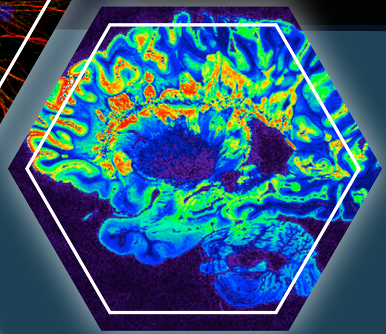
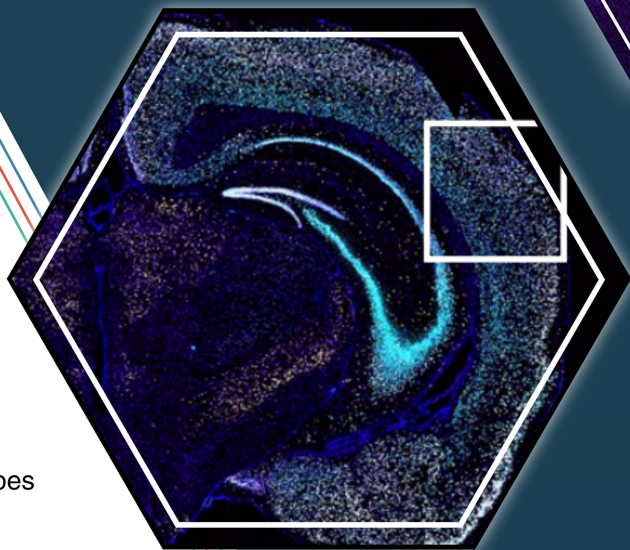
AUGUST 2021

Toolmakers Newsletter





ISSUE 03

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BRAIN INITIATIVE

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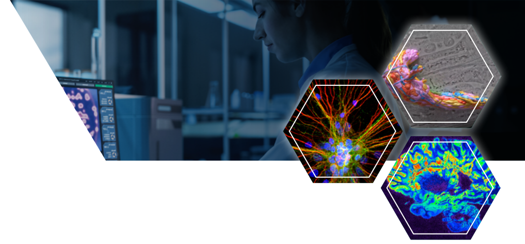


Welcome to the Toolmakers Newsletter!

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

In our third issue, we describe four exciting tool advancements: a miniature two-photon fiber-coupled microscope for 3D neural imaging in freely moving animals, by Dr. Emily Gibson; BARseq and MAPseq, new methods for mapping long-range projections at the resolution of a single neuron, by Drs. Xiaoyin Chen and Anthony Zador; novel implantable micro-coils for stimulating cortical neurons magnetically by Dr. Shelley Fried; and the Phase Calculator Plugin, a new open source tool for studying local field potential (LFP) oscillations, developed by Dr. Alik Widge.

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

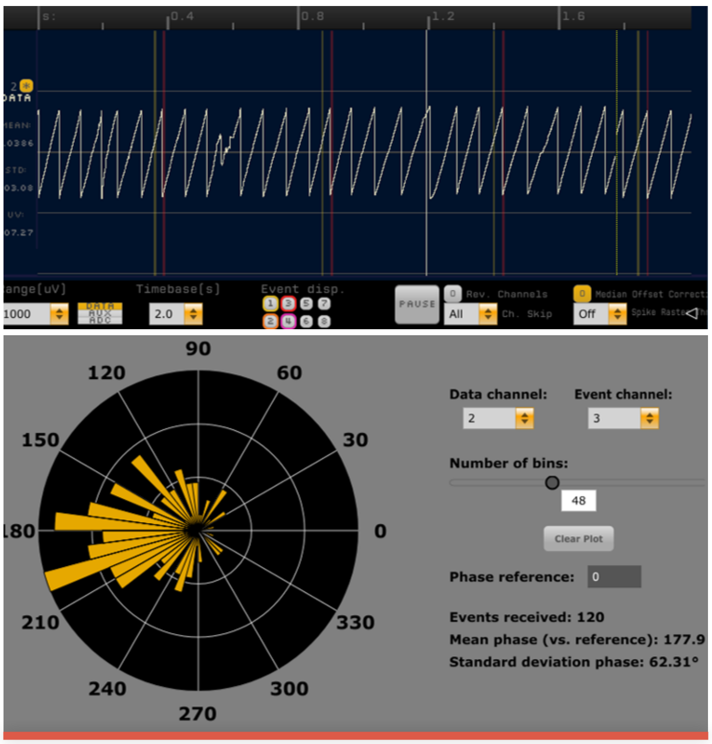
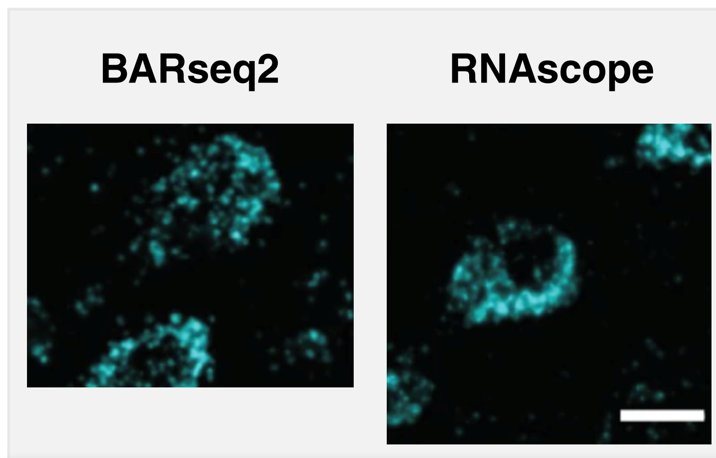


Image Left: LFP Phase Calculator Plugin software interface. Credit: https://github.com/tne-lab/phase-calculator.

Image Below: Representative images of BARseq2 detection of the Slc17a7 gene compared to RNAscope. Credit: Sun et al., 2021.



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:** Confocal image of BARseq2 detection of multiplexed mRNAs in the mouse brain. Credit: Sun et al., 2021.

Miniature two-photon fiber-coupled microscope for 3D neural imaging in freely moving animals — Dr. Emily Gibson

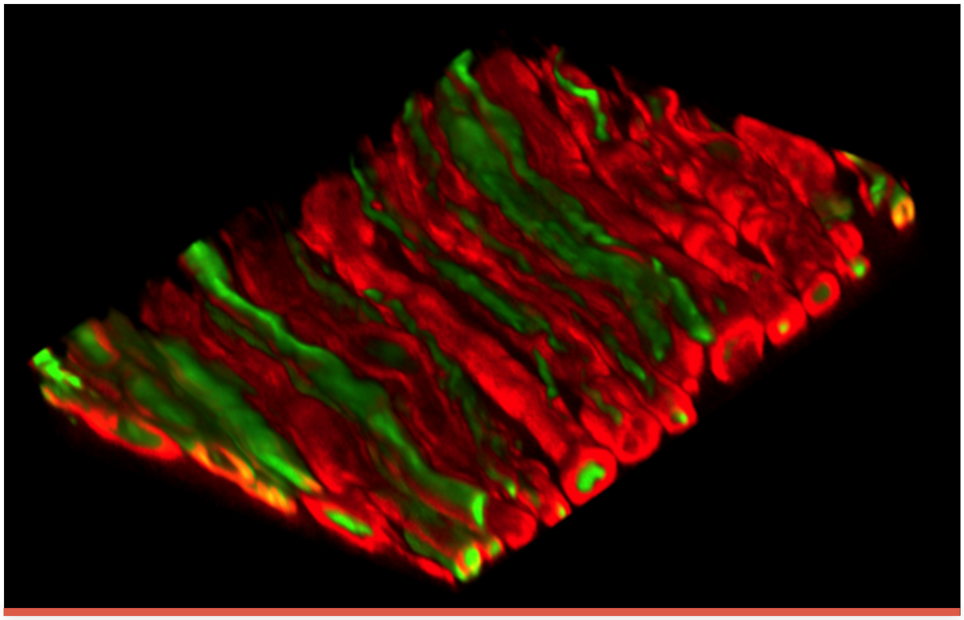
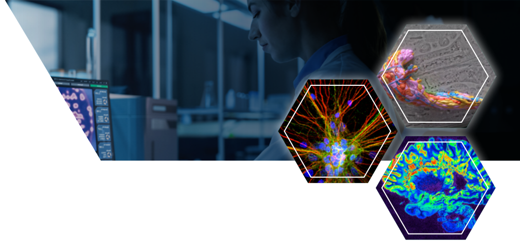


Image: Cross-section of axons in the mouse sciatic nerve. Image from the Gibson Biophotonics Lab.

At the University of Colorado Anschutz Medical Campus, Dr. Emily Gibson is developing miniature two-photon fiber-couple microscopes capable of 3D neural imaging. Specifically, Dr. Gibson and her team are improving this technique in freely moving animals, as opposed to traditional head fixed approaches. Her new tool, dubbed 2P-FCM, is ultra-lightweight, weighing less than four grams. This new microscope uses electrowetting lens technology to achieve the goal of obtaining high resolution 3D images by enabling high-speed variable focusing without any moving parts. Altogether, this approach has resulted in a compact design that packs a powerful punch. So far, Dr. Gibson's team has demonstrated this is an effective tool in the mouse model. To take this research even further, Dr. Gibson is currently working to disseminate the technology to five beta users for testing in different animal models, including prairie voles and songbirds. In addition to her lab's BRAIN Initiative funding, Dr. Gibson and her collaborator, Dr. Diego Restrepo, as well as Karl Kilborn, co-president of 3i (Intelligent Imaging Innovations, Inc.), recently received a Small Business Innovation Research grant to commercialize these miniature microscopes. This grant will also play a role in the dissemination of this research to other neuroscience laboratories. Dr. Gibson told the University of Colorado, "The idea is to turn it into an easy-to-use commercial product and make it available to labs around the world. For me, that is what is most rewarding about this work."



Mapping long-range projects at single neuron resolution using BARseq and MAPseq — Drs. Xiaoyin Chen & Anthony Zador

It wasn't long ago that Dr. Anthony Zador from Cold Spring Harbor Laboratory (CSHL) created MAPseq, an RNA-Seq-based method for high-throughput mapping of projection neurons as a part of his work studying the auditory cortex, decision making, and the connectome. Now, Dr. Zador and his postdoctoral researcher Dr. Xiaoyin Chen (also from CSHL) have developed the next generation of MAPseq called BARseq. BARseq is capable of mapping long-range projections of thousands of neurons in a given brain area at the resolution of a single neuron. BARseq can even correlate projections to gene expression, as demonstrated in their recent paper published in *Nature Neuroscience*. Drs. Zador and Chen (and their team) achieve this incredible resolution through cellular barcoding and sequencing. Specifically, BARseq uses genetic barcodes that label cells, making it possible to make high resolution maps. These methods allow comparison of projections across neuronal subtypes within an animal, across individual animals, and across genotypes. Overall, this technological breakthrough will likely change the shape of neuroscience and neuroanatomy research in years to come. Dr. Zador's team currently offers MAPseq services through a CSHL core facility and may offer BARseq service in the future. Furthermore, they welcome other labs to adopt both methods on their own.

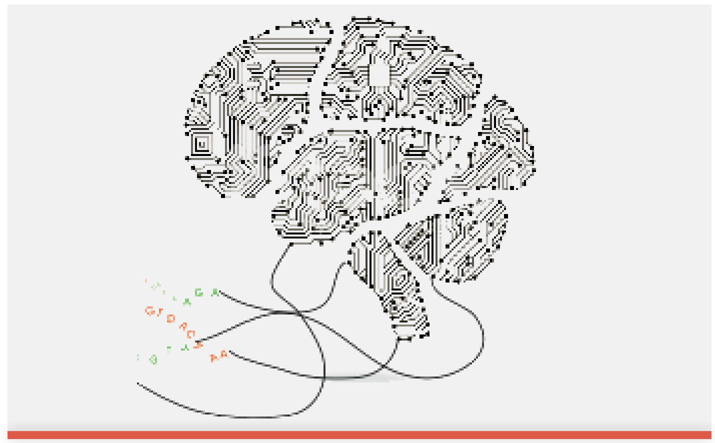


Image: A neural circuit graphic.
Credit: http://zadorlab.labsites.cshl.edu.

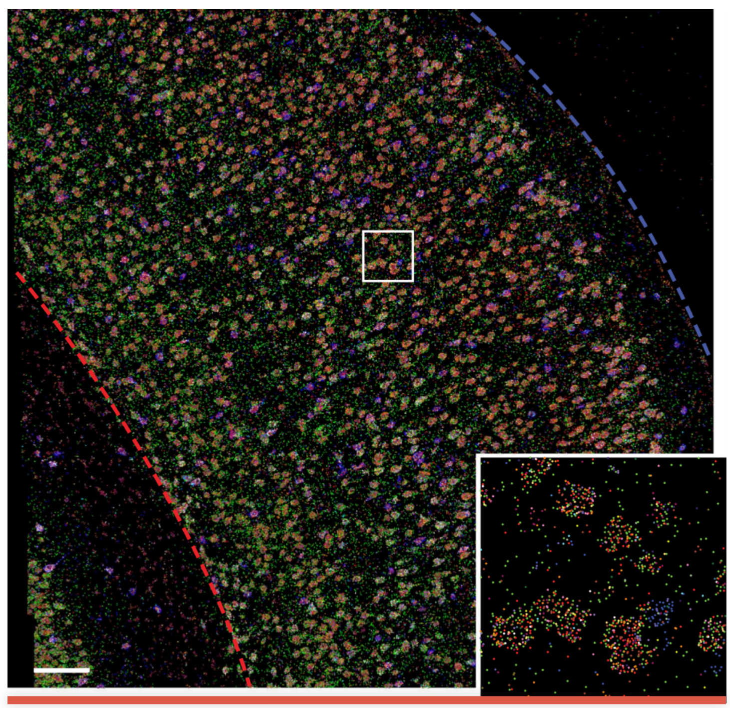


Image: A representative confocal image of multiplexed detection of 24 different mRNAs in the mouse auditory cortex using BARseq. Credit: Sun et al., 2021.

Micro-coils for magnetic stimulation of cortical neurons — Dr. Shelley Fried

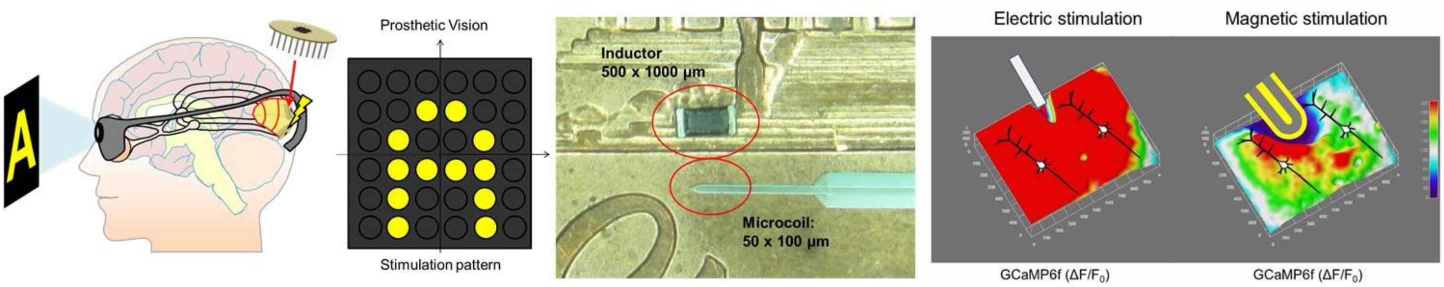


Image: Schematic image of the placement, size, and stimulation output of Dr. Shelly Fried's magnetic microcoils. Credit: https://friedlab.mgh.harvard.edu/.

At Harvard University's Neural Prosthetic Research Lab, Dr. Shelley Fried and his team are developing neurotechnology to help restore vision in the blind. To accomplish this, Dr. Fried first developed micro-coils that can be implanted into the cortex. One thing that sets these micro-coils apart is that they use magnets to stimulate neurons. Magnetic micro-coils have two important advantages over conventional micro-electrodes: not only are magnetic fields less susceptible to changes in the surrounding environment (such as body's response to a pathogen), but they also can be shaped to selectively target specific types of neurons and drive activity *in vivo*. This research first hit the neuroscience scene in 2016 when Dr. Fried and his team's paper came out in *Science Advances*. But the story hasn't stopped there. Since they first developed the magnetic micro-coils, they have worked on how coil design influences neuronal selectivity. Research has shown that the coil design itself shapes the spatial extent of cortical activation. V-shaped coils enhance selective activation of vertical pyramidal neurons over horizontal axons, while W-shaped coils enhance selectivity even further (although slightly reducing the strength of stimulation). Dr. Fried's ultimate goal is to use these micro-coils as cortical prosthetic devices that can help restore vision in people. So, what's the next step? To achieve this goal, Dr. Fried's research must move out of proof-of-concept testing in the mouse model and into non-human primates, and eventually, humans. In the coming years, Dr. Fried plans to design and develop a micro-coil array that is suitable for implantation into the human visual cortex and establish both its safety and efficacy. Without a doubt, these magnetic micro-coils may be paradigm shifting for visual protheses.

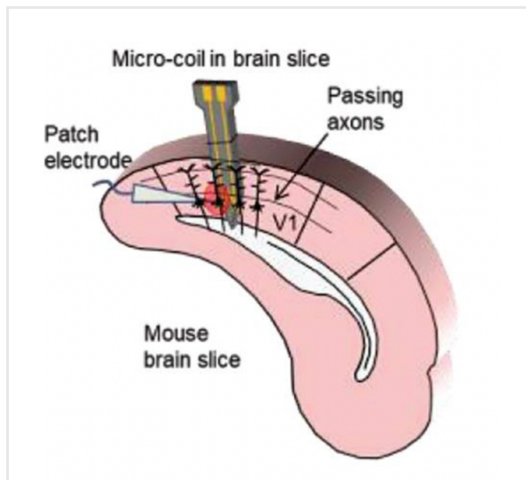
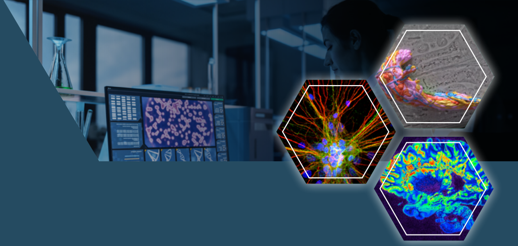


Image: Schematic representation of the *ex vivo* test configuration. Micro-coils were positioned in the primary visual cortex of a mouse brain slice and a patch electrode was used to record neural responses of targeted pyramidal neurons to the magnetic stimulation. Credit**:** Lee et al., 2018.



Open-source tool to precisely lock experimental perturbations to the phase of ongoing LFP oscillations — Dr. Alik Widge

TNE LAB
Translational NeuroEngineering

Video: Dr. Alik Widge explains how critical the BRAIN Initiative has been to his research.

In the realm of new tools that are driving open science efforts, Dr. Alik Widge and his team at the University of Minnesota have built a new open-source software tool for the Open Ephys GUI used to precisely lock perturbations (including optical/electrical/magnetic stimulation, behavioral triggering, and more) to the phase of ongoing local field potential (LFP) oscillations. The Phase Calculator Plugin is part of a larger Toolbox for Oscillatory Real-time Tracking and Estimation, or TORTE. This plugin can be found on GitHub, and is maintained by Widge's Translational NeuroEngineering Lab. This tool has been successfully used on neural data gathered from a variety of animal model systems including the rat, monkey, and human. By using the Phase Calculator Plugin, researchers can elucidate the basics of brain communication via oscillatory coherence patterns. This open-source tool is not only more accurate than other published methods, but it is also written in C++ for high speed and low latency closed loop applications. Additionally, it is part of a large, well-supported infrastructure (Open Ephys) that offers compatibility with a wide range of recording and stimulating devices used in animals and humans. This new tool can be applied to clinical studies in humans, such as testing novel neurostimulation designs in patients undergoing deep brain stimulation treatment for epilepsy or movement disorders. This exciting advance in open-sourced science is sure to open even more doors in the world of neurotechnology.

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!