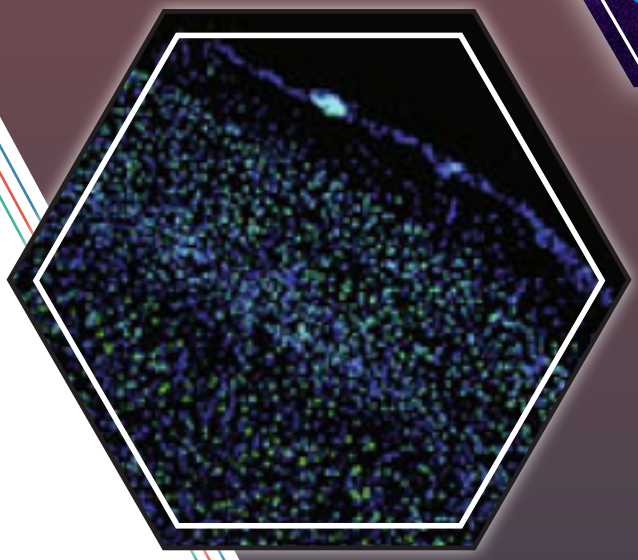
NOVEMBER 2021

Toolmakers Newsletter



ISSUE 04

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BRAIN INITIATIVE

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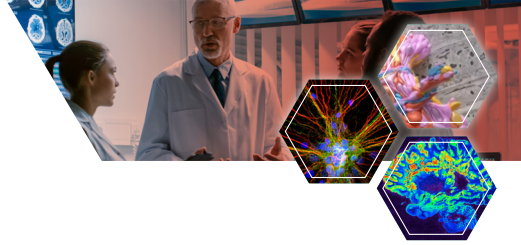


Welcome Back to the Toolmakers Newsletter!

Welcome to the final *Brain Research Through Advancing Innovative Neurotechnologies*® (BRAIN) Initiative Alliance Toolmakers Newsletter of 2021!

In this issue, we will tell you about four more exciting tool advancements in neuroscience: Craniobot, a robotic platform for automated cranial microsurgery and See-Shells, transparent skulls for cortical imaging by Dr. Suhasa Kodandaramaiah; modular recording systems with soft, flexible polymer electrode arrays by Dr. Loren Frank; sciMAP-ATAC, a new method to spatially resolve epigenomic profiles of single cells in intact tissue by Casey Thornton and Dr. Andrew Adey; and reagents to map neural connections at the level of individual cells and synapses by Dr. Alison Barth.

Let's explore the latest breakthroughs from these BRAIN investigators!

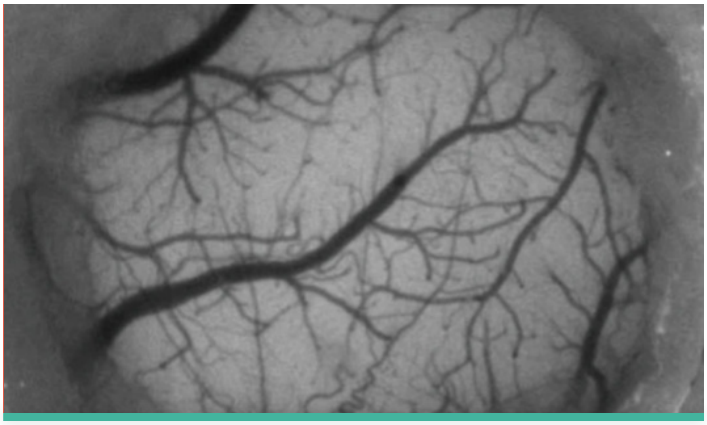
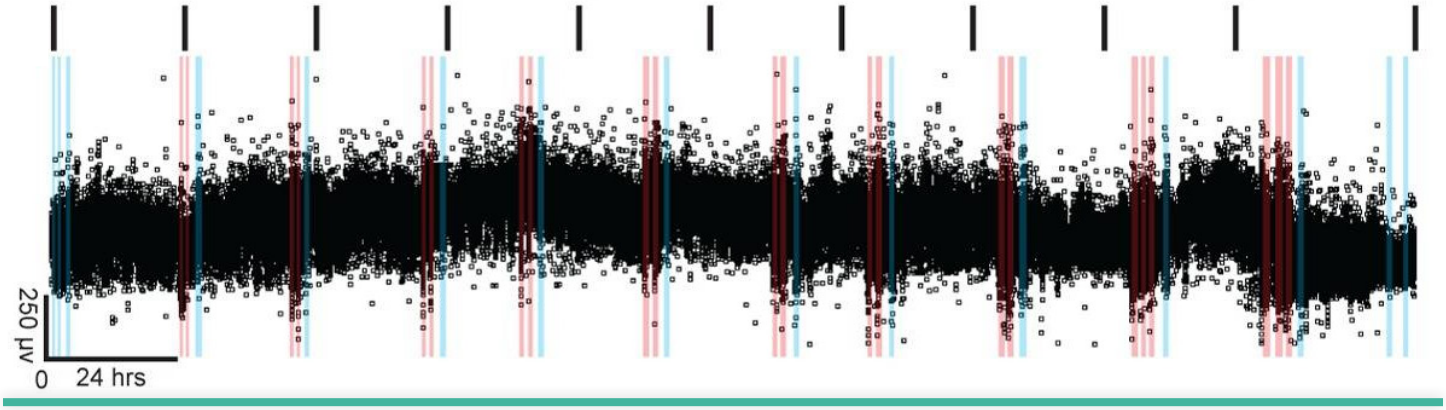


Image Above: Photographs taken from a Thy1-GCaMP6f mouse with a chronically implanted See-Shell. Credit: Ghanbari et al., 2019, Scientific Reports.

Image Below: Spike amplitude (bandpass filtered 300–6,000 Hz) over length of continuous recording using a new modular polymer electrode array. Credit: Chung et al., 2019, Neuron.



On the front cover: **Top Right Hexagon:** An image still from a video of the C. elegans brain, including every nerve and muscle fiber, being reconstructed by serial-section electron microscopy. Credit: Daniel Witvliet, University of Toronto and Harvard University, 2020. **Top Central Hexagon:** Four-week-old rat cortical neurons labeled for dendrites (red), axons (green), and nuclei (blue). Credit: Karthik Krishnamurthy, Davide Trotti, Piera Pasinelli, Thomas Jefferson University, 2020. **Bottom Right Hexagon:** A pseudo-colored image of high-resolution gradient-echo MRI scan of a fixed cerebral hemisphere from a person with multiple sclerosis. Credit: Govind Bhagavatheeshwaran, Daniel Reich, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 2016. **Bottom Central Hexagon:** DAPI and SATB2 staining of mouse primary somatosensory cortex from sciMAP-ATAC sections. Credit: Thornton et al., 2021, Nature Communications.

Robotic platforms for automated cranial microsurgery and transparent polymer skulls for neural interfacing: Craniobot and See-Shells — Dr. Suhasa Kodandaramaiah

At the University of Minnesota in the Biosensing and Biorobotics Laboratory, Dr. Suhasa Kodandaramaiah and his team are perfecting new technologies: Craniobot and See-Shells. Craniobot is a robotic platform for automated cranial microsurgeries. The platform uses a low force contact sensor to profile the skull surface and uses this information to perform micrometer-scale precise milling operations, within minutes. See-Shells are transparent polymer skulls that allow for cortex-wide neural interfacing. The seminal paper describing Craniobot was published in *Scientific Reports* in 2019, while the paper describing See-Shells came out in *Nature Communications* later that same year. Neural computations that occur simultaneously across the cerebral cortex are critical for mediating cognition, perception, and a variety of sensorimotor behaviors. However, prior to Craniobot and See-Shells, simultaneous monitoring and perturbation of neural activity from multiple cortical regions was technologically challenging. Craniobot and See-Shells have been shared with several groups across the nation, including labs at the National Institutes of Health (NIH), Stanford University, Massachusetts Institute of Technology (MIT), Johns Hopkins University, University of Colorado Boulder, and Princeton University. Dr. Kodandaramaiah and his lab provide starter kits that have fully assembled implantable devices and raw materials for making dozens more. He hopes to continue his BRAIN Initiative work and develop commercial versions of both pieces of technology.

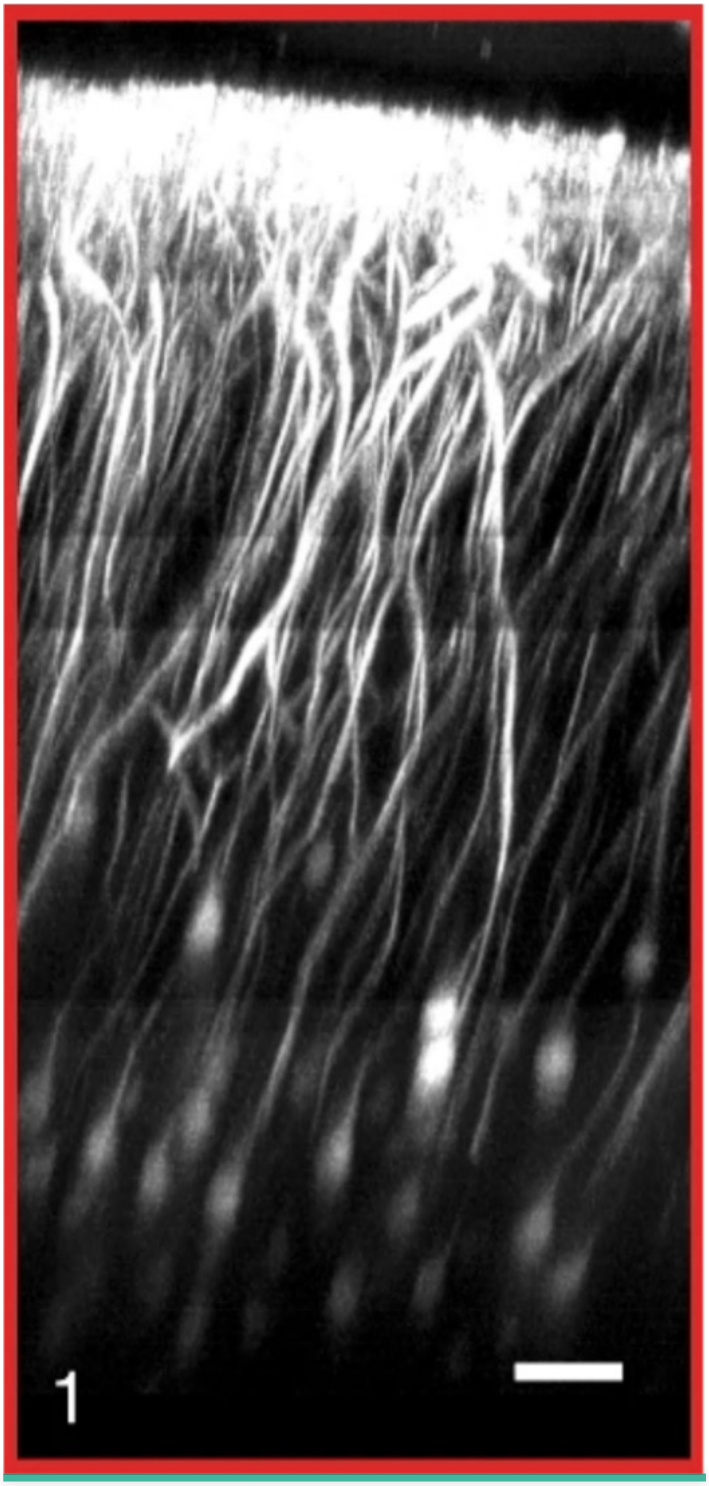


Image: Image of a whole cortical column of a Thy1-YFP mouse implanted with a See-Shell. Imaging conducted two weeks after implantation. Credit: Ghanbari et al., 2019, Nature Communications.

Modular recording systems with soft, flexible polymer electrode arrays for recording from hundreds of neurons distributed acoss the brain — Dr. Loren Frank

Dr. Loren Frank from the University of California, San Francisco recently developed new biocompatible polymer electrode arrays, electronics, software, and surgical approaches that make it possible to record from up to 1,024 channels simultaneously. The introductory paper for this polymer electrode array system was published in *Neuron* in 2019. Thanks to Dr. Frank and his team, scientists can now yield high quality recordings from hundreds of neurons across multiple brain regions in behaving rats 24 hours a day, seven days a week. The system can also maintain high-quality recordings for over 160 days. This high throughput approach allows for the mass collection of large datasets from awake animals engaging in tasks and complex behaviors. Dr. Frank's lab is currently distributing these electrodes to about 20 other labs for testing. These beta-users' feedback will be used to further refine the devices. So far, the utility of Dr. Frank's polymer electrode array has been demonstrated in rats, and now the system is being developed for mice, songbirds, and non-human primates. Dr. Frank's long-term goal is to disseminate these devices to the entire research community. To learn more, check out the Frank lab's Journal of Video Editing (JOVE) article and video about chronic implantation of multiple flexible polymer electrode arrays here.

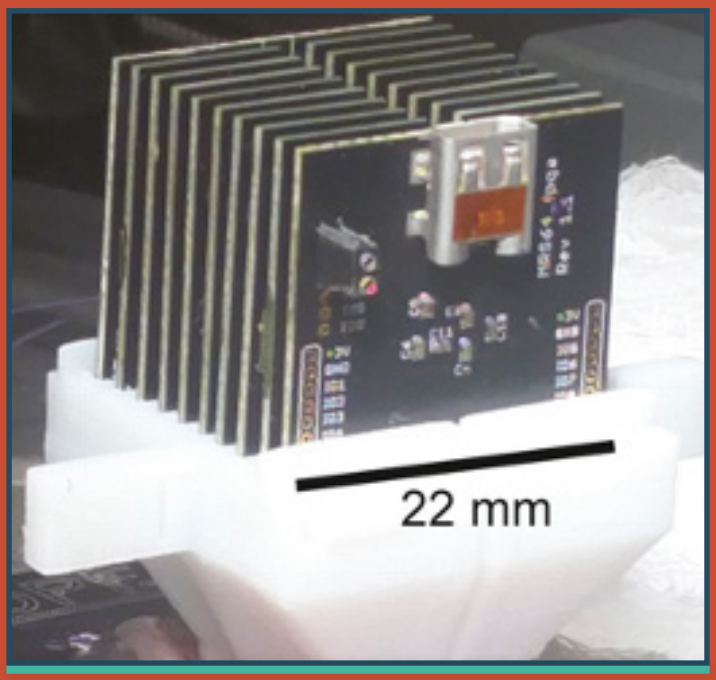


Image: Full 1,024-channel, 16-module recording system stacked into FPGA head stage (SpikeGadgets LLC) during implantation of the new polymer electrode array. Credit: Chung et al., 2019, Neuron.

Spatially-resolved epigenomic profiles of single cells in intact tissue using sciMAP-ATAC — Casey Thornton and Dr. Andrew Adey

Casey Thornton is a rising star and Ph.D. Candidate in the lab of Dr. Andrew Adey at Oregon Health and Science University. Together, Thornton, Dr. Adey, and their team developed sciMAP-ATAC, or single-cell combinatorial indexing on Microbiopsies Assigned to Positions for the Assay for Transposase Accessible Chromatin. This method allows for highly scalable, spatially resolved, single-cell profiling of chromatin states. High-throughput single cell genomic assays can resolve the heterogeneity of cell states in complex tissues, including brain tissue. However, with most current methods, the spatial orientation within the network of interconnected cells is lost. Thus, Thornton and her team developed a novel method for capturing spatially resolved epigenomic profiles of single cells within intact tissue and applied this method to generate non-neuronal cell taxonomy atlases of human and mouse cortex. The seminal paper for this project was published in *Nature Communications* earlier this year. A step-by-step protocol describing the sciMAP-ATAC methods can be found at Protocols.io. Further, all data, along with single cell analyses, will be made available through the BRAIN Initiative Cell Census Network (BICCN). Some of their single-cell ATAC-seq data is available here.

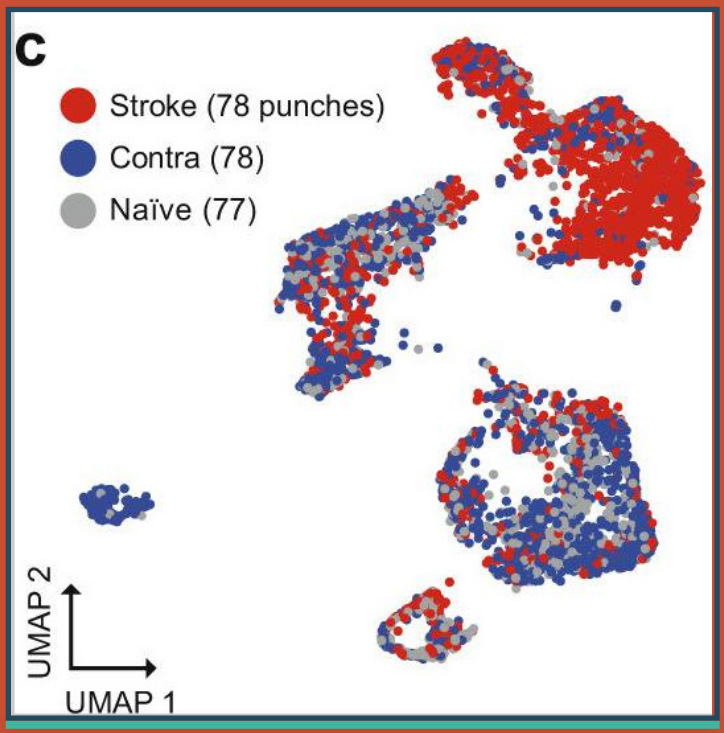
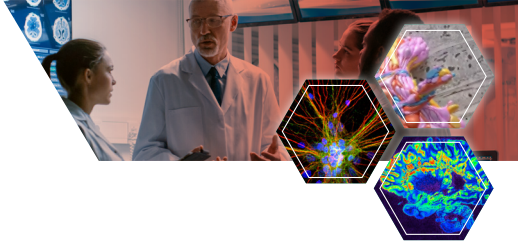


Image: Two-dimensional visualization of cells from ischemic mouse brain tissue (stroke and contralateral hemispheres) and naïve control mouse brain tissue using sciMAP-ATAC modeling tools. Credit: Thornton et al., 2021, Nature Communications.

Video: Casey Thornton explains the importance of the BRAIN Initiative in the sciMAP-ATAC project.



Genetically-encoded reagents for high throughput connectomics — Dr. Alison Barth

Video: Dr. Barth discusses the utlity of her new reagents for cell-type specific research and the role of the BRAIN Iniative.

At Carnegie Mellon University, Dr. Alison Barth has been working on updating the neuroscientific approach to quantitative connectomics by labeling synapses with incredible precision. Specifically, she and her team developed new genetically encoded reagents for fluorescence-synapse labeling and connectivity analysis in brain tissue. These reagents are designed for compartment-specific localization of synapses across diverse neuron types in the mammalian brain. The paper introducing this technology was published in *eNeuro* in 2019. Dr. Barth and her team now have high-resolution images of labeled, virally transduced neurons that can be used for three dimensional reconstructions of postsynaptic cells, automated detection of synaptic puncta, and multichannel fluorescence alignment of dendrites, synapses, and presynaptic neurites to assess cell-type specific connectivity. This technology has important implications in the evaluation of changes in synaptic connectivity during learning and in mouse models of neurological disorders such as Alzheimer's and Parkinson's disease. Moreover, identification of a vast number of fluorescently labeled, input- and target-specified synapses offers a multitude of new and exciting opportunities for data analysis and machine learning.

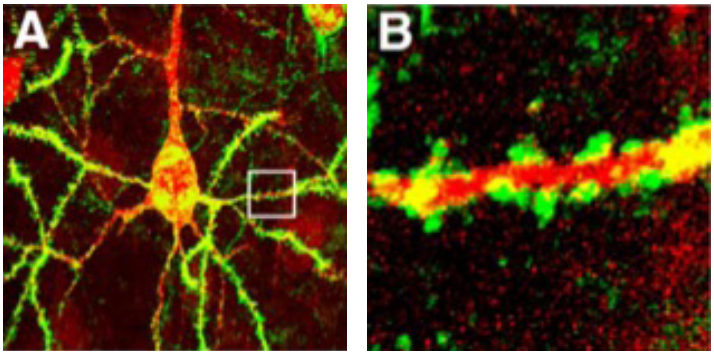


Image: Confocal image of a fluorogen-activating protein (FAP)-coupled targeting sequence labeled pyramidal neuron. Credit: Kuljis et al., 2019, eNeuro.

Excited by the potential of the tools in this issue?! Stay tuned for our next issue and explore more products of BRAIN Initiative discoveries in our Toolmakers' Resources page!