Boston University Neurophotonics Center

Annual Report 2020-21

BU Neurophotonics Center

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Message From the Director

While the Boston University Neurophotonics Center (NPC) has just completed its fourth year of operation, this is our third annual report. Due to all the upheaval during the pandemic, we did not complete an annual report last year. As such, this annual report is covering activities from the last 2 years from July 2019 through June 2021.

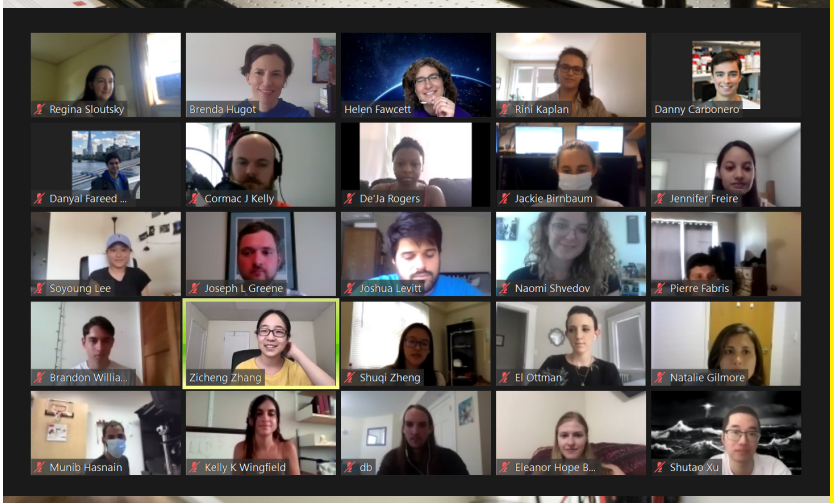
A major development for the NPC over the last two years was the arrival of Professor Anna Devor and her team – including Martin Thunemann, Kivilcim Kilic and Natalie Fomin-Thunemann – in CILSE. I am very excited to have the Devor lab here at BU and to have Anna's assistance as the Associate Director of the NPC. Her creativeness in the neurophotonics space, particularly in microscopy methods and animal models, and the Devor team's openness to collaboration and helping others will greatly benefit the members of the NPC. While the onset of the pandemic caused a great deal of delay in moving the Devor lab to BU and then in setting up all the equipment, they are now fully up and running and already bringing in new large grants funded through NIH BRAIN Initiative.

The last two years has also seen continued growth in the NPC community, now engaging 46 faculty at BU and their trainees. This growth over the last two years arose from the addition of new faculty that we welcome to BU (Abdoulaye Ndao, Hadi Nia, and Timothy O'Shea) as well as the growth of faculty interested in working with the NPC in adopting functional near infrared spectroscopy (fNIRS) and related human focused neurophotonic technologies into their research programs (Lou Awad, David Chung, Claudio Ferre, Simone Gill, David Greer, Deepak Kumar).

Supporting the growth of fNIRS activities within the NPC, we obtained a $5.9 million award from the NIH BRAIN Initiative for developing and deploying "The Neuroscience of Everyday World- A novel wearable system for continuous measurement of brain function." This award is directly engaging the labs of Boas, Cronin-Golomb, Ellis, Kiran, Somers and Yücel; and the technologies we are advancing under this grant are immediately impacting the efforts of many other groups at BU including the labs of Awad, Ferre, Gill, Kumar, Lewis, Sen and Tager-Flusberg. You can read much more about these exciting developments in the feature article in this annual report.

Another big development was the establishment of the NPC Core Facility. By the end of 2019, the NPC instrumentation was being extensively used by many groups and we did not have a manageable scheduling system in place, nor did we have sufficient infrastructure to maintain the high level of usage. Leading up to the start of the July 2020 fiscal year, we established the NPC Core Facility policies and obtained approval from the University to operate as a core facility. We have just completed the first year of operation and were approved to continue into our second year. The available instruments and policies are all easily found on the bu.edu/neurophotonics website. Importantly, the scheduling system put in place is very effective, and the cost recovery model will help ensure that we can maintain the high level of service that this facility provides to the community. The NPC continues to subsidize members, particularly junior members and those developing new ideas. The NPC subsidized approximately 50% of the activities during the 2020-2021 fiscal year. We expect that the total dollar amount of the subsidy will stay about the same but that the percentage will decrease as more and more grant funded users utilize the core. A critical component of this core model that will benefit all members is that it helps us purchase major new equipment every few years, augmenting what we can obtain by, for example, shared instrument grants.

In the following pages you will also learn about the several faculty projects that have engaged the NPC and the resultant collaborative publications and grants. I very much enjoy working with this community, and as we more fully emerge from the pandemic I look forward to the in-person gatherings and the creative new ideas that will emerge during those interactions.



At a Glance

47
Faculty Members

68
Students in NRT

14
Projects Supported

$13.5M
Collaborative Grants Funded

52
Publications from NPC Faculty Collaborations

WHO WE ARE

Over the past year, the BU Neurophotonics Center (NPC) has continued its vigoruos pursuit of its mission: to build and support an interdisciplinary community that can develop and broadly deploy impactful photonics technologies in the neurosciences to advance our understanding of how the brain works in health and in disease.

As always, we never would have achieved what we have in the past year without the excellent work of technical directors Anderson Chen and Meryem Yücel and staff members Parya Farzam and John Jiang.

We are also excited to welcome new and returning staff scientists.

Kivilcim Kilic is returning to the NPC after a brief excursion to the West Coast. She was instrumental in launching the NPC and we are excited to have her back with us on the East Coast.

We also welcome Martin Thunemann to the NPC. He joined the department of Biomedical Engineering in 2020. He received his PhD in Biochemistry from Eberhard Karls Universität Tübingen, Germany. During his graduate studies, Dr. Thunemann gained extensive knowledge in molecular biology, cell culture, cardiovascular physiology, mouse transgenesis and the Cre/lox system. He joined Dr. Devor laboratory at UCSD in 2015, first as a postdoctoral fellow, later – as a Project Scientist. He has been leading a number of bioengineering efforts including those based on multiphoton imaging and multiplexed electrophysiological recordings in awake behaving mice, and will be assisting the NPC community in the adoption of these methods.

Leadership

David Boas, Ph.D.
Director

Anna Devor, Ph.D.
Associate Director

WHO WE ARE

Technical Directors

Anderson Chen, Ph.D.

Meryem Yücel, Ph.D.

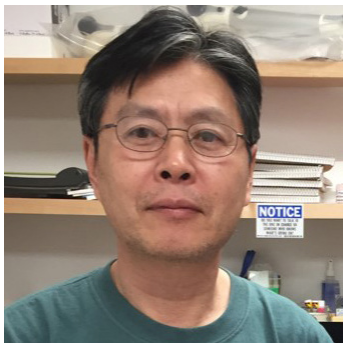
Scientists

Martin Thunemann, Ph.D.

Kıvılcım Kılıç, Ph.D.

Staff

Parya Farzam
fNIRS Specialist and Administrative director



John Jiang
Lab Manager

Faculty

Lou Awad
Assistant Professor (Director, Neuromotor Recovery Laboratory)

Works to develop, test, and translate rehabilitation technologies and interventions for people living with impaired neuromotor control.

Thomas Bifano
Professor (ME, MSE, BME)

Deformable mirrors; Microelectromechanical systems (MEMS); Adaptive optics; Biphotonic microscopy; Astronomical telescope instrumentation; Laser wavefront control

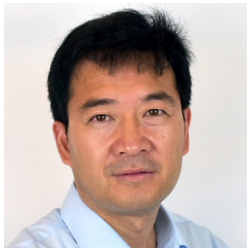
Irving Bigio
Professor (BME, ECE)

Medical application of optics, lasers and spectroscopy; Biophotonics; Nonlinear optics; Applied spectroscopy; Laser physics

David Boas
Professor (BME, ECE)
Director of Neurophotonics Center

Neurophotonics; Biomedical Optics; Oxygen delivery and consumption; Neuro-vascular coupling; Physiological Modeling

Anderson Chen
Lecturer (BME, MNI Facility Manager)
The Micro and Nano Imaging (MNI) Facility suite is a central teaching and research facility with a focus on optical imaging metrology of biological materials ranging from tissues to individual molecules



Ji-Xin Cheng
Professor (ECE, BME, MSE)

Molecular spectroscopic imaging technologies; Label-free microscopy; Medical photonics; Neurophotonics; Cancer metabolism; Photonics for infectious diseases

Jerry Chen
Assistant Professor of Biology

Large-scale neuronal networks; Sensorimotor integration; Decision making; Neurodevelopment; Non-linear microscopy

Ji-Xin Cheng
Professor (ECE, BME, MSE)
Molecular spectroscopic imaging technologies, Label-free microscopy, Medical Photonics, Neurophotonics Cancer metabolism, Photonics for infectious diseases

David Chung
Medical Doctor (BMC, Neurology)

Cerebral aneurysms, Stroke, Traumatic Brain injury, Neuromonitoring

Alice Cronin-Golomb
Professor (Psychological & Brain Sciences)

Neural correlates of perception and cognition in aging and age-related neurodegenerative disease

Alberto Cruz-Martin
Assistant Professor of Biology

Neural circuits; Sensory processing; Visual pathways

Ian Davison
Assistant Professor of Biology

Pheromones and innate social behaviors; Cortical computations and plasticity

Faculty

Allison Dennis
Assistant Professor (BME, MSE)

Nanobiotechnology; Fluorescent biosensing; Fluorescence resonance energy transfer (FRET); Quantum dot chemistry; Fluorescence microscopy; Single molecule sensing/imaging

Anna Devor
Assistant Professor (BME)

Cellular and systems-level neuroscience, microscopy, physiological underpinning of noninvasive imaging

Michael Economo
Assistant Professor (BME)

Neural circuits, Cognitive function, Neurodevelopmental disorders

Andrew Emili
Professor Biochemistry and Biology
Director of Center for Network Systems Biology

Molecular Interaction Networks, Precision Mass Spectrometry, Proteomics, Systems Biology.

Helen Fawcett
Research Assistant Professor, ME

Biodetection, Optics, Nanoscale lithography and imaging, Photonics applications.

Claudio Ferre
Assistant Professor (DOT)

Development of manual skills in typically developing children and children with disabilities (e.g., cerebral palsy)

Chris Gabel
Assistant Professor (Physiology & Biophysics)

Femtosecond laser surgery and optical neurophysiology for the study of the nervous system of the nematode worm C. elegans

Simone Gill
Associate Professor (Medicine)

We are interested in how people's bodies and environmental demands influence walking and motor functioning across the lifespan.

David Greer
Professor (BMC)
Chair and Chief of Neurology

Predicting recovery from coma after cardiac arrest, brain death, and multiple stroke-related topics, including acute stroke treatment and stroke prevention.

Lee Goldstein
Assoc. Professor (Neurology, BME, ECE)

The role of abnormal protein aggregation in chronic degenerative disorders of aging

Xue Han
Assoc. Professor (BME)

Neurotechnology; Optical neural modulation; Optogenetics; Neural prosthetics; Neural network dynamics; Brain rhythms; Neurological and psychiatric diseases; Cognition

Michael Hasselmo
Director of Center for Systems Neuroscience

The role of oscillatory dynamics and neuromodulatory regulation in cortical mechanisms for memory-guided behavior

Faculty

Mark Howe
Assistant Professor (Psychological & Brain Sciences)

Basal ganglia circuit mechanisms for learning and action

Swathi Kiran
Professor (Department of Speech, Language, and Hearing Sciences)

Bilingual aphasia; Aphasia rehabilitation; Functional neuroimaging; Language recovery; Impairments in naming, reading, writing

Deepak Kumar
Movement & Applied Imaging Lab

Development of more effective and personalized treatment interventions that reduce disability and directly impact patient care

Laura Lewis
Assistant Professor (BME)

Developing computational and signal processing approaches for neuroimaging data that enable new kinds of analyses of human brain physiology and function at subsecond timescales

Sam Ling
Assistant Professor (Psychological & Brain Scientists)

Imaging human behavior to explore how the brain mediates between the "buzzing confusion" of the visual world and our limited processing power

Jerome Mertz
Professor (BME, ECE)

Development and applications of novel optical microscopy techniques for biological imaging

Abdoulaye Ndao
Assistant Professor (ECE)

Light-matter interaction for digital imaging and medical diagnostics

Hadi Nia
Assistant Professor (BME, MSE)

Interface of physical sciences and molecular biology with a focus on links between mechanical forces and cell biology in health and disease.

Timothy O'Shea
Assistant Professor (BME)

Developing new treatments for brain and spinal cord disorders by engineering glia to perform specific reparative functions

Siddharth Ramachandran
Professor (ECE, MSE)

Optical physics of guided waves; Micro- and nano-structured optical fibers; High-power fiber lasers and fiber sensors; Biomedical imaging and microscopy with optical fibers

Steve Ramirez
Assistant Professor (Psychological & Brain Sciences)

Revealing the neural circuit mechanisms of memory storage and retrieval, and artificially modulating memories to combat maladaptive states

Darren Roblyer
Assistant Professor (BME)

Optical functional imaging; Diffuse optics and spectroscopy; Monitoring of therapies in oncology; Non-invasive monitoring of tumor metabolism

Faculty

Michelle Sander
Assistant Professor (ECE, MSE)

Femtosecond lasers; Ultrafast photonics and nonlinear processes; Fiber and integrated optics; Frequency combs; Infrared spectroscopy and biomedical applications

Benjamin Scott
Associate Professor (Psychological & Brain Sciences)

Develop and apply new technologies to study the neural basis of cognition and complex learned behavior

Kamal Sen
Associate Professor (BME)

Neural coding of natural sounds; Neural discrimination; Population coding of natural sounds

David Somers
Professor & Chair (Psychological & Brain Sciences)

Functional MRI, psychophysics, and computational modeling to investigate the mechanisms underlying visual perception and cognition

Robert Stern
Professor (Neurology)
Director of CTE

Long-term effects of repetitive brain trauma in athletes, including the neurodegenerative disease

Chantal Stern
Professor (Psychological & Brain Sciences)
Using fMRI to study how the normal brain encodes, stores and subsequently recognizes visual, spatial and verbal information

Helen B. Tager-Flusberg
Director of Center for Autism Research

The phenotypic characteristics of the Language, communication and associated social-cognitive deficits in autism (ASD) and other neurodevelopmental disorders

Lei Tian
Assistant Professor (ECE)

Computational imaging and sensing; Gigapixel, 3D microscopy; Compressive imaging; Phase retrieval; Imaging through complex media; X-ray phase imaging

Benjamin L. Wolozin
Professor (DPET)

Focused on the role of RNA binding proteins and translational regulation in disease processes

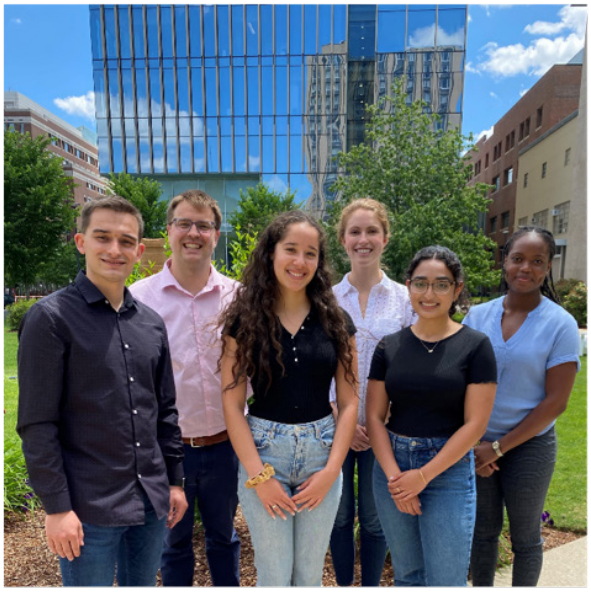
John A. White
Professor & Chairman (BME)

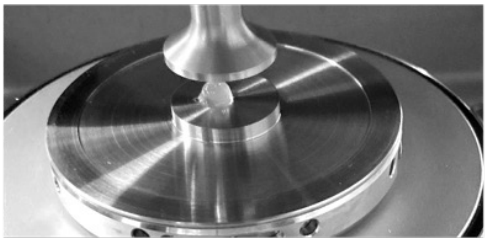
Mechanisms of episodic memory; Pathophysiology of epilepsy; Computational neuroscience; Design of real-time instrumentation; Imaging of activity in neurons and astrocytes

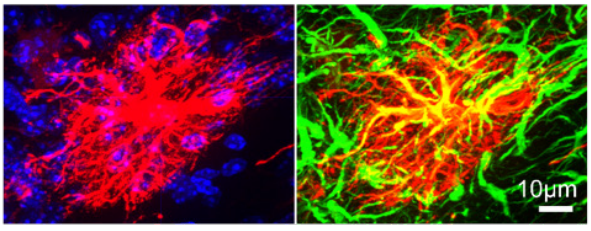
Meryem Yücel
Assistant Professor (BME)

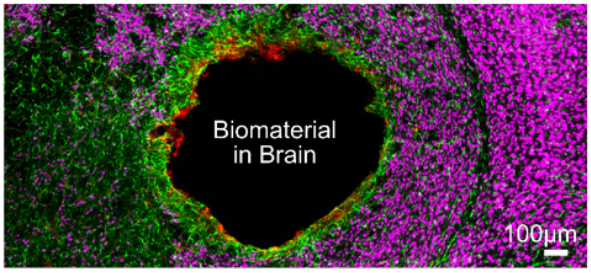
Functional neuroimaging (fNIRS, fMRI, EEG); fNIRS signal processing; cognitive neuroscience

Tim O'Shea









Tim O'Shea is an assistant professor in the biomedical engineering department who started at BU in Fall 2020 and subsequently joined the Neurophotonics Center as a faculty member in January 2021. Tim leads the Glia Engineering Lab which is focused on developing new treatments for brain and spinal cord disorders by engineering the functions of glia. Glia are a collection of cells in the brain and spinal cord that interact directly with neurons as well as peripheral cells to ensure healthy nervous system function. In spinal cord injury and stroke, damage to neural tissue destroys large volumes of glia and these cells are not naturally replenished resulting in the formation of lesions that do not support recovery. Dysfunctional glia can also contribute to progression of a variety of neurological diseases such as Alzheimer's, Parkinson's disease and Multiple Sclerosis. Although glia are critically important cells for healthy nervous system function, glia have historically been considered only supporting players in what has classically been neuron-centric neuroscience research but recently the spotlight has shifted their way.

In the lab Tim and his students are studying glia in the context of injury, degenerative diseases and foreign body responses using in vivo rodent models. As part of this work, they are also developing new bioengineering tools that can regulate glia functions and serve as new therapies. Biomaterials are the foundation of their bioengineering toolkit and the group is currently working on synthesizing and characterizing a variety of glycan-based biomaterials that are composed of polymers with biologically inspired supramolecular functionalities that afford tunable physiochemical and biological properties. The lab also maintains transgenic neural cell lines that are used in transplantation studies and interrogating glia-biomaterial interactions. The lab applies the bioengineering tools

Steve Ramirez

they develop to models of stroke and spinal cord injury in the mouse and incorporates cutting edge cell and molecular techniques such as immunohistochemistry (IHC) and transcriptomics to evaluate therapeutic outcomes.

Tim and his lab are excited to be involved in the BU Neurophotonics community. Since joining at the start of this year Tim has already initiated collaborations with leading imaging experts in the Neurophotonics center to apply advanced imaging techniques such as 2 photon microscopy, optical coherence tomography and ultrasound to study functional outcomes of a promising glia repair strategy in cortical and sub-cortical stroke injury models. Tim and his team look forward to working on other collaborative projects with the Neurophotonics center in the coming years.

If you ask ***Steve Ramirez*** what he likes most about working in the Neurophotonics Center at Boston University, he won't hesitate in telling you it's the camaraderie and the sense of shared support that pervade the place.

"I really enjoy that the community embraces this kind of collegial and team-oriented approach to science which I love. People here are very comfortable with sharing success," says Ramirez, an assistant professor of Psychological and Brain Sciences at BU and principal investigator of the Ramirez Group in the Center.

"It's like a trip to Mars. One person alone doesn't get to Mars. You need all the people in NASA. Have you seen the videos of everyone in a NASA control room celebrating an achievement together, jumping up and down and high-fiving each other? In my world, that's how all of science should be."

And in the Neurophotonics Center, he adds, that's how science is.

Indeed, there's no shortage of success to be shared. Since moving his lab to BU in 2017 – since returning home, as it were; he had been an undergraduate here and

was well acquainted with both the systems neurology program and the Photonics Center – he and his group have gone from strength to strength, particularly in looking at neural circuit mechanisms of memory storage and retrieval and how these might be manipulated in treating a range of psychiatric diseases and disorders.

Basically, they want to know, can we selectively edit memories? Like in the science fiction movies Total Recall and Eternal Sunshine of the Spotless Mind but here in the real world, using lasers and genetic engineering. For example, can we identify and suppress fear memories associated with post-traumatic stress disorder? The answer appears to be a resounding yes. Ramirez and his team have made tremendous strides, not only in demonstrating the fundamentals of how such an approach might work but also in advancing ever closer to practical application.

Even more recently, they have used the cutting-edge technologies in the lab to show how certain social interactions may help access previously held memories: an intriguing finding, especially considering the isolation many have experienced during the COVID-19 pandemic.

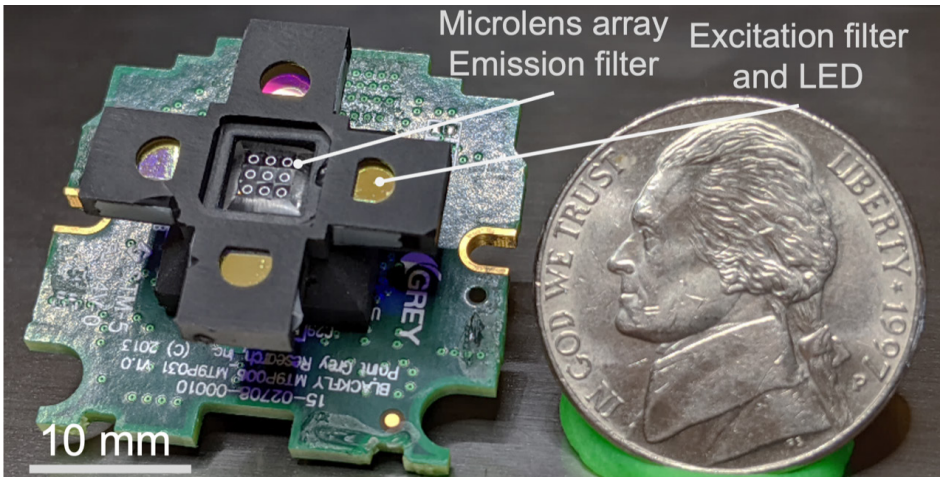
"The intersection between memory and the social dimension of the world is a very powerful one," Ramirez says. "Both are well studied on their own, but the intersection between the two is less well so. The fact is, socializing can strengthen what already exists in the brain, including memories. We now think we've found a mechanism in animal models to bring memories back online through socializing."

In discussing his lab's many achievements, Ramirez returns to the idea of community and the importance of working together as a community – very consciously including the younger generation of scientists, who in other environments don't always have the freedom to contribute as fully as they are able.

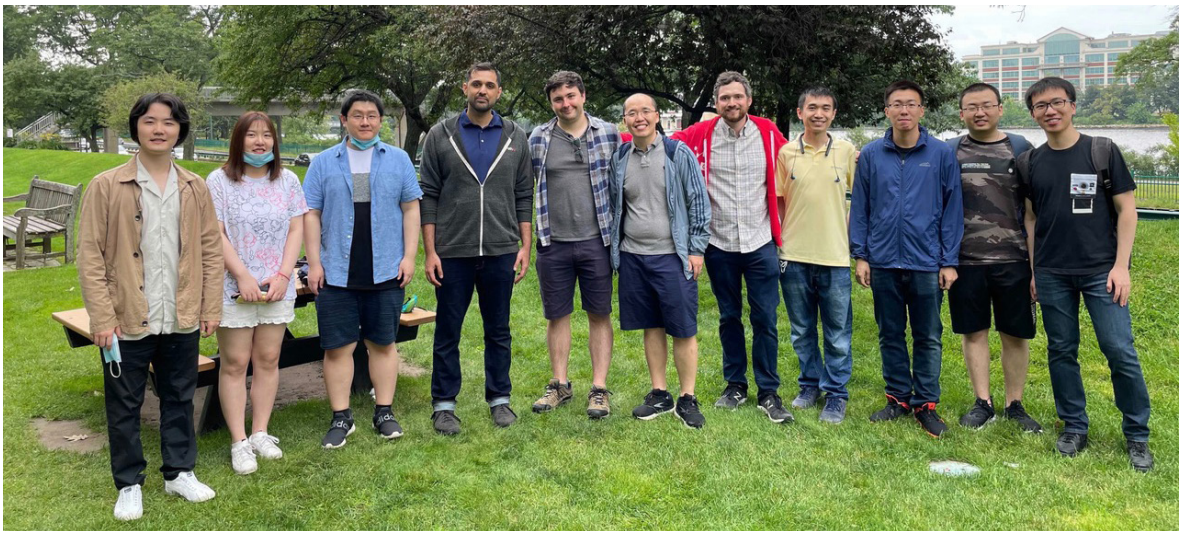
"I like to tell students, 'Let's think big,'" he says. 'We can get to Mars. Now what would it look like to get to Jupiter?' The students here are so remarkably good at thinking big and being proactive about research. It really is a testament to the culture of the Neurophotonics Center, their graduate programs and all the different umbrellas at BU."

Lei Tian

When ***Lei Tian*** joined Boston University's Electrical and Computer Engineering department in 2016, he never imagined his work would take him into the neurosciences. But when the Neurophotonics Center at BU launched the following year, bringing together a multidisciplinary team from all four corners of the university, he couldn't help but get involved.



Faculty Profiles



"When I started with BU, neuroscience was not one of my ambitions," he says. "I was thinking about other things." After a series of conversations with NPC faculty, though, he realized the potential impact of his work in neuroscience studies. "A lot of people these days talk about how super-important data is for the biomedical science. After talking with researchers in the Neurophotonics Center, I realized that, if we can help them process the data better, they can see more, understand more, in the studies they are doing."

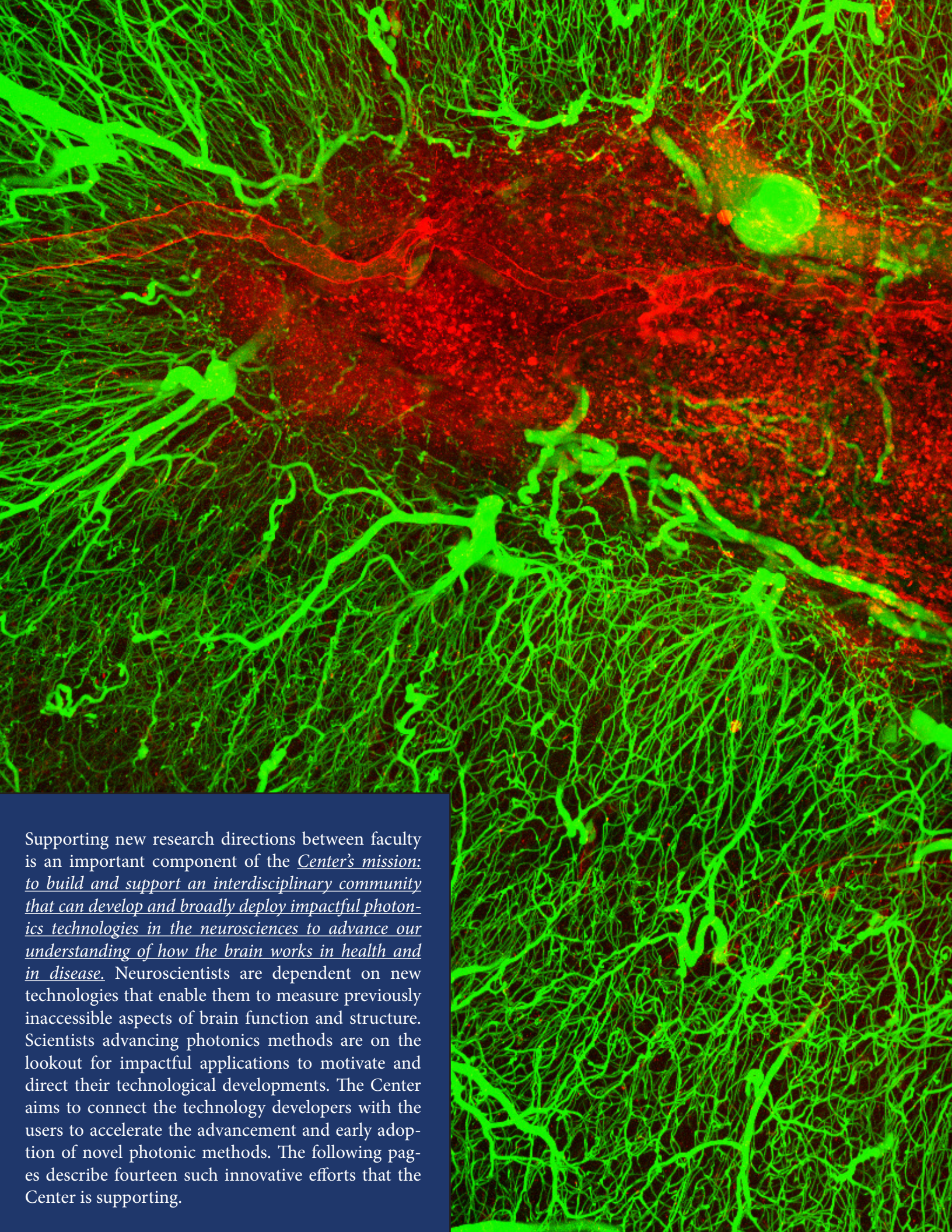
The main thrust of Tian's research has always been computational imaging, developing computational algorithms and optical imaging technologies that work together synergistically to address a host of applications. For instance, one of the threads of his work has been the development of a computational label-free microscope combining programmable illumination, multiple-scattering physical modeling and advanced reconstruction algorithms to enable tomographic reconstruction of unstained biological samples – work that was recognized by an NSF CAREER award in 2019.

Today, in collaboration with investigators from across the NPC, Tian and his group are creating cutting-edge solutions for studies producing very different kinds of neuroimaging data – and, in doing so, advancing the state of the art for computational imaging.

Just one example: In an October 2020 issue of Science Advances, Tian's group, in collaboration with Ian Davison's team in the Neurophotonics Center and NPC director David Boas, reported a wearable microscope for use in mouse models. Wearable instrumentation has recently made considerable waves in the neurosciences: not least because it enables studies in freely moving animals, yielding insights into the brain that would not have been possible in conventional imaging studies, where the animals are typically physically constrained. But because of engineering and other challenges inherent to miniaturized wearable microscopes, many of the instruments developed for such applications have been limited in application.

Tian and colleagues tackled these challenges decisively in the 2020 Science Advances paper, in which they describe wearable instrumentation called the Computational Miniature Mesoscope, or CM2. (The acronym doubles as a reference to the area of coverage it provides – 1 centimeter squared – which is approximately the area of a mouse's brain.) In developing the CM2, they employed computational imaging – augmenting the optics with algorithms – to facilitate a robust design enabling single-shot 3D imaging across an 8 mm by 7 mm field of view with a 2.5-mm depth of field with high resolution.

Ultimately, they hope to wield the technology to image large populations of neurons across the entire brain cortex of a mouse, potentially opening the door to an array of new neuroscience applications.



Supporting new research directions between faculty is an important component of the *Center's mission: to build and support an interdisciplinary community that can develop and broadly deploy impactful photonics technologies in the neurosciences to advance our understanding of how the brain works in health and in disease.* Neuroscientists are dependent on new technologies that enable them to measure previously inaccessible aspects of brain function and structure. Scientists advancing photonics methods are on the lookout for impactful applications to motivate and direct their technological developments. The Center aims to connect the technology developers with the users to accelerate the advancement and early adoption of novel photonic methods. The following pages describe fourteen such innovative efforts that the Center is supporting.

Neurophotonics Center-Supported Research Projects

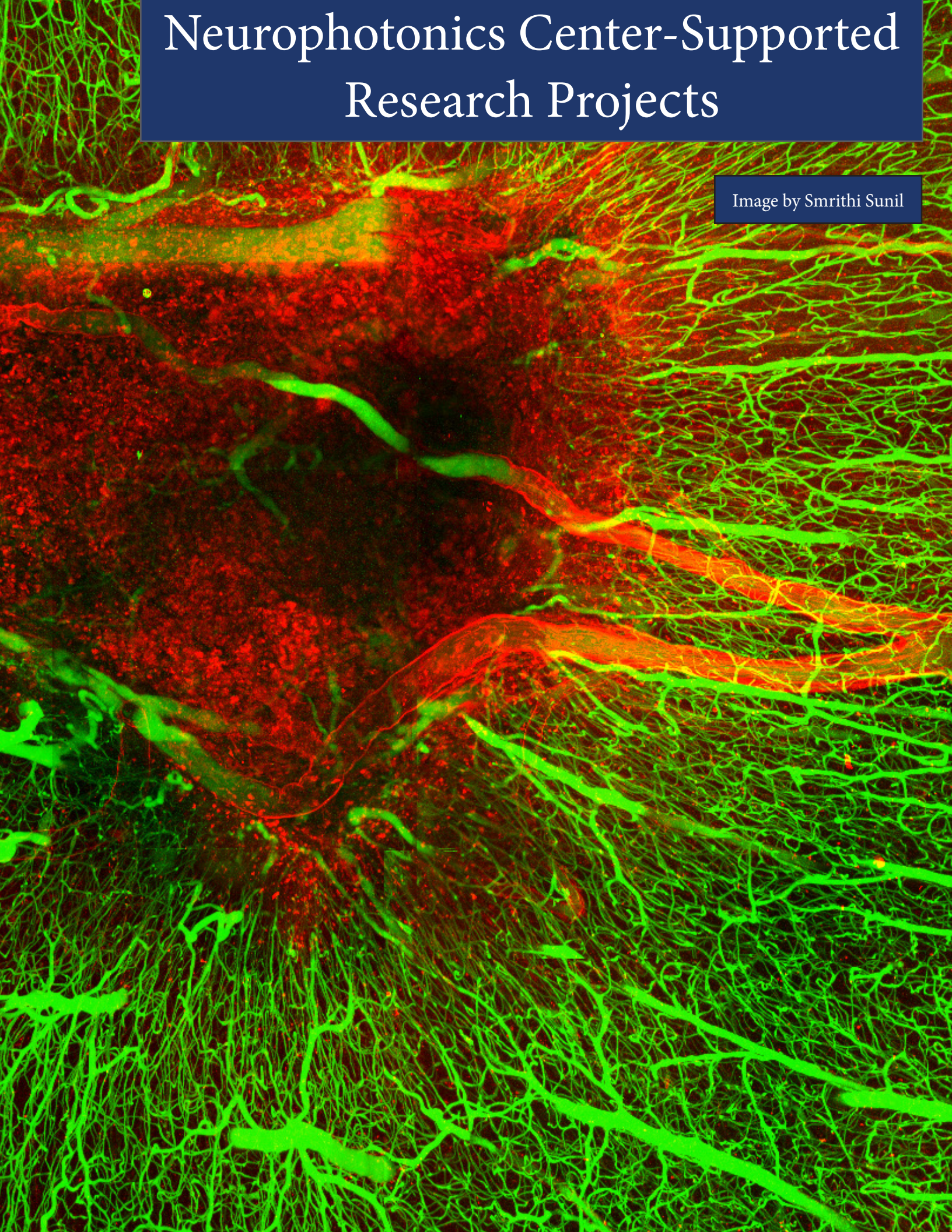
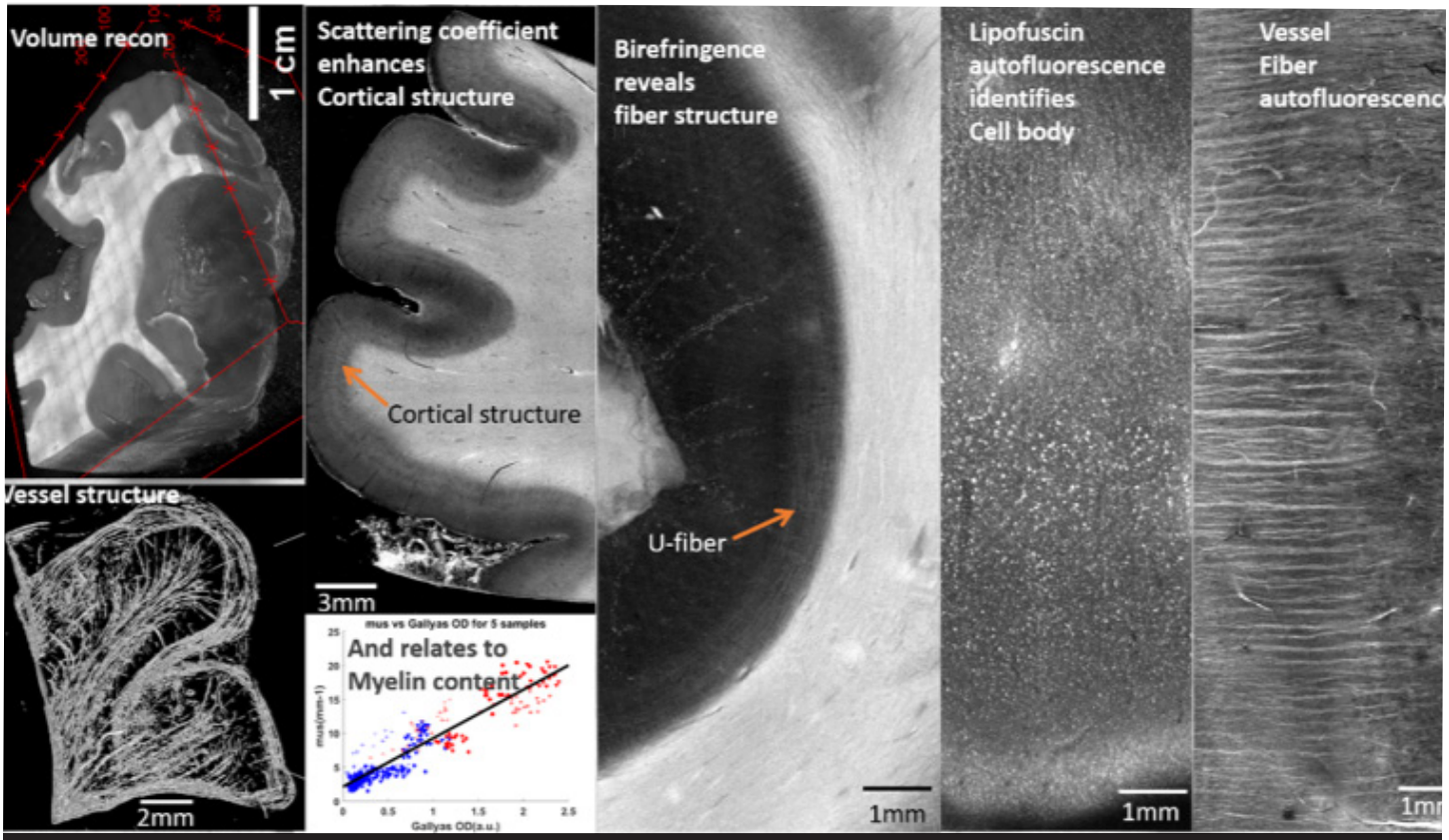


Image by Smrithi Sunil

Summary of Supported Projects



Serial Sectioning OCT

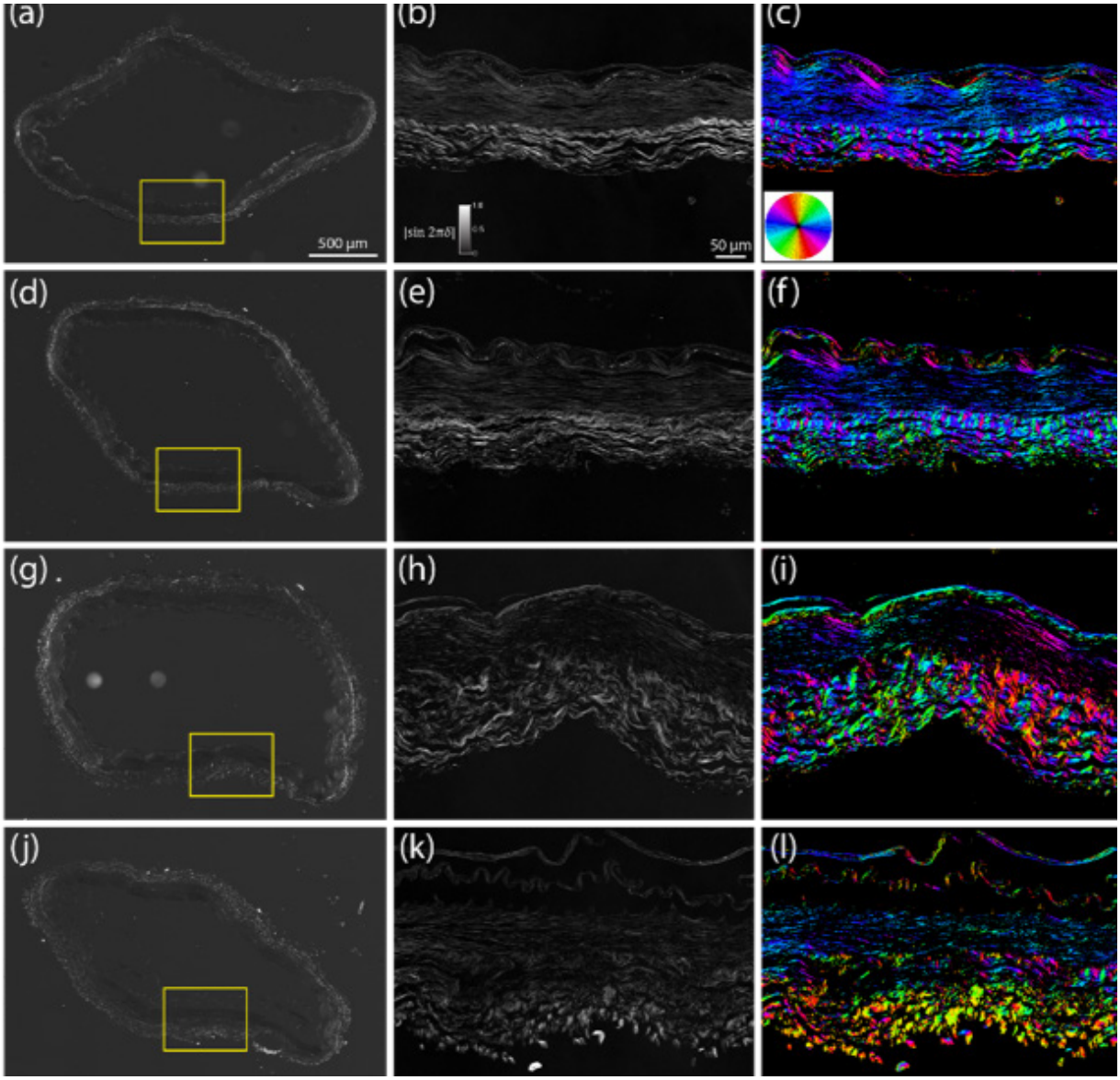
Structural Microscopy of four of the support projects.

The cells, dendrites, and axons in the human brain are structured into cytoarchitectonic and myeloarchitectonic areas, based on cell type, size, density, and the density of myelin sheath surrounding the axons. Those structural components are the substrate for cognitive competencies and the specific locations of neuropathological processes. Despite significant advances in imaging technology in the past decades, our understanding of human brain structures at 1-100 μm scale, in which neurons are organized into functional cohorts, is still limited. Quantitative features such as cell and myelin density have only been reported in a small number of subjects and over a small region of the brain. In the neurophotonics center we aim to develop and utilize a fully automated imaging pipeline that supports a human brain cell census network by linking the macro-scale MRI with micro-scale and multiplexed immunohistochemistry.

The imaging infrastructure at the Neurophotonics Center consists of a serial sectioning PSOCT-2P microscope system that generates multiple contrasts simultaneously, including volumetric reconstruction, scattering coefficient maps, birefringence, autofluorescence of vessels, axonal fibers and cell bodies, and so on. From these contrasts, various data-mining algorithms are being developed to extract features of human brain such as vessel and fiber structure, cortical layers, myelin content and cell density. **David Boas** and his team utilize this imaging system to further our understanding of the multi-level brain structure and provide landmarks for bridging MRI to immunohistochemistry. This project runs in collaboration with **Bruce Fischl** at MGH and **Kwanghun Chung** at MIT.

Quantitative birefringence microscopy

Irving Bigio and his team has developed a custom quantitative birefringence microscopy (qBRM) system for label-free imaging of anisotropic structures in biological tissues. This system, which is a resource available to other researchers at BU, is equipped with variable-ellipticity polarizers in the illumination and detection arms, which enable two complimentary configurations: (1) real-time, qualitative imaging with circular polarizers of opposite handedness; and (2) quantitative imaging with six images taken under different light-polarizations states. For neuroscience applications, qBRM has been utilized for high-resolution imaging of myelinated axons within brain sections as well as collagen fibers in the adventitia of cerebral artery sections. As breakdown of these structural components is an important factor in many neurodegenerative diseases, we anticipate that qBRM will provide new insights into the progression of these diseases in human or animal tissues. In the figure below, qBRM was applied for studying Alzheimer's disease (AD) progression in human anterior cerebral arteries (ACAs): (a-c) normal control; (d-f) early-stage AD; (g-i) middle-stage AD; (j-l) late-stage AD. (a,d,g,j) show qualitative images of entire ACA sections. (b,e,h,k) show relative retardance, and (c,f,i,l) show optic-axis orientation maps.

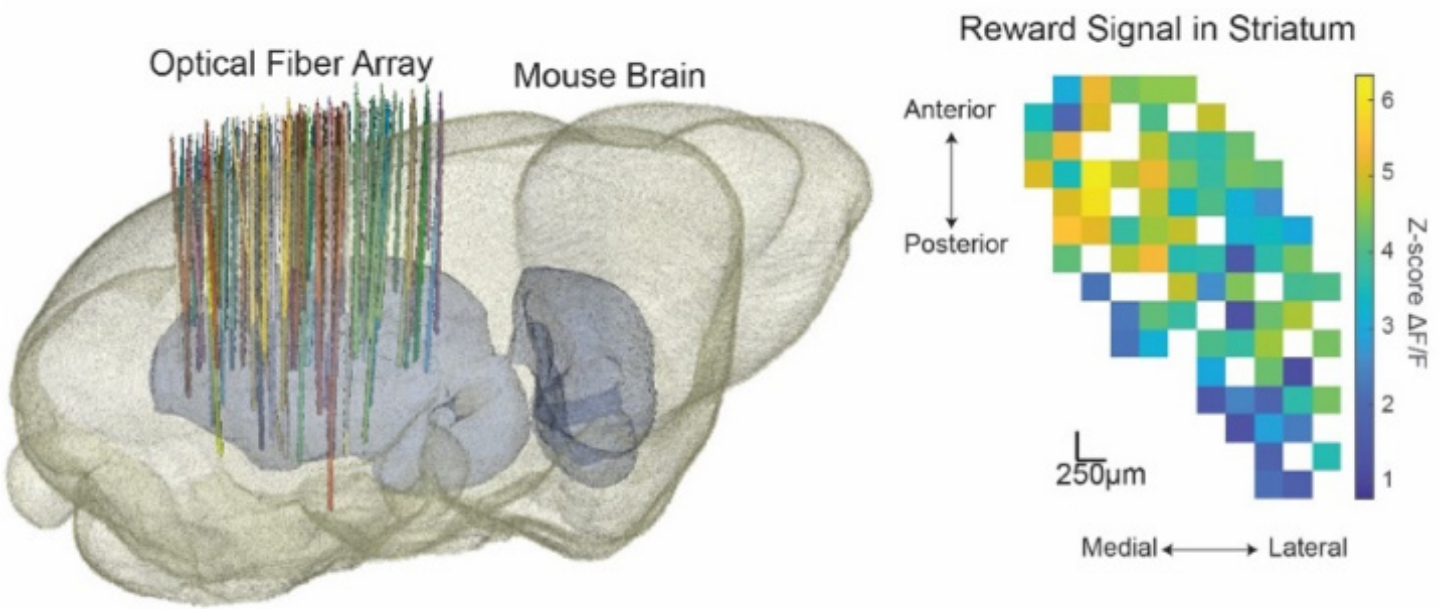


Large Scale Fiber Photometry

Complex behaviors such as motivation and decision making are supported by cell-type specific neural dynamics in widely distributed neural circuits. A major challenge for systems neuroscience is to capture these large-scale dynamics at high resolution across deep, 3-dimensional brain volumes during behavior. Current optical imaging methods which leverage fluorescent neural activity indicators are limited to sampling from small tissue volumes or superficial regions of cortex. Members of **Mark Howe's** lab in collaboration with the Boas lab, have developed a new approach based on fiber photometry, that enables optical measurements from genetically encoded sensors of neurotransmitter release and neural activity from hundreds of targeted locations across arbitrarily sized 3-dimensional brain volumes in behaving mice. They are applying it to answer fundamental questions about how neural dynamics in basal ganglia circuits regulate movement, goal-directed and habitual behaviors, and adaptive learning.

The new approach uses micro-3D printed plastic frames to precisely position arrays of over 100 small (37-50 micron) diameter optical fibers with uniform density across a deep 3D tissue volume. Arrays are surgically implanted into mice which express cell-type and neurotransmitter specific fluorescent indicators. High sensitivity CMOS cameras are used to image changes in fluorescence through each fiber, on timescales of 10s of milliseconds, which reflect local neural activity from small regions around each fiber tip. Stable measurements can be made over several weeks as head-fixed mice perform decision making tasks guided by sensory cues. As indicated in the figure above, the positions of each fiber tip in the array can be precisely localized in the brain with post-experiment imaging.

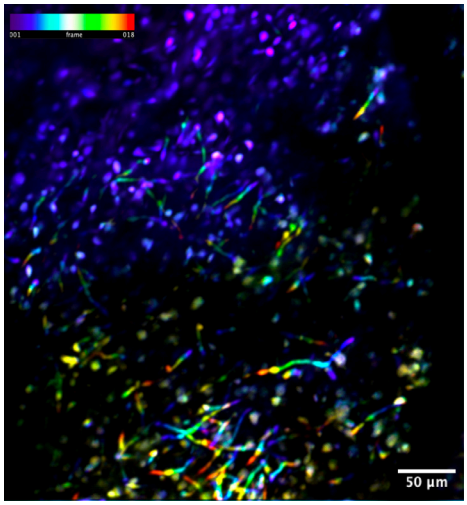
With this new technique, the **Howe** lab is now investigating the large-scale dynamics of dopamine and acetylcholine release in the striatum, a large deep brain nucleus in the basal ganglia (blue in figure above). For the first time, they can observe how these neuromodulators evolve in space and time across 100s of cubic millimeters to modulate critical functions ranging from movement control to reinforcement learning. The figure below shows the spatial distribution of dopa-



minergic reward signals measured from fibers at many locations across the A/P and M/L striatum axes in a behaving mouse. Imaging capabilities are currently being expanded to support multi-color imaging of red and green fluorescent indicators in the same tissue, enabling investigation of how large-scale neuromodulation influences post-synaptic signaling in distinct basal ganglia cell types. This approach can be easily adopted by the neurophotonics community and is applicable to addressing a wide range of basic questions in systems neuroscience. Future directions will extend the capability to enable precise optical manipulations neural activity across large deep brain volumes.

Adult Neurogenesis and Neuroblast Migration

Adult neurogenesis has garnered widespread interest over the past few decades for its potential in regenerative treatment for degenerative nervous system pathologies. However, obstacles to studying neuroblast migration and functional integration in-vivo have created a gap in knowledge that impedes the therapeutic localization and incorporation of neuronal stem cells into functioning circuitry. Over the past year **Ben Scott** and his team have employed advancements in multiphoton microscopy and genetic engineering to evaluate living, transgenic zebra finch songbirds as a naturalistic model for the study

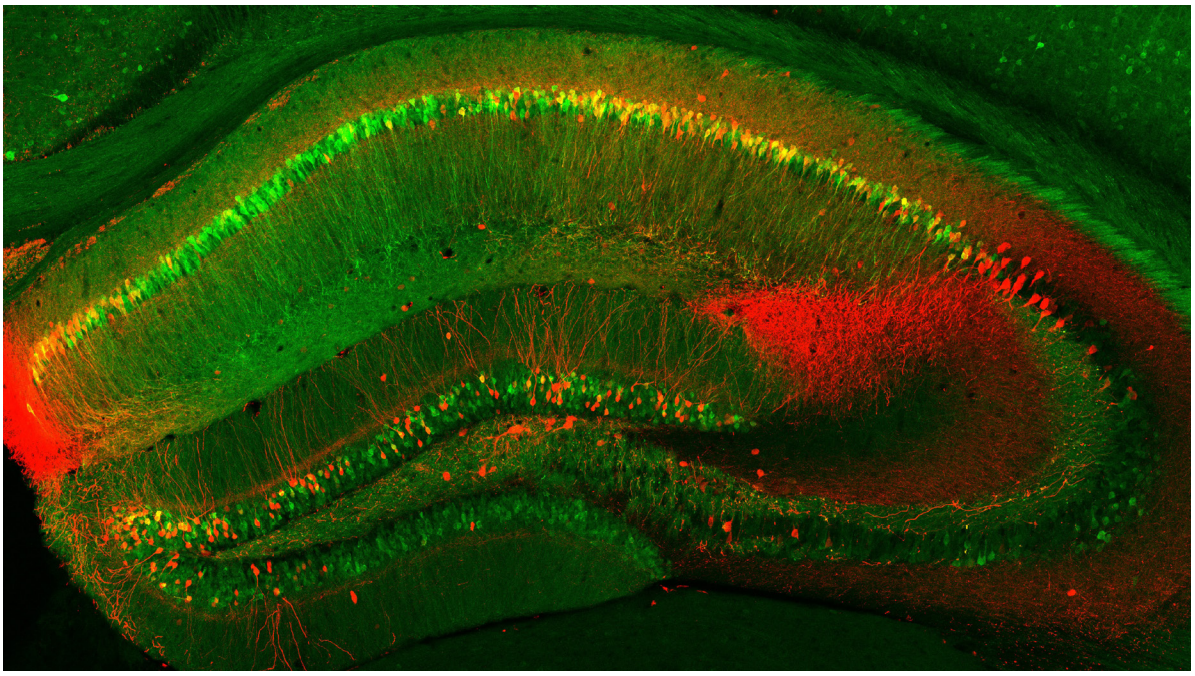


of adult neurogenesis and adult neuroblast migration, overcoming many obstacles to the in-vivo imaging of this biological phenomenon.

Zebra finches have extensive neurogenesis throughout their lives. Tens of thousands of new neurons are added to song system pre-motor circuitry during the song learning period alone. To access this superficial population of behaviorally relevant migratory neuroblasts, the team implanted cranial windows over the HVC nucleus of transgenic zebra finches that densely express green fluorescent protein (GFP) in different cell types. With immunohistochemistry, they verified that migratory neuroblasts were labeled in these transgenic zebra finches. Using the Bruker Investigator two-photon microscope at the Neurophotonics Center, they captured large volumetric time-lapses of this neuroblast migration in the hippocampus, ventricular zone, and HVC (see the image below). Their analysis yielded hundreds of migratory cells in three spatial dimensions across time from a single bird's imaging session, which is orders of magnitude larger than in previous work and revealed neuroblast migration in the zebra finch hippocampus for the first time.

Formation and Retrieval of Memories

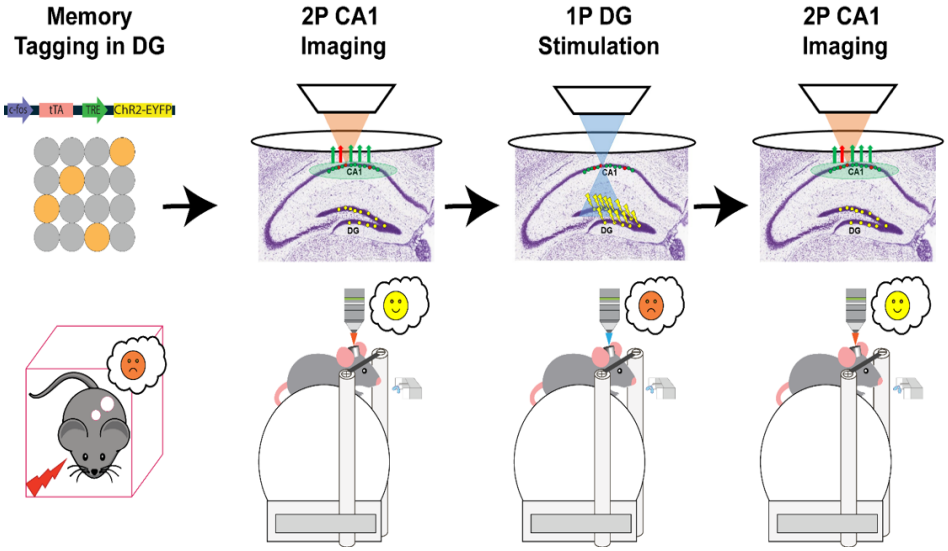
Understanding the basic mechanisms of memory function requires recording from populations of neurons in the hippocampus, a brain region crucial for the formation and storage of memories. In vivo optical imaging methods provide the opportunity for large-scale recording of neural activity from thousands of neurons in the mouse hippocampus during memory formation. Previous research has indicated that specific neurons, expressing the activity-dependent, learning-related gene c-Fos are activated during initial learning, and that reactivating these cells drives memory recall. For this reason, these c-Fos cell ensembles are believed to form part of the memory trace, or engram, in the brain. Until recently, identifying and recording from these engram cells in the intact brain has been limited by current technology. Now, with multiphoton imaging, it is possible to both identify engram cell populations and record their neural activity during learning and memory retrieval. **Steve Ramirez**, **Ben**



and two-photon imaging to observe population and engram cell activity in hippocampal CA1, the output region of the hippocampus, during engram reactivation. With this approach, they can observe downstream population and engram network activity during behavioral manipulation to understand the hippocampal outputs driving the behavioral changes. This study will help elucidate the mechanisms that lead to different behaviors despite activating similar engram neurons in upstream regions such as DG.

Scott and their collaborative team utilize a novel approach combining two-photon calcium imaging with the activity-dependent genetic strategy to access engram cells and to image activity of these engram cells during learning and memory recall. This approach will provide novel insight into how patterns of activity in engram cells drive the formation of memories, and how their sustained reactivation drives the retrieval of these memories.

In a related project, **John White** and his team are investigating the neuronal networks altered by engram manipulations and their behavioral manifestations. To understand engram manipulations, the pathway from stimulation to behavior can divided into two questions: 1) how does engram stimulation drive the hippocampal output region? and 2) how do hippocampal outputs correlate with behavior? While memory and spatial navigation have been correlated with patterns of activity in the hippocampus, the hippocampal network activity during the artificial manipulation of memory has not been studied. The **White** lab use single-photon stimulation



Multimodal Approaches

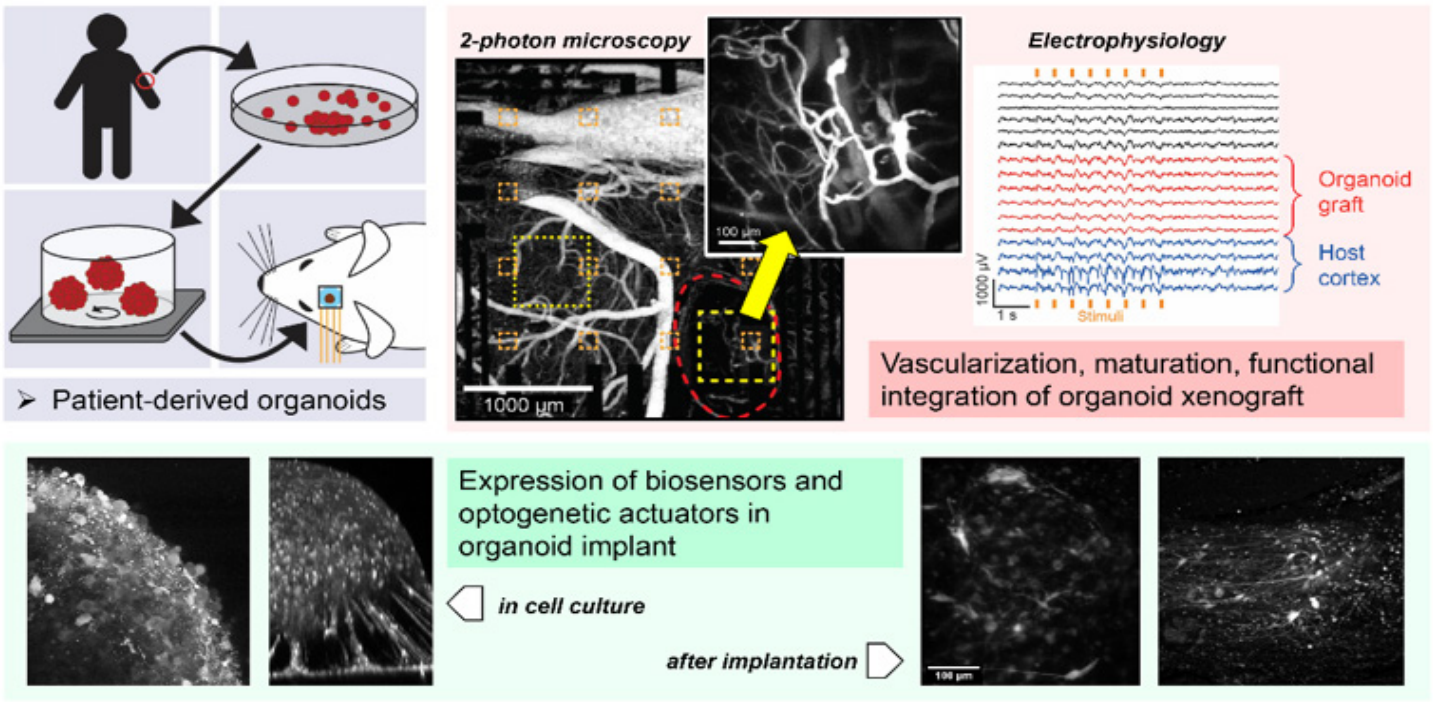
iPSC-Derived Brain Organoids

Cortical organoids, 3-dimensional neuronal cell cultures derived from human induced pluripotent stem cells, have recently emerged as promising models of human brain development and dysfunction.

Xue Han and her team grow 3D iPSC-derived midbrain organoids that upon differentiation exhibit midbrain phenotype and consist of a diverse cellular population complete with dopaminergic neurons and glia. They transduce the organoids with no-associated virus (AAV) vectors to express fluorescent markers or calcium indicator GCaMP.

Ben Wolozin's lab has developed methods to reproduce the pathology and pathophysiology of Alzheimer's disease using 3 dimensional sphroid assemblies of human neurons, astrocytes and microglial cells. These spheroids exhibit classic markers of tau pathology characteristic of Alzheimer's disease including hyper-phosphorylated tau, oligomeric tau and fibrillar tau. Organoids and spheroids can be maintained and studied in the dish for months. Ultimately, their growth and development are limited by the lack of vascularization. The absence of blood vessels limits their oxygenation and often renders the organoid core necrotic, interfering with further maturation. Therefore, organoids have been implanted into mouse brain, where they were vascularized, which enabled further growth and development, including generation of functional synapses between xenograft and host neurons (Mansour, et al., 2018, Nat Biotech 36: 432-41). This approach enables longitudinal studies, for which effective multimodal recording technologies are crucial.

Martin Thunemann and **Anna Devor** collaborate with the **Han** and **Wolozin** teams on multimodal monitoring of cortical organoids transplanted into mouse cortex using transparent graphene microelectrode arrays and two-photon imaging. This project also runs in collaboration with Duygu Kuzum and Alysson Muotri at UC San Diego. The team implant single organoids into the retrosplenial cortex of adult immunodeficient mice, place a graphene array (fabricated by the Kuzum's lab) bonded to coverglass on top of implant and



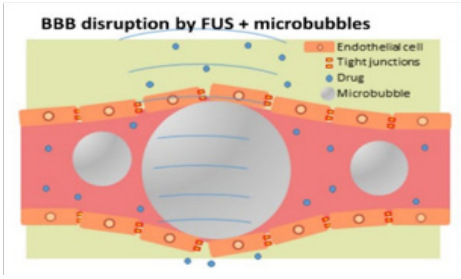
Multimodal Approaches

surrounding host cortex, and monitor the implant using electrophysiological recordings and two-photon imaging over many weeks. They perform recordings of local field potentials and multi-unit activity during spontaneous activity and in response to sensory stimulation. As the implantation site is close to visual cortex, they are able to record electrical activity in host cortex and organoid implant in response to photic stimulation of the contralateral eye. Using two-photon imaging with intravascular Alexa 680-Dextran, they observe vascularization within the implantation site. Imaging of organoid implants that were transduced with adeno-associated virus encoding fluorescent proteins before implantation show sustained transgene expression. This novel combination of stem cell and neurorecording technologies provides a unique opportunity for comprehensive evaluation of the development, maturation, and functional integration of human neuronal networks within the mouse brain.

FUS-BBB Opening, Neuroinflammation and the Neurovascular Response

The blood-brain barrier (BBB) controls which biologics are able to pass from the blood stream into the brain parenchyma. **Nick Todd** at Brigham and Women's uses focused ultrasound (FUS) as an emerging-technology that allows non-invasive and controlled opening of the BBB for delivery of therapeutics that would not otherwise reach the brain.

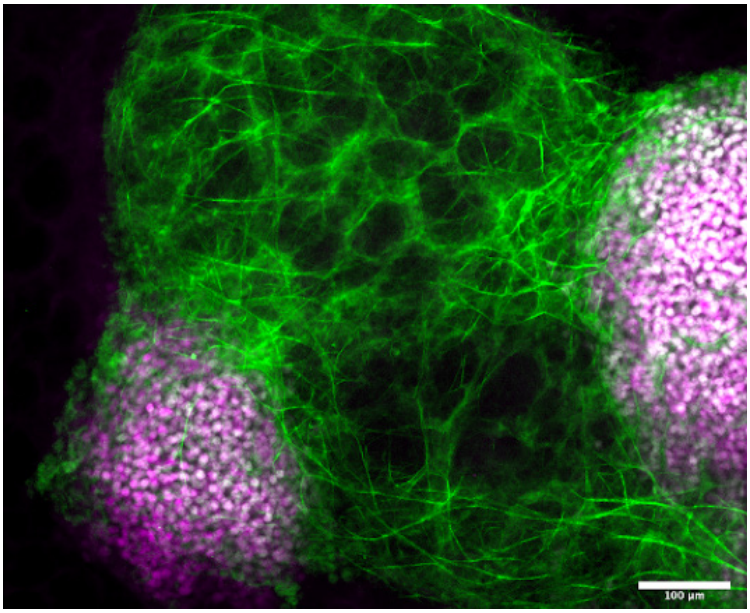
In collaboration with **Martin Thunemann** and **Anna Devor**, the Todd lab aim to better understand the relationships between FUS-BBB opening, neuroinflammation, and alteration of cerebral blood flow regulation so that the field of FUS-BBB opening can be moved forward safely into new applications. (pO2) using Phosphorescence Lifetime Imaging Microscopy with the Oxyphor-2P probe.



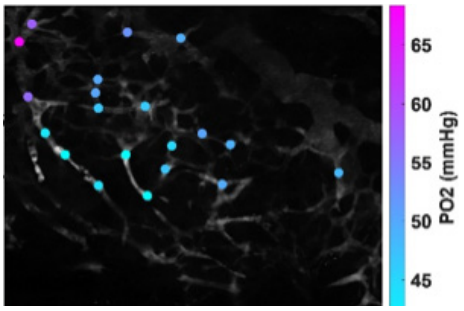
Applications Beyond Neuroscience

Ex vivo Lung Imaging

How does lung metastasis alter the properties and function of the lung at the alveolar level? And how does this remolding of the lung microenvironment affect tumor growth and treatment response? Hadi Nia and his team aim at answering these critical questions by developing novel model systems to probe the lung function and properties at the alveoli level, and how they change by hematogenous lung metastasis at different steps of tumorigenesis. The figure to the right shows a two-photon image of two breast cancer metastatic nodules (in blue) and how they remodel the structure of the alveoli surrounding them (in green).



Applications Beyond Neuroscience



In vivo Measurement of Mechanical Stresses in Tumors

A recently identified physical abnormality in fibrotic tumors is an elevated level of tensile and compressive solid stresses, defined as the mechanical stresses generated and transmitted by the solid components of the tumor within itself and surrounding tissues. These stresses are found to promote tumor progression and impede drug delivery by compressing blood vessels, increasing invasiveness of cancer cells, stimulating tumorigenic pathways, and inducing neuronal damage. However, the origins and consequences of solid stresses are still poorly understood due to a lack of appropriate measurement tools. Despite the recent progress in measuring solid stress ex vivo and in vitro, the in vivo measurement of solid stress in tumors is an unmet need. In this project, the **Nia** lab use intravital multi-photon microscopy and optical coherence tomography at NPC to quantify the intratumoral mechanical stresses in vivo. This will lead to better understanding of the origins and consequences of mechanical stresses and how they evolve in different stages of tumorigenesis.

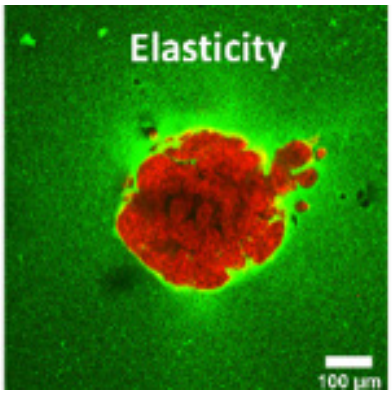
Tumor Vascularization and Oxygenation

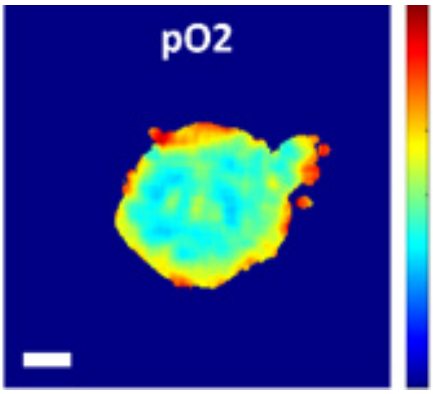
Abnormal angiogenesis has been characterized as a hallmark of cancer and its alleviation can be a necessary factor for a successful response. The vasculature is responsible for supplying oxygen and nutrients throughout the body and removing waste. Cancer cells can override this natural signaling and co-opt the vascular system in order to support its development. Tumor vasculature commonly has abnormal structural and function, characterized by excessive leakiness, enlarged vessels, and abnormal branching order. While many tumors are characterized by hypoxia, little is known about intravascular oxygenation. **Darren Roblyer** and his team aim to look at the relationship of structural vasculature properties such as length and diameter compared to intravascular partial pressure of O2 (pO2) using Phosphorescence Lifetime Imaging Microscopy with the Oxyphor-2P probe.

ECM Mechanics and Cell Metabolism

Invasive cancers respond to their microenvironment via metabolic plasticity, and metabolism is known to respond to changes in the mechanics of the fibrous extracellular matrix (ECM). The **Roblyer** lab study the relationship between ECM mechanics and tumor metabolism with respect to invasion in breast cancer spheroids.
They fabricate tumor spheroids in varying densities of collagen microenvironments and use multiphoton imaging to perform measurements of collagen organization and cell metabolism in 3D cell cultures of breasts cancer invasion using second harmonic generation (SHG) and fluorescence lifetime imaging microscopy (FLIM).

The outcomes of this project will advance our fundamental understanding of breast cancer progression and offer new avenues of investigation for pharmacological intervention.

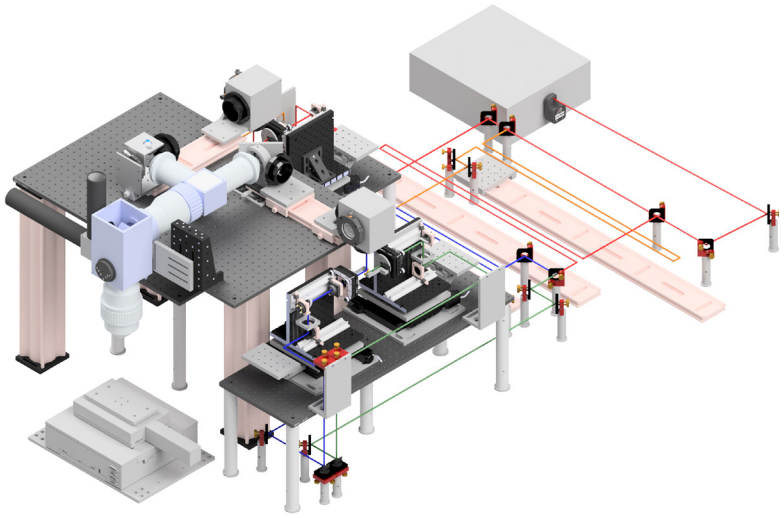




Proof-of-principle Optical Imaging Technology

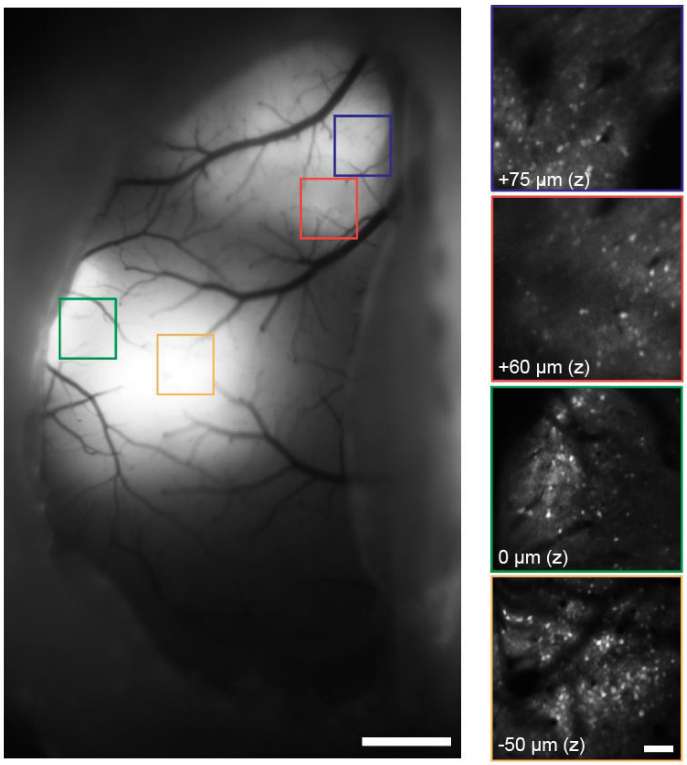
Imaging Neuronal Dynamics across Multiple Brain Areas with Two-photon Resolution

In order to understand how the brain functions as a whole, it is necessary to monitor the patterns of neuronal activity across the brain with cellular resolution. Jerry Chen and his team are developing a novel large field of view two-photon microscope for imaging neuronal dynamics across multiple brain areas.



The key advancements in capabilities compared to previous technologies are:

1) True simultaneous imaging of four brain regions across a 5mm field of view, sufficient to cover mouse sensorimotor cortex. Previous systems have demonstrated only sequential imaging across a similar field of view.
2) Because of this simultaneous imaging capacity, the Chen lab are able to image neural dynamics at high speeds (30Hz). This is 3-4x faster than other large field of view imaging systems that rely on sequential imaging.
3) All four field of views are independently positionable across 3 dimensions which allows us to target any combination of brain areas for imaging. The only other previous quad-region imaging system had fixed field of views and was applied for imaging only a single brain region.

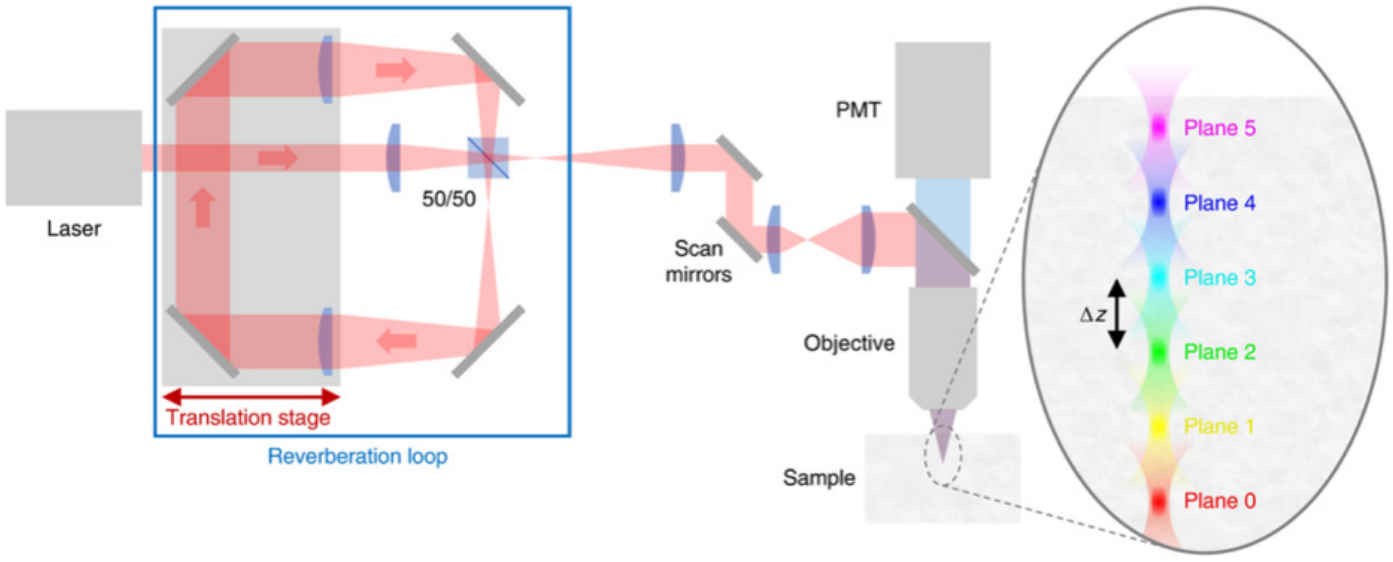


Three-Photon Reverberation Microscopy

In comparison to two-photon microscopy, three-photon microscopy provides superior depth penetration, due to the longer excitation wavelength it uses, and higher order nonlinear dependence of its signal. Previous demonstrations have successfully used three-photon microscopy for calcium imaging of relatively small neural populations in the mouse hippocampus.

Jerome Mertz and his team seek to broaden the application of three-photon imaging to larger populations of neurons. Recording of neuronal activity from large populations is key to understanding complex brain functions. To that end, the **Mertz** lab aim to record calcium transients from multiple depths simultaneously using reverberation microscopy.

In reverberation microscopy, a single pulse of light enters a partially-transmitting cavity, which creates multiple copies of the original pulse that are delayed in time from one another (see the figure below). Since each of the copies has looped through the weakly-focusing cavity a different number of times, they will each focus at a slightly different depth in the sample. The time delay between the copies provides a means of distinguishing which signal came from each depth post-hoc. Three-photon reverberation microscopy could potentially allow for recording of neuronal activity in the cortex and hippocampus simultaneously, a tool that can be exploited for a variety of neuro-biological studies.



NPC Faculty Collaborative Publications

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1. Lin, P., Ni, H., Li, H., Vickers, N.A., Tan, Y., Gong, R., Bifano, T. and Cheng, J.X., 2020. **Volumetric chemical imaging in vivo by a remote-focusing stimulated Raman scattering microscope**. Optics Express, 28(20), pp.30210-30221

2. Lin, P., Ni, H., Li, H., Tan, Y., Vickers, N.A., Bifano, T. and Cheng, J.X., 2021, March. **Volumetric chemical imaging in vivo by a deformable mirror-based remote-focusing stimulated Raman scattering microscope.** In Advanced Chemical Microscopy for Life Science and Translational Medicine 2021 (Vol. 11656, p. 116561N). International Society for Optics and Photonics.

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3. Beaulieu, Devin R., Ian G. Davison, Kıvılcım Kılıç, Thomas G. Bifano, and Jerome Mertz."**Simultaneous multiplane imaging with reverberation two-photon microscopy**." Nature Methods 17, no. 3 (2020): 283-286. https://doi.org/10.1038/s41592-019-0728-9

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4. Rodriguez, C., Chen, A., Rivera, J.A., Mohr, M.A., Liang, Y., Sun, W., Milkie, D.E., Bifano, T.G., Chen, X. and Ji, N., 2020. **An adaptive optics module for deep tissue multiphoton imaging in vivo**. bioRxiv.

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5. Xiao, S., Lowet, E., Gritton, H.J., Fabris, P., Wang, Y., Sherman, J., Mount, R., Tseng, H.A., Man, H.Y., Mertz, J. and Han, X., 2021. **Large-scale voltage imaging in the brain using targeted illumination**. bioRxiv.

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6. Xue Y, Davison IG, Boas DA, Tian L. **Single-shot 3D wide-field fluorescence imaging with a Computational Miniature Mesoscope**. Sci Adv. 2020;6(43):eabb7508. PMID: 33087364

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11. S. Sadegh, M. Yang, C. Ferri, M. Thunemann, P. Saisan, Z. Wei, E. Rodriguez, S. Adams, K. Kiliç, D. Boas, S. Sakadžić, A. Devor, and Y. Fainman, "**Efficient non-degenerate two-photon excitation for fluorescence microscopy**," Opt. Express 27, 28022-28035 (2019). https://doi.org/10.1364/OE.27.028022

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30. Sunil, S., Erdener, S.E., Lee, B.S., Postnov, D., Tang, J., Kura, S., Cheng, X., Chen, I.A., Boas, D.A. and Kilic, K., 2020. **Awake chronic mouse model of targeted pial vessel occlusion via photothrombosis**. Neurophotonics, 7(1), p.015005. https://doi.org/10.1117/1.NPh.7.1.015005
31. Yang, J., Chang, S., Chen, I.A., Varadarajan, D., Wang, H., Magnain, C., Fischl, B., Costantini, I., Pavone, F., McKee, A.C. and Chen, S.C., 2021, March. **Feature enhancement volumetric visualization of human brain sample with serial sectioning spectral domain optical coherence tomography**. In Optical Techniques in Neurosurgery, Neurophotonics, and Optogenetics (Vol. 11629, p. 116290Y). International Society for Optics and Photonics.
32. Giblin, J., Chen, A., Park, S.W., Kilic, K., Jiang, J. and Boas, D.A., 2021, March. **Interlaced two-photon volumetric scanning for measurement of capillary network dynamics**. In Optical Techniques in Neurosurgery, Neurophotonics, and Optogenetics (Vol. 11629, p. 116290I). International Society for Optics and Photonics.
33. Sunil, S., Erdener, S.E., Cheng, X., Kura, S., Tang, J., Jiang, J., Karrobi, K., Kılıç, K., Roblyer, D. and Boas, D.A., 2020. **Stroke core revealed by tissue scattering using spatial frequency domain imaging. NeuroImage**: Clinical, p.102539.

NPC Faculty Collaborative Publications

Swathi Kiran and Helen B. Tager-Flusberg

34. Butler, L.K., Kiran, S. and Tager-Flusberg, H., 2020. **Functional Near-Infrared Spectroscopy in the Study of Speech and Language Impairment Across the Life Span: A Systematic Review**. American Journal of Speech-Language Pathology, pp.1-28. https://doi.org/10.1044/2020_AJSLP-19-00050

Xue Han and Ji-Xin Cheng

35. Jiang, Y., Lee, H.J., Lan, L., Tseng, H.A., Yang, C., Man, H.Y., Han, X. and Cheng, J.X., 2020. **Optoacoustic brain stimulation at submillimeter spatial precision**. Nature Communications, 11(1), pp.1-9 http://dx.doi.org/10.1101/459933

Ji-Xin Cheng and John White

36. Shi, L., Jiang, Y., Fernandez, F.R., Chen, G., Lan, L., Man, H.Y., White, J.A., Cheng, J.X. and Yang, C., 2021. **Non-genetic photoacoustic stimulation of single neurons by a tapered fiber optoacoustic emit-ter. Light**: Science & Applications, 10(1), pp.1-13.

Lei Tian and Ji Yi

37. Matlock, A., Sentenac, A., Chaumet, P. C., Yi, J., & Tian, L. (2020). **Inverse scattering for reflection intensity phase microscopy**. Biomedical Optics Express, 11(2), 911-926. https://doi.org/10.1364/BOE.380845

38. Song, W., Matlock, A., Fu, S., Qin, X., Feng, H., Gabel, C.V., Tian, L. and Yi, J., 2020. **LED array reflectance microscopy for scattering-based multi-contrast imaging.** Optics Letters, 45(7), pp.1647-1650. https://doi.org/10.1364/OL.387434

39. Shain, W., Vickers, N., Li, J., Han, X., Bifano, T., Mertz, J. (2018). **Axial localization with modulated-illumination extended-depth-of-field microscopy.** Biomedical Optics Express 9(4), 1771-1782. https://dx.doi.org/10.1364/BOE.9.001771

40. Cheng, S., Fu, S., Kim, Y.M., Song, W., Li, Y., Xue, Y., Yi, J. and Tian, L., 2021, May. **Deep-learning Augmented Reflectance Microscopy for Label-free Multiplexed Cytometry.** In CLEO: Applications and Technology (pp. ATu4L-3). Optical Society of America.

Xue Han and Jerome Mertz

41. Xiao, S., Gritton, H., Tseng, H.A., Zemel, D., Han, X. and Mertz, J., 2021, March. **Single-shot high-contrast multiplane imaging with a z-splitter prism. In Three-Dimensional and Multidimensional Microscopy**: Image Acquisition and Processing XXVIII (Vol. 11649, p. 1164906). Interna-tional Society for Optics and Photonics.

42. Tsang, J.M., Gritton, H.J., Das, S.L., Weber, T.D., Chen, C.S., Han, X. and Mertz, J., 2021. Fast, **multiplane line-scan confocal microscopy using axially distributed slits**. Biomedical Optics Express, 12(3), pp.1339-1350.

43. Xiao, S., Lowet, E., Gritton, H.J., Fabris, P., Wang, Y., Sherman, J., Mount, R., Tseng, H.A., Man, H.Y., Mertz, J. and Han, X., 2021. **Large-scale voltage imaging in the brain using targeted illumination**. bioRxiv.

44. Xiao, S., Gritton, H., Tseng, H.A., Zemel, D., Han, X. and Mertz, J., 2020. **High-contrast multifocus microscopy with a single camera and z-splitter prism.** Optica, 7(11), pp.1477-1486.

Anna Devor and Xue Han

45. Thunemann, M., Wilson, M., Puppo, F., Pizzo, D.P., Rickner, H., Bortz, E., Mansour, A.A., Wolozin, B., Han, X., Gage, F.H. and Muotri, A.R., 2021, April. **Multimodal Monitoring of Human Brain Organoids Implanted in Mice Using Transparent Microelectrodes.** In Optics and the Brain (pp. BM2B-4). Optical Society of America.

Xue Han and Kamal Sen

46. Gritton, H.J., Nocon, J.C., James, N., Lowet, E., Abdulkerim, M.E., Sen, K. and Han, X., 2020. **Oscillatory activity in alpha/beta frequencies coordinates auditory and prefrontal cortices during extinction learning.** bioRxiv

Xue Han and John White

47. Shroff, S.N., Das, S.L., Tseng, H.A., Noueihed, J., Fernandez, F., White, J.A., Chen, C.S. and Han, X., 2020. **Voltage imaging of cardiac cells and tissue using the genetically encoded voltage sensor Archon1**. iScience, p.100974. https://doi.org/10.1016/j.isci.2020.100974

48. Keaveney, M.K., Rahsepar, B., Tseng, H.A., Fernandez, F.R., Mount, R.A., Ta, T., White, J.A., Berg, J. and Han, X., 2020. **CamKIIα Positive Inter-neurons Identified via A microRNA Based Viral Gene Targeting Strat-egy.** Journal of Neuroscience. Vancouver DOI: https://doi.org/10.1523/JNEUROSCI.2570-19.2020

Bob Stern and Lee Goldstein

49. Alosco, M.L., Cherry, J.D., Huber, B.R., Tripodis, Y., Baucom, Z., Kowall, N.W., Saltiel, N., Goldstein, L.E., Katz, D.I., Dwyer, B. and Daneshvar, D.H., 2020. **Characterizing tau deposition in chronic traumatic encephalopathy (CTE): utility of the McKee CTE staging scheme.** Acta Neuropathologica, pp.1-18. https://doi.org/10.1007/s00401-020-02197-9

50. Adams, J.W., Alosco, M.L., Mez, J., Alvarez, V.E., Huber, B.R., Tripodis, Y., Adler, C.H., Kubilius, C., Cormier, K.A., Mathais, R. and Nicks, R., 2020. **Association of probable REM sleep behavior disorder with pathology and years of contact sports play in chronic traumatic encephalopathy**. Acta neuropathologica, 140(6), pp.851-862.

Darren Roblyer and Irving J. Bigio

51. Tabassum, S., Tank, A., Wang, F., Karrobi, K., Vergato, C., Bigio, I.J., Waxman, D.J. and Roblyer, D., 2021. **Optical scattering as an early marker of apoptosis during chemotherapy and antiangiogenic therapy in murine models of prostate and breast cancer.** Neoplasia, 23(3), pp.294-303.

NPC Faculty Collaborative Publications and Grants

Chris Gabel and Lei Tian

52. Song, W., Matlock, A., Fu, S., Qin, X., Feng, H., Gabel, C. V., Tian, L., Yi, J., Popescu, G., Park, Y., & Liu, Y. (2021). **Programmable LED array reflectance microscopy for multi-contrast imaging.** School Psychology International., 11653. https://doi.org/10.1117/12.2578905

GRANTS:

The table below summarizes the NPC Center, New Collaborative, and Ongoing Collaborative grants. Additional grants to NPC Director Boas are included as well as they contribute to the resources of the Center that are made available to NPC members. During the 2020 and 2021 academic year.

PI	AWARD TITLE (FULL)	SPONSOR	FISCAL YEAR	Funds
BOAS DAVID	MICROSCOPIC FOUNDATION OF MULTIMODAL HUMAN IMAGING	NIH/National Institute of Neurological D	SEP 2020	159,390.00
BOAS DAVID	ESTABLISHING AN FNIRS ECOSYSTEM FOR OPEN SOFTWARE-HARDWARE DISSEMINATION	NIH/National Institute of Neurological D	JAN 2020	334,081.00
BOAS DAVID	IMPROVING HUMAN FMRI THROUGH MODELING AND IMAGING MICROVASCULAR DYNAMICS	NIH/National Institute of Neurological D	AUG 2020	109,772.00
BOAS DAVID	ACOUSTO-OPTIC MODULATED INTERFEROMETRIC DCS (IDCS) OPERATING AT 1064 NM	NIH/National Institute of Neurological D	OCT 2020	132,000.00
BOAS DAVID	TIME-GATED DIFFUSE CORRELATION SPECTROSCOPY FOR FUNCTIONAL IMAGING OF THE HUMAN BRAIN	NIH/National Institute of Neurological D	JAN 2020	125,309.00
BOAS DAVID	NONINVASIVE FAST OPTICAL CORRELATES OF NEURAL AND NEUROVASCULAR ACTIVITY	Facebook Technologies, LLC	APR 2020	97,148.00
BOAS DAVID	MONTE CARLO SIMULATIONS OF THE EFFECT OF NEURAL ACTIVATION AND VASCULAR DILATION ON THE DIFFUSE CORRELATION SPECTROSCOPY SIGNAL MEASURED NON-INVASIVELY IN THE HUMAN HEAD	Facebook Technologies, LLC	MAR 2020	72,090.00
BOAS DAVID	FIBER-BASED LASER SPECKLE CONTRAST IMAGING	Facebook Technologies, LLC	APR 2020	241,131.00
BOAS DAVID	THE NEUROSCIENCE OF EVERYDAY WORLD- A NOVEL WEARABLE SYSTEM FOR CONTINUOUS MEASUREMENT OF BRAIN FUNCTION	NIH/National Institute of Biomedical Ima	SEP 2021	2,476,388.00
BOAS DAVID	THE IMPACT OF MICROVASCULAR (DYS)REGULATION ON CEREBRAL FLOW AND OXYGEN HETEROGENEITY	NIH/National Institute of Neurological D	JUL 2021	632,670.00
BOAS DAVID	IMAGING AND ANALYSIS TECHNIQUES TO CONSTRUCT A CELL CENSUS ATLAS OF THE HUMAN BRAIN	Massachusetts General Hospital	AUG 2021	663,184.00
CHEN JERRY	NEUROTECHNOLOGY HUB: NEMONIC: NEXT-GENERATION MULTIPHOTON NEUROIMAGING CONSORTIUM	University of California, Santa Barbara	NOV 2021	221,076.00
CHENG JI-XIN	UNVEILING THE MECHANISMS OF ULTRASOUND NEUROMODULATION VIA SPATIALLY CONFINED STIMULATION AND TEMPORALLY RESOLVED RECORDING	NIH/National Institute of Neurological D	JUL 2021	654,740.00
DEVOR ANNA	TRANSPARENT NEURAL INTERFACE FOR IN VIVO INTERROGATION OF HUMAN ORGANOIDS	NIH/National Eye Institute	AUG 2021	270,342.00
DEVOR ANNA	EFFECTS OF INTRINSIC AND DRUG-INDUCED NEUROMODULATION ON FUNCTIONAL BRAIN IMAGING	NIH/National Institute on Drug Abuse	JUN 2021	808,089.00
DEVOR ANNA	MICROSCOPIC FOUNDATION OF MULTIMODAL HUMAN IMAGING	NIH/National Institute of Mental Health	JUN 2021	1,231,107.00
FERRE CLAUDIO	CODEVELOPMENT OF SENSORY AND MOTOR FUNCTION IN INFANTS AT RISK FOR CEREBRAL PALSY	NIH/National Institute of Neurological D	FEB 2021	208,839.00
HOWE MARK	STRIATUM WIDE DYNAMICS AND NEUROMODULATION OF CELL-TYPE SPECIFIC STRIATUM POPULATIONS DURING LEARNING	NIH/National Institute of Mental Health	APR 2021	700,662.00
KUMAR DEEPAK	MIND YOUR WALK INTERVENTION FOR COMMUNITY-BASED MANAGEMENT OF KNEE OA: A FEASIBILITY STUDY	NIH/National Institute of Arthritis & Mu	SEP 2021	178,462.00
MERTZ JEROME	SPECKLE-FREE PHASE-CONTRAST ULTRASOUND IMAGING	NIH/National Institute of General Medica	SEP 2020	235,800.00
MERTZ JEROME	FAST, LARGE-SCALE NEURONAL IMAGING WITH MULTI-Z CONFOCAL MICROSCOPY	NIH/National Institute of Biomedical Ima	NOV 2021	899,777.00
MERTZ JEROME	MULTI-LAYER NEURONAL IMAGING WITH REVERBERATION MULTIPHOTON MICROSCOPY	NIH/National Institute of Neurological D	DEC 2021	857,796.00
SANDER MICHELLE	POPULATION IMAGING OF ACTION POTENTIALS BY NOVEL TWO-PHOTON MICROSCOPES AND GENETICALLY ENCODED VOLTAGE INDICATORS	NIH/National Institute of Neurological D	JAN 2020	1,742,013.00
TIAN LEI	A COMPUTATIONAL MINIATURE MESOSCOPE FOR LARGE-SCALE BRAIN MAPPING IN BEHAVING MICE	NIH/National Eye Institute	AUG 2020	247,500.00