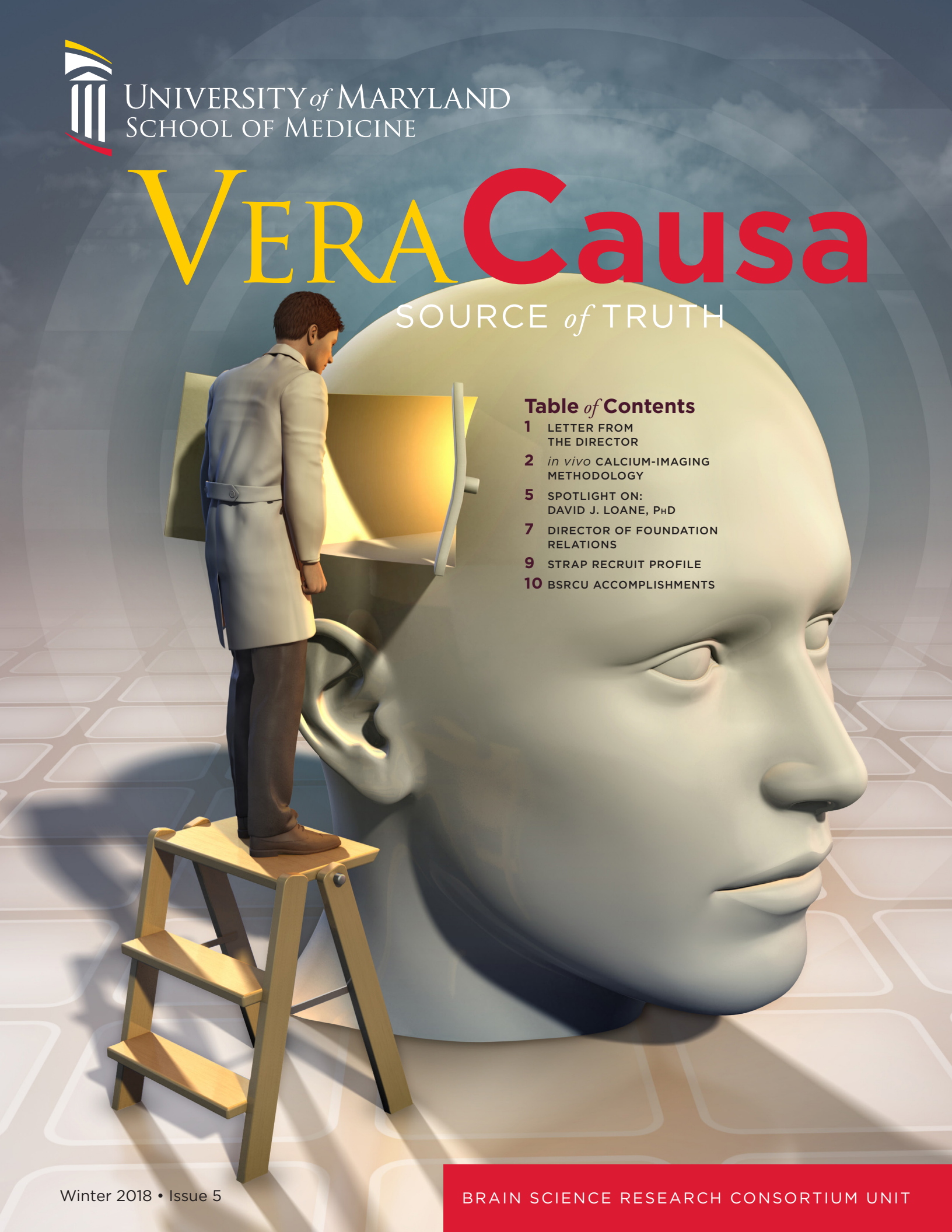


UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

VERA Causa

SOURCE of TRUTH

Table of Contents

Winter 2018 • Issue 5

BRAIN SCIENCE RESEARCH CONSORTIUM UNIT

LETTER FROM THE DIRECTOR

Welcome to a new issue of *Vera Causa,* a publication of the Brain Science Research Consortium Unit (BSRCU) at the University of Maryland School of Medicine (UMSOM). Since its inception in 2014, the BSRCU has served as an effective stir-plate on the laboratory bench of how to increase collaborative, interdisciplinary research in the brain sciences. Opportunities have been created by the BSRCU in the form of small seed funding, and through a variety of seminars, work group discussions, and symposia, serving to both expand existing brain science research and create new research space. Guided by the steady hand of the Executive Membership, the BSRCU has evolved to become a catalyst for new ideas and to provide a structure around which brain sciences can coalesce.

In this issue of *Vera Causa,* we highlight the initiatives of the BSRCU Pain and Addiction work group, which has brought an emerging new technology to our School, that of calcium-imaging. Using miniature endoscopes on awake behaving animals possessing genetically encoded calcium indicators, these scientists are able to measure neuronal activity with very high spatial and temporal resolution, providing key insight into how large ensembles of neurons work to produce coordinated behaviors.

Also in this issue, we profile one of our BSRCU members, **David Loane, PhD,** an Associate Professor in Anesthesiology, and faculty member at the Shock, Trauma and Anesthesiology Research (STAR) Center at the UMSOM. Dr. Loane and his team are conducting pioneering work in their own right: the discovery that microglial cells are an indicator of neurodegenerative diseases and linked to Traumatic Brain Injury (TBI) can help lead us to treatments for brain disorders that affect millions.

Finally, we are very happy to introduce four new faces to the BSRCU Executive Membership: **Peter B. Crino, MD, PhD,** who is Professor and Chair of the Department of Neurology, and **Tracy L. Bale, PhD,** who is Professor of Pharmacology and Psychiatry, and the Director of the newly established Center for Epigenetic Research in Child Health and Brain Development. We would also like to welcome **Linda Chang, MD, MS,** Professor of the Department of Diagnostic Radiology and Nuclear Medicine, and Vice Chair for Faculty Development, and **Cynthia F. Bearer, MD, PhD,** the Cobey Chair in Neonatology within the Department of Pediatrics. All four of these individuals are commanding leaders in their respective fields, and they bring new depth and dimension to the range of expertise at the BSRCU leadership table. We welcome them warmly to the BSRCU, and look forward to many years of productive interactions by their side.

I hope you enjoy this issue of *Vera Causa* and, on behalf of the BSRCU Executive Committee, best wishes for a wonderful 2018.

Bankole A. Johnson, DSc, MD

Director, Brain Science Research Consortium Unit

The Dr. Irving J. Taylor Professor and Chair, Department of Psychiatry

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

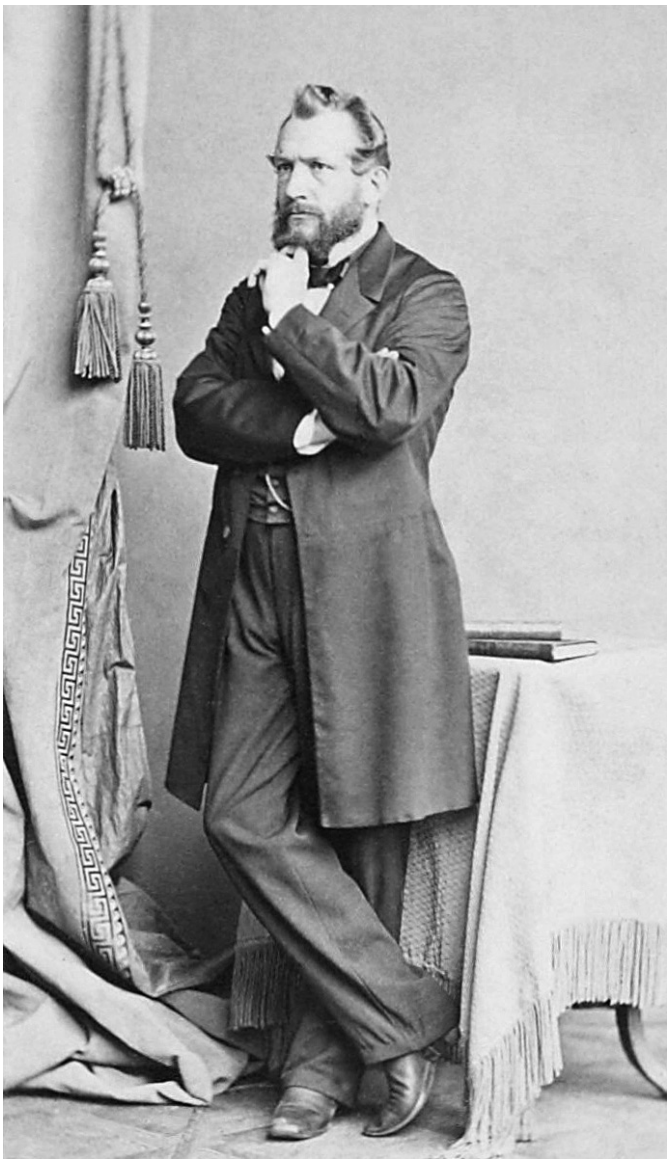
RESHAPING BEHAVIORAL NEUROSCIENCE WITH *in vivo* CALCIUM-IMAGING METHODOLOGY:

Real-time neuronal communication in awake, freely behaving rodents

The most exciting phrase to hear in science, the one that heralds new discoveries, is not "Eureka!" but "That's funny…"

The German physicist Emil du Bois-Reymond (1818-1896) is renowned for his discovery of action potentials, the electrical basis of excitable membranes common to all animals, and is arguably the father of modern electrophysiological methods. A stalwart academic authority during his time, he gave several probing speeches, the most famous of which was delivered in 1880 before the Royal Prussian Academy of Sciences. In this speech, he flipped on a bright and unflattering fluorescent light to reveal that the all-hallowed scientific enquiry, considered by most to be our only approach to truth, was a blunt and imperfect tool with hard and impassable limits on truth-seeking endeavors. He delineated seven "World Riddles" that he deemed would never be able to be addressed by science or philosophy — among those questions, the ultimate nature of matter and of force, and the origin of simple sensations, language, and intelligent thought.

Within this same historical timeframe, and while his laboratory technician was out on a leave of absence, British physiologist Sydney Ringer was conducting a series of experiments to replicate data published by his own laboratory just a year prior. Frustrated by his apparent lack of ability to maintain the pulsatile activity of an excised animal heart, Ringer went back to his technician's logs to carefully examine notes, only to realize that his rather sloppy technician had not used distilled water in conducting his experiments, as any good scientist would have done in those days. Ringer writes, "After the publication of a paper in the Journal of Physiology… I discovered, that the saline solution which I had used had not been prepared with distilled water, but with pipe water supplied by the New River Water Company… [which] contains minute traces of various inorganic substances."

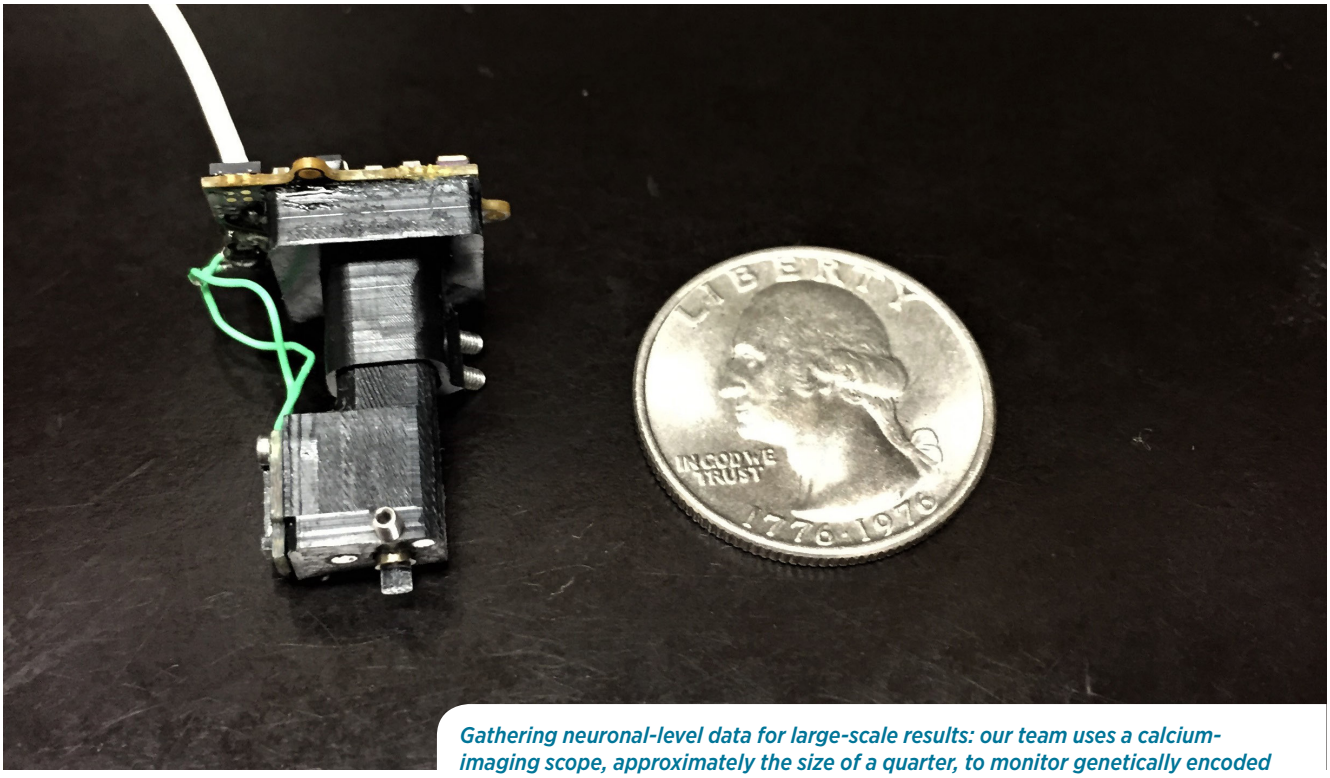


Emil du Bois-Reymond. (2017, December 3). In Wikipedia, The Free Encyclopedia. Retrieved December 14, 2017, from https://en.wikipedia.org/w/index.php?title=Emil_du_Bois-Reymond&oldid=813514982.

Realizing the methodological misstep, and after a careful characterization of those inorganic constituents, Ringer began varying the concentrations of those elements and compounds to derive the perfect saline solution for a viable *ex vivo* heart — the eponymous aqueous solution we now know as "Ringer's Solution." Three years following du Bois-Reymond's proclamation of the unknowable, Ringer published a seminal compilation of works that are now acknowledged as the flash point for modern understanding of the role of calcium in the contraction of the heart.

Today we appreciate the inextricable role that calcium plays across a range of crucial biological functions — most notably, as a key messenger that accompanies cells throughout the duration of their entire lifespan from fertilization to the end of the life cycle. Importantly, calcium is also ubiquitous in the brain as a central figure in neuronal communication, at the heart of how the brain performs the most basic functions. Although it is unlikely that a simple understanding of calcium dynamics could explain the origins of life, it is bringing us closer to an understanding of the origins of one very elusive topic of scientific study: that of how behavior emerges from neuronal ensembles.

Neuroscientists have understood for many years that nerve cell communication constitutes the basis of fundamental brain function and, thus, behavioral output. But the human brain does not possess just a few nerve cells: with the typical human brain topping in at about 100 billion neurons, large-scale neuronal communication is not easy to track. The question of how and with whom large groups of neurons communicate to produce coordinated behavior has eluded us. Knowing that calcium plays an essential role in neuronal communication (without it, nerve cells do not transduce information), and with the advent of new imaging technology and genetically-encoded calcium indicators, neuroscientists have begun to use calcium dynamics as a proxy for neuronal communication to paint a larger picture of how individual neurons work to produce an organism's coordinated, goal-directed activity. This elegant modern technological advancement gives a significant edge over previous attempts to understand how the brain works, and has the potential to fundamentally re-shape the field of behavioral neuroscience. Now, thanks in part to the Brain Science Research Consortium Unit (BSRCU), the University of Maryland School of Medicine (UMSOM) has access to this pioneering approach.



Gathering neuronal-level data for large-scale results: our team uses a calcium-imaging scope, approximately the size of a quarter, to monitor genetically encoded calcium indicators. How does brain activity produce behavior? We aim to find out.

In early 2015, the Executive Membership of the BSRCU voted unanimously to seed the implementation of advanced calcium imaging methodologies for pre-clinical applications. This project represents a group effort, and is led by several faculty in Anatomy & Neurobiology, **(1 Joseph Cheer, PhD, 2 Dennis Sparta, PhD, 3 Mary Kay Lobo, PhD, 4 Michael Shipley, MD, and 5 Adam Puche, PhD)** and Pharmacology **(6 Brian Mathur, PhD).** In a very short period, the investment is already yielding a bumper crop of scientific productivity, including a National Institute on Mental Health R01 grant, a CHDI Foundation contract, an IMHRO grant, and two published manuscripts. Because this technique allows for the interrogation of systems-level questions in awake, freely-moving animals, brain function can be captured in real-time to address a wide range of questions. Some examples of the type of questions being addressed by our faculty include the role of specific cell circuits in social distress modification of reward-guided behavior, the role of cell subtypes in the encoding of actions and habits, and the role of neurons implicated in attention in the modulation of sensory (olfactory) function. This technology is also being used to probe the most vexing neuropsychiatric disorders, including drug and alcohol use and abuse and depression. Importantly, this technique allows for the recording of neuronal activity over periods of weeks, or even months — to understand how the brain changes as a function of disease or trauma. And the applications will not stop there: plans are to extend the current platform to include collaborations with various faculty across the UMSOM, opening wide the door of questions that could be addressed using this technology.

"Ignoramus et ignorabimus." This is the phrase that du Bois-Reymond used in his speech in 1880 to describe the things that science "does not know, nor will ever know." With the advent of new technologies bringing us increasingly closer to understanding several of those "unknowables," one can only imagine that if he gave that speech today, du Bois-Reymond's list would be much shorter.

— AMB

Scientists work in the lab to monitor the brains of mice and understand the bigger picture, like what happens during the decision-making process. How do mice perform daily, routine functions, like deciding which path to take?

Faculty Leading the Way in Advanced Calcium Imaging Methodologies

1 Dr. Cheer

2 Dr. Sparta

3 Dr. Lobo

4 Dr. Shipley

5 Dr. Puche

6 Dr. Mathur

REFERENCES

Carafoli E (2002) Proc Nat Acad Sci 99:1115-1122.

Miller DJ (2004) J Physiol 555:585-587.

Ringer S (1883) J Physiol 4:29–43.

Levin-Schwartz Y, Sparta D, Cheer JF, Adali T (2017) Proc IEEE 103:1478-1493.

SPOTLIGHT ON:

David J. Loane, PhD

Changing the Face of Traumatic Brain Injury (TBI) Research

Photo Credit: Nuajé Visions Photography

These days, every individual is a smart-phone slinger: we invest hundreds of dollars into our palm-sized data command centers, and purchase cases, screen protectors, and even insurance policies to prevent mishaps. And, should we ever drop our phones, either shattering the case or causing a blurred screen — all chaos breaks loose.

Like with our phones, our brains require a high level of protective care, and understanding the wiring of our information hubs is no easy feat, particularly when our reset buttons are hit.

What happens to our brains when we experience a fall or a blow to the head?

How do these types of traumatic brain injury, known as TBI, contribute to the development of a spectrum of brain diseases, including Alzheimer's disease and dementia?

David J. Loane, PhD, Associate Professor in the Department of Anesthesiology, and member of the Shock, Trauma and Anesthesiology Research (STAR) Center, University of Maryland School of Medicine (UMSOM), is devoted to answering these questions and more.

He currently conducts sophisticated brain research at molecular and cellular levels to uncover the functions of both a healthy and injured brain — all in order to better understand what happens when we experience our own technical malfunctions and, most important, how we can fix them.

By way of this perspective, Dr. Loane serves as an exponentially advanced, neurological help desk: his specific research focuses on the rising theme of neuroinflammation and the role of microglial cells in the injured brain. Microglia are the primary innate immune cells in the central nervous system that defend the brain from injury and infection by performing protective "garbage collection" activities and other immunoregulatory functions.

Not only are microglial cells critical for brain development and neuroprotection, but they also play a reverse role as well: they can contribute to the neuropathology of several age-related neurodegenerative disorders.

As Dr. Loane explains, when microglial cells in the injured brain become over-activated, they release reactive oxygen species and other inflammatory mediators that can kill neurons — these neurotoxic mediators have been implicated in the pathogenesis of Alzheimer's and Parkinson's disease, and other neurodegenerative disorders.

"By understanding the molecular mechanisms that regulate microglial cell function, we may be able to engineer better drugs or other advanced treatment strategies that could stimulate neuroprotective functions after brain trauma, even as monumental as tissue repair and regeneration.

This would be a game changer for TBI."

— David J. Loane, PhD
Associate Professor

"Neurotoxic microglia upregulate NOX2, an enzyme system that produces high levels of reactive oxygen species. Our pre-clinical studies demonstrate that NOX2 is a critical regulator of microglial function and, when we inhibit NOX2 activity, we can switch neurotoxic microglial cells to neuroprotective cells that improve long-term neurological recovery in brain-injured animals," said Dr. Loane. "By understanding the molecular mechanisms that regulate microglial cell function, we may be able to engineer better drugs or other advanced treatment strategies that could stimulate neuroprotective functions after brain trauma, even as monumental as tissue repair and regeneration. This would be a game changer for TBI."

Currently, Dr. Loane is paving the way in this field of research by studying animals in a pre-clinical setting. He and his team conduct their studies with genetically engineered mice, known as knock-outs, so that they can analyze the effects of selective removal of specific genes in microglial cells. As a result, they're able to study the neuroinflammatory responses to TBI in a very precise and controlled manner.

In this way, his team uses clinically relevant and reproducible injury models in their studies, and follow the recovery of each animal using sophisticated motor and cognitive tests that mimic key neurological functions that are impaired in humans after brain injury.

"We are able to evaluate the motor and cognitive functions of injured mice," said Dr. Loane, "and then study their brains, using histological techniques to determine the levels and type of microglial activation in injured mice. We are also able to grind up tissue biopsies, and then analyze the expression patterns of genes and proteins in individual cell types, as a sort of molecular and cellular fingerprint, to understand how brain injury evolves after a TBI and how microglial cells contribute to ensuing tissue loss and neuropathology."

Dr. Loane uses the flow cytometry core facility at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, in his research to profile the immune response in the injured brain. This advanced flow cytometry-based technology allows his team to characterize phenotypic and functional responses in individual cells within the complex tissue microenvironment of the injured brain. It can also be used to get a molecular snapshot within individual cells (e.g., microglia versus infiltrating immune cells) by sorting cells for downstream genomic or proteomic analyses.

"Given the heterogeneity of microglial activation following brain trauma, it is now essential to study these cells at an individual or sub-population level in order to understand their functional responses after TBI. The use of flow cytometry and genomics platforms is allowing us to get a better handle on the multi-faceted role of microglia, both during the secondary injury and neurotoxic phase — but also during the recovery phase after a TBI," Dr. Loane said.

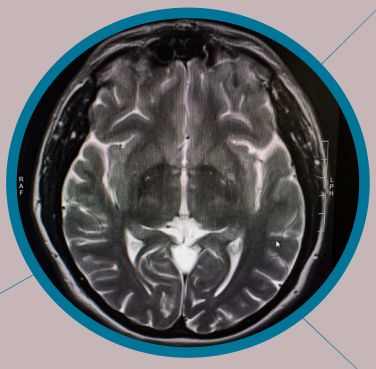
The urgency of Dr. Loane and his team's efforts are monumental: at the end of the day, rates of brain disorders are only expected to increase. To date, more than 5 million Americans are living with Alzheimer's disease and, by the year 2050, projections estimate this already startling number to rise as high as 16 million (http://www.alz.org/facts/overview.asp), and that's simply data on one isolated disorder.

It's for this exact reason that Dr. Loane devotes long hours in the lab, and applies himself to tackling research initiatives at almost every angle, including asking questions like: "Do microglial cells drive the chronic effects of brain injury, or do they respond to it?"

This type of perspective opens up a new realm of thinking, and it's why Dr. Loane has been so successful throughout his career.

While admittedly there is still so much to answer, UMSOM is proud to host such a cross-collaborative team of pioneering scientists, inclusive of Dr. Loane, and we eagerly anticipate the advancement of providing treatments for brain diseases — one research initiative at a time.

— LC



A DEDICATED UMSOM RESOURCE

Director of Foundation Relations

It is no secret that the majority of large grants for scientific and medical research come from the NIH and other federal agencies. However, as that pool of funding becomes increasingly competitive, private foundations and other non-government grants can fill funding gaps during lean times, keep work going while a principal investigator applies for government funds, or support a pilot project designed to obtain data necessary to compete for larger grants.

Because every grant submission is a direct reflection on the principal investigator and all others involved, as well as a representation of the University of Maryland School of Medicine (UMSOM), preparing and writing grants of any size requires a significant time commitment.

For that reason, the UMSOM Office of Development provides a dedicated resource to assist faculty with private foundation grant submissions.

Sarah Bradley, Director of Foundation Relations for UMSOM, is available to help with all aspects of private foundation and non-government funding, ranging from identification of opportunities to direct communication with foundations and final grant submission and stewardship. Sarah has ten years of medical writing and communications experience, and is the former director of a medical education company.

"My mission is to realize significant growth in foundation funding for research, programs, and educational initiatives at the local, regional, and national levels," she says. "My job is to make it easier and less time-consuming for our faculty to apply for these opportunities."

Please contact Sarah Bradley to schedule an individual meeting at (410) 706-0107 or by email at sbradley@som.umaryland.edu.

Sarah Bradley
Director of Foundation Relations

UMSOM Development Offices
31 S. Greene Street, 3rd Floor
Baltimore, MD 21201

7 Strategies for Successful Foundation Grant Submissions

1. Request a meeting with the Director of Foundation Relations to initiate a search for foundation funding opportunities.
2. Choose your applications wisely — don't try to fit a round peg into a square hole.
3. Request information from the Director of Foundation Relations on previously funded grants, specific application guidelines and eligibility, granting limitations, and any internal processes.
4. Work with the Director of Foundation Relations to contact the foundation to discuss your idea.
5. Identify other faculty who have applied to and/or received grants from a foundation you are interested in for tips and suggestions on their grant process.
6. When applicable, seek collaboration with other Departments, Institutes, Programs, and Organized Research Centers.
7. Utilize the Director of Foundation Relations to assist with writing, editing, setting up online application accounts, preparing attachments such as nonprofit letters and other required documents, ensuring the proposal is ready for routing, and tracking the submission in the grantor's system.

MORE...

FEDERAL AND FOUNDATION FUNDING OPPORTUNITIES

WOULD YOU LIKE TO KNOW WHAT'S AVAILABLE FOR FUNDING IN THE BRAIN SCIENCES?

PLEASE VISIT THE FOLLOWING LINK FOR A LIST OF FUNDING OPPORTUNITIES BY THE NIH, NSF, AND MORE.

MEDSCHOOL.UMARYLAND.EDU/MEDIA/SOM/DEPARTMENTS/PSYCHIATRY-/DOCUMENTS/BSRCU-OPEN-RFA.PDF

Spread the word – and let's start collaborating!

NEW STRAP RECRUIT PROFILE

Tracy Bale, PhD

LEADING SCIENTIST IN BRAIN DEVELOPMENT

STRAP recruit **Tracy Bale, PhD,** is Professor of Pharmacology and Psychiatry, and Director of the Center for Epigenetic Research in Child Health and Brain Development. She obtained her PhD in Neurobiology from the University of Washington, and completed her postdoctoral training with Dr. Wylie Vale and the Salk Institute. The University of Maryland School of Medicine (UMSOM) recruited Dr. Bale from University of Pennsylvania, where she was a Professor of Neuroscience. She also co-directed the Penn Center for the Study of Sex and Gender in Behavioral Health and was the Director of Research for the BIRCWH Faculty Scholars.

A nationally-recognized neuroscientist, Dr. Bale is respected for her research on stress as a risk factor for neurodevelopmental disorders and neuropsychiatric disease. She has been the recipient of several awards, including the development award for early career achievement and promise by the Society for Neuroscience, the Richard E. Weitzman Memorial award by the Endocrine Society, the Medtronic Award from the Society for Women's Health Research and, most recently, the Daniel H. Efron Research Award from the American College of Neuropsychopharmacology.

Dr. Bale's lab has developed mouse models to study vulnerability to stress dysregulation, while also assessing sex-specificity, developmental timing, and epigenetic mechanisms involved in programming of the brain, placenta, and sperm in response to stress. Her research has provided novel insight into the increased neurodevelopmental risk to males following prenatal insults, such as maternal stress, and the role of placental sex (XX vs. XY) in buffering effects of gestational insult. Her lab identified OGT expression in the placenta as critical in providing protection to female offspring. Her lab is also making important discoveries linking paternal stress experience to offspring dysregulation through novel epigenetic markers in the sperm. Recently, Dr. Bale has focused on bridging basic and clinical research, translating her work on epigenetic markers in the sperm, and collaborating with Dr. Neill Epperson to mechanistically examine the impact of early life adversity on neuropsychiatric disease in women.

"We are off to a tremendous start with the STRAP initiative, and are very excited to be able to attract these first teams of outstanding individuals who are nationally and internationally recognized," says **E. Albert Reece, MD, PhD, MBA,** Executive Vice President for Medical Affairs, UM Baltimore, John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine.

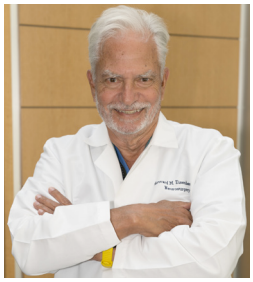
NEW AND NOTEWORTHY ACCOMPLISHMENTS OF THE BSRCU

Peter Crino, MD, PhD

Peter J. Crino, MD, PhD, Chair, Department of Neurology, and his team recently identified new blood-based protein biomarkers designed to accurately distinguish epileptic seizures from other neurological events. This exciting new enhancement to an existing diagnostic was reported in the December 2, 2017 issue of *Business Insider.*

Meaghan Creed, PhD

Meaghan Creed, PhD, Assistant Professor of the Department of Pharmacology, is the 2017 winner of Science & PINS Prize for Neuromodulation, which recognizes pioneering research on the biology of underlying addication. The findings were discussed in her prize-winning essay, "Toward a Targeted Treatment for Addiction."



Mary Kay Lobo, PhD

Together with her research team, Mary Kay Lobo, PhD, Associate Professor, Anatomy and Neurobiology, recently published an article in the December 2017 issue of the high-profile journal *Neuron*. Her team identified increases in a protein involved with mitochondrial fission in the brains of cocaine-exposed mice and human post-mortem tissue. Importantly, by disrupting the activity of this protein in cocaine-exposed mice, the researchers were able to block the animals' heightened sensitivity to, and seeking of, cocaine. These provocative findings suggest a potential new therapeutic treatment for Cocaine Use Disorder: that of disrupting mitochondrial fission.

Howard Eisenberg, MD

Howard Eisenberg, MD, Professor and Chair of Neurosurgery, is the Principal Investigator for a pivotal study that has received FDA approval to use focused ultrasound to treat Parkinson's disease. The title is "A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease With Unilateral Lesioning of the Globus Pallidum Using the ExAblate Neuro System," and is a multi-center (n=110 proposed) randomized study of the safety and efficacy of MR guided focus ultrasound (GPi lesion) for the treatment of Parkinson's disease.

CHECK US OUT ON THE WEB!

Keep abreast of the latest BSRCU happenings, receive the newsletter directly to your email, and join our growing member database by going to:
http://medschool.umaryland.edu/BSRCU/

QUESTIONS? COMMENTS? IDEAS?

Annabelle (Mimi) Belcher, PhD
Assistant Professor of Psychiatry

110 South Paca Street, Room 4-N-101 | Baltimore, Maryland 21201
Phone: 410-328-6837 | Email: abelcher@som.umaryland.edu

Managing Editor and Writer:
Lisa Cleary; lcleary@som.umaryland.edu

Consulting Scientific Editor and Writer:
Annabelle (Mimi) Belcher, PhD; abelcher@som.umaryland.edu

Contributing Writer:
Sarah Bradley, Director of Foundation Relations
sbradley@som.umaryland.edu

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

medschool.umaryland.edu