NRC newsletter

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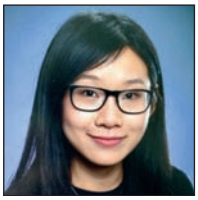
Harnessing the Power of Brain Immunity in Health and Diseases

Mengdi Fei, PharmD & Long-Jun Wu, PhD



Fei

Wu

Abstract: Recent advances in neuroimmunology have revealed the intricate crosstalk between the central nervous system (CNS) and the immune system, crucial for brain development, homeostasis, and disease progression. Microglia, the primary immune cells of the CNS, interact with neurons to play diverse roles in both normal physiology and pathological conditions. Our research utilizes advanced genetic and imaging tools to investigate how microglia sense and regulate neuronal activity, and explores their clinical implications in neurological disorders. By better understanding the mechanisms underlying microglia-neuron communication in health and diseases, we hope to identify microglia-specific targets to develop therapeutic strategies for brain diseases.

Introduction

Our understanding of the relationship between the brain and immune system has drastically changed over the past decades. In the past, the brain was considered to be an "immune-privileged" organ that is protected from the blood-brain barrier. It is now understood that the brain and immune system crosstalk extensively to maintain brain homeostasis, regulate circuit function, trigger inflammatory responses, and contribute to pathogenesis of neurological disorders. A key player involved in these neuroimmune interactions is the microglia, the highly dynamic resident immune cells of the CNS (**Fig. 1**). Microglia originate from the yolk sac and migrate to the CNS during embryogenesis, where they persist throughout adulthood. Once established in the brain, microglia are maintained through an efficient self-renewal process, contributing to brain homeostasis and regulation of neuronal function. Microglia use their dynamic processes to constantly survey the surrounding microenvironment and act as the first line of immune defense against neuronal insults. In addition to performing immune functions, microglia are able to modulate neuronal activity and shape neuronal structures by interacting with various neuronal compartments, such as the neuronal somata and synapses. Considering the diverse and complex roles that microglia play in the brain, many of which remain poorly understood, our laboratory is dedicated to unraveling the mechanisms and functions underlying microglia-neuron interactions, or broadly neuroimmune inter-

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Circadian Control of Metabolism via Clock Function in the Hypothalamus

Kristin Eckel-Mahan, PhD

Eckel-Mahan

Abstract: The circadian clock is a 24 hour (24h) time keeping system in the body, which controls cellular metabolism and tissue-specific functions necessary for energy balance. Growing evidence from individuals with chronic circadian disruption (such as night or rotating shift work) has revealed that disruption of our 24h cycle increases our risk of acquiring metabolic diseases and disorders, including obesity, type II diabetes, and cardiovascular disease. My laboratory is working in both the brain and in peripheral organs to better understand the protective roles of the circadian clock and its function in the context of healthy aging metabolism. Using chromatin immunoprecipitation and single nuclei RNA sequencing, some of our recent studies have identified a prominent role for the circadian protein BMAL1 in the paraventricular nucleus of the hypothalamus in driving rhythmic expression of endocrine factors, such as oxytocin, which help to maintain body-wide rhythms and energy balance.

Circadian (from the Latin phrase "*circa diem*", or "about a day") rhythms occur in most organisms, and are in sync with the earth's rotation on its axis, which takes approximately 24 hours. Mammalian organisms are entrained to the earth's 24h light/dark cycle by a small region of the brain's hypothalamus, called the suprachiasmatic nucleus (SCN). Ultimately, reception of light by the SCN via innervation of neurons transmitting signal from the retina to the SCN via the retinohypothalamic tract, helps synchronize a variety of molecular, behavioral, and physiological rhythms across the body, including rhythmic food intake, hormone secretion, and rhythmicity of the sleep/wake cycle.

While humans generally show rhythms in sync with the 24h rotation of the earth, chronotype (that is, one's behavioral rhythm preference) varies widely across individuals. For example, the term "lark" is often used to refer to individuals who perform optimally on an early-to-bed, early-to-rise schedule, while other individuals (often referred to as "owls") prefer going to bed late and rising later in the morning. Though circadian chronotype varies considerably, adherence to a regular sleep/wake cycle appears to be important, regardless of chronotype (Roenneberg & Merrow, *Curr. Biol.* 26:R432, 2016). A large and growing number of epidemiological studies support the idea that adherence to a regular circadian cycle is important for metabolic health. Higher incidence of several metabolic diseases is associated with chronic circadian disruption, and behaviors that interfere

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Director's Column

Byrne

From the Director, John H. Byrne, PhD

As the Director of the Neuroscience Research Center (NRC), I am privileged to witness firsthand the profound impact that neuroscience research has on our state. The NRC, which serves as a collaborative platform that unites over 300 faculty members from diverse disciplines across our institution, also builds connection within our community through brain awareness events. Currently, our Center is filled with optimism as we are about to embark on a transformative step forward in our collective fight against one of the most pressing health challenges: dementia.

In March, the Texas Legislature passed Senate Bill 5 and Senate Joint Resolution 3, marking bipartisan support for the establishment of the Dementia Prevention and Research Institute of Texas (DPRIT). This legislation introduced by Tom Craddick of the Texas House of Representatives (District 82) and Joan Huffman of the Texas Senate (District 17) proposes a $3 billion initiative modeled after the highly successful Cancer Prevention and Research Institute of Texas (CPRIT). Just as CPRIT has propelled Texas to the forefront of cancer research, DPRIT has the potential to position our state as a national leader in dementia research and care. In May, Texas Governor Greg Abbott signed DPRIT into law. The funding, however, is contingent on voter approval on the November ballot.

Over 500,000 Texans are currently affected by some form of dementia, particularly Alzheimer's disease (AD) and vascular dementia, and numbers are expected to rise significantly in the coming decades. It is especially troubling as Texas ranks 3rd nationally in AD cases and 2nd in AD-related deaths. The economic and emotional toll on families is profound, with millions of caregivers providing essential support for their loved ones. DPRIT aims to alleviate this burden by funding innovative research, developing effective treatments, and ultimately finding a cure. Importantly, the recent legislative efforts underscore the state's commitment to addressing these escalating challenges by funding research over a 10-year period.

Many individuals played a pivotal role in advocating for the establishment of DPRIT, but space constraints allow for only mentioning a few. **Ashley McPhail**, Vice President of Strategy and Administration at the Texas Medical Center (TMC), was instrumental in leading and fostering collaboration across the TMC. **LaTanya Love, MD**, interim president of UTHealth Houston, has fostered UTHealth Houston's strength in dementia research and prevention. **Louise D. McCullough, MD, PhD**, Chair of Neurology at UTHealth Houston's McGovern Medical School, participated in testimony advocating for the formation of DPRIT; an opportunity made possible by **Scott Forbes**, Sr. Vice President, and **Kara Crawford**, Vice President, both from the Office of Governmental Relations at UTHealth Houston.

We have identified more than 100 basic and clinical scientists across the seven schools of UTHealth Houston who are poised to play a pivotal role in this initiative, and plan to leverage our multidisciplinary expertise to develop creative solutions for prevention, early detection, and treatment of dementia-related disorders. For example, researchers at the **McWilliams School of Biomedical Informatics (SBMI)**, led by X**iaoqian Jiang, PhD**, chair in the Department of Health Data Science and Artificial Intelligence, are currently studying how Alzheimer's disease is connected to multiple chronic diseases by building risk trajectory maps for patients using clinical data and electronic health records. Another group, led by Dr. Jiang and **Zhongming Zhao, PhD**, are using Deep Learning Models (advanced AI) to integrate brain imaging data with genetic information. This approach seeks to uncover the genetic underpinnings of Alzheimer's disease and cognitive decline and identify potential biomarkers for early detection.

Faculty at **McGovern Medical School** are also investigating risk factors like Post Traumatic Stress Disorder (PTSD), Traumatic Brain Injury (TBI), Parkinson's disease, and cerebrovascular disease to better understand how they contribute to dementia progression. Indeed, most departments within the medical school are home to faculty studying these risk factors including Anesthesiology, Diagnostic and Interventional Imaging, Integrative Biology and Pharmacology, Neurobiology & Anatomy, Neurology, Neurosurgery, Psychiatry and Behavioral Sciences, and others. Importantly, several clinical trials are targeting early-stage AD. Building upon previous research in TBI and stroke, a group led by **Paul E. Schulz, MD**, professor of neurology, is exploring the potential of stem cell therapy to reduce inflammation and preserve memory function in early-stage AD. In addition, **GQ Zhang, PhD**, Vice President & Chief Data Scientist at UTHealth Houston, is collaborating with **Cui Tao, PhD**, Professor from the SBMI, on a National Institute on Aging grant to build a proposed Alzheimer's disease Clinical Trial Simulation (ACTS) framework, providing a standardized, accessible, and reusable platform for AD trial design and simulation.

In addition, researchers at the **School of Dentistry**, including **Neha Parikh, PhD**, associate professor in the Department of Diagnostic & Biomedical Sciences, as well as McGovern Medical School, are examining the relationship between the oral and gut microbiome with cognitive decline, aiming to identify microbial factors that may influence the onset and progression of Alzheimer's disease and dementia.

Carolyn Pickering, PhD, RN, professor and Isla Carrol Turner Chair in Gerontological Nursing at the **Cizik School of Nursing**, and her team are investigating the behavioral and psychological symptoms associated with AD. Their research identifies patterns and triggers of these symptoms, aiming to improve caregiver strategies and patient care, as well as identifying environmental and situational factors that influence symptom expression.

The **School of Public Health (SPH)** is also importantly contributing to dementia research and care by studying the effects of integrated palliative care for Parkinson's-related dementia, a project led by **Adriana Pérez, PhD**, professor in the Department of Biostatistics and Data Science. In addition, **Rafael Samper-Ternent, MD, PhD**, associate professor in the Department of Management, Policy, and Community Health, examines recruiting strategies and demographic characteristics of participants in clinical trials relating to dementia care.

The diverse research efforts mentioned above underscore UTHealth Houston's alignment with the DPRIT initiative. We are pleased to announce that UTHealth Houston is launching a DPRIT Seed Funding Program with an initial investment of $500,000 to generate preliminary data and thereby best position our investigators to be competitive for DPRIT funding. Nine awards of $50,000 will be given with a six-month window of support. In addition, five mini-grants of $10,000 will be provided to support smaller projects.

Beyond the promise of DPRIT, the NRC is focused on developing impactful programs for the upcoming academic year. Our Executive Committee recently met to establish the theme for our annual graduate course, the Neurobiology of Disease. The topic this year will be, "Dementia Prevention and Research," and will feature UTHealth Houston, Baylor College of Medicine, and Houston Methodist Research Institute faculty members covering research from the cellular basis of network abnormalities to novel imaging techniques and caregiver support. The course is open to graduate and medical students, postdoctoral fellows, residents, and faculty members. Course information will be listed on our website in the coming weeks. The NRC will be honored to host our Distinguished Lecture Speaker this year, **Joshua A. Gordon, MD, PhD**, Chair of the Department of Psychiatry at Columbia University Vagelos College of Physicians and Surgeons, and former Director of the National Institute of Mental Health (NIMH). To end the year, we will again host our annual, multi-institutional, Neuroscience Poster Session, in December. More details will be posted soon on our website. It is with great hope that this year continues to bring excitement and momentum towards advancing public brain health awareness and real solutions for care and treatment of dementia and related diseases.

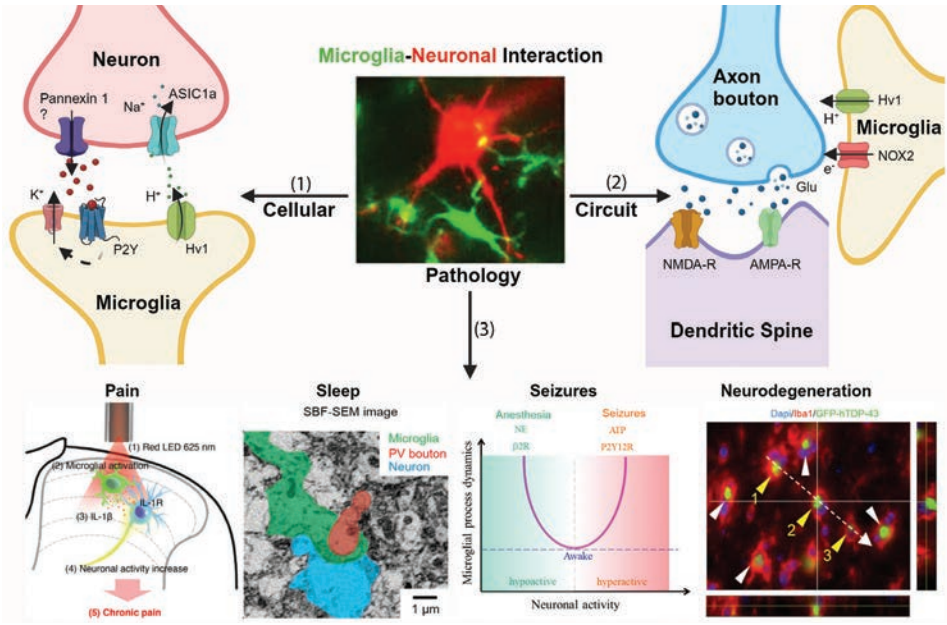

Figure 1. Neuroimmune interaction at cellular, circuit, and system levels. (1) Molecular signaling of microglia-neuron communications at the cellular level. For example, neuronal release of ATP/ADP can be sensed by microglial P2Y receptors, while microglial proton extrusion via Hv1 channel can activate acid-sensing ion channels (ASIC1a) in neurons. (2) Microglia in synaptic function and neuronal circuits. Microglial processes can dynamically interact with synapses, regulating synaptic function and remodeling. (3) Neuroimmune mechanism of neurological disorders. Microglia and macrophages are key players in brain diseases, such as pain, seizures, and neurodegeneration.

action, in both normal and diseased brains (Zhao et al., *Trends Neurosci.* 47:181, 2024).

Microglia dampen neuronal activity in seizures and epilepsy

Microglia play an important role not only in responding to but also regulating neuronal activity when neurons are in both hyperactive and hypoactive stages (**Fig. 2**). Our previous studies have demonstrated that when neurons become hyperactive, microglia interact with active neurons through different types of interactions, including microglial process extension, convergence, and pouches (Eyo and Wu, *Prog. Neurobiol. 179*:101614, 2019). Using a combination of high-resolution live cell imaging, electrophysiology and behavioral analysis, we identified the molecular mechanisms underlying microglial process extension in response to hyperactive neuronal activity. Specifically, neurons release glutamate from presynaptic terminals that activates NMDA receptors on postsynaptic sites, leading to calcium influx and ATP release, which attract microglial process extension towards neurons through microglial P2Y12 receptors. By using P2Y12 knockout mice, we found that P2Y12 receptor deficiency worsened acute seizures with associated reduction in microglial process extension (Eyo et al., *J. Neurosci.* 34:10528, 2014). Our results suggested that microglial process extension and their contact with neurons play a neuroprotective role in seizures. This is further supported by another study using microglia ablation approaches. By depleting microglia from three different transgenic mouse lines, we found the severity of both acute and chronic seizures was exacerbated. However, re-population of microglia reversed the deleterious effect of microglial depletion on acute seizures, suggesting that microglia are beneficial in controlling seizures (Wu et al., *Brain Behav. Immun.* 89:245, 2020). More recently, we found that microglia Ca^{2+} activity is critical for the phagocytosis of dying neurons that may affect the comorbidity of epilepsy such as memory impairment (Umpierre et al., *Neuron* 112:1959, 2024). Our findings provide a foundation for future therapeutic research targeting microglia in epilepsy and similar neurological diseases.

Microglia promote neuronal activity via synaptic shielding

As we unravel the complex roles that microglia play in regulating neuronal hyperactivity, we became interested in the less explored area on the role of microglia-neuron interactions in the hypoactive state, such as anesthesia. Utilizing genetic tools, along with two-photon imaging, we discovered that microglia increase their process surveillance during anesthesia (Liu et al., *Nat. Neurosci.* 22:1771, 2019). We further showed that during anesthesia and its emergence, microglia exhibit increased interactions with neuronal somata and dendrites, extending their processes and forming more bulbous ending contacts. These morphological changes correlate with neuronal hyperactivity during the emergence phase from anesthesia. Using the combination of two photon imaging with electron microscopy, we discovered that microglia specifically insert their processes between inhibitory boutons and neuronal somata, transiently shielding GABAergic inhibitory inputs to enhance neuronal activity during anesthesia emergence. To further test the role of microglia in response to anesthesia, we used microglia ablation and neuronal calcium imaging techniques to determine neuronal activities in mice with and without microglia. Similar to what we initially hypothesized, microglia-ablated mice failed to show neuronal hyperactivity that is observed in control mice during emergence from anesthesia, suggesting that microglia are critical players in regulating neuronal activity post-anesthesia (Haruwaka et al., *Nat. Neurosci.* 27:449, 2024). These findings have potential clinical implications as delirium, characterized by hyperactive, hypoactive or mixed symptoms, is a common and serious complication in patients undergoing anesthesia. By understanding the functional role of microglia in regulating neuronal activity under anesthesia, we could potentially develop novel strategies to manage or prevent post-anes-

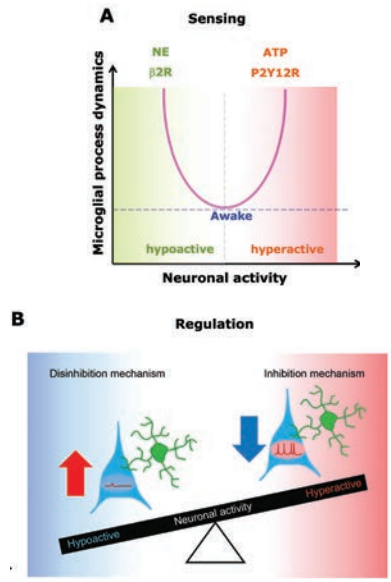

Figure 2. Microglia sense and regulate neuronal activity to maintain homeostasis. (A) Both neuronal hyperactivity and hypoactivity increase microglial process dynamics via differential mechanisms. (B) Microglia regulate neuronal activity to maintain brain homeostasis. During a hyperactive period, microglia can dampen neuronal activity through an inhibition mechanism. During a hypoactive period, microglia can promote neuronal activity through a disinhibition mechanism.

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thesia complications.

Neuroprotective function of microglia in neurodegeneration

Triggering receptor expressed on myeloid cells 2 (TREM2), a surface phagocytic receptor exclusively expressed on microglia within the CNS, is implicated in various neurodegenerative diseases, yet its function remains unclear. One of our lab's research focuses is exploring the role of microglial TREM2 in neurodegeneration, such as amyotrophic lateral sclerosis (ALS) (Xie et al., *Mol. Neurodegener.* 18:75, 2023). As ALS is characterized by the abnormal accumulation of TAR DNA-binding protein 43 (TDP-43) aggregates in the CNS, we used transgenic and viral-transduction mouse models overexpressing TDP-43 to investigate microglial TREM2 function in TDP-43-induced neurodegeneration. We demonstrated that TREM2 is critical for mediating microglial phagocytosis of pathological TDP-43. This was supported by findings from TREM2 knockout mice, which showed a significantly reduced number of TDP-43 containing microglia compared to wild-type mice, resulting in greater pathological TDP-43 accumulation, worsened motor dysfunction, and increased mortality. Furthermore, we found TREM2 physically interacts with TDP-43 in both mouse and ALS human tissue, identifying TDP-43 as a potential new ligand for microglial TREM2 (Xie et al., *Nat. Neurosci.* 25:26, 2022). Our results suggest that boosting TREM2 function, for example with anti-TREM2 agonist antibodies, could be a promising therapeutic approach for neurodegenerative diseases like ALS.

Conclusion

Neuroimmune interactions are critical for maintaining homeostasis and play a key role in the initiation and progression of neurological disorders. By investigating the molecular signaling involved in microglia-neuron communication, the role of microglia in synaptic function and neuronal circuits, and the neuroimmune mechanisms underlying neurological disorders, we aim to decipher the complex neuroimmune interactions at cellular and system levels in both healthy and diseased states. Our ultimate goal is to leverage advanced techniques and interdisciplinary collaboration to develop novel therapeutic strategies for treating brain diseases.

About the Authors

Long-Jun Wu, PhD *is the C. Harold and Lorine G. Wallace Distinguished University Chair, Professor, and Founding Director of the Center for Neuroimmunology and Glial Biology (CNG) at the Institute of Molecular Medicine, UTHealth Houston McGovern Medical School. He received a PhD in Neurobiology from the University of Science and Technology of China and completed postdoctoral trainings at the University of Toronto and Harvard Medical School. He was Professor of Neurology and Neuroscience at the Mayo Clinic prior to joining UTHealth Houston in 2024 where he founded the CNG, an interdisciplinary research center dedicated to understanding the brain's immune system for treating brain diseases.*

Mengdi Fei, PharmD *is a research assistant at the Institute of Molecular Medicine, UTHealth Houston McGovern Medical School. She holds a PharmD and BS in Immunology from the University of Toronto. Before joining UTHealth Houston, she worked in a clinical practice at the Princess Margaret Cancer Centre and is currently focusing on research in neuroimmunology in glioma.*

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with a regular circadian cycle, such as shift work or "social jet lag" (adhering to social pressures that interfere with maintenance of a regular 24h schedule) are associated with increased disease risk (Roenneberg et al., *Curr. Biol.* 22:939, 2012; Van Dycke et al., *Curr. Biol.* 25:1932, 2015; van Amelsvoort et al., *Int. J. Obes. Relat. Metab. Disord.* 23:973,1999; Parkes, *Scand. J. Work Environ. Health* 28:64, 2002; Karlsson et al., *Int. Arch. Occup. Environ. Health* 76:424, 2003; Sharifian et al., *J. Circadian Rhythms* 3:15, 2005; Suwazono et al., *Obesity* 16:1887, 2008; Litinski et al., *Sleep Med. Clin.* 4:143, 2009; Ruger & Scheer, *Rev. Endocr. Metab. Disord.* 10:245, 2009; Scheer et al., *Proc. Natl. Acad. Sci. USA* 106:4453, 2009; Eckel et al., *Curr. Biol.* 25:3004, 2015; Parsons et al., *Int. J. Obes.* 39:842, 2015; Ribas-Latre & Eckel-Mahan, *Mol. Metab.* 5:133, 2016).

So why does a disruption of our circadian cycle increase our risk for certain diseases, such as type II diabetes, and certain forms of cancer? Ultimately, physiological rhythms are maintained by molecular and metabolic rhythms occurring at the single cell level across tissue both in the brain and in the peripheral organs. The SCN of the brain consists of two very small lobes of approximately 20,000 neurons. Divided into "core" and "shell" regions, this area of the brain expresses specific neurotransmitters including vasoactive intestinal peptide (VIP) and vasopressin (AVP), which work to synchronize cells within the region, but also in the larger context of the hypothalamus and surrounding brain regions (Ono et al., *Front. Neurosci.* 15:650154, 2021). Whereas light is the strongest driver of rhythms in the SCN and the brain, nutrient intake and exercise are strong "Zeitgebers," or "time-givers" for peripheral clocks, such as the liver and muscle. These Zeitgebers help keep a cellular, transcriptional and translational negative feedback loop operating in sync, wherein the transcriptional factors Brain and Muscle ARNTL Like 1 (BMAL1) and Circadian Locomotor Output Cycles Kaput (CLOCK) heterodimerize to promote transcription of thousands of genes, including their own negative regulators, which at the protein level subsequently block transcriptional activation by the CLOCK:BMAL1 heterodimer. Global loss of some of these circadian genes results in arrhythmicity and accelerated aging (Kondratov et al., *Genes Dev.* 20:1868, 2006), while tissue-specific loss of some results in an array of tissue-specific metabolic defects (Paschos et al., *Arntl. Nat. Med.* 18:1768, 2012; Lamia et al., *Proc. Natl. Acad. Sci. USA* 105:15172, 2008; Marcheva et al., *Nature* 466:627, 2010). In short, a precise, yet adaptable cellular 24h cellular clock is at work in mammalian cells across the body, and necessary for the proper function of almost every cellular pathway studied. Disrupting our circadian rhythm interferes with timed regulation of these pathways, leading to altered tissue-specific metabolism and communication between peripheral clocks and the brain clocks.

Our laboratory is very interested in how cell- and tissue-specific rhythms contribute to healthy aging and prevent metabolic disease. We rely heavily on rodent models of circadian disruption in our studies to answer these questions. Early studies in rodents show that lesions of the SCN results in a loss of all rhythms in energy intake, water intake, melatonin release from the pituitary, and sleep and wakefulness. While these studies show the importance of rhythms in the SCN for many physiological rhythms in mammals, the importance of other hypothalamic regions in driving rhythmicity has not been as thoroughly investigated. Some experiments looking at the role of the circadian clock in extra-SCN hypothalamic areas showed that loss of BMAL1 in an extra-SCN nucleus of the hypothalamus, the paraventricular nucleus (PVN), resulted in complete behavioral arrhythmicity when mice were analyzed for locomotion rhythms in their home cages by infrared sensors attached to the cage top (Kim et al., *Nat. Commun.* 11:3794, 2020). This finding was the first demonstration that the PVN, known for regulating hunger and satiety, temperature, and stress behavior (in addition to numerous other processes) could modulate body-wide rhythms in metabolism. In addition to a loss of rhythms in activity, energy intake patterns were completely destroyed, and the mice gained weight within only a few weeks of losing circadian rhythmicity in this region.

Some ongoing studies in our laboratory have expanded on these initial findings to better understand what the central circadian proteins are doing to drive rhythms in the PVN, which ultimately control rhythmicity in metabolic tissues body-wide. In particular, we utilize two techniques, chromatin immunoprecipitation

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("ChIP") and single nuclei sequencing to better understand which cells in the PVN are highly rhythmic in gene expression, as well as the roles of the circadian transcription factor BMAL1 in this region of the brain. The circadian clock is known to control a number of rhythmic cellular processes, but an understanding of its role in PVN rhythmicity is extremely limited.

ChIP, a process that involves isolating a specific transcriptional modifying protein from cells or tissues while bound to its target DNA, provided evidence that the circadian clock protein BMAL1 binds to many different genes in the PVN of the hypothalamus. Single nuclei RNA-seq (snRNA-seq) is a method commonly used to analyze gene expression in individual cell types of a tissue. In some of our recent studies, we isolated the PVN at two different times of the day, the late sleeping/fasting phase, and the late waking/eating phase for nocturnal mice. As a result, we were able to observe thousands of genes expressed in a diurnally variant manner in individual cell types of the PVN. In combination with ChIP-seq experiments, we were able to determine that many of the specific genes that showed diurnal variation in expression were likely regulated by BMAL1, based on its occupancy at those genetic loci (Van Drunen et al., *Cell Rep*. 43:114380, 2024) (**Fig. 1**).

While many interesting gene targets were both altered in expression based on time of day, and regulated by circadian clock proteins, several endocrine and paracrine factors emerged from these studies as factors potentially relevant for the arrhythmicity, weight gain, and arrhythmic eating of our mice that lacked circadian rhythms in the PVN. One of these factors, oxytocin (OXT, often referred to as the "love" hormone) has captured our attention based on its known regulatory role in satiety, stress response, and lipolysis. OXT is predominantly produced by the pineal gland, a downstream target of the PVN, and studies by our group have shown a loss of its diurnal secretion in the context of PVN circadian disruption. Interestingly, restoration of OXT rhythms in our mutant mice restored circadian behavior (**Fig. 2**) and reduced food intake, consistent with its role in satiety. While OXT is just one of many interesting molecules that we are pursuing, metabolic rhythms controlled by the clock are likely due to many endocrine, paracrine, and autocrine factors that work both within and outside tissues to preserve rhythmicity in specific tissues.

In summary, evidence is growing that disruption of our circadian clock increases our risk of metabolic disease, resulting in insulin resistance, obesity, and cardiovascular disorders, among other manifestations of impaired metabolic homeostasis. My laboratory hopes to better understand how to improve our circadian cycle to counteract these effects. There are some known behavioral and pharmacological opportunities for improving circadian "robustness," or amplitude. For example, while some natural flavonoids have been used to improve circadian robustness in preclinical studies (He et al., *Cell Metab*. 23:610, 2016), behavioral modifications (such as time-restricted feeding) have also been shown to improve circadian robustness at the cell- and tissue-specific levels. Understanding how these approaches impinge on the clock to improve metabolic health could be highly instrumental in helping individuals with sleep disorders or circadian disruption, as well as those with pre-existing metabolic disease.

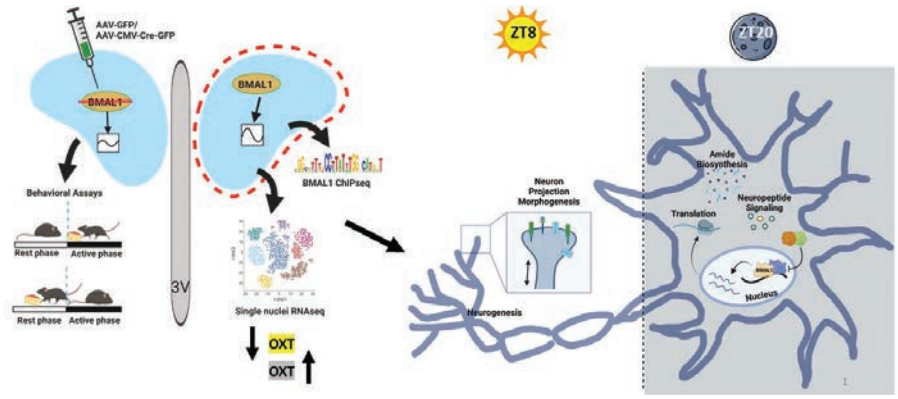


Figure 1. Circadian transcription factor BMAL1 promotes rhythmicity in the PVN. The effects of loss of BMAL1 in the PVN of the hypothalamus was tested behaviorally and molecularly (left). Whether animals moved or ate during the active or the rest phase was measured. Rhythms in BMAL1 activity in the PVN were also tested using chromatin immunoprecipitation ("ChIP-seq"). Single nuclei RNA-seq assays were performed on PVN taken at ZT8 (Zeitgeber time 8, which is the late resting phase for nocturnal rodents) or ZT20 (Zeitgeber time 20, which is the late active phase for nocturnal rodents). This approach revealed that genes important for neuronal projections and connectivity were upregulated during the late resting phase, wherease genes involved in translation of new proteins and cell signaling tended to be higher during the late active/feeding phase. These approaches also led to the discovery of many diurnally variant, BMAL1-controlled genes across numerous cell types in the PVN. Gene annotation revealed many genes under circadian control involved in a variety of cellular processes (right).

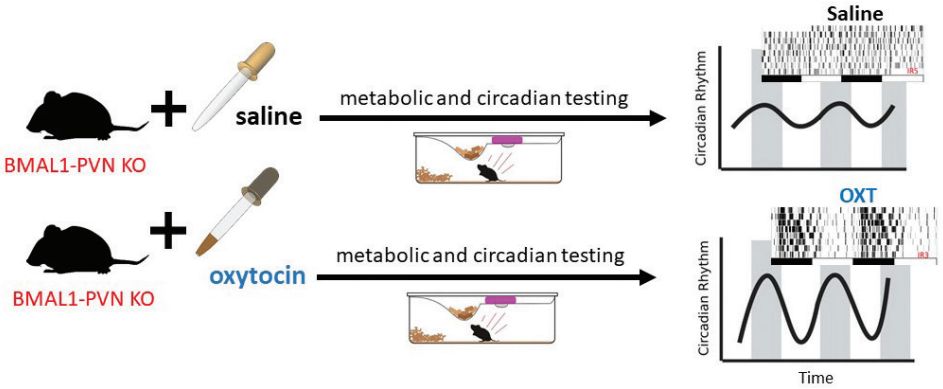


Figure 2. Restoring oxytocin (OXT) rhythms in PVN BMAL1-deficient mice restores rhythmicity. Mice lacking BMAL1 in the PVN with impaired rhythms in OXT release were administered exogenous OXT to mimic natural rhythms in OXT production (scheme on left). When measured for metabolic and circadian activity in metabolic and circadian cages, OXT was able to rescue the circadian activity defects resulting from a loss of BMAL1 in the PVN. Right: light and dark shading refer to the light/dark cycle across several days, with oscillating traces indicating the amplitude of changes in activity during the light/dark cycle. Data under "Saline" and "OXT" labels reveal the home cage activity of mice at different stages of the light/dark cycle in the presence or absence of exogenously-administered OXT in PVN BMAL1-deficient mice.

About the Author

Kristin Eckel-Mahan, PhD *acquired her BA at the University of Colorado at Boulder and her PhD in Pharmacology from the University of Washington, Seattle, where she studied the importance of circadian regulation in hippocampal learning and memory. She performed a postdoctoral fellowship at the University of California, Irvine, where she continued to study the protective functions of the circadian clock in the context of metabolic disease. She started her laboratory at the Institutes of Molecular Medicine at UTHealth Houston in 2015, and remains there as an Associate Professor. She currently serves as the Director of the Graduate School of Biomedical Sciences Molecular and Translational Biology Program, and Associate Director for the Houston Nutrition and Obesity Research Center.*

grants & awards

Alexis Bavencoffe, PhD, assistant professor of integrative biology and pharmacology, received funding from the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) for a project titled, "Regulation of nociceptor excitability by macrophage migration inhibitory factor as a therapeutic strategy for chronic pain treatment after spinal cord injury."

Shivika Chandra, MD, associate professor of neurology, received support from the Michael J. Fox Foundation for a grant titled, "Black and African Americans connections to Parkinson's disease: a project of the global Parkinson's genetics program." Dr. Chandra also received funding from the Parkinson's Foundation for a grant titled, "PD (Parkinson's disease) GENEration genetic registry."

Mission Connect awarded funding to several NRC faculty in the Department of Physical Medicine and Rehabilitation. **Shuo-Hsiu (James) Chang, PhD**, associate professor, was awarded funding for the project, "Muscle synergy-based electrical stimulation for post-stroke locomotor training." **Gerard E. Francisco, MD,** The Wulfe Family Chair, received funding for the project, "Safety and feasibility of supervised, home-based, paired taVNS with upper limb exoskeleton rehabilitation after stroke." **Sheng Li, MD, PhD**, professor and vice chair of discovery and advancement, received funding for a project titled, "BreEStim for stroke motor recovery."

J. Chase Findley, MD, associate professor of psychiatry and behavioral sciences and assistant dean for Educational Programs, and **Robert D. Spears, PhD**, professor and associate dean for Student and Academic Affairs at the School of Dentistry, were recently inducted into the 2025 class of The University of Texas Kenneth I. Shine, MD, Academy of Health Science Education; a special recognition by the University of Texas System for their teaching excellence and commitment to enhancing health science education.

Stuart M. Fraser, MD, assistant professor of pediatrics and director of the Pediatric Stroke Clinic, received funding from the International Alliance for Pediatric Stroke Inc. to study the "Tolerability of transcranial direct current stimulation in pediatric stroke survivors."

Melba Hernandez-Tejada, PhD, associate professor of psychiatry and behavioral sciences, received funding from the United States Department of Defense for a project titled, "Neuromodulation + prolonged exposure therapy: evaluation of a technology-enhanced, entirely remote 2-week integrated treatment for pain and PTSD."

Harry Karmouty-Quintana, PhD, director of the Pulmonary Center of Excellence and associate professor of biochemistry and molecular biology, received the Transformational Project Award from the American Heart Association to study Alzheimer's disease. The project is titled, "Linking NUDT21 depletion to 3'UTR shortening and cerebrovascular dysfunction in Alzheimer's disease."

Sunil Krishnan, MD, professor and John P. and Kathrine G. McGovern Distinguished Chair in neurosurgery, and **Yuri Mackeyev, PhD**, assistant professor of neurosurgery, received a Cancer Prevention and Research Institute of Texas (CPRIT) grant titled, "Protecting the GI tract with a C60 fullerene derivative to facilitate dose-escalated abdominopelvic radiotherapy." The goal of the project is to use a serinol derivatized fullerene as a radioprotector in GI malignancies.

Juneyoung Lee, PhD, assistant professor of neurology, received a R01 grant from the NIH National Institute on Aging (NIA) for a projected titled, "Impact of the gut microbiome on B cell-mediated neuroinflammation in cerebral amyloid angiopathy." This project will investigate if B cells are involved in neuroinflammation and amyloid pathology in cerebral amyloid angiopathy through the gut microbiota-immune-brain axis.

Raja Mehanna MD, associate professor of neurology, assistant director of the Movement Disorder Fellowship, co-director of the Deep Brain Stimulation and Advanced Therapies Program, and director of Movement Disorder Curriculum, was named a Texas Super Doctors 2024 as featured in Texas Monthly.

Majid Momeny, PhD, instructor at the Institute of Molecular Medicine (IMM), received research funding from the Neuroendocrine Tumor Research Foundation to study the role of dual specificity phosphatase 6 (DUSP6) in neuroendocrine tumors. DUSP6 drives tumor progression and therapy resistance, making it a promising biomarker target for future therapies and treatment.

Rodrigo F. Morales, PhD, professor of neurology, received an award from the NIH/NIA for a grant titled, "Seeding activity of misfolded A β in eyes of Alzheimer's disease patients." This project will evaluate the prion-like seeding activity in eyes from Alzheimer's disease patients and other individuals displaying brain amyloid pathology.

Elizabeth Noser, MD, associate professor of neurology, received a grant from The University of Texas Foundation, Inc. to fund the UTHealth Houston Stroke Institute Educational Outreach Program.

Eunsu Park, PhD, assistant professor of neurosurgery, received a Cerebrovascular Research Grant from The Aneurysm and AVM Foundation (TAAF) for a project titled, "Targeting cell adhesion molecules for treating brain arteriovenous malformation." The goal of this grant is to study the mechanism by which cell adhesion molecules mediate macrophage infiltration, exacerbating brain arteriovenous malformation (bAVM)-caused intracerebral hemorrhage (ICH).

Roy F. Riascos-Castaneda, MD, MBA, professor of radiology and neurosurgery and chief of neuroradiology, was recently elected as the president of the Ibero Latin American Society of Diagnostic and Therapeutic Neuroradiology (SILAN) for 2024-2026.

Psychiatry and Behavioral Sciences faculty members, **Joy M. Schmitz, PhD**, professor, and **Luba Yammine, PhD**, associate professor, along with **Francisco Versace, PhD**, professor at The University of Texas MD Anderson Cancer Center Department of Behavioral Science, recently received funding from the NIH for a project titled, "Repurposing semaglutide for the treatment of cocaine use disorder:

a pilot mechanistic study."

Claudio Soto, PhD, Huffington Distinguished University Chair, professor of neurology, and director of the Mitchell Center for Alzheimer's Disease and Related Brain Disorders, was recently awarded the Robert A. Pritzker prize for Leadership in Parkinson's Research by the Michael J. Fox Foundation.

Kartik Venkatachalam, PhD, professor of integrative biology and pharmacology, recently received funding from the NIH/NIA for two projects studying Alzheimer's disease related dementias: (1) "Neuropathology in tauopathies stem from depolarization-induced alterations in the planar distribution of phosphoinositides," and (2) "Metal responsive transcription factors in neurodegeneration."

Heather E. Webber, PhD, assistant professor of psychiatry and behavioral sciences, recently received a Brain and Behavior Research Foundation Young Investigator Grant for a project titled, "Orexin receptor antagonism and relapse-related outcomes in stimulant use disorder." This study will be the first to assess the effects of suvorexant during early withdrawal from stimulant use in treatment-seeking patients entering residential treatment for stimulant use disorder.

Yuanzhong Xu, PhD, assistant professor at the IMM-Center for Neuroimmunology and Glial Biology, received funding from the NIH for a project titled, "Hypothalamic prodynorphin neurocircuits integrating defensive behaviors."

Graduate & Medical Students, Postdoctoral Fellows & Residents

Anik Banerjee, PhD, a postdoctoral fellow with co-mentors **Juneyoung Lee, PhD**, assistant professor of neurology, and **Louise D. McCullough, MD, PhD**, professor and chair of neurology, received a 2025 American Heart Association (AHA) Postdoctoral Fellowship for a project titled, "Gut microbiota-mediated disruption of Peyer's patch-specific IgA+ plasma cells after stroke." This project aims to directly investigate the immunoregulatory roles of IgA^+ plasma cells within the specialized niches of the central nervous system in the context of post-stroke inflammation.

Kamand Khalaj, MD, MPH, a neuroradiology resident, received the American Society of Neuroradiology (ASNR) 2025 Member in Training Travel Award at the annual meeting in Philadelphia for her abstract: "Differentiating LITT-related necrosis from avastin-related cytotoxicity, radiation necrosis, and recurrent glioblastoma using apparent diffusion coefficient values."

Andrew Ngo, MD, a neuroradiology fellow, received the Texas Society for Neuroradiology (TSNR) First Place of Certificate of Recognition for Scientific Presentation at the 2025 annual meeting in Houston for a project titled, "Vessel wall remodeling index as a complementary quantitative method to differentiate intracranial arterial pathologies in high-resolution vessel wall MRI." Co-authors from UTHealth Houston included **Elham Tavakkol, MD**, research fellow, **Kamand Khalaj, MD, MPH, Laura Ocasio, MD**, adjunct assistant professor, **Andrew Rodriguez, MD**, neuroradiology fellow, **Arash Kamali, MD**, associate professor, **David E. Timaran Montenegro, MD**, assistant professor, and **Roy F. Riascos-Castaneda, MD, MBA**, professor.

Antonio Pagán, PhD, a postdoctoral fellow in the Department of Psychiatry and Behavioral Sciences, received a K99 award from the NIH for his project titled, "Psychosocial and neural mechanisms for a culturally and linguistically adapted treatment for bilingual Latino young adults with autism." This project aims to develop ¡Iniciando! La Adultez, an evidence-based therapy program tailored for bilingual Latino young adults with autism spectrum disorder.

MeKenzie Peshoff, a PhD student in the lab of **Long-Jun Wu, PhD**, C. Harold and Lorine G. Wallace Distinguished University Chair and Professor & Founding Director of the Center for Neuroimmunology and Glial Biology at the Institute of Molecular Medicine, received a NIH/NINDS F31 Predoctoral Fellowship award for a grant titled, "Understanding the role of triggering receptor expressed on myeloid cells 2 (TREM2) on microglia and macrophages in gliomas."

Andres Rodriguez, MD, a neuroradiology fellow in the Department of Radiology, received the American Society of Neuroradiology (ASNR) 2024 Spine Outstanding Project Award at the May meeting in Las Vegas for a project titled, "Prevertebral hematoma: a new biomarker for prediction of clinical outcomes in upper cervical spine trauma."

Ruth Yanes Bengoa, MD, MPH, clinical research coordinator and former MPH student at the UTHealth Houston Institute for Stroke and Cerebrovascular Diseases, received the Bernard J. Tyson Career Development Award at the International Stroke Conference in Los Angeles.

Every year, the NRC recognizes medical and graduate students with two special awards. The "Graduate Student Brain Awareness Outreach Award" is awarded to students who exhibit remarkable dedication to brain awareness activities in their community. This year, the award was given to **Madison Shyer**, a student in the lab of **Paul E. Schulz, MD**, professor of neurology. Madison participated in The McGovern Health Museum Summer Internship program, and as a representative of the Neuroscience Program, she connected with Houston-area high school students to introduce the fundamentals of neuroscience.

The "Distinguished Medical Student in the Neurosciences Award" honors fourth-year medical students for excellence in neuroscience research while in medical school. This year, the award was presented to two equally deserving students. **Megan Goyal** was acknowledged for her research examining the relationship between body mass index (BMI) and the clinical presentation and outcomes of encephalitis in adults. Megan performed her research in the lab of **Rajesh K. Gupta, MD**, associate professor of neurology. **Megan Jiao** was also awarded for her exceptional effort to help develop a virtual reality (VR)-based intervention to improve cognition and behavior in children and adolescents with ADHD. Megan performed her work under mentorship of **Renee J. Flores, MD**, associate professor of geriatric and palliative medicine.

Brain Night for Kids at The Health Museum

March 13, 2025

The NRC appreciates our incredible volunteers! The event was attended by over 500 children and parents this year. Guests participated in a variety of demonstrations at 18 different stations and took home brain related souvenirs. A huge thank you to our 53 volunteers from various institutions and departments including Biochemistry and Molecular Biology, Neurobiology and Anatomy, Pediatrics, Psychiatry and Behavioral Sciences, and the Children's Learning Institute.

Brain Night Cont.

Donna Wood Retires

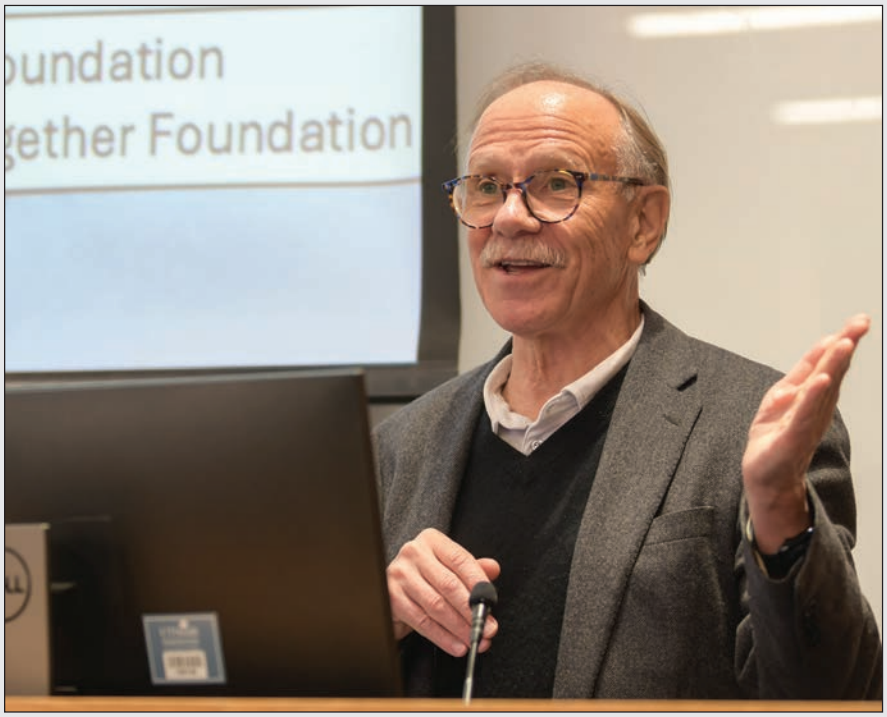
After 17 years of dedicated service to both the Neuroscience Research Center and Department of Neurobiology and Anatomy, **Donna Wood**, Sr. Coordinator of Special Programs, has announced her retirement. As the face of the NRC for several years, Donna has always brought warmth and professionalism to every event and program. We will all miss our dear friend and colleague, but wish her the very best in this next chapter, as she plans to spend more time with family and her darling grandchildren.

Donna Wood (center) with Anne Hart (left) and Jack Byrne (right)

Cheves Smythe Distinguished Lecture

April 8, 2025

Fred "Rusty" Gage, PhD, the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases at the Salk Institute for Biological Studies, was the keynote speaker for the 2025 Cheves Smythe Distinguished Lecture on April 8, 2025. The lecture, hosted by the Office of Research Affairs, was titled, "Aging as a Major Risk for Dementia."



29th Annual Neuroscience Forum

Youth Mental Health: Navigating the Storm and Stress of Adolescence

April 2, 2025

Jeff R. Temple, PhD, Professor and Associate Dean for Clinical Research at the School of Behavioral Health Sciences, led an educational forum with key experts and panelists: **Funlola Are, PhD**, Assistant Professor in the Department of Psychiatry and Behavioral Sciences, **Dana DeMaster, PhD**, Associate Professor in the Department of Pediatrics and The Children's Learning Institute, **Melissa Peskin, PhD**, Professor and Vice Chair of Health Promotion & Behavioral Sciences at the School of Public Health, and **Cesar Soutullo, MD, PhD**, John S. Dunn Professor, Vice Chair and Chief of Child & Adolescent Psychiatry, and Director of the ADHD Outpatient Program in the Department of Psychiatry and Behavioral Sciences.

If you missed the in-person event, a link to the recording is available on our website.

news & information

In May, the UTHealth Houston Center for Eating Disorders, established by the Faillace Department of Psychiatry and Behavioral Sciences and in collaboration with the Division of Adolescent Medicine in the Department of Pediatrics, hosted a 2025 update conference: Bridging the Gap. The conference focused on two distinct tracks for attendees: Medical and Therapy, focusing on evidenced-based treatments and clinical applications. The course directors, **Asha Davidson, MD, MPH,** assistant professor of pediatrics and medical director of the Center, and **Zach Appenzeller, PsyD,** assistant professor of psychiatry and behavioral sciences and founding director, were joined by esteemed experts.

The 2025 University of Texas System Artificial Intelligence (AI) Symposium in Healthcare, held in May, highlighted the latest breakthroughs in AI across research, education, and clinical care. Important topics included discussions on UTHealth System AI collaboration strategy, nationwide AI collaboratives, AI's impact on healthcare, and bringing AI from innovation to bedside. Breakout sessions featured the potential for AI's role in clinical trials and drug discovery, medical imaging and diagnostics, clinical operation, literacy and education, and the relevance of AI governance and regulation. Event leadership and speakers included UTHealth Houston NRC faculty members from the School of Biomedical Informatics (SBMI): **Xaioqian Jiang, PhD,** associate vice president for medical AI chair, **Hongfang Liu, PhD,** professor, and **Jiajie Zhang, PhD,** dean and professor. Speakers also included SBMI faculty **Elmer Bernstam, MD,** professor, **Susan H. Fenton, PhD,** professor and vice dean for education, **Arif Harmanci, PhD,** assistant professor, **Yejin Kim, PhD,** assistant professor, **Kirk Roberts, PhD,** associate professor, **Shayan Shams, PhD,** assistant professor, **Muhammad Walji, PhD,** professor and chair of clinical and health informatics, in addition to **Martin J. Citardi, MD,** professor and chair of otorhinolaryngology at the Medical School, and **Amar Yousif, MBA,** VP and CIO UTHealth Houston.

The Brain Health Research Group, a new, collaborative initiative created by The Stroke Institute, and led by **Fadi Musfee, MD, PhD, MPH,** assistant professor of epidemiology at the School of Public Health, started meeting every month to explore various topics related to the advancement of brain health. These meetings are open to junior faculty, students, and fellows with the goal of fostering innovation and support for the next generation of researchers.

Nitin Tandon, MD, professor of neurosurgery and vice president of strategy and development at UTHealth Houston Neurosciences, joined an expert panel of speakers at the latest offering of the Meeting of the Minds NeuroNetworking Series: Advancements in Brain Cancer Research. The event, hosted in May by the Educational and Research Initiatives for Collaborative Health (ENRICH) at Rice University, highlighted the latest breakthroughs in neuro-oncology. Other panelists included Vinay K. Puduvalli, MD, professor and chair of neuro-oncology at MD Anderson Cancer Center, and Christina Tringides, PhD, assistant professor of materials science and nanoengineering at Rice University.

Marina Zhukova, PhD, assistant professor of psychiatry and behavioral sciences, partnered with the Houston Public Library to curate a collection of children's and adolescent literature for inpatient psychiatric units at UTHealth Houston Harris County Psychiatric Center (HCPC) and the John S. Dunn Behavioral Health Sciences Center at UTHealth Houston. The goal of the project is to provide positive coping mechanisms through books.

Upcoming Events

Join us for our Fall 2025 Seminar Course

Current Topics in the Neurobiology of Disease course

"Dementia Prevention and Research"

Tuesdays at Noon; MSB 7.037

Open to Everyone; More info on our website

Distinguished Lecture in the Neurosciences

October 21, 2025 | MSB 3.001 | Noon

Circuits and Computation: A Neuroscientist's View of the Future of Psychiatry

Joshua Gordon, MD, PhD

Chair of the Department of Psychiatry at Columbia University Vagelos College of Physicians and Surgeons, Executive Director of the New York State Psychiatric Institute, and Psychiatrist-in-Chief at New York-Presbyterian Hospital-Columbia University Irving Medical Center

SAVE THE DATE!

31st Annual Neuroscience Poster Session

Saturday, December 6, 2025

UTHealth Houston Denton A. Cooley, MD and Ralph C. Cooley, DDS University Life Center

UTHealth Houston | Baylor College of Medicine | Rice University

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

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