desimone Lab, to measure neural activities and their interactions across wider areas.

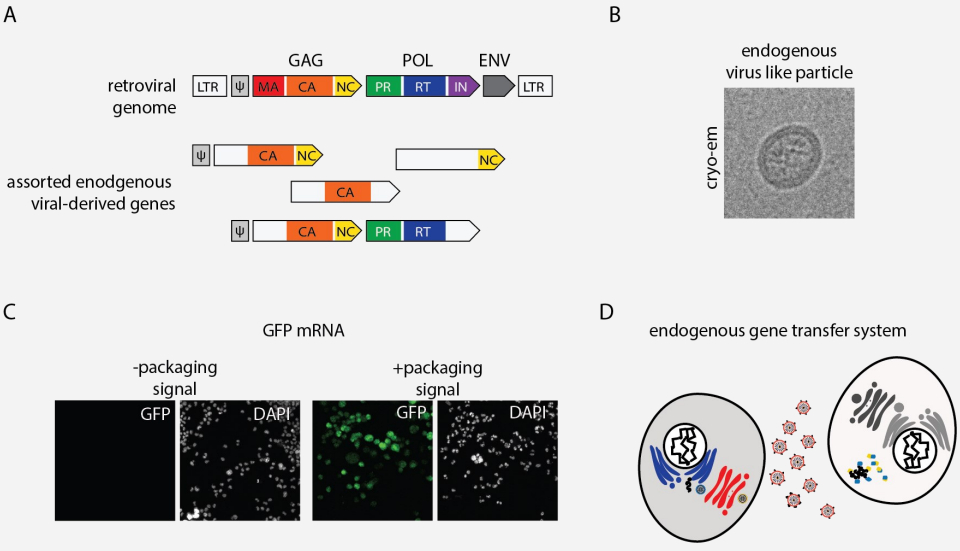
For additional information on Targeted Projects, please visit:
http://scsb.mit.edu/research/targeted-projects/

Michael Segel, Ph.D. | Feng Zhang Laboratory, Broad Institute of MIT and Harvard

EXPLOITING RETROELEMENTS FOR TARGETED GENE INSERTION

Large scale genome-wide DNA sequencing studies have begun to untangle the specific sequences of genetic code that underlie autism spectrum disorder. Moreover, recent advances in genome engineering enable high precision manipulation of genetic information in cells. Despite these two parallel advances in molecular medicine, the challenge of *delivering* gene-based therapies to correct or reverse the disorder-causing mutations in the central nervous system remains a significant barrier for developing novel therapies for autism spectrum disorder.

My Simons Fellowship research focuses on developing strategies of gene delivery in the central nervous system. An ideal gene delivery system would be non-immunogenic and capable of delivering a range of genetic cargo to the central nervous system. To identify such a system, we have focused on identifying endogenous mechanisms of gene transfer—a system by which one cell communicates to another using genetic information. If actively used by humans for intercellular communication, such a system would likely be safe and well-tolerated as a gene delivery vector. With these search parameters, we have identified a panel of human proteins derived from retroviral-like elements that are abundant in the central nervous system, detectable in adult blood plasma, and are highly conserved across mammals (Figure 1A). In addition, many of these candidate proteins form capsid-like structures, as detected by electron microscopy, are secreted by cells *in vitro*, and are able to package specific RNA sequences (Figure 1B).



Leveraging these endogenous viral-like particles, we have developed a reprogrammable delivery vector called SEND (**S**elective **E**ndogenous e**N**capsidation for cellular **D**elivery) that can efficiently deliver specific mRNA cargo to cells (Figure 1C, 1D). We are currently understanding the biodistribution of these particles in an *in vivo* context to determine whether they can be targeted to the central nervous system. Ultimately, we hope to leverage these viral-like particles to deliver gene therapy and manipulate the causative genetic mutations in autism spectrum disorder.

Figure 1. A. Schematic outlining the retroviral-derived proteins embedded in the human genome. All of the identified endogenous proteins lack one or more essential domains of a bona-fide retrovirus. **B.** Representative cryogenic electron micrograph shows that some of these endogenous viral-derived proteins can spontaneously form capsid-like structures. **C.** Representative images show that SEND can deliver specific mRNA cargo of interest, such as GFP, given that the mRNA cargo contains the essential sequence-specific packaging signal. **D.** Schematic highlighting that these newly identified human proteins may be endogenous intercellular communication systems—capable of mediating intercellular gene transfer.

Xuyu Qian, Ph.D. | Christopher Walsh Laboratory, Currently HHMI Fellow of the Helen Hay Whitney Foundation

CHARACTERIZING THE FUNCTIONS OF NOVEL NEURODEVELOPMENTAL DISEASE-ASSOCIATED GENE KIF26A

By studying individuals affected with neurodevelopmental disorders and identifying the associated mutations, the Walsh lab has established expertise in discovering novel genes that play key functions in human brain development. We recently discovered a patient cohort with biallelic mutations in the KIF26A gene. The affected individuals displayed a spectrum of brain malformations including polymicrogyria, dilated ventricles and cerebral atrophy (Figure 1A). KIF26A is a kinesin protein that lacks ATPase activity and its function in the central nervous system has not been characterized, despite the fact that it is specifically expressed in early and mid-gestation by migrating excitatory neurons in the developing cortex.

To investigate KIF26A's function in human brain development, I created KIF26A knockout (KO) hPSC lines and generated forebrain organoids to compare with isogenic controls. I found KO organoids exhibited altered lamination and aberrant excitatory neuron radial migration (Figure 1B), as well as elevated apoptotic cell death. At the molecular level, KIF26A modulates these cellular processes by sequestering signaling pathway proteins and complexes onto microtubules, suppressing their activity in signal transduction. In mouse embryonic cortex with shRNA knockdown of Kif26a, I observed similarly arrested radial migration in a cell-autonomous manner, but the knockdown didn't induce increase in apoptosis (Figure 1C). To explore the underlying molecular mechanisms, I performed single-cell RNA sequencing on these organoids and discovered cell type-specific transcriptional changes in migrating and maturing excitatory neurons upon loss of KIF26A, underscoring its function in modulating multiple signaling cascades related to neuronal survival (Figure 1D). Our results uncovered an unexpected role of KIF26A in brain development and offered mechanistic explanation for the clinical manifestation of patients with mutations in KIF26A.

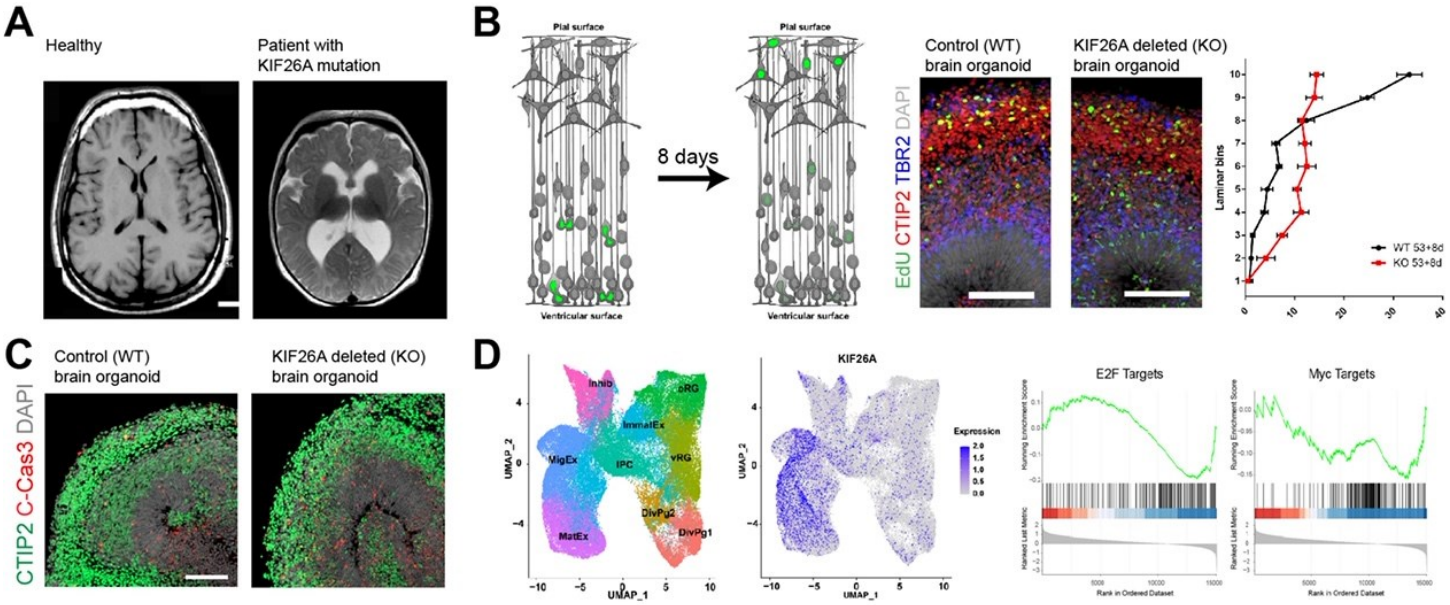


Figure 1. A. A patient with biallelic mutation in KIF26A showed congenital brain malformation. **B.** EdU pulse-chase labeling in human brain organoids showed defective neuronal migration caused by KIF26A deletion. **C.** KIF26A deletion induced elevated apoptotic cell death (red) in brain organoids. **D.** Single-cell RNA-seq in organoids revealed that KIF26A was specifically expressed by excitatory neurons and induced cell type-specific gene expression changes in key pathways regulating cell survival.

UPCOMING EVENTS: FALL 2021

COLLOQUIUM SERIES

SEPTEMBER

15 - Joshua Hartshorne, Ph.D.
Boston College

OCTOBER

6 - Barbara Landau, Ph.D.
Johns Hopkins University

27 - Constance Smith-Hicks, M.D., Ph.D.
Kennedy Krieger Institute, Johns Hopkins University

NOVEMBER

10 - Lauren Weiss, Ph.D.
University of California San Francisco

DECEMBER

8 - Nirao Shah, Ph.D.
Stanford University

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

LUNCH SERIES

September 24, 2021— **Sophie Bridgers, Ph.D.**
Simons Postdoctoral Fellow, Laura Schulz Laboratory, Department of Brain and Cognitive Sciences, MIT

October 15, 2021 – **John Gabrieli, Ph.D.**
Grover Hermann Professor, Health Sciences and Technology; Professor, Brain and Cognitive Sciences; Investigator, McGovern Institute; Director, Athinoula A. Martinos Imaging Center

November 19, 2021 – **Alan Jasanoff, Ph.D.**
Professor, Biological Engineering, Brain and Cognitive Sciences, Nuclear Science and Engineering; Associate Investigator, McGovern Institute; Director, Center for Neurobiological Engineering

December 3, 2021— **Shaoyu Lin, Ph.D.**
Simons Postdoctoral Fellow, Kwanghun Chung Laboratory, Picower Institute, 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**