NRC newsletter

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Cellular Basis of Network Abnormalities in Alzheimer's Disease

Keran Ma, PhD

Ma

Abstract: Alzheimer's disease is associated with neuronal network abnormalities and cognitive impairment. Technological advances in the field of systems neuroscience have enabled the investigation of neural dynamics and microglial modulation of neuronal activity in awake behaving mice. Understanding neuronal and microglial contributions to network abnormalities in the Alzheimer brain may lead to novel therapeutic interventions to restore cognitive function.

Alzheimer's disease (AD) is a devastating neurodegenerative disease that results in progressive memory loss, confusion, aggression, anxiety, depression, and death. FDA approved drugs for treating AD provide limited efficacy by targeting the cholinergic and glutamatergic systems for temporary symptomatic relief or by targeting beta-amyloid in mild AD cases to slow disease progression. There is an urgent need for alternative therapeutic strategies.

Although AD patients suffer from irreversible hippocampal and cortical degeneration resulting in learning and memory impairments, they experience lucid moments at early and moderate stages of the disease, as well as paradoxical lucidity shortly before death. These lucid episodes cannot be explained by the sudden regeneration of neurons or the removal of neurotoxic beta-amyloid and tau aggregates, but likely represent the emergence of healthy neuronal network interactions for temporary reversal of cognitive impairment. In support of cognitive fluctuations in AD patients reflecting neuronal network alterations, AD patients exhibiting neuronal network hyperexcitability manifested as seizures and subclinical epileptiform activity have faster cognitive decline (Vossel et al., *Ann. Neurol*. 80:858, 2016). Furthermore, AD patients and mouse models of AD also showed impaired learning and memory associated with altered synchronized activity of neuronal assemblies, known as brain oscillations. Particularly, the power of gamma oscillations and the phase-amplitude coupling of theta-gamma oscillations are

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Discovering How Neurons Regulate Autophagy

Andrea KH Stavoe, PhD

Stavoe

Abstract: Neuronal health and function decline with age, which are exacerbated in age-related neurodegenerative diseases such as Alzheimer's disease. Our research focuses on autophagy, a cellular pathway that is especially critical in neurons to recycle damaged proteins and organelles to maintain homeostasis and function. We previously found that autophagy decreases with age in neurons, but that we can restore these age-related decreases by ectopically expressing a single protein, WIPI2, in neurons from aged mice. We are interested in elucidating how neurons regulate autophagy and if we can mobilize these pathways to restore neuronal health and function during aging.

Neurons are highly specialized cells that are polarized, metabolically active, post-mitotic, and must survive the lifetime of a human. Thus, neurons are especially sensitive to the routine stressors they experience and have developed extensive quality control systems to maintain their integrity. Autophagy is an evolutionarily conserved degradative pathway that maintains neuronal homeostasis by sequestering damaged proteins and organelles and delivering cargo to lysosomes for degradation. Importantly, specifically knocking out autophagy components in murine neurons leads to neuronal death and axon degeneration (Hara et al., *Nature* 441:885, 2006; Komatsu et al., *Nature* 441:880, 2006). Furthermore, autophagy has been implicated in age-related neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases (HD) (Menzies et al., *Neuron* 2:1015, 2017; Nixon, *Nat. Med.* 19:983, 2013; Yamamoto & Yue, *Annu. Rev. Neurosci.* 37:55, 2014), which combined affect 50 million Americans each year (Brown et al., *Health Perspect.* 113:1250, 2005; Meek et al., *Pharmacotherapy* 18:68, 1998).

Despite the implication of this pathway in neurodegenerative disease, autophagy has been predominately studied in yeast and mammalian cell culture in response to acute stressors such as starvation. Studying the autophagy pathway in yeast and immortalized cell

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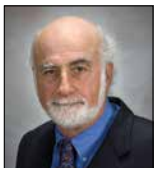
Director's Column



Byrne

From the Director, John H. Byrne, PhD

In this special issue of the Newsletter, I am delighted to share the Director's Column with the newly appointed Chairman of the Vivian L. Smith Department of Neurosurgery, ***Jacques J. Morcos, MD****, as he outlines his plans and goals for this ever-growing department at McGovern Medical School. Dr. Morcos is also holds the titles of Kathrine G. McGovern Distinguished Chair, Co-Director of UTHealth Houston Neurosciences, and Director of Cerebrovascular and Skull Base Surgery. I hope you enjoy learning about his plans as much as I did, and look forward to seeing you at one of the several upcoming events hosted by the NRC this spring.*

Morcos

Jacques J. Morcos, MD

I did not join UTHealth Neurosciences (UTHN) on a whim. After all, from 1995 till 2023 I had stayed at the same institution, the University of Miami, Department of Neurosurgery. There, I had risen to become Co-Chair of the department, had a phenomenal clinical practice, including national and international referrals, enjoyed a thriving career in education, teaching and clinical research. Yet, UTHN had an appeal that was hard to ignore. There was this phenomenal group of professionals dedicated to the advancement of the academic mission of an enterprise rooted in an expanding city, Houston, and centered right in a healthcare conglomerate that has no equal in the world, the Texas Medical Center. There was this partnership between McGovern Medical School and UT, a massive State University, with the largest non-profit hospital network in the city, Memorial Hermann. There was the Vivian L. Smith Department of Neurosurgery, brilliantly designed to comprise a collaborative group of neurosurgeons, pain specialists, neurologists, neurointensivists, radiation oncologists, neuropsychologists, basic and translational researchers, supported by advanced practice providers, nurses, residents, fellows and staff. UTHN had been the agent of many breakthroughs: the first integrated stroke program in Texas, the first discovery of a genetic mutation linked to brain aneurysms, the first use of robotic SEEG in epilepsy in the state, the first use in the region of advanced PET scanning for Alzheimer's disease, a dedicated clinic for the study of cluster headaches, the multidisciplinary establishment of the Texas Institute for Restorative Neurotechnologies (TIRN), and on and on. It is no surprise that the department is ranked 4th in the nation in 2023 on the Blue Ridge report for NIH funding.

What are my goals? I have many, but they all boil down to a single mission: Help make this department a beacon of academic, clinical and educational neurosurgery in the nation and worldwide. It is my very strong conviction that there is currently enormous untapped potential, that with the right catalysts and restructuring, the mission is within reach. The roadmap for me is best thought out along five lanes: Clinical, Research, Education, Engagement, Administrative.

On the Clinical front, there are ongoing efforts in recruiting several key Faculty. A Chief of Neurosurgical Spine Division is needed. There has been great interest, interviews are ongoing and an appointment is near. The ideal candidate will be a stellar academician with proven leadership skills. We are also interviewing for more junior faculty positions for our Memorial City and Southeast MH campuses, to better serve the community in these areas. We will continue a very close collaboration with Orthopedics Spine at the Texas Medical Center (TMC) and other sites, as synergy between our divisions is for the greater good. We are actively recruiting for the position in Functional neurosurgery and looking for a rising star that will own and expand the Deep Brain Stimulation (DBS) program, and move us in new directions beyond Parkinson's disease, such as novel therapies for addiction and neuropsychiatric diseases, as well as Brain Machine Interface possibilities. It is said that Talent is hitting a target that nobody else can hit, while Genius is hitting a target that nobody else can see. We are indeed looking for a neurosurgical "eagle" to join our innovative functional group. Our brain tumor program is in need for a third neurooncologist to serve our brain tumor patients better and strengthen our clinical trials and research portfolio, and that search is ongoing. The spirit and proven track record of "multidisciplinary" work that I established at the University of Miami will continue here. In the near future, I clearly see and will plan the establishment of several Centers of Excellence (COE) and Institutes involving Neurosciences: A Skull Base Institute (including ENT, Oculoplastics, NeuroOphthalmology, Neuroradiology, Radiation Oncology, Neurooncology, Neuropathology, Neuroendocrinology and many others); Center for Cranial Nerves Disorders (Trigeminal Neuralgia and Hemifacial Spasm); Center for Moyamoya disease and Bypass Surgery (with Stroke Neurology, Cerebrovascular scientists, and others); Brain Tumor Institute; Neurocritical Care Institute; and others.

On the Research side, we have 19 brilliant PhD researchers engaged in avant-garde innovative work in most aspects of neurosciences. I appointed this summer **Hui-Wen Lo, PhD** in the new position of Vice-Chair for Research. Together we are restructuring and bolstering our research enterprise. In particular, as one of the most productive research groups in the UT system, we are actively looking for more bench space and personnel to expand the research efforts and realize goals more easily. We are expanding administrative support for our researchers. One of my specific goals, while interviewing for this position, was to establish a physical space we would name "CINE" (Center for Innovation and Neuroscience Education). This space would be a nexus for hands-on cadaveric courses and education, augmented by Virtual Reality and Augmented Reality stations, with a view to create possibilities of device development and industry sponsorship.

On the Education side, we currently take three neurosurgery residents per year. Based on future clinical and research volume and expansion of resident coverage into other campuses, we may consider expanding that number. But prior to that, we are eagerly looking at establishing a pre-residency fellowship program and my goal is to eventually have a CAST approved post-residency Fellowship in each one of our subspecialties.

On the Engagement side, I believe we need an expanded and well targeted program that increases the visibility of UTHN. This is done through traditional marketing (social media, brochures, regular media such as TV,…) and combined neuroscience outreach programs to physicians, the patients and the public (webinars and in-person events). Furthermore, we must establish a well run Neuroscience Center for Second Opinions and International Programs, to make the clinical expertise available among our talented Faculty available to the nation and the world.

Finally, a well-coordinated internal Administrative structure of governance is needed to achieve excellence in the above stated goals. I have already appointed a Director for each of our subdivisions. I have recruited talent to lead medical illustrations, nurse management, APPs and others. The excellent relationship that Neurosurgery has with Neurology, under the leadership of **Louise McCullough, MD, PhD**, and Ophthalmology, under the leadership of **Timothy McCulley, MD**, will continue to get stronger. UTHN will eventually have a center for Scholarly Excellence with three subdivisions: Editorial Office, Clinical Research and Data Management, and Clinical Trials Division.

In conclusion, I believe this department is poised for more greatness in its future. Maya Angelou stated that "courage is the mother of all virtues, because without courage, none of the virtues can be exercised consistently." Courage can certainly have many forms, one of which is to not fear change. Regardless of where this journey takes us, the journey will take place in a spirit that respects and upholds the following values: openness, trust, pride in differences, altruism, hard work, surgical excellence, innovation, mentorship. And if that occurs, then the legendary and distant sky will indeed be a faraway limit.

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reduced with cognitive decline (**Fig.1**; Palop & Mucke, *Nat. Rev. Neurosci.* 17:777, 2016; Goodman et al., *Front. Aging Neurosci.* 10:101, 2018). Recent genomic and gene expression studies have identified many pathways and cell types associated with AD. However, the mechanisms by which these genetic variants and changes in gene expression alter cell, circuit, and network functions remain largely unexplored. Taking advantage of the rich datasets from genomic and sequencing studies in AD patients, research in my laboratory focuses on functional changes in neurons and microglia resulting from disease-associated genetic variants and gene expression changes. We are investigating the consequences of these changes on cell and circuit function that underlie abnormal brain oscillations and network hyperexcitability that are associated with cognitive impairment in the AD brain.

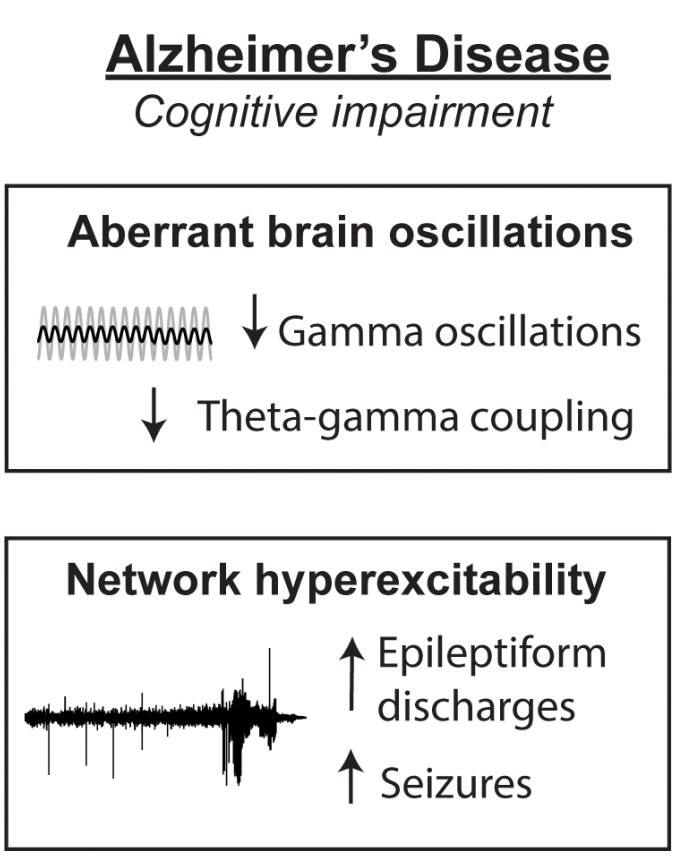

Figure 1. Functional abnormalities in the Alzheimer brain. The Alzheimer brain is characterized by aberrant brain oscillations such as decreases in the power of gamma oscillations and theta-gamma phase frequency coupling, and network hyperexcitability, which are associated with cognitive decline.

Restoring brain oscillations and network excitability in AD is a novel therapeutic approach that offers alternative and complementary options to current treatments. Accumulating evidence indicates that inhibitory interneuron dysfunction contributes to network and cognitive deficits in AD (Palop & Mucke, *Nat. Rev. Neurosci.* 17:777, 2016; Gabitto et al., *Nat. Neurosci.* 27:2366, 2024). The brain relies on oscillatory activity, generated by inhibitory interneurons, to organize information flow and precisely time neuronal firing required for cognitive processing. Specifically, gamma oscillations, which depend on the activity of parvalbumin (PV) inhibitory interneurons, increase during memory encoding and predict memory formation in humans and mice. We and others have shown that enhancing PV inhibitory interneuron function by genetic manipulation (Nav1.1BAC) or optogenetic stimulation at 40 Hz improved multiple aspects of the AD disease phenotype. This includes increased gamma oscillatory activity, decreased network hyperexcitability, reduced pre-mature mortality, lowered beta-amyloid plaque load and improved cognitive functions in mouse models of AD (Martinez-Losa et al., *Neuron* 98:75, 2018; Cardin et al., *Nature* 459:663, 2009; Verret et al., *Cell* 149:708, 2012). Inhibitory interneurons play a critical role in supporting brain oscillations associated with cognition.

Besides inhibitory interneurons, genome-wide association studies (GWAS) highlight microglia as the most important cell type relevant to late-onset AD (LOAD), which accounts for more than 95% of AD cases. Validation of GWAS identified risk loci also implicated microglia in LOAD and that AD disease variants of microglia-expressing genes may contribute to the disease independent of beta-amyloid pathology. How do microglia, the immune cells in the brain, cause neuronal dysfunction in the AD brain? We and others have recently shown a previously unknown physiological role of microglia in modulating neuronal activity. Microglia suppress neuronal hypersynchrony and network hyperexcitability through surveillance and process motility directed towards neurons. Without such microglial modulation of neuronal activity, the network becomes hyperexcitable, leading to seizures (Merlini et al., *Nat. Neurosci.* 24:19, 2021; Badimon et al., *Nature* 586:417, 2020). Network hyperexcitability and seizures are observed in both AD and models of reduced microglia-neuron interactions. Interestingly, a large-scale human single-nucleus sequencing study identified 12 microglial transcriptional states, 3 of which showed significantly altered fractions of microglia in AD patients, including reduced microglia in the "neuronal surveillance" state (Sun et al., *Cell* 186:4386, 2023). Taken together, these studies highlight microglia as the cell type most associated with LOAD and that their interactions with neurons through microglia surveillance could be altered in AD, leading to neuronal network disturbances and related cognitive impairment.

Furthermore, GWAS identified the microglia-expressing gene, triggering receptor expressed on myeloid cells 2 (TREM2), as an AD risk gene implicated in AD pathogenesis, which has been validated and confirmed by multiple studies. Genetic variants of TREM2, particularly the R47H variant, strongly increase AD risk by 2-4 fold. One of the projects in my laboratory focuses on targeting microglia-neuron interactions to restore network abnormalities in AD. We hypothesize that the TREM2 gene risk variant R47H induces cognitive impairment in AD by altering microglial responses to neuronal activity resulting in dysregulation of neuronal synchronization, abnormal brain oscillations, and network hyperexcitability.

Both inhibitory interneurons and microglia dysfunction are involved in AD pathogenesis, as well as epilepsy and psychiatric disorders. Although impaired inhibitory function has been suggested as a key mechanism of network dysfunction in AD and related

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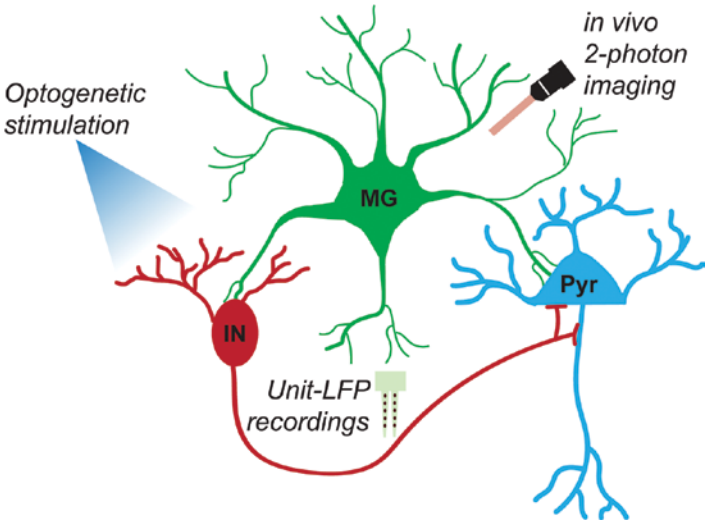

Figure 2. Investigation of cellular function and interactions in health and disease. Advanced systems neuroscience tools including *in vivo* two-photon imaging, high density electrophysiological recordings (unit-LFP), and optogenetics are utilized to investigate cellular activity and cell-cell interactions in wildtype mice and mouse models of Alzheimer's disease. IN: inhibitory interneurons; MG: microglia; Pyr: pyramidal neurons

models, and enhancing PV inhibitory interneurons has beneficial effects in mouse models of AD, little is known about the cellular and circuit mechanisms of inhibitory dysfunction leading to network abnormalities in AD. The main reason for this gap in knowledge is the major technological barrier of simultaneously examining the activity of distinct and well-identified cell types *in vivo* while recording network alterations during behavior. Similarly, studying altered microglia-neuron interactions in AD have been met with technological barriers of *in vivo* functional studies in behaving mice at the cellular and network levels.

To address this technological barrier, my laboratory uses *in vivo* two-photon imaging of neuronal activity and microglia process motility, *in vivo* electrophysiological recordings of neuronal activity and local field potential, and optogenetics for manipulating neuronal activity in awake behaving mice (**Fig. 2**). Experimental mice are either head-fixed or free-moving during imaging and recording sessions, and their behavior is assessed in either virtual reality or physical paradigms. We employ the latest advances in viral vectors to transduce cell-type specific fluorophores, calcium indicators, and opsins. These imaging and recording techniques generate large datasets that are analyzed using MATLAB- and Python-based algorithms and custom codes. In addition, we are also exploring machine learning methods, such as tracking mouse behavior using DeepLabCut and jointly analyzing synchronized behavior and cell activity data using CEBRA, to determine neural dynamics underlying behavior and cellular dysfunction leading to behavioral alterations in Alzheimer's disease mouse models.

Taking advantage of state-of-the-art technological advances in systems neuroscience, we will gain an unprecedented mechanistic understanding of functional deficits at the cellular, circuit, and network levels, as well as maladaptive interactions between different cell types that result in network dysfunction in various mouse models of AD. We aim to restore network function and behavioral abnormalities in AD by preserving cell function and their interactions.

About the Author

Keran Ma, PhD *is an assistant professor in the Department of Neurobiology and Anatomy at the UTHealth Houston McGovern Medical School. Dr. Ma received a PhD from the University of Toronto and completed postdoctoral training at the Gladstone Institutes/University of California, San Francisco. Dr. Ma's research career has been focused on translational research in Alzheimer's disease, investigating disease pathophysiology and various therapeutic approaches. She was awarded a K99/R00 Pathway to Independence Award from the National Institute on Aging, Rising STARs Award from the UT System, and research grants from the Alzheimer's Association and the Texas Alzheimer's Research and Care Consortium.*

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lines was critical to dissecting the core components of this complex pathway. However, these experimental systems cannot be used to interrogate how the autophagy pathway is differentially regulated in distinct tissues and cell types or in the context of intact, physiologically relevant surroundings. Unsurprisingly, much less is known about how autophagy is regulated in differentiated cells and under basal conditions. As unique, highly differentiated cells, neurons represent a powerful model to interrogate these fundamental questions. While recent progress has firmly linked autophagy and aging in general (Chang et al., *eLife* 6:e18459, 2017; Hansen et al., *Nat. Rev. Mol. Cell Biol*. 19:579, 2018), little is known about how this essential homeostatic mechanism is affected by aging in neurons. Further, neurons, as post-mitotic cells with unique homeostatic demands and significantly higher rates of basal autophagy, appear to regulate autophagy differently than non-neuronal cells. Thus, neurons are uniquely poised to answer this fundamental question in cellular biology.

There are fundamental unanswered questions about neuronal autophagy. What unique mechanisms do neurons engage to tightly orchestrate autophagy? How do those mechanisms change during aging? How can we modulate neuronal autophagy to increase nervous system healthspan in the context of normal aging and neurodegenerative diseases?

Prior work has focused on applying the regulatory pathways that have been extensively studied in non-neuronal cells to neurons to ectopically upregulate neuronal autophagy without significant success. However, those efforts assume that neurons do not use distinct molecular mechanisms to uniquely modulate autophagy to meet their distinctive needs. Thus, the regulatory pathways that neurons evolved to dynamically modulate autophagy have gone undiscovered, leaving potential therapeutic targets for neurodegenerative diseases untapped. In yeast and mammalian cell culture, autophagy is studied in the context of cellular stress, predominately starvation, as it upreg-

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ulates autophagy to detectable levels. These stress-related pathways act through mTORC1, a master regulator of cell growth that senses the metabolic state of the cell. Inhibitors of mTORC1, such as rapamycin and Torin, robustly induce autophagy in yeast and immortalized cells. However, cellular stressors such as proteotoxic stress, starvation, and mTORC1 inhibitors do not induce autophagy in primary mammalian neurons (Maday et al., *J. Cell Biol.* 196:407, 2012; Maday & Holzbaur, *J. Neurosci.* 36:5933, 2016; Tsvetkov et al., *PNAS* 107:16982, 2010). While mTOR has other important roles in neurons, distinct molecular pathways regulate neuronal autophagy.

To address this current gap in knowledge, my laboratory will use the model organism *Caenorhabditis elegans* complemented with mammalian neuron culture from mice. My previous work has established the power of both model organisms to study neuronal autophagy, especially in the context of aging and disease. In *C. elegans* neurons, I identified how autophagy cell-autonomously directs specific neurodevelopmental programs. In one neuron, PVD, autophagy is required to restrict axon outgrowth. In contrast, in a different neuron, AIY, autophagy is required for proper clustering of presynaptic vesicles. Further, I uncovered a cellular pathway that contributes to the spatial confinement of autophagy to presynaptic regions of the neuron: KIF1A, the synaptic vesicle-specific kinesin, is required to transport ATG9 (the only transmembrane protein in the core autophagy pathway and a critical autophagy component) to presynaptic sites in the axon to facilitate autophagosome formation at presynaptic sites (Stavoe et al., *Dev. Cell* 38:171, 2016).

Additionally, my previous work in murine primary neuron culture found that the rate of autophagosome biogenesis decreases drastically with age in mouse dorsal root ganglion (DRG) neurons. Remarkably, I discovered that ectopic overexpression of a single autophagy pathway component, WIPI2B, in neurons from aged mice restored the rate of autophagosome biogenesis to that of neurons from young adult mice – an unexpected, breakthrough finding. We were further surprised to find that early autophagy stages were not affected by aging and that WIPI2 rescue of autophagosome biogenesis was dependent on its phosphorylation state. Phosphorylation of WIPI2 affected its ability to interact with membranes and the duration of time WIPI2 resided at developing autophagosomes (Stavoe et al., *eLife* 8:e44219, 2019). I will leverage both systems in the proposed research to take advantage of the ease of *in vivo* microscopy and genetic tractability in *C. elegans* and the advanced imaging and biochemical techniques available in mammalian neuron culture. Together, these orthogonal systems provide an unparalleled opportunity to uncover the molecular mechanisms of neuronal autophagy during aging and neurodegenerative disease.

About the Author

Andrea KH Stavoe, PhD *is an assistant professor in the Department of Neurobiology and Anatomy at the UTHealth Houston McGovern Medical School. She earned a MPhil and a PhD in Cell Biology from Yale University and completed postdoctoral training in cellular neuroscience at the University of Pennsylvania. Her research is focused on how neurons modulate the autophagy pathway to maintain their function during aging and how we can manipulate this pathway therapeutically to ameliorate age-related neurodegenerative diseases and cognitive decline. Dr. Stavoe was awarded a F32 postdoctoral training fellowship, as well as the prestigious NIH Pathways to Independence Award (K99/R00), both from the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Stavoe has also been awarded a Rising STARs Award from the UT system.*

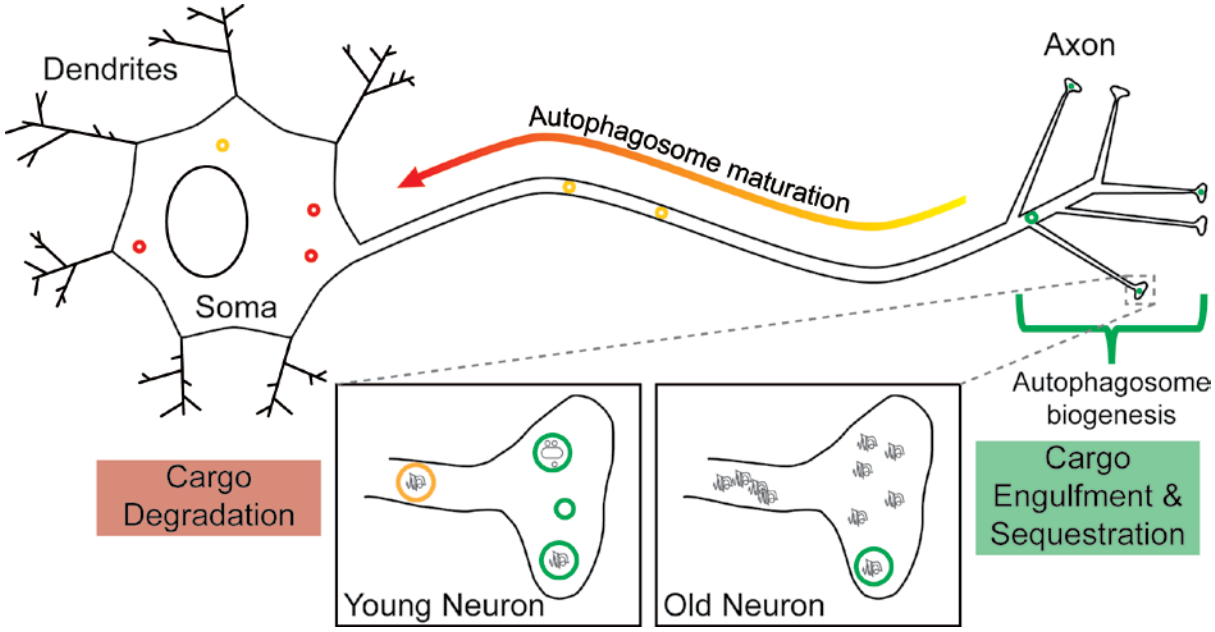


Figure 1. Model for axonal autophagy in neurons. The *de novo* formation of a double-membrane autophagosome occurs predominately in the distal axon and/or at presynaptic sites in neurons. Once the autophagosome has engulfed cargo and completed formation, effectively sequestering cargo from the cytosol, autophagosomes begin transport to the cell soma along microtubules by the retrograde microtubule motor cytosolic dynein. During retrograde transport, autophagosomes encounter and fuse with lysosomes, which are present in the axon in an increasing gradient of degradative competence as autophagosomes are transported closer to the soma. Upon delivery to the cell body, matured autolysosomes complete degradation of their contents, and resulting molecular building blocks are recycled into new proteins and organelles. Autophagosome biogenesis decreases in the distal axon with age, resulting in an accumulation of damaged and aggregated proteins and organelles in the axon, which can subsequently lead to loss of neuronal function and neurodegeneration.

grants & awards

The 2024 awardees for the Champions of the Clinical Learning Environment included NRC faculty members: **Dean Atkinson, MD**, assistant professor of psychiatry and behavioral sciences, **Pedro Balaguera, MD**, assistant professor of neurology, **Melissa Christie, MD**, assistant professor of neurology, **Brandi Karnes, MD**, assistant professor of psychiatry and behavioral sciences, **John Lincoln, MD, PhD**, associate professor of neurology, and **Teresa Pigott, MD**, professor of psychiatry and behavioral sciences. This award acknowledges faculty who have significantly influenced third-year McGovern Medical School students by cultivating a professional and stimulating learning environment.

Tatiana Barichello, PhD, associate professor of psychiatry and behavioral sciences, received an award from the National Football League Players Association (NFLPA) for a grant titled, "Decoding gut-brain biomarkers and developing a minimally intrusive gut microbiome sampling: Enhancing cognitive well-being in athletes." This project aims to explore the relationships between gut health, neurological markers such as the blood-brain barrier, glial cells, neurons, and behavior, providing insights into how gut health might influence the risk of sports-related concussions, muscle injuries, athletic performance, and recovery in athletes.

Tatiana Barichello, PhD, associate professor of psychiatry and behavioral sciences, and **Rodrigo F. Morales, PhD**, professor of neurology, received an award from the National Institutes of Health (NIH)/National Institute on Aging (NIA) for a project titled, "Infection-driven mechanisms associated with Alzheimer's disease (AD) pathology," and will provide valuable insights into the role of infections in AD and the immune system's involvement in dementia. Dr. Barichello and Dr. Morales also received a grant from the Texas Alzheimer's Research and Care Consortium (TARCC) for a project titled, "Unraveling the influence of delirium in Alzheimer's disease pathogenesis." This research investigates whether delirium caused by infection or surgery increases the brain's vulnerability to AD.

Jennifer E.S. Beauchamp, PhD, RN, Nancy B. Willerson Distinguished Professor in Nursing at the Cizik School of Nursing, received an award from the UTHealth Office of Global Health Initiatives for a grant titled, "Let's talk about stroke." This grant aims to address the significant gap in stroke recognition and education in El Salvador, a country where stroke is a leading cause of death and disability. This project will develop and evaluate a culturally tailored online stroke health course in Spanish, focusing on the RÁPIDO acronym to improve stroke knowledge and early recognition among healthcare providers and students in El Salvador. The project's success could serve as a model for expanding stroke education across other Spanish-speaking countries, potentially reducing disparities in stroke outcomes.

Spiros Blackburn, MD, associate professor of neurosurgery, received an award from the Brain Aneurysm Foundation for a project titled, "Life expectancy after subarachnoid hemorrhage: Damage vs repair."

Peng R. Chen, MD, professor of neurosurgery, and **Eunhee Kim, PhD**, assistant professor of neurosurgery, received a R21 award from the NIH/National Institute of Neurological Disorders and Stroke (NINDS) for a project titled, "EndMT as a target to treat human brain arteriovenous malformations." The goal of this grant is to test if targeting EndMT by calpain inhibition can be a potential therapeutic approach to treat human bAVMs.

Kristin Eckel Mahan, PhD, associate professor at the IMM-Center for Metabolic and Degenerative Diseases, received an NIH grant for a project titled, "Circadian regulation of astrocytic adenosine kinase in the irradiated and cancer brain." This project will examine circadian regulation of adenosine activity and its response to irradiation in the context of glioblastoma.

Gabriel R. Fries, PhD, assistant professor of psychiatry and behavioral sciences, received the 2024 Dean's Teaching Excellence Award. In addition, Dr. Fries received the John S. Dunn Foundation Collaborative Research Award in conjunction with the Gulf Coast Consortia with **Agenor Limon, PhD**, associate professor and vice chair for research at the University of Texas Medical Branch at Galveston. Their project is titled, "Exploring excitatory to inhibitory synaptic ratio as a novel target in bipolar disorder and suicide." The goal of this award is to encourage new collaborations in the Gulf Coast region.

Vijayasree V. Giridharan, PhD, MPharm, assistant professor of psychiatry and behavioral sciences, was awarded the TARCC Junior Investigator Research Award to investigate the significance of innate lymphoid cells in AD pathology and how can these cells be manipulated to combat the disease.

Georgene W. Hergenroeder, PhD, associate professor of neurosurgery, received an award from the NIH/NINDS for a grant titled, "Discovery of biomarker signatures prognostic for neuropathic pain after acute spinal cord injury."

Seema Jacob, PsyD, assistant professor of psychiatry and behavioral sciences, received a research career development award from the Texas Child Mental Health Care Consortium to support the development and implementation of UT-Early Parent Education (UT-EPE). UT-EPE is a parent intervention for preschoolers with the most common psychiatric diagnoses (i.e. anxiety, atten-

tion deficit hyperactivity disorder [ADHD] and behavior and mood dysregulation). Dr. Jacob will be working with **Cesar A. Soutullo, MD, PhD**, John S. Dunn Professor of Psychiatry and Behavioral Sciences and Vice Chair and Chief of Child and Adolescent Psychiatry, to pilot this intervention in the Child and Adolescent Mood Disorders Program (ChAMP) clinic.

Rodrigo F. Morales, PhD, professor of neurology, received a grant from the USDA/Animal and Plant Health Inspection Service (APHIS) for a grant titled, "Screening of strain-specific anti chronic wasting disease (CWD) prion molecules." The main goal of this project is to identify anti-prion molecules with specific activities against CWD prion strains.

Cesar A. Soutullo MD, PhD, John S. Dunn Professor of Psychiatry and Behavioral Sciences and Vice Chair and Chief of Child and Adolescent Psychiatry, was recently awarded the American Academy of Child and Adolescent Psychiatry (AACAP) Distinguished Fellow Award, the highest honor from the AACAP to recognize a career in teaching, research and clinical excellence. His group also received gifts from the Vivian L. Smith Foundation and The Favrot Fund to support the creation of the ChAMP clinic. ChAMP is a Measurement-Based model clinic established as a quality improvement project to improve adherence and outcomes in children and adolescents with mood disorders (depression and bipolar) and other conditions recently associated with them, such as ADHD and anxiety.

Peeyush K. Thankamani Pandit, PhD, assistant professor of neurosurgery, received a R21 award from the NIH/NINDS for a proposal aimed to identify the role of epigenetically programmed brain endothelial cells in guiding neuronal progenitors. Additionally, this study will examine the capacity of these cells to support the survival and migration of transplanted neural progenitors in the stroke-affected brain.

Heather E. Webber, PhD, assistant professor of psychiatry and behavioral sciences, was an American College of Neuropsychopharmacology (ACNP) Travel Awardee. This special award is given to distinguished young scientists and allowed her to travel to Phoenix, AZ for their annual meeting. Dr. Webber was also awarded support through the National Alliance for Research on Schizophrenia and Depression (NARSAD), Brain and Behavior Research Foundation Young Investigator Grant. Her project was titled, "Orexin receptor antagonism and relapse-related outcomes in stimulant use disorder." In addition, Dr. Webber received an internal seed grant from the Faillace Department of Psychiatry and Behavioral Sciences for a project titled, "A pilot study of transcranial magnetic stimulation plus episodic future thinking for methamphetamine use disorder." Furthermore, she received a NIH K01 (Mentored Research Scientist Development Award) for a project, "Identifying electrophysiological targets for transcranial magnetic stimulation in cocaine use disorder."

Jin H. Yoon, PhD, associate professor of psychiatry and behavioral sciences, along with **Chukwuemeka Okafor, PhD, MPH,** assistant professor at UTHealth San Antonio, received an award from the NIH/National Institute on Drug Abuse (NIDA) for a project titled, "Development of a behavioral economic intervention to improve HIV-related behaviors among sexual minority men." The study will assess the behavioral economic intervention, Episodic Future Thinking, to improve HIV-related behaviors such as drug use, PrEP initation and adherence, and risky sexual behavior.

Graduate & Medical Students,
Postdoctoral Fellows & Residents

The Dee S. and Patricia Osborne Endowed Scholarship in the Neurosciences was awarded at the 30th Annual Neuroscience Poster Session to **Takese McKenzie** (1st Place; lab of **Jian Hu, PhD**, professor of cancer biology, MD Anderson Cancer Center), **Vicky Chuong** (2nd Place; lab of **Fabricio H. Do Monte, DVM, PhD**, associate professor of neurobiology and anatomy), and **Stephen Farmer** (3rd Place; lab of **Sheng Zhang, PhD**, associate professor at the IMM-Center for Metabolic and Degenerative Diseases). All students are part of The University of Texas MD Anderson Cancer Center UTHealth Houston Graduate School of Biomedical Sciences.

Ari Dienel, PhD, a postdoctoral fellow in the lab of **Devin W. McBride, PhD**, associate professor of neurosurgery, recently received an American Heart Association Career Development Award.

Dounya Jalloul, a PhD candidate in the laboratory of **Michael Beierlein, PhD**, professor of neurobiology and anatomy, received the 2024 Terry J. Crow, PhD, Scholarship in Neuroscience. Ms. Jalloul received the scholarship for her outstanding scholastic achievements.

Max A. Skibber, MD, a former 4th year medical student working under **Charles S. Cox, Jr., MD**, the George & Cynthia Mitchell Distinguished Chair in Neurosciences, received 2024 Distinguished Medical Student in the Neurosciences award from the UTHealth Houston Neuroscience Research Center for his research achievements.

Sithara Thomas, PhD, a postdoctoral fellow in the lab of **Peeyush K. Thankamani Pandit, PhD**, assistant professor of neurosurgery, received a 2-year postdoctoral fellowship award from TARCC. The proposal will investigate the role of vascular dysfunctions in triggering and accelerating AD pathology. Additionally, it will study the effect of angiogenesis in a mouse model of AD.

Public Forum

August 29, 2024

The NRC hosted our annual Public Forum titled, "Connecting Your Brain to Computers," at The Health Museum on August 29, 2024. Our panelists are pictured (left to right): **Jacob Robinson, PhD**, Co-Founder and CEO of Motif Neurotech, Professor of Electrical and Computer Engineering and Bioengineering at Rice University; **Nitin Tandon, MD**, Professor and VP of Strategy and Development at UTHealth Houston Neurosciences, Director of the Epilepsy Surgery Program at Memorial Hermann – Texas Medical Center, Co-Director of the Texas Comprehensive Epilepsy Program, and Co-Director of the Texas Institute for Restorative Neurotechnologies; **Matt Angle, PhD**, Founder and CEO of Paradromics.

Distinguished Lecture

October 22, 2024

The NRC hosted our annual Distinguished Lecture in the Neurosciences on October 22, 2024 at McGovern Medical School. Our distinguished guest, **Grégoire Courtine, PhD**, Professor at the Swiss Federal Institute of Technology (EPFL) and Director of .NeuroRestore, held a captive audience during his lecture, "The Neuron that Repairs the Central Nervous System." Dr. Courtine is pictured here with NRC Director and professor of neurobiology and anatomy, **Jack Byrne, PhD**, and **Nitin Tandon, MD**, VP of Strategy and Development, UTHealth Houston Neurosciences and Professor of Neurosurgery.

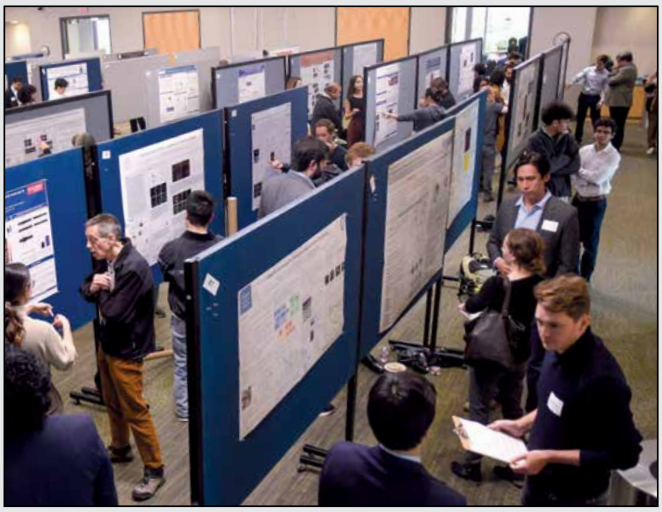
Society for Neuroscience Reception

In October, the NRC hosted a reception at the Society for Neuroscience's annual meeting in Chicago, IL, held at the Chicago Yacht Club.

30th Annual Neuroscience Poster Session

Saturday, December 7, 2024
UTHealth Cooley University Life Center

The NRC hosted our 30th Annual Neuroscience Poster Session which included faculty, residents, postdoctoral fellows, graduate and medical students, as well as undergraduate students, from three Texas Medical Center institutions. The large group included the Departments of BioSciences, Psychological Sciences, and Electrical and Computer Engineering at Rice University, the Department of Neuroscience at Baylor College of Medicine, and the UTHealth Houston Neuroscience Research Center. A record breaking 104 research posters were presented to faculty judges from each institution and prizes were awarded for the best poster presentations in each category. Congratulations to all of the winners from the 30th Annual Neuroscience Poster Session!



Faculty judges from Baylor College of Medicine, Rice University, and UTHealth Houston.

Presenters who received 1st, 2nd, or 3rd place prizes in their categories.

news & information

The 7th Annual UTHealth Houston Symposium on Aging Research was held in October and highlighted ongoing and innovative clinical and basic aging research. The event included a keynote address by **Nicolas Musi, MD**, professor of medicine and director of Endocrinology, Diabetes & Metabolism, Cedars-Sinai Medical Center, as well as several presentations by NRC Faculty members: **Yejin Kim, PhD**, assistant professor of health data science and artificial intelligence at the SBMI; **Jose Felix Morono Manchon, PhD**, assistant professor of neurology; **Andrea K. Stavoe, PhD**, assistant professor of neurobiology and anatomy.

The Carmel Dyer, MD, Lecture Series, held in November and hosted by the UTHealth Houston Institute on Aging, featured a presentation by renowned neuroradiologist **Roy F. Riascos-Castaneda, MD, MBA**, professor of diagnostic and interventional imaging, titled, "Neuroradiology of Alzheimer's Disease."

In partnership with Baylor College of Medicine, the first and only Injury Control Research Center in Texas has been established by the Centers for Disease Control and Prevention at UTHealth Houston. The new Violence and Injury Prevention Research (VIPR) Center will be a special collaboration between the institutions, community, and policymakers, and will be led by director, **Jeff Temple, PhD**, associate dean for clinical research at UTHealth Houston School of Behavioral Health Sciences, and co-director, **Melissa Peskin, PhD**, professor and vice chair of health promotion and behavioral sciences at UTHealth Houston School of Public Health. The center's focus will be on preventing adverse childhood and community experiences, violence across the lifespan, suicide, and firearm violence.

The UTHealth Houston Institute on Aging joined the Walk to End Alzheimer's in November, highlighting their joint efforts to raise awareness and funds for this debilitating disease. Physicians, researchers, community members, and caregivers united for this important community wide event.

UTHealth Houston NRC Executive Committee

Nguyen

The NRC would like to extend our gratitude to UTHealth Houston NRC Executive Committee Member, **Vuvi H. Nguyen, MS, PhD**, as she rolls off the Executive Committee. Dr. Nguyen is an associate professor in the Department of Diagnostic and Biomedical Sciences at the UTHealth Houston School of Dentistry. The NRC has appreciated her service on this Committee for the past several years.

Parikh

We would also like to welcome **Neha Parikh, MS, PhD** to the Executive Committee. Dr. Parikh is an associate professor in the Department of Diagnostic and Biomedical Sciences at the UTHealth Houston School of Dentistry. Her research program assesses the progressive role of poor oral health, microbial dysbiosis and systemic inflammation in Alzheimer's disease. Besides scientific and educational research, she enjoys teaching and mentoring dental students. We are thrilled to have her participation in this leadership role.

Upcoming Events

Brain Night for Kids -

Free Event for Families

Thursday, March 13th 6-8pm

The Health Museum
1515 Hermann Dr.
Houston, TX 77004

Free Public Forum

Youth Mental Health: Navigating the Storm & Stress of Adolescence

Wednesday, April 2, 2025 11:30am-1pm

McGovern Medical School; Room 2.006

Led by Jeff Temple, PhD

Associate Dean of Clinical Research
Director, Center for Violence Prevention
School of Behavioral Health Sciences

Panelists include:

Funlola Are, PhD
Dana DeMaster, PhD
Melissa Peskin, PhD
Cesar Soutullo, PhD

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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Neuroscience Research Center

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Questions? Comments?

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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 Houston. 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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