

BreESTim: An Innovative Neuromodulation Technique for Management of Neuropathic Pain

Sheng Li, MD, PhD



Li

Abstract: Breathing-controlled electrical stimulation (BreESTim) is developed based on discoveries about the systemic effects of voluntary breathing and the physiological interactions with body systems. Our results have demonstrated that BreESTim produces effective analgesic effects with restoration of autonomic dysfunction via central neuromodulatory mechanisms.

Neuropathic pain (NP) after spinal cord injury (SCI) is common and debilitating. It is characterized by spontaneous and ongoing pain, and described as burning, shooting, prickling or electrical. This type of pain can result from innocuous stimuli (allodynia) and/or exaggerated pain in response to noxious stimuli (hyperalgesia). About 65 to 85 percent of SCI patients experience neuropathic pain, and in about a third of them, the pain is severe. It doesn't resolve over time, and in some cases it worsens. Neuropathic pain has increasingly been recognized as an important contributor to suffering, poor rehabilitation outcomes and reduced quality of life. Medication fails to provide sufficient relief and has side effects, which makes the search for non-pharmacological interventions important. Different non-invasive neuromodulation techniques via peripheral or central electrical stimulation, such as transcranial Direct Current Stimulation (tDCS), have been used. However, their effectiveness is still limited and controversial. According to a recent meta-analysis, persons with SCI have an average pain reduction of 1.33 units on a 0 – 10 visual analog scale (VAS) after the 5 or 10 days of tDCS treatment.

Electrical stimulation (EStim) therapy, which uses small electrodes to send electrical currents through the skin to target certain muscle groups or nerves, has a broad range of applications in rehabilitation to achieve functional and therapeutic goals, from spasm relaxation to pain management. However, traditional EStim functions more locally and the effect is short-lasting. The analgesic effect is usually limited to the treated area

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The Role of Mitochondrial Dysfunction in the Neurobiological Basis of Bipolar Disorder

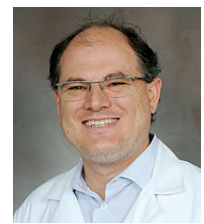
Giselli Scaini, PharmD, MS, PhD, Gabriel R. Fries, PhD, João L. de Quevedo, MD, PhD



Scaini



Fries



de Quevedo

Abstract: Bipolar disorder (BD) affects approximately 4.8% of the population, which results in significant costs to the healthcare system in the United States and is associated with high morbidity and mortality. BD involves a complex pathology with several biological pathways, including the interaction of molecular, cellular, and behavioral mechanisms with susceptibility genes, environmental stressors, and biological mechanisms such as mitochondrial dysfunction. Several studies have demonstrated that a viable pool of mitochondria is fundamental for cellular metabolism and neuronal survival and that this mitochondrial pool plays critical roles in adult neurogenesis, a vital process for hippocampal function and the formation of new episodic memories. Therefore, we aimed to understand how mitochondrial quality control contributes to cell survival and death in BD.

Bipolar disorder (BD) is a severe and disabling condition that affects around 1-4% of the population and is associated with high morbidity and mortality. Among 14-59% of individuals with BD report suicidal ideation, with 25-50% attempting suicide, and almost 20% dying from suicide. BD is characterized by changes in mood that alternate between mania or hypomania, depression, and mixed states, often associated with functional impairment. The clinical hallmark of the BD diagnosis is the presence of manic or hypomanic episodes. During the episode of mania or hypomania, patients can present symptoms related to elevated mood, including euphoria, feelings of greatness, hyperactivity, increased sexual activity, decreased need for sleep, risky behaviors, irritability, and aggression. On the other hand, episodes of depression are characterized by symptoms of anhedonia (an inability to feel pleasure), sadness, vegetative

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Director's Column - Virtual Neuroscience

From the Director, John. H. Byrne, PhD



These are certainly unprecedented times. As I write this column, it is summer in Houston, COVID-19 cases have risen in our city, and the start of a new academic year is upon us. Traditionally, this is a time of great anticipation, where new graduate students begin their training, and faculty and research staff return from summer conferences and

workshops invigorated with new ideas to push the frontiers of neuroscience research. This year however, resiliency planning and flexibility are at the forefront of our preparations for an uncertain period of virtual neuroscience.

It is fair to say that COVID-19 has had a disastrous effect on neuroscience research and biomedical research in general. Labs have been forced to weather months-long closures at most universities across the United States and around the world. Graduate training has also been severely affected with classes either cancelled or moved exclusively online, along with departmental seminar series. The entire research and academic environment has been greatly interrupted, with a disproportionate negative effect for female scientists, scientists that work in the lab, and those that have young children at home (Myers et al., 2020, *Nat Hum Behav*).

Following suit, spring and summer conferences and workshops have been cancelled or changed to virtual formats. For example, the Society for Neuroscience cancelled their annual, highly attended meeting this fall. Cold Spring Harbor Laboratory, which is known for hosting multiple courses and meetings throughout the year, and excels at creating personal connections and collaborations, has decided to shift many of their events online. In addition, the Federation of European Neuroscience Societies (FENS) hosted their annual meeting as a Virtual Forum through an online platform. Of benefit to those who attended this conference virtually, FENS has made the content available for three months online, allowing participants to attend more symposia than they could have in person. Sessions still included live Question and Answer portions, and posters were interactive, allowing live-chat with the authors. Many networking and development sessions were included as well. It is entirely possible that many of these new virtual accommodations become permanent fixtures of large-scale conferences moving forward.

While some changes have been easier to navigate than others, there are certainly instances where the advantages of the in-person component cannot be replicated. For example, NIH study sections and other review groups have gone virtual, but they have been challenging not having the face-to-face interactions. At a recent study section meeting that I attended, we were given extra breaks to reduce "Zoom fatigue." Although video conferencing platforms have allowed us to keep our scientific and educational missions moving forward, zoom fatigue is real. In addition, these platforms cannot help with hands-on lab work that frequently involves small groups of scientists working in close proximity. At the new virtual scientific conferences and

meetings, what will substitute for those hallway and meal-time discussions, and the beer with a colleague after an afternoon session?

We all look forward to the day when we can return to something approaching pre-COVID times. Here is where a massive investment in biomedical research is necessary to stop COVID-19, and, in general, protect society from future pandemics. Part of that investment should be to examine the effects of COVID-19 on the brain. Finally, we will need support from the NIH and other state and federal agencies to provide funds to stimulate research programs and thereby help make up for the lost productivity caused by COVID-19.

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At the local level, task force committees across UTHealth have been created to best determine how to safely proceed with education, research and training in the current dynamic environment, and as classes resume in the fall. All six UTHealth schools, along with Auxiliary Enterprises, the Office of Postdoctoral Affairs, the Office of International Affairs, and our administrative support teams have worked cooperatively to find solutions to minimize the disruptions.

On the educational front, this past spring, lectures and seminar courses were rapidly transitioned to virtual classrooms with great success, due to enormous efforts from the faculty and the previous online availability of many components including lecture videos of medical school courses. New guidelines were also made for laboratory research. For example, researchers were and remain required to wear face masks and social distance within their own lab space. Limits have been placed on the number of individuals who can be in the lab at any given time. To accommodate these restrictions, lab members are required to work in shifts, which include evenings and weekends, resulting in great disruptions to graduate student and postdoctoral research projects. While researchers maintain these social distancing guidelines, leaders are working to ensure support and oversight for all lab members and staff. One example is that the MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences is asking for faculty to privately arrange work schedules and meetings based on the needs of those in their research labs and where possible, advisors have been encouraged to identify a senior lab member who can be present in the same shift as more junior lab members. In addition, reopened labs are adjusting their research projects to ones that require less team interactions, as additional disruptions are expected for the remainder of the year.

Clinical neuroscience has also seen major shifts. In some cases, recruiting healthy subjects for clinical research has been challenging as fewer people feel comfortable participating during this time. Our department of psychiatry and behavioral sciences, as well as other clinical departments at UTHealth, have rapidly embraced the use of telemedicine. Most of their patients were quickly converted to this platform, allowing for increased

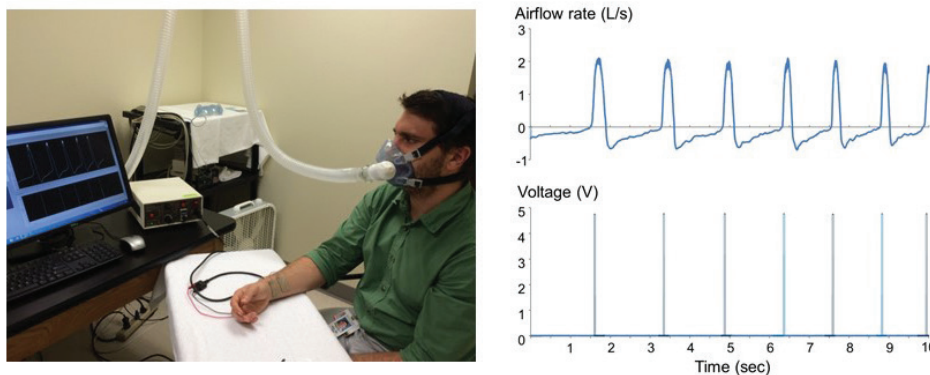
access and continuum of care, despite a worldwide pandemic and need for social distancing. Even though it took great effort to install these measures, the added value can be considerable and long-lasting. Of particular benefit to our local community, this department generously offered free telemedicine sessions to all employees and trainees of UTHealth. In addition, Salih Selek, MD, and Scott Lane, PhD, are leading an online study titled, "UTHealth Community Attitudes Toward COVID-19 and Mental Well-Being," which aims to better understand how the pandemic has affected UTHealth faculty, students, and staff, including how often they feel stressed, anxious, or depressed, their personal social distancing efforts, sleep habits, and daily news consumption.

At the NRC, we are making necessary alterations to our events for the 2020-2021 academic year. Our annual Neurobiology of Disease Course, traditionally held in-person at the McGovern Medical School in the fall, will be held virtually this year. This is the case for most graduate courses being held this fall at UTHealth. In addition, our Distinguished Lecture in the Neurosciences has been moved from October 2020 to May 2021. Updates to our other fall 2020 events, including the multi-institution Neuroscience Poster Session, are pending. We will continue to evaluate and update as needed.

During these difficult times, it has been encouraging to see how everyone at UTHealth has come together to help one another. May this sense of community continue long after this pandemic.

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Figure 1. BreESTim Experimental Setting.



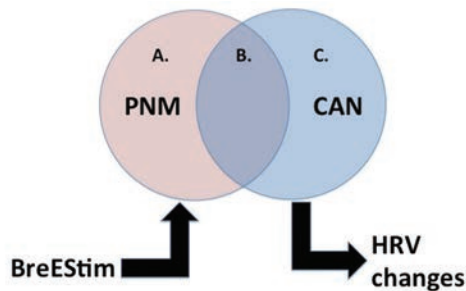
This figure depicts the experimental setting with the BreESTim treatment. A subject breathes through a facemask (left panel) to collect breathing signals. When the airflow rate (right upper panel) reaches a predetermined threshold, the central controller sends a command to the electrical stimulator leading to subsequent electrical stimulation delivered through the surface electrode to the median nerve transcutaneously (right lower panel).

or limb and lasts about an hour. Based on discoveries about the systemic effects of voluntary breathing and the physiological interactions among body systems during voluntary breathing, we have invented a protocol called BreESTim – breathing-controlled electrical stimulation – to augment the effects of electrical stimulation in patients with spasticity and neuropathic pain. Briefly, in the BreESTim treatment (Fig. 1), a single-pulse of painful electrical stimulus is triggered and delivered to the target area when the air flow rate of each individual breath reaches a certain threshold during forceful voluntary inhalation. Patients themselves control the intensity of electrical stimulation, to increase the intensity gradually to a painful, but tolerable level. As compared to conventional electrical stimulation, the novelty of BreESTim is that electrical stimulation is delivered only during the window of voluntary inhalation.

We have tested BreESTim in a series of studies, comparing the effects of EStim-only or Breathing-only. We compared the electrical pain threshold between BreESTim and EStim after one session of treatment in pain-free healthy subjects in a cross-over design. All subjects received both BreESTim and EStim to the median nerve at the wrist of the dominant side in a random order with at least one week apart. The intensity and dose of electrical stimulation were comparable between BreESTim and EStim. We observed an increase in the electrical pain threshold in the hands on both the treated side and contralateral side after the BreESTim treatment, but no change in either hand after the EStim treatment.

We also tested the pain-free healthy subjects with BreESTim vs Breathing-only using the same experimental design. The results consistently showed electrical pain threshold increased only with BreESTim treatment. Subsequently, we further compared the analgesic effects between EStim and BreESTim in a cohort of SCI subjects (paraplegia or tetraplegia) with chronic neuropathic pain (Li et al., 2016, *J Pain Res*). On average, reduction in VAS was 2.6 for 14.2 hours after BreESTim treatment, while it was 0.8 for 1.9 hours after EStim. The results confirmed that BreESTim had a better and longer-lasting analgesic effect as compared to EStim.

Collectively, these results suggest that BreESTim has systemic de-sensitization effects for analgesia. The analgesic effect of BreESTim is attributed to intrinsic physiological interactions between the respiratory and sensory/pain systems that are activated and integrated by coupling of electrical stimulation during this particular window of voluntary inhalation. Distinctly different from autonomic breathing, during voluntary breathing, such as talking and singing, humans voluntarily suppress autonomic breathing by activating the cortical respiratory center of the brain. These same cortical and subcortical areas that are activated during voluntary breathing are also involved with muscle tone, posture, mood, pain, speech, heart beats and other functions. For example, the insula and anterior cingulate cortex (ACC) are activated during voluntary breathing, among other brain areas, according to brain imaging studies. The ACC and

Figure 2. Illustration of Interactions Between Pain Neuromatrix (PNM) and Central Autonomic Network (CAN).

(A) Upon pain induction, the PNM is diffusely activated. It is susceptible to BreEstim influence. (B) The PNM–CAN of shared structures, such as the insula and ACC, are specifically activated in chronic SCI. (C) The CAN helps regulate the autonomic system. BreEstim is expected to modulate the PNM, including the shared PNM–CAN areas, to produce analgesic effects, and thus changes in heart rate variability (HRV) parameters as well.

the insula are also known to selectively process the aversive quality of noxious stimulation, but do not influence sensation of the stimulation. When aversive stimulation is delivered during activation of the insular cortex, item-specific anterograde amnesia to the stimulation occurs. In other words, the memory of the noxious stimulation is impaired or “forgotten” after BreEstim. Subsequently, the feeling of noxious stimulation is altered and habituated, leading to analgesic effects of BreEstim. Findings of concomitant changes of autonomic function with induced analgesia further support the response of the insula and ACC during BreEstim (see details below). As such, BreEstim likely integrates several internal coping mechanisms, including: 1) activation of internal pain modulation mechanisms; 2) electrical stimulation effect; 3) anterograde amnesia of pain stimulation; 4) habituation of aversive stimuli; 5) central neuromodulatory mechanisms. As a result, BreEstim increases pain threshold and pain tolerance, resulting in analgesic effects.

Some voluntary breathing-activated brain areas, such as the insula and ACC are involved in both the pain neuromatrix and the central autonomic network (Fig. 2). Due to shared areas in both networks, people demonstrate autonomic responses when anticipating pain or experiencing pain. An example of this would be changes in skin blood flow. It is therefore expected that analgesic effects could be accompanied by modulation of autonomic functions. Heart rate variability (HRV), the physiology variance in the inter-beat intervals, is a tool for quantitative assessment of autonomic function. Furthermore, an increasing number of studies have supported HRV as a potential biomarker for pain.

To further investigate whether BreEstim-induced analgesic effects are accompanied by modulation of the above mentioned shared pain and autonomic networks, we compared changes in the pain scale (VAS) and HRV parameters between BreEstim and Breathing-only treatments in a cohort of SCI subjects with chronic neuropathic pain (SCI+NP) in a cross-over design (Karri et al., 2018, *J Pain Res*). In this study, SCI+NP subjects wore the same facemask during both Breathing-only and BreEstim treatments on separate days with an interval of a week. The only difference was that subjects received an electrical stimulation in the BreEstim treatment, while no electrical stimulus was delivered in the Breathing-only treatment. The BreEstim treatment produced analgesic effects with concomitant increase in parasympathetic functions, while no effects on neuropathic pain or HRV parameters were observed after the Breathing-only treatment. The results support the association between pain and autonomic networks and BreEstim-induced modulation in these

networks. In other words, pain reduction is accompanied by restoration of autonomic balance in SCI+NP subjects.

An interesting set of results were observed when we compared the analgesic effects and associated HRV changes between SCI+NP subjects and pain-free healthy subjects after the active BreEstim treatment (Karri et al., 2019, *Neuromodulation*). As expected, BreEstim produced pain reduction in SCI+NP subjects and increased pain threshold in pain-free healthy subjects. Pain reduction in SCI+NP subjects was associated with increased parasympathetic function, however there was no HRV changes in healthy subjects. This study further suggests that the shared areas of pain and autonomic networks had maladaptive plasticity in SCI subjects with chronic neuropathic pain. It also indicates that their dysfunction could be modulated by BreEstim.

Taken together, our series of studies demonstrate that BreEstim produces effective analgesic effects with restoration of autonomic dysfunction via central neuromodulatory mechanisms. In our on-going study on the long-term effect of BreEstim treatment, the pilot data showed that neuromodulatory effect of BreEstim could be accumulated and result in prolonged analgesic effects over a week after the 10-day treatment. BreEstim has potential to be an effective neuromodulation technique for management of neuropathic pain after spinal cord injury.

Acknowledgement: Research studies were supported in part by grants from Mission Connect, a program of TIRR Foundation, and NIH/NICHD/NCMRR R21HD087128

Disclosure: Sheng Li holds the following two BreEstim patents: U.S. Patent No. 8,229,566 “Method and Apparatus of Breathing-Controlled Electrical Stimulation for Skeletal Muscles”, issued on 7/24/2012; U.S. Patent No. 8,588,919 “Method and Apparatus of Breathing-Controlled Electrical Stimulation for Skeletal Muscles” Divisional of Application No. 12/146,176 (issued as U.S. Patent 8,229,566).

About the Author

Sheng Li, MD, PhD, is a professor of Physical Medicine and Rehabilitation, Attending Physician at TIRR Memorial Hermann Hospital, and Director of Neurorehabilitation Research Laboratory. Dr. Li received his MD from Beijing Medical University, Beijing, China. He obtained his PhD in Kinesiology from The Pennsylvania State University, and subsequently completed a postdoctoral research fellowship in Neurorehabilitation at Rehabilitation Institute of Chicago with a focus on spasticity management and stroke rehabilitation. Dr. Li's primary clinical focus is spasticity management and neurorehabilitation after neurological impairments.

grants & awards

Congratulations to the 76 NRC Faculty Members, from 10 different departments, that received the 2020 Dean's Teaching Excellence Award. For a complete list, please visit our website.

Hyochol "Brian" Ahn, PhD, Theodore J. and Mary E. Trumble Professor in Aging Research, UTHealth School of Nursing, has recently received two grants from the NIH/NINR for projects entitled, "Self-Administered Transcranial Direct Current Stimulation for Pain in Older Adults with Knee Osteoarthritis: A Phase II Randomized Sham-Controlled Trial," and "Combination Therapy of Home-based Transcranial Direct Current Stimulation and Mindfulness-based Meditation for Self-management of Clinical Pain and Symptoms in Older Adults with Knee Osteoarthritis." He is also the subcontract PI on a grant from the NIH/NIA to examine "Ethnic Differences in Responses to Painful Stimuli." Dr. Ahn is also a Co-Investigator, with PI **Melba Hernandez-Tejada, PhD**, associate professor of psychiatry and behavioral sciences, on a grant from the department to study the "Management of Chronic Pain and PTSD in Gulf War Veterans with tDCS+Prolonged Exposure."

Leomar Y. Ballester, MD, PhD, assistant professor of pathology and laboratory medicine, and **Yoshua Esquenazi, MD**, assistant professor of neurosurgery, received an award from the UTHealth Center for Clinical and Translational Sciences (CCTS) Pilot Project Awards Program to study the relationship between glioma and the gut-brain axis.

Spiros Blackburn, MD, associate professor of neurosurgery, with Co-Investigator, **Roy F. Riascos-Castaneda, MD**, professor of diagnostic and interventional imaging, received grant funding from PILLAR-XT for their project, "Automation of Extracorporeal Filtration of Subarachnoid Hemorrhage via Spinal Catheter Extension."

Peng R. Chen, MD, associate professor of neurosurgery, received a grant from the NIH/NINDS for a machine learning study, "Non-invasive Detection of Cerebral Aneurysm Recurrence after Endovascular Treatment Using Automated Image Processing."

April Crawford, PhD, associate professor and director of strategic initiatives & program implementation at the Children's Learning Institute (CLI), received a grant from the Texas Workforce Commission and The Elkins Foundation to teach the latest child development strategies to more than 850 infant and toddler specialists and teachers working in at-risk communities in Texas.

Valentin Dragoi, PhD, Rochelle and Max Levit Distinguished Professor in the Neurosciences, department of neurobiology & anatomy, received the NIH BRAIN Initiative Award (NINDS) for his project, "Optogenetic Manipulation of Cortical Feedback to Examine Network Function and Behavior." In addition, Dr. Dragoi also received the University of Texas Systems STARS Award for support for equipment and lab infrastructure.

Gabriel R. Fries, PhD, assistant professor of psychiatry and behavioral sciences, recently received an Institutional Scholar

Award for a project titled, "Neuronal DNA Methylation Biosignature of Suicide in Bipolar Disorder" from the UTHealth CCTS. He also received the CCTS Pilot Award for his project, "Accelerated Aging in Bipolar Disorder: Translating Findings from the Clinic to the Laboratory."

Bhanu Priya Ganesh, PhD, assistant professor of neurology, received funding from the NIH/NINDS for their project, "Mast Cell Signaling Connects the Brain and Gut Post-Stroke."

Georgene W. Hergenroeder, PhD, associate professor of neurosurgery, received funding from the NIH/NINDS for her project, "Discovery of Biomarker Signatures Prognostic for Neuropathic Pain after Acute Spinal Cord Injury."

Juan J. Herrera, PhD, assistant professor of diagnostic and interventional imaging, received a grant from Lexicon Pharmaceuticals to examine drug efficacy for the treatment of pain after spinal cord injury. He also received a grant from Hope Bioscience for a project entitled, "Attenuating Allodynia Following Spinal Cord Injury by Adipose-Derived Mesenchymal Stem Cells (HB-AdMSC) Treatment."

Cameron B. Jeter, PhD, associate professor of diagnostic and biomedical sciences at the UTHealth School of Dentistry, received the Geriatric Research Program for Junior Faculty award to study the oral microbiome in patients with dementia from the Harry E. Bovay Jr. Foundation.

Arash Kamali, MD, assistant professor of diagnostic and interventional imaging, received the 2020 Dean's Research Award for the medical student summer research program at UTHealth. In addition, he was given an award, as one of the top 33 academic faculty researchers in the USA, to attend the Academy Council for Early Career Investigators in Imaging (CECI2) class of 2020 in Washington, DC in May.

Balveen Kaur, PhD, professor of neurosurgery, received a grant from the Beckman Institute Research of the City of Hope for her project, "Overcoming Barriers of Virotherapy by Next-Generation oHSV Expressing E-Cadherin." In addition, Dr. Kaur received funding from the NIH/NINDS for their project titled, "Optimizing Oncolytic Virus Therapy for Glioblastoma."

Scott D. Lane, PhD, professor of psychiatry and behavioral sciences, and **Consuelo Walss-Bass, PhD**, professor of psychiatry and behavioral sciences, received a grant from the McManus Charitable Trust for a project titled, "In vitro and in vivo Evidence of Neurotoxicity in Substance Abuse." In addition, Dr. Lane and **Joy M. Schmitz, PhD**, professor of psychiatry and behavioral sciences, received a four-year grant from the NIH/NIDA for a project entitled, "Pioglitazone as an Adjunct to CBT for Cocaine Relapse Prevention and Neuroprotection."

grants&awards

Ying Liu, MD, PhD, assistant professor of neurosurgery, received funding from the NIH/NINDS for her project titled, “Reconnecting the Injured Cervical Spinal Cord by Transplanted Human iPSC-Derived Neural Progenitor.”

Devin W. McBride, PhD, assistant professor of neurosurgery, received support from the Brain Aneurysm Foundation for his grant, “Preventing Platelet Activation Improves Function after Subarachnoid Hemorrhage in Mice.”

Louise D. McCullough, MD, PhD, Roy M. and Phyllis Gough Huffington Distinguished Chair and professor of neurology, received the American Heart Association’s prestigious Merit Award to investigate whether the maternal microbiome influences stroke risk in offspring. In addition, Dr. McCullough, along with Robert Bryan, PhD (Baylor College of Medicine), was awarded a grant from the NIH to study the gut-brain connection in dementia and aging.

Rodrigo F. Morales, PhD, associate professor of neurology, has recently received two grants for his work examining infectious prions. From the NIH/NIAID, he received an award to assess shedding, retention and spreading of chronic wasting disease prions in the environment. Support from the Creutzfeldt-Jakob Disease Foundation will allow his group to explore the zoonotic potential of porcine-derived materials from animals exposed to infectious prions.

Scott D. Olson, PhD, assistant professor of pediatric surgery, along with co-investigator Caleb J. Bashor, PhD (Rice University), received an NIH/NINDS grant for a project titled, “Reshaping MSC Surface Expression Profiles to Target Inflammation Following CNS Trauma.”

Alan R. Prossin, MBBS, assistant professor of psychiatry and behavioral sciences, received a five-year grant through the NIH Helping to End Addiction Long-term Initiative (HEAL) to discover which proteins in a patient’s blood can be a predictor of pain after surgery.

João L. de Quevedo, MD, PhD, professor of psychiatry and behavioral sciences, received funding from the NIH/NIMH for a grant titled, “Neural-Derived Extracellular Vesicles MicroRNAs in Bipolar Disorder: A Peripheral Window Into the Brain.”

Roy F. Riascos-Castaneda, MD, professor of diagnostic and interventional imaging, with Kirk Roberts, PhD, assistant professor at UTHealth School of Biomedical Informatics, received an NIH grant for their project titled, “Fine-Grained Spatial Information Extraction for Radiology Reports.”

Yanning Rui, PhD, assistant professor of neurosurgery, received funding from the NIH/NINDS for her project titled, “Role of Autophagy in THSD1-Mediated Intracranial Aneurysm.”

David I. Sandberg, MD, professor of pediatric neurosurgery and co-director of the Pediatric Brain Tumor Program at the University of Texas MD Anderson Cancer Center, received the 2020 Houston Men of Distinction Annual Award, a research award that will support his work on local drug delivery into the brain to treat recurrent malignant brain tumors in children.

Amrou Sarraj, MD, associate professor of neurology, received the prestigious “Stroke Care in Emergency Medicine Award” from the American Stroke Association for his project, “Optimization Methodologies to Enhance Endovascular Thrombectomy Access in the United States.” In addition, Dr. Sarraj, along with Co-Investigator **Clark Sitton, MD**, associate professor of diagnostic and interventional imaging, received funding from SELECT 2 for their project, “A Randomized Controlled Trial to Optimize Patient’s Selection for Endovascular Treatment in Acute Ischemic Stroke.”

Giselli Scaini, PharmD, PhD, instructor of psychiatry and behavioral sciences, recently won a travel fellowship award from the Society of Biological Psychiatry (SOBP). Recognizing the importance of training a new generation of psychiatric academics, the SOBP awards the travel fellowship to an early career investigator annually.

Sudhakar Selvaraj, MD, PhD, assistant professor of psychiatry and behavioral sciences, received grant funding from the NIH/NIMH for a grant entitled, “TMS-EEG Investigation of Prefrontal Cortical Excitability in Depression and rTMS treatment Response.” Raymond Cho, MD, from Baylor College of Medicine, is the PI.

Rachael Sirianni, PhD, assistant professor of neurosurgery, received a grant from the Morgan Adams Foundation for her project, “Biomimetic Microenvironments to Model Leptomeningeal Metastasis in Pediatric Neuro-Oncology.” Dr. Sirianni also received funding from the NIH/NINDS for the project, “Targeting Leptomeningeal Metastasis in Medulloblastoma,” and from the National Institute of Child Health & Human Development for the project, “Intrathecal Delivery of Radiation Sensitizing Nanoparticles in Pediatric Neuro-Oncology.”

Claudio Soto, PhD, professor of neurology, received a grant from the NIH/NIA entitled, “Comprehensive Diagnosis of Alzheimer’s Disease by Detection of Misfolded Oligomers in Biological Fluids.” He also has received funding from the Michael J. Fox Foundation for the project, “Differential Diagnosis of Parkinson’s Disease and Multiple System Atrophy by Detection of Conformational Strains of Misfolded Alpha-Synuclein.”

Argy Stampas, MD, assistant professor of physical medicine and rehabilitation, recently received a grant from the Craig H. Neilsen Foundation for a project titled, “Transcutaneous Tibial Nerve Stimulation for Spinal Cord Injury Neurogenic Bladder.” Dr. Stampas also received funding from the Administration for Community Living, National Institute on Disability, Independent Living, and Rehabilitation Research for his project titled, “Rehabilitation Research and Training Center on Health and Function for People with Physical Disabilities Focused on Neurogenic Lower Urinary Tract Dysfunction.” In addition, he has received funding through the UTHealth KL2 Award and Mission Connect, a project of the TIRR Foundation, for his project, “Reducing Anticholinergic Bladder Medication Use in Spinal Cord Injury with Home Neuromodulation.”

Nitin Tandon, MD, professor and vice chair of neurosurgery, received a grant from the NIH/NINDS for a project titled, "A Unified Cognitive Network Model of Language."

Andrey Tsvetkov, PhD, assistant professor of neurology, received a grant from the NIH/NINDS for the study of "Nuclear Sphingosine Kinase 2 in Huntington Disease." He also received funding from the NIH/NIA to study "NAAG Peptidase, Chemobrain, and Alzheimer's Disease."

Akihiko Urayama, PhD, assistant professor of neurology, received funding from the NIH to examine the brain's clearance system in order to understand how to reverse age-related inflammation, treat vascular dementia and enhance recovery after brain injury.

Jiaqian Wu, PhD, associate professor of neurosurgery, received a grant from the NIH/NINDS for her project, "Delineating the Heterogeneity of Reactive microAstrocytes in Spinal Cord Injury."

Jay-Jiguang Zhu, MD, professor and director of neuro-oncology, with Xiaobo Zhou, PhD, professor at UTHealth School of Biomedical Sciences, received funding from the National Cancer Institute for a study titled, "A Quantitative Imaging Informatics System for Understanding Pseudo/True Progression" in glioblastoma patients.

POSTDOCS AND GRAD STUDENTS

Fan Bu, PhD, under the mentorship of **Jun Li, PhD**, associate professor of neurology, received the American Heart Association Postdoctoral Fellowship for their project titled, "The Role of Endothelial Ras-Related C3 Botulinum Toxin Substrate 1 (Rac1) in Post-Stroke Recovery and Angiogenesis."

Natasha Kharas, an MD/PhD candidate in the laboratory of **Valentin Dragoi, PhD**, professor of neurobiology and anatomy,

is the second recipient of the Terry J. Crow, PhD Scholarship in Neuroscience, an award established in honor of the late Dr. Crow, professor emeritus in the Department of Neurobiology and Anatomy at McGovern Medical School.

Monica Goss, PhD, under mentorship of **Sean Marrelli, PhD**, professor of neurology, received a Postdoctoral Research Fellowship from the American Heart Association for her project titled, "Regulation of Leptomeningeal Collaterals by the Endothelial Mechanosensor, Piezo1."

Emily Mendez, a UTHealth GSBS MD/PhD candidate, with mentors **Consuelo Walss-Bass, PhD**, and **Scott D. Lane, PhD**, received an NIH/CCTS TL1 fellowship award for her project entitled, "Investigating Human Neuron-Specific Gene Expression Signatures of Cocaine-Induced Neurotoxicity in Postmortem Brain and Induced Pluripotent Stem Cell-Derived Neurons."

Alexandre Paim Diaz, MD, PhD, a postdoctoral research fellow with mentor, **Jair C. Soares, MD, PhD**, professor and chairman of psychiatry and behavioral sciences, received the New Investigator Award from the International Society for CNS Clinical Trials and Methodology (ISCTM), which aims to raise up the next generation of leaders focused on the critical aspects of clinical trials design in CNS drug development.

Heather Soder, PhD, a postdoctoral fellow with mentors **Scott D. Lane, PhD**, and **Joy M. Schmitz, PhD**, received a two-year grant from the NIH/NIDA for her project, "Developing Adaptive Interventions for Cocaine Cessation and Relapse Prevention via Neuroimaging."

Nicole Stephens, a graduate student in the laboratory of **Cameron B. Jeter, PhD**, received the Legacy Scholarship from the Army Women's Foundation in support of her graduate studies.

UTHEALTH NRC BRAIN AWARENESS OUTREACH AWARD

This annual award honors a graduate student in the MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences who has exhibited an exceptional interest and effort in brain awareness and neuroscience outreach activities. This year, two outstanding students received this award.



Melissa Franch

Ms. Franch has exhibited exceptional outreach efforts and service to her community through membership on the GSBS Neuroscience Program Student Council, by volunteering at the NRC Brain Night for Kids and GSBS Science Night, and for her roles as a Teaching Assistant for both the UTHealth School of Dentistry Neuroanatomy course and GSBS Summer Biomedical Academy. She is a passionate advocate for Autism Spectrum Disorder and Mental Health Disorders. Ms. Franch is a PhD candidate in the Neuroscience Program, conducting research in the laboratory of Valentin Dragoi, PhD (Neurobiology & Anatomy).



Jamie Wright

Ms. Wright is a fervent volunteer in the Hydrocephalus community. She founded the Houston Hydrocephalus Association Community Network, and has been a part of the planning committee for the annual Houston WALK to End Hydrocephalus since it started eight years ago. She has traveled to Haiti to help treat children with hydrocephalus alongside neurosurgery teams from Children's Memorial Hermann Hospital and UT Health McGovern Medical School. She has actively served on the Hydrocephalus Association Patient Partner Committee, the Hydrocephalus Association Translate to Transform Planning Committee, and has been a Consumer Reviewer for the Department of Defense Peer Reviewed Medical Research Program. Ms. Wright is an MD/PhD student in the Neuroscience Program, conducting research with her faculty mentor, Dianna Milewicz, MD, PhD (Internal Medicine - Medical Genetics).

In the Spotlight

26th Annual Neuroscience Poster Session Saturday, December 7, 2019 UTHealth Cooley University Life Center

The NRC was pleased to host the 26th Annual Neuroscience Poster Session. This year, for the first time, undergraduate students from the Rice University Department of BioSciences joined our diverse group of postdoctoral fellows, graduate and medical students, and other researchers from throughout UTHealth, the Department of Neuroscience at Baylor College of Medicine, and the Departments of Biosciences, Psychology, and Electrical and Computer Engineering at Rice University. Eighty research posters were presented to faculty judges from each institution and prizes were awarded for the best poster presentations in each category. Local businesses and restaurants generously provided door prizes and gift certificates for those presenting posters.

Congratulations to all of the winners from the 21st Annual Neuroscience Poster Session!

FOR A COMPLETE LIST OF WINNERS, PLEASE VISIT OUR WEBSITE.



Jonathan Flynn, PhD, assistant teaching professor at Rice University, posing with the three award winners from Rice University's Neuroscience Program in the Department of BioSciences.



Group photo of presenters from all three institutions.



Group photo of faculty judges from all three institutions.



The NRC Reception at the 49th annual meeting of the Society for Neuroscience was held on October 22, 2019 at the Chicago Yacht Club. This casual event brings together past and present UTHealth NRC members, grad students and postdocs to provide a means of promoting collaborations and scientific exchange.

news & information

Please visit our website for a list of recent publications from UTHealth NRC Faculty Members.

Cesar Arias, MD, PhD, Margaret and Herbert DuPont Chair in Infectious Disease and professor of internal medicine, has been named the editor-in-chief of *Antimicrobial Agents and Chemotherapy*, an interdisciplinary journal produced by the American Society for Microbiology.

The Association of Academic Psychiatrists (AAP) has named **Gerard E. Francisco, MD**, professor and chair of the department of physical medicine & rehabilitation (PM&R), as its 2020 Distinguished Academician. Dr. Francisco received the award for achieving distinction and peer recognition by virtue of excellence as a teacher, researcher, and administrator. He was presented the award at the 14th ISPRM World Congress and 53rd AAP Annual Meeting.

A recently published paper from **David W. Marshak, PhD**, professor of neurobiology and anatomy, and colleagues, was featured on the cover of the *Journal of Comparative Neurology*, a leading neuroanatomy journal. The paper is titled, "Wide-field amacrine cell inputs to ON parasol ganglion cells in macaque retina."

Amrou Sarraj, MD, associate professor of neurology, earned the Italian Society of Neurology (SIN) Article of the Month for December 2019. Dr. Sarraj's paper "Optimizing patient selection for endovascular treatment in acute ischemic stroke (SELECT): A prospective, multicenter cohort study of imaging selection," was

originally published in the *Annals of Neurology*.

The National Network of Depression Centers (NNDC) elected **Jair Soares, MD, PhD**, Pat R. Rutherford, Jr. Chair in Psychiatry, to its executive committee. The NNDC aims to reduce suffering from depression through the power of networking. The organization connects members to advance scientific discovery and to provide stigma-free, evidence-based care to patients with depressive and bipolar illnesses.

Cesar A. Soutullo, MD, PhD, professor of psychiatry and behavioral sciences, is Co-investigator of the Texas Child Mental Health Care Consortium, funded by Senate Bill 11, to foster collaboration among our state medical schools, promote and coordinate mental health research, and help address workforce issues. The Site PI is **Jair Soares, MD, PhD** and the Network PI is Madhukar Trivedi, PhD, from UT Southwestern.

Barbara J. Stoll, MD, the H. Wayne Hightower Distinguished Professor, stepped down as dean of the McGovern Medical School at UTHealth at the end of June. The entire UTHealth community is grateful for her outstanding contributions and advancement of the school through her oversight of the implementation of new curriculum and faculty recruitment.

The UTHealth School of Public Health and UT Austin College of Pharmacy are partnering to offer students the opportunity to earn a Master of Public Health (MPH) while pursuing their Doctor of Pharmacy (PharmD) degree. This is the first PharmD-MPH program in the state of Texas.

CONTINUED FROM PAGE 1: SCAINI, FRIES & DE QUEVEDO

symptoms, and psychomotor retardation. Mixed episodes manifest as simultaneous states of mania and depression.

Several studies have proposed that BD is a progressive condition, and the delay in the diagnosis and unsuitable treatment can result in recurring mood episodes, persistent subthreshold symptoms, development of co-morbidities, and progression of the disease with cognitive impairment and functional decline. The last few years have witnessed significant progress in the understanding of BD pathophysiology, although its precise etiopathology remains unknown. Several studies have suggested that the pathophysiology of BD is orchestrated by several mechanisms, including multiple genetic, neurochemical, and environmental factors that act synergistically.

Multiple studies over more than 50 years have highlighted mitochondrial dysfunction as a common pathway in BD's pathophysiology, supporting the "mitochondrial hypothesis". Mitochondria are more than just the powerhouse of the cell. They are intimately embedded in signaling cascades and programs that operate within the cell, and are considered a central platform in the execution of diverse cellular events. When mitochondria are functional, fusion and fission of mitochondria occur in a constant and balanced manner to adapt to environmental,

metabolic, and neuroendocrine stressors and stress mediators. As soon as individual parts of the mitochondria pool turn dysfunctional, damaged mitochondria become spatially isolated and can be distinguished on a morphological basis from the rest. This leads to degradation by a selective process, called mitophagy, in order to minimize accumulation of cellular debris and subsequent damage. This mitochondrial quality control mechanism is of particular importance for post-mitotic tissues such as neurons and muscle cells, and the impairment on this machinery has been associated with normal aging and correlated with the development of a wide range of age-related diseases.

Given the need to establish a complete picture of the relevant processes and alterations in mitochondrial pathways that result in BD, our research group at the Translational Psychiatry Program at the Faillace Department of Psychiatry and Behavioral Sciences at McGovern Medical School of UTHealth is performing studies to delineate if changes in mitochondrial dynamics and function might affect multiple cellular processes, which could determine disease progression and severity, as well as premature aging observed in BD. Through a series of studies (Fries et al., 2019, *Bipolar Disord*; Scaini et al., 2018, *Neuropsychopharm*; Scaini et al., 2017, *Transl Psychiatry*; Fries et al., 2017, *Transl Psychiatry*) our work has suggested that patients

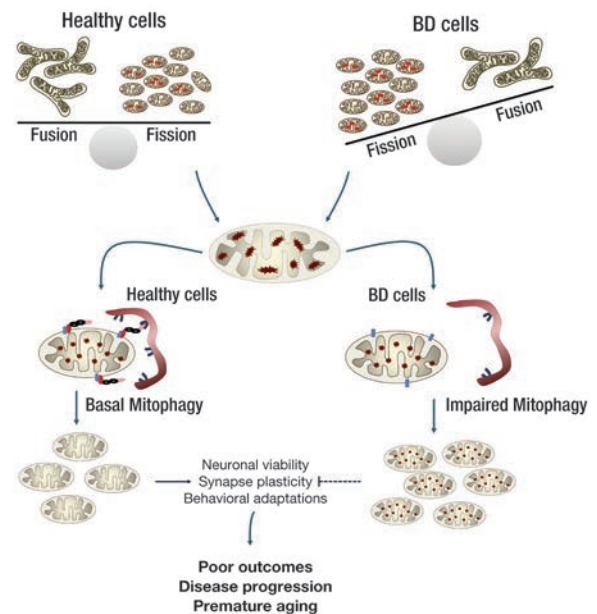
with BD present an impairment of mitochondrial breakdown signaling through the mitochondrial quality control failure, which is correlated with poor outcomes. We have found that the levels of proteins governing mitochondrial fission and fusion are significantly altered in BD, causing an imbalance in mitochondrial fission and fusion towards fission, culminating in an increase in mitochondrial fragmentation. Furthermore, reduced levels of proteins responsible for the removal of damaged mitochondria via the mitophagy pathway, followed by apoptosis activation, were demonstrated in the same cohort of BD patients. Moreover, we found a link between the severity of BD and issues with mitochondrial function. When the severity of manic and depressive symptoms increased, alterations on the mitochondrial quality control related proteins rose as well. This study highlighted the significant correlation between mitochondrial alterations with a decrease in functional status.

As described above, the accumulation of abnormal mitochondria resulting from perturbations in the mitochondrial quality control could be seen as a crucial nodal point in premature aging in patients diagnosed with BD. In this line, our group discovered that patients with BD have been shown to present accelerated epigenetic aging in blood compared to controls, with significant correlations found between two biological aging markers: DNA methylation and mitochondrial DNA (mtDNA) copy number. Although no differences have been found in the cerebellum of patients, we found an epigenetic aging acceleration in the postmortem hippocampus of patients with BD compared with controls. Contrary to our a priori findings in the periphery, our study in postmortem hippocampus of BD patients showed a reduction in the mtDNA copy number that was not associated with epigenetic aging. However, significant correlations were detected between another biological aging marker, telomere length, with epigenetic aging and mtDNA, suggesting hippocampal crosstalk between markers that is distinct from that seen in blood.

Overall, our results support the hypothesis that mitochondrial function, in part, acts in the BD pathogenesis feedback loop and could independently determine the course of the disease, progression, and premature aging (Fig. 1). Further studies should explore which mechanisms and proteins are similarly affected or expressed in particular subsets of brain cells versus

peripheral cells to establish if the peripheral cells mimic complex mechanistic alterations in brain cells of BD patients. Based on our current work, we believe that the relationship between mitochondrial dysfunction and BD is a scientific frontier ripe for the development of endophenotype-based therapeutic interventions.

Figure 1: Schematic representation of mitochondrial quality control in healthy cells and Bipolar Disorder (BD).



In healthy cells, the balance between the opposing processes of fusion and fission maintains the overall morphology of mitochondria and ensures the maintenance of a healthy mitochondrial pool. In BD cells, however, an imbalance in mitochondrial fission and fusion towards fission has been described, suggesting that BD patients have an increase in the mitochondria fragmentation followed by a decrease in the levels of mitophagy proteins and an increase in the caspase-3 protein levels in PBMCs. These changes could initiate a vicious cycle where numerous systems and mechanisms intensify and accelerate cellular damage, synaptic dysfunction, and impaired neurogenesis, resulting in progressive structural brain changes and cognitive decline thought to contribute to the neuroprogression of BD.

About the Authors

Giselli Scaini, PharmD, MS, PhD, is an instructor of psychiatry and behavioral sciences and a translational researcher in the field of biological psychiatry. Dr. Scaini received her PharmD, MS, and PhD, in Health Science from the University of Southern Santa Catarina (UNESC, Brazil). In 2015 she joined UTHHealth as a postdoctoral research fellow. Her current research aims to delineate connections between mitochondrial dysfunction and molecular changes with neuroanatomical and neurophysiological changes in psychiatric disorders.

Gabriel R. Fries, PhD, is an assistant professor of psychiatry and behavioral sciences and a translational researcher in the field of biological psychiatry. Dr. Fries received his MS and PhD in Biochemistry from the Federal University of Rio Grande do Sul, Brazil. He also completed a research fellowship at the Max Planck

Institute of Psychiatry in Germany, before joining UTHHealth in 2015 as a postdoctoral research fellow and later as an Instructor. His research focuses on the epigenetic basis of mood disorders, with a particular interest in bipolar disorder and molecular mechanisms of stress.

João L. de Quevedo, MD, PhD, is a professor and vice chair of Faculty Development and Outreach in the Department of Psychiatry and Behavioral Sciences. He is both the Director of the Translational Psychiatry Program and the Treatment-Resistant Mood Disorders Program, part of the Center of Excellence on Mood Disorders. He completed his MD, residency training in psychiatry, fellowship in psychopharmacology, and PhD in Biological Sciences (Biochemistry) all from the Federal University of Rio Grande do Sul in Porto Alegre, Brazil. Dr. de Quevedo specializes in the pathophysiology of mood disorders and develops experimental treatments that can be used in the clinic.

Upcoming Events

Current Topics in the Neurobiology of Disease- GS14 1021 The Microbiome and the Brain

Tuesdays 12:00 p.m. – 1:00 p.m., via WebEx videoconference

Course Director: Cameron B. Jeter, PhD

Open to graduate and medical students, postdoctoral fellows, and residents. This course is an integrated approach to neurological diseases, which includes background information as well as the diagnosis, treatment, and biological mechanisms of the disease under study. The topic for Fall 2020 is “The Microbiome and the Brain.” The human microbiota is comprised of all microorganisms living in the body. Amazingly, dynamic changes in the microbiota can alter brain physiology and behavior. Microbes release metabolites and microbiota-derived molecules to further trigger host-derived cytokines and inflammation in the central nervous system, which contribute greatly to the pathogenesis of host brain disorders. In this seminar course, content experts will discuss the role of the human microbiome in various neurological conditions.

27th Annual Neuroscience Poster Session

Saturday, December 5, 2020, 10 a.m. to Noon

The UTHealth Cooley University Life Center, 7440 Cambridge St., Houston, TX 77054

Participating Institutions: Baylor College of Medicine, Rice University, UTHealth

UTHealth NRC 25th Annual Free Public Forum: Innovative Brain Stimulation Strategies to Treat Neuropsychiatric Disorders

Saturday, April 24, 2021, 10:30 a.m. to Noon

The UTHealth Cooley University Life Center, 7440 Cambridge St., Houston, TX 77054

João de Quevedo, MD, PhD, professor and director, translational psychiatry program, at McGovern Medical School Louis A. Faillace, MD Department of Psychiatry and Behavioral Sciences, will moderate a panel of leading UTHealth physicians and researchers on new treatment strategies for neuropsychiatric disorders.

UTHealth NRC 2020 Distinguished Lecture in the Neurosciences Ed Boyden, PhD, Y. Eva Tan Professor in Neurotechnology at MIT

May 26, 2021, 4 p.m. at UTHealth McGovern Medical School Building, 3.001

Dr. Boyden leads MIT's Synthetic Neurobiology Group (syntheticneurobiology.org), which develops tools for analyzing and repairing complex biological systems such as the brain, and applies them systematically to reveal ground truth principles of biological function as well as to repair these systems.

We welcome notices of your neuroscience seminars, grand rounds, research colloquia, and conferences (sponsored by UTHealth, the Texas Medical Center, and area institutions) for our calendar (<https://med.uth.edu/nrc/eventcal/>). Please send the event name, contact details, date, time, and place to UTHealth.NRC@uth.tmc.edu.

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Questions? Comments?

Contact us at 713-500-5538

or E-mail: UTHealth.NRC@uth.tmc.edu

This Newsletter is distributed by mail to individuals and groups engaged in neuroscience research within the TMC and worldwide and features research, neuroscience accomplishments and outreach efforts performed at UTHealth. Past issues are available on the NRC website.

If you prefer to receive a digital copy through email, please contact UTHealth.NRC@uth.tmc.edu with your information.

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Editor: Anne Hart, PhD

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The Neuroscience Research Center is a component of
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Director: John H. Byrne, PhD

Editor: Anne Hart, PhD

Sr. Coordinator, Special Programs: Donna Wood

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