

Sequelae During Stroke Recovery: Post-Stroke Cognitive Impairment and Pain

Seema Aggarwal, PhD & Deniz Dishman, PhD



Aggarwal



Dishman

Abstract: Of the estimated 800,000 stroke victims in the US, 85% survive but most are left with chronic disability affecting their function and quality of life, and that presents barriers to participation in critically

needed rehabilitation. Under-recognized post-stroke complications include post-stroke pain and cognitive decline. Our research aims to provide important and timely evidence to advance pain and cognition assessment and interventions in stroke survivors, and ultimately enable participation in rehabilitation.

It is estimated that in the U.S. there are upwards of 800,000 stroke survivors each year, and fortunately, due to advances in stroke treatment, 85% of these victims survive. More than half of the survivors are left with moderate to severe disability or cognitive impairments. Stroke is the number one cause of long-term disability and averages a lifetime cost of \$180,000 as most are left with conditions that require chronic care. Although stroke rehabilitation is critical for motor and cognitive recovery within the first year to prevent functional and cognitive decline, only a third of stroke survivors participate in outpatient stroke rehabilitation and over half do not receive the recommended rehabilitation within 6 months after being discharged from hospitals (Ayala et al., *MMWR Morb. Mortal. Wkly. Rep.* 67:575, 2018). To date, despite developed and globally promoted evidence-based guidelines, post-stroke care in the U.S. remains fragmented. In the U.S., there lacks a standardized timeline for post-stroke recovery services, and little has been done for survivors outside of inpatient rehabilitation. Furthermore, most stroke survivors have limited access to inpatient rehabilitation, skilled nursing facilities, outpatient rehabilitation, or in-home health services because of costs and/or transportation barriers. For instance, the uninsured are more likely to experience mortality in the hospital than those with private insurance and are less likely to receive stroke rehabilitation. Without rehabilitation, stroke survivors lose

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Agitated Delirium: Is Inflammation a Mechanism?

Sandra K. Hanneman, PhD, RN, Allen Huang, BSN & David Hui, PhD



Hanneman



Huang



Hui

Abstract: Agitated delirium is a complication of illness that is highly distressing to patients, families, and healthcare professionals. The mechanism(s) of delirium in the context of critical illness and/or end-of-life is not clear. We are investigating inflammation as a mechanism and as a predictor of response to pharmacological treatment for agitated delirium.

As early as 500 BC, Hippocrates observed the acute onset of cognitive deficits and behavioral disturbances, which he called *phrenitis*, associated with such physical illnesses as fever, head trauma, and toxin exposure. The word *frenzy* is derived in various etymologies from *phrenitis* and describes well the phenomenon of agitated delirium. Different labels for delirium have been used over the intervening millennia, but the defining characteristics that distinguish delirium from other neuropsychiatric syndromes remain as observed by Hippocrates: its acute onset of altered cognition and behavior in the context of physical illness.

Cognitive manifestations of delirium include deficits in attention and language, disorientation, and disruptions in arousal states. Motor manifestations form the basis of the most familiar subtypes of delirium, best understood along a spectrum of agitation: hyperactive (agitated), hypoactive, and mixed delirium. In hyperactive delirium, patients exhibit a range of behaviors from heightened anxiety to pulling out catheters to violently lashing out at others. Psychotic features such as hallucinations may also be present. In contrast, hypoactive delirium is characterized by apathy, withdrawal, and slowed verbal and motor responses. Mixed delirium possesses fluctuating characteristics of both hyperactive and

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Director's Column

From the Director, John H. Byrne, PhD



The UTHealth Houston NRC is a university-wide center where diverse and multidisciplinary research is conducted to further the understanding of the brain and brain disorders. Established in 1992, the NRC serves as an “umbrella organization,” which brings together neuroscience researchers within UTHealth Houston to promote research, education and outreach. Over the past several issues of the *NRC Newsletter*, we have highlighted neuroscience research and collaborations from the School of Public Health and the School of Biomedical Informatics, two of the six institutions at UTHealth Houston. In this issue, we are pleased to feature neuroscience research from the Cizik School of Nursing. In addition, we will describe our expanded programs at the NRC and plans for the remainder of the academic year.

The first scientific article in this issue, co-authored by Seema Aggarwal, PhD, and Deniz Dishman, PhD, both assistant professors in the Department of Research, discuss their research to increase participation in post-stroke rehabilitation and enhance outcomes in cognitive impairment and pain during a critical recovery period. The second scientific article is co-authored by Sandra K. Hanneman, PhD, RN, Professor in the Department of Research, David Hui, MD, Professor in the Department of Palliative, Rehabilitation and Integrative Medicine at MD Anderson Cancer Center, and Allen Huang, BSN, an Honors Student at the School of Nursing. These authors discuss their ongoing investigation of inflammation as a mechanism of agitated delirium, a common complication of illness, as well as inflammation as a predictor of a patient's response to pharmacological treatment. Both articles present potential strategies for improvements in quality of life with illness, and have potential to significantly serve a large portion of our population.

As the six institutions continue to grow and expand their neuroscience research programs, the NRC has mirrored this expansion through programming topics and events. For example, this fall, our annual graduate level course, “Current Topics in the Neurobiology of Disease,” featured research and advances in the emerging field of the Neurobiology of HIV. There is a growing group here at UTHealth Houston that is focusing on the neurological and cognitive difficulties associated with HIV infection and the impact of HIV infection on the brain. Joy M. Schmitz, PhD, Professor and Director of the Center for Neurobehavioral Research on Addictions, Jordan E. Lake, MD, Associate Professor of Infectious Diseases, and Rodrigo Hasbun, MD, MPH, Professor of Infectious Diseases, our course co-directors, assembled a comprehensive program of expert lecturers. Thirteen faculty from UTHealth Houston, Baylor College of Medicine, and institutions across the nation shared their research as it related to HIV-associated neurocognitive disorders, biological therapies for HIV, and the psychosocial impacts of HIV infection. Much gratitude is given to our UTHealth NRC Members that participated in the course. Dr.

Hasbun opened the course by providing an overview of the neurocognitive disorders in people living with HIV/AIDS. Dr. Lake, with her lecture titled, “HIV 101,” provided a thorough background and base understanding of HIV for which the course was built upon. James Langabeer, II, PhD, MBA, Professor at the School of Public Health, shared information about the local HEROES (Houston Emergency Opioid Engagement System) program and the existing treatment gaps in opioid use disorder.

In December, we hosted our annual Neuroscience Poster Session. This event is in its 28th year and continues to develop into a larger, more inclusive, program ever year. We have grown from a small poster session for UTHealth Houston graduate students and postdoctoral fellows, to the largest neuroscience poster session in the Texas Medical Center including Baylor College of Medicine and Rice University. One of the major additions this year was the inclusion of graduate students from the University of Houston. Attendees continue to benefit from the experience and professional development that comes with presenting one's research, and are also provided a great opportunity for networking and collaboration with other major institutions. We look forward to seeing this event continue to evolve and hope you will join us for our next Poster Session.

Next on the horizon is our annual Brain Awareness Event, “Brain Night for Kids,” a collaboration with The Health Museum, scheduled for March 16, 2023. This free educational program provides elementary-aged children with an exciting opportunity to engage in hands-on activities, teaching them about the brain and nervous system. In addition, our annual Public Forum will be held on Saturday, April 15, 2023, and will update the public on “Post-COVID Brain Health.” We are very pleased that Antonio Teixeira, MD, PhD, Professor and Director of the Neuropsychiatry Program, will moderate this timely program. Also on the horizon, we are looking forward to a visit from Ann Graybiel, PhD, Institute Professor at the Massachusetts Institute of Technology and Investigator at the McGovern Institute, as part of our Distinguished Lecture series later this spring. Please check our website and subscribe to our monthly calendar, for more information about these upcoming events.

grants & awards

NRC faculty were among four recipients of a NIH BRAIN Initiative award to establish a coordinating unit for biostatistics, informatics, and engagement (CUBIE) as part of the larger NIH BRAIN Initiative Cell Atlas Network (BICAN). The project's PI is **GQ Zhang, PhD**, vice president and chief data scientist for UTHealth Houston, with co-leaders **Hua Xu, PhD**, associate dean for innovation at the School of Biomedical Informatics (SBMI), and **W. Jim Zheng, PhD**, professor at the SBMI. Additional investigators include **Rashmi Abeysinghe, PhD**, assistant professor of neurology, **Licong Cui, PhD**, associate professor at the SBMI, **Yan Huang, PhD**, assistant professor at the SBMI, **Xiaojin Li, PhD**, assistant professor of neurology, **Cui Tao, PhD**, professor at the SBMI, and **Shiqiang Tao, PhD**, assistant professor of neurology.

Five NRC faculty members were selected as the 2022 awardees for the Champions of Clinical Learning Environment at UTHealth Houston. **Kawal Bir, MD**, assistant professor of psychiatry and behavioral sciences, **Shivika Chandra, MD**, assistant professor of neurology, **Gregory Hestla, MD**, assistant professor of psychiatry and behavioral sciences, **John Lincoln, MD**, associate professor of neurology, and **Louise McCullough, MD, PhD**, professor of neurology and Roy M. and Phyllis Gough Huffington Distinguished Chair, were among 24 total recipients. These faculty were described as exceptional role models and praised for exemplifying professional and compassionate behavior.

Four awards were granted to NRC faculty members from the UT System Board of Regents' Faculty Science and Technology Acquisition and Retention (STARs) Program. **Juneyoung Lee, PhD**, assistant professor of neurology, **Keran Ma, PhD**, assistant professor of neurobiology and anatomy, and **Rodney Ritzel, PhD**, assistant professor of neurology, all received Rising STARs awards. **Vasanthi Jayaraman, PhD**, professor of biochemistry and molecular biology and John S. Dunn Chair, received a Translational STARs award.

Two NRC faculty members recently received funding through the Cancer Prevention and Research Institute of Texas (CPRIT). **Christopher Alvarez-Breckenridge, MD, PhD**, assistant professor of neurosurgery at MD Anderson and affiliate of the Graduate School of Biomedical Sciences (GSBS) Immunology Program, received the Early Clinical Investigator Award for his research in neurosurgery. **Jian Hu, PhD**, associate professor of cancer biology at MD Anderson and affiliate of the GSBS Cancer Biology and Neuroscience Programs, received a High-Impact/High-Risk Research Award for his project, "Restoration of phagocytosis function of glioma-associated microglia/macrophage by activating QKI-PPARb-RXRa."

H. Alex Choi, MD, associate professor of neurosurgery, was awarded a grant from the NIH to identify biomarkers in patients at risk for a serious secondary neurological complication called delayed cerebral ischemia (DCI) which can arise after a subarachnoid hemorrhage (SAH).

Carmen W. Dessauer, PhD, Chair ad interim and professor of integrative biology and pharmacology, received funding from the NIH for a grant titled, "Regulation of adenylyl cyclase signaling." This MIRA award mechanism is a 5-year award for established investigators. It will fund projects that examine the scaffolding of adenylyl cyclase activity with TREK-1 potassium channels that controls cardiac pace-making and that also has significant relevance to synaptic plasticity.

Deniz Dishman, PhD, assistant professor of research at the Cizik School of Nursing, received an award from the PARTNERS (Providing Advancement Resources To Nursing Education, Research and Students) Organization for pilot research to explore quantitative EEG analysis and brain mapping in stroke survivors reporting shoulder pain.

Yoshua Esquenazi, MD, assistant professor of neurosurgery, has been awarded a grant from StacheStrong for a project titled, "A prospective, longitudinal, multi-institutional observational study to correlate alterations of the human structural and functional connectome with clinical outcomes in adults undergoing neurosurgical resection of WHO II-IV glioma."

J. Chase Findley, MD, associate professor of psychiatry and behavioral sciences, received the 2022 John P. McGovern Award as an exceptional clinical teacher. This award is given annually to outstanding UTHealth Houston clinical faculty members as chosen by the senior medical class.

Gabriel R. Fries, PhD, assistant professor of psychiatry and behavioral sciences, received a seed grant from the UTHealth Faillace Department of Psychiatry & Behavioral Sciences for a project titled, "Longitudinal DNA methylation and epigenetic aging changes associated with treatment and improvement of suicidal ideation in hospitalized patients with mood disorders." In addition, Dr. Fries also received a Pilot Grant from the McGovern Medical School Research Committee for a project, "Leveraging an ongoing longitudinal study of suicidal ideation to identify transcriptomic signatures of symptom improvement in hospitalized patients with mood disorders." Further, Dr. Fries received an Emerging Scholar Travel Award from the National Network of Depression Centers (NNDC) to attend their annual meeting in Ann Arbor, MI.

Jane Hamilton, PhD, associate professor of psychiatry and behavioral sciences, was awarded a diversity, equity, and inclusion grant from Houston Methodist. Her team, in collaboration with the UTHealth School of Public Health faculty, **Shreela Sharma, PhD**, and **Wes McWhorter, DrPH**, will work with community partners to improve health for people who previously experienced chronic homelessness.

Sandra K. Hanneman, PhD, RN, professor of research at the Cizik School of Nursing, was selected by the University of Texas System Board of Regents to receive a 2022 Regents' Outstanding Teacher Award. Dr. Hanneman was nominated for excellence in shaping

the next generation of nurses and for advancing nursing school research initiatives.

Mary Kay Koenig, MD, professor of pediatrics and director of the Center for the Treatment of Pediatric Neurodegenerative Disease, received funding from the 3billion End the Diagnostic Odyssey Grant to provide genetic testing for rare diseases.

Radha Korupolu, MD, associate professor of physical medicine and rehabilitation, received funding from the NIH National Center for Complementary and Integrative Health for a grant titled, "Mindfulness meditation training and home practice in persons with spinal cord injury: A pilot study." The major goal of this project is to study the feasibility and acceptability of mobile app-guided mindfulness exercises in people with spinal cord injury who have chronic pain. In addition, Dr. Korupolu, along with **Nuray Yozbatiran, PT, PhD**, associate professor of physical medicine and rehabilitation, received a Mission Connect grant for a project titled, "Safety and feasibility of paired vagus nerve stimulation with rehabilitation for improving upper extremity function in people with cervical spinal cord injury."

Devin W. McBride, PhD, assistant professor of neurosurgery, received a 1-year, Brain Aneurysm Foundation 2022 Grant.

Asia McCleary-Gaddy, PhD, director of the Office of Diversity and Inclusion and assistant professor of psychiatry and behavioral sciences, received the National Diversity Council DEI Champions Award. This award honors professionals who are passionate about creating an impact in the field of diversity and inclusion.

Louise D. McCullough, MD, PhD, professor and chair and the Roy M. and Phyllis Gough Huffington Distinguished Chair in the Department of Neurology, co-director of UTHealth Houston Neurosciences, and NRC Executive Committee Member, was recently honored with the 2022 American Heart Association Basic Research Prize in acknowledgment of her outstanding contributions to the advancement of cardiovascular science and exceptional leadership of a cardiovascular basic science laboratory.

Rodrigo F. Morales, PhD, associate professor of neurology, has recently been awarded several grants: (1) "Exploring new uses for PMCA and RT-QuIC diagnosis: prion strain discrimination and soil contamination," from the USDA/APHIS. (2) "Cross-seeding between bacterial and mammalian amyloids," from the Alzheimer's Association. (3) "Going up in smoke: assessing the ability of incineration to inactivate CWD prions from carcasses," from the United States Geological Survey. (4) "Effect of COVID-19 in AD, PD and associated protein misfolding" from the Texas Alzheimer's Research and Care Consortium. **Tatiana Barichello, PhD**, associate professor of psychiatry and behavioral sciences, is also a PI on this grant. (5) "Development of a high throughput system for screening anti-prion molecules," from the Creutzfeldt-Jakob Disease Foundation.

Eunsu Park, PhD, assistant professor in neurosurgery, received an award from the NIH/NINDS for a project titled, "Microglia/macrophages as target to prevent intracerebral hemorrhage in KRAS mutation-induced brain arteriovenous malformations." The research goal is to develop treatment options for brain arteriovenous malformation (bAVM)-associated intracerebral hemorrhage by modulating the activation/infiltration of

microglia/macrophages in mutant KRAS-induced bAVM.

Co-lead investigators **Eva M. Sevick, PhD**, professor and Nancy and Rich Kinder Distinguished Chair of Cardiovascular Disease Research at the Institute of Molecular Medicine (IMM), and **Manish N. Shah, MD**, associate professor of pediatric neurosurgery, along with **Banghe Zhu, PhD**, assistant professor at the UTHealth IMM Center for Molecular Imaging, received a grant from the NIH/NINDS to deploy a new optical imaging technique, fluorescence cap-based transcranial optical tomography (fCTOT), to understand the role that cerebrospinal fluid flow dynamics play in post-hemorrhagic hydrocephalus in order to develop prevention, progression, and treatment strategies.

Claudio Soto, PhD, professor of neurology, renewed funding from the NIH/NIAID as the Program Director, Principal Investigator, Project 2 and Director of Administrative Core for a grant titled, "Pathogenesis, transmission and detection of zoonotic prion diseases." The main goal of this iteration of the PPG is to study the molecular and cellular mechanisms responsible for chronic wasting disease (CWD) prion replication, to address the diversity and potential for adaptation of CWD prion strains, and to assess the risk posed to humans from established and emergent strains and their adapted derivatives. Dr. Soto also received funding from the Van Andel Institute as a site PI for a project titled, "The contribution of the vermiform appendix to Parkinson's disease." The main goal of this project is to determine the mechanisms by which α -synuclein pathology in the vermiform appendix contributes to Parkinson's disease (PD). In addition, Dr. Soto was recently awarded a grant from the NIH/NIA for a project titled, "Production and distribution of well-characterized polymorphic variants of alpha-synuclein aggregates."

Jiaqian Wu, PhD, associate professor of neurosurgery, received funding from the NIH/NINDS for a grant titled, "CNS exosome-mediated adaptive immunity in Alzheimer's Disease." Dr. Wu serves as a co-investigator on this project; Yongjie Yang, PhD and Alexei Degtarev, PhD, both from Tufts University, serving as the grant PIs.

Luba Yamine, PhD, associate professor of psychiatry and behavioral sciences, received funding from the NIH/NIDA for a grant titled, "A randomized controlled trial of exenatide as an adjunct to nicotine patch for smoking cessation and prevention of post-cessation weight gain."

The UTHealth Houston Children's Learning Institute (CLI) has received grant funding from the National Science Foundation for their project titled, "Breaking stereotypes through culturally relevant storytelling: optimizing out-of-school time STEM experiences for elementary-age girls to strengthen their STEM interest pathways." **Gloria Yeomans-Maldonado, PhD**, assistant professor of pediatrics, and **Tricia Zucker, PhD**, Harriet and Joe Foster Distinguished Professor in the Department of Pediatrics and co-director of the CLI, are co-PIs for the new grant.

Han Zhang, MD, professor of neurobiology and anatomy, is the 2022 recipient of the John H. Freeman Award for Faculty Teaching. This award is chosen by the senior medical class to recognize an outstanding basic science faculty member. This is Dr. Zhang's seventh time receiving this award.

Graduate Students & Postdoctoral Fellows

Solmaz AghaAmiri, PhD, a postdoctoral researcher in the Center for Translational Cancer Research at the IMM, is the 2022 recipient of North American Neuroendocrine Tumor Society (NANETS) Theranostics Investigator Grant. Her proposal is titled, "Overcoming MGMT resistance in NETs with a tumor-targeted drug." Dr. AghaAmiri's mentor is **Ali Azhdarinia, PhD**, associate professor in the Center for Translational Cancer Research, and co-mentor is Daniel Halperin, MD, medical oncologist at MD Anderson.

Elliot Murphy, PhD, a postdoctoral fellow in the lab of **Nitin Tandon, MD**, professor of neurosurgery and Chair ad interim, received first place in the 2022 President's Award for Excellence in Postdoctoral Research, named by the Postdoctoral Association and the Office of Postdoctoral Affairs at UTHealth Houston. Eunju Kim, PhD, a postdoctoral fellow with mentors Zheng Chen, PhD, and **Seung-Hee Yoo, PhD**, assistant professor of psychiatry and behavioral sciences, received the third-place award.

Camila N. de Lima, PHD, a postdoctoral fellow in the lab of **Gabriel R. Fries, PhD**, assistant professor of psychiatry and behavioral sciences, received a Brain & Behavior Research Foundation Young Investigator Grant titled, "Molecular mechanisms underlying accelerated epigenetic aging in bipolar disorder: a transcriptomic and neuroanatomical study." Dr. de Lima also received the New Investigator Award from the American Society of Clinical Psychopharmacology (ASCP) which is a travel and career development award to attend the annual meeting of the ASCP.

UTHEALTH HOUSTON NRC 2022 DISTINGUISHED MEDICAL STUDENT IN THE NEUROSCIENCES AWARD



Recipients of the UTHealth Houston NRC 2022 Distinguished Medical Student in the Neurosciences awards, Avram Bukhbinder, MD, and Anam Haque, MD, with Jack Byrne, PhD, Director of the UTHealth Houston NRC. Dr. Bukhbinder pursued neuroscience research in the lab of Dr. Paul E. Schulz in the Department of Neurology. He intends to continue contributing to clinical and translational research during his residency in child neurology at Massachusetts General Hospital. Dr. Haque pursued her neuroscience research in the lab of Dr. Rajesh Gupta in the Department of Neurology. She is continuing her research in the field of Pediatric Neurology.

UTHealth Houston NRC Executive Committee

The UTHealth NRC would like to welcome two new faculty members to our Executive Committee: **Michael A. Jacobs, PhD**, Professor in the Department of Diagnostic and Interventional Imaging at the McGovern Medical School, and **Vuvi H. Nguyen, PhD**, Assistant Professor in the Department of Diagnostic and Biomedical Sciences at the School of Dentistry.

We would like to extend our deepest gratitude and best wishes to former UTHealth Houston NRC Executive Committee Members, **Cameron Jeter, PhD**, and **Ponnada A. Narayana, PhD**, as they recently completed their service on this committee.



Jeter

will certainly be a wonderful asset in her new role in Kansas.

Dr. Jeter recently joined the Kansas Health Science Center, Kansas College of Osteopathic Medicine as Professor of Biomedical Sciences and Director of Academic Outcomes. Dr. Jeter's involvement with the UTHealth Houston NRC has been extraordinarily valuable over the past two decades; from her time as a graduate student volunteer for Brain Night for Kids through her service as a Member of the Executive Committee. She



Narayana

but also volunteering countless hours as a volunteer for our many annual events, including our most recent Neuroscience Poster Session. The NRC is grateful for his continued service over the past several decades.

Dr. Narayana has recently transitioned to the role of Professor Emeritus following retirement from his many roles at UTHealth Houston, including Professor of Diagnostic and Interventional Imaging, Vice-Chair for Research and the Director of Magnetic Resonance Research at McGovern Medical School. Dr. Narayana has served on this committee since its inception, not only providing invaluable guidance and direction,

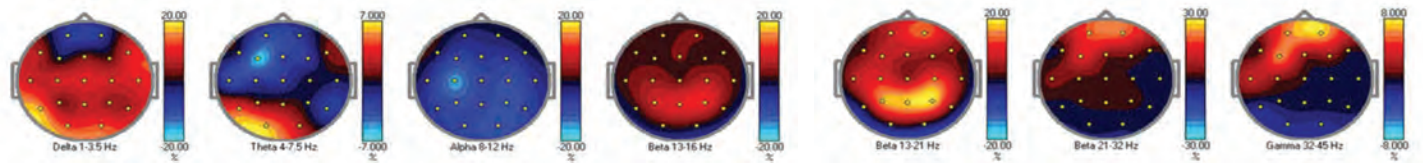


Figure 1. Brain mapping from qEEG analysis of neuropathy patients with the neuropathic biomarker.

Arrows show somatosensory strip. Image courtesy of Sarah Prinsloo, PhD.

physical function and cognition, have reduced quality of life, and are at risk of a second stroke. However, there is growing evidence that stroke survivors who are greater than 6 months post-stroke can realize long-term improvements in physical function with intensive therapy (Hall et al., *Cerebrovasc. Dis.* 42:247, 2016).

Despite the importance of stroke rehabilitation to functional outcomes, many stroke survivors have reduced access to this crucial care. More than half of all stroke survivors experience reduced mobility and are often dependent on a caregiver. In addition, most patients cannot afford the average cost of outpatient stroke rehabilitation, which is approximately \$17,000 during the first year after discharge from inpatient settings and is not covered by all forms of health insurance. Importantly, only 71% of stroke patients who live in rural Texas have access to outpatient stroke rehabilitation services.

Because stroke survivors often have other underlying chronic conditions (diabetes, hypertension, cardiac disease, obesity), the added stroke-related disabilities make their post-stroke management quite complex. The convolution of managing their care can leave some complications untreated or unrecognized. For example, persistent pain after stroke is reported in 30-50% of survivors, and significantly impacts patients' function, ability to participate in rehabilitation, and quality of life. Pain can be centrally mediated such as neuropathy, musculoskeletal as from contractures, or both central and musculoskeletal as is thought to occur with shoulder pain. Post-stroke pain is often underdiagnosed, inappropriately treated, or untreated altogether, mostly because the unclear pathophysiology leaves clinicians with a poor understanding of the causes. Additionally, variability in methodologies and pain conditions confounding current evidence leaves clinicians without the ability to effectively assess and treat post-stroke pain. Pain after stroke inhibits movement, which is critical to maintaining function and decreasing the irreversible effects of contracture. We recently completed a retrospective data analysis of 824 stroke survivors admitted to a large, urban, acute care facility, and preliminary findings demonstrate that close to half of these patients reported pain at time of discharge (Prinsloo et al., under review, *Cancer*).

In efforts to address the gap in knowledge regarding the causes of post-stroke pain, we have initiated a pilot study funded by PARTNERS (Providing Advancement Resources To Nursing Education, Research, and Students) of the UTHealth Science at Houston Cizik School of Nursing, examining the feasibility of quantitative EEG analysis (qEEG) in stroke survivors with post-stroke shoulder pain. In this preliminary study, we will be looking for spatial patterns in qEEG brain maps (see Figure

1) of post-stroke shoulder pain patients. qEEG spatial patterns related to pain perception have been found in other pain conditions such as a pancreatic cancer pain (De Vries et al., *J. Pain Res.* 6:815, 2013), lower back pain (Mayaud et al., *Eur. Spine J.* 28:2487, 2019; Teixeira et al., *Pain Med.* 23:558, 2022), head and neck cancer pain (Prinsloo et al., *Brain Topogr.* 32:283, 2019), tonic muscle pain (Li et al., *Front. Comput. Neurosci.* 10:45, 2016), and most recently in chemotherapy induced neuropathy (Prinsloo et al., *Integr. Cancer Ther.* 13:30, 2014; Prinsloo et al., *Cancer* 123:1989, 2017; Prinsloo et al., *J Pain Symptom Manage.* 55:1276, 2018). Upwards of 30% of those with post-stroke shoulder pain have pain refractory to any available intervention (Maxwell & Nguyen, *Curr. Phys. Med. Rehabil. Rep.* 1:1, 2013). We hope that finding central processes related to post-stroke pain will aid in the development of effective treatments as well as enable the identification of patients who would be most responsive to these interventions. It is our long-term plan to provide important and timely evidence that advances pain assessment and interventions in stroke survivors and enables participation in rehabilitation.

Another significant contributor to the complexity of post-stroke recovery is post-stroke cognitive impairment (PSCI). PSCI occurs in nearly half of all stroke patients within the first 6 months of injury (Mellon et al., *BMC Neurol.* 15:31, 2015; Lo et al., *Neurology* 93:e2257, 2019) and 1 in 5 stroke patients develop dementia (Craig et al., *J. Neurol. Neurosurg. Psychiatry* 93:180, 2022). Cognitive disabilities impact independence and impede quality of life, including returning to work. We examined the impact of stroke rehabilitation on PSCI in our stroke population. We reviewed 690 medical records of inpatient stroke rehabilitation patients and found that the odds of cognitive improvement for patients who received ≥ 186 average total therapy minutes per day were 2.09 times greater than those for patients who received ≤ 152 total therapy minutes (95% CI 1.17-3.71, $p=0.012$) (Aggarwal et al., *Stroke* 52(Suppl_1):AP69, 2021). This study highlights the need for inpatient stroke rehabilitation for cognitive improvement.

Home-based stroke rehabilitation using telehealth technologies (e.g., telerehabilitation) increases access to stroke rehabilitation because it can be performed remotely and is less costly than rehabilitation in the clinical setting. Studies have shown that stroke survivors who receive telerehabilitation have similar upper extremity (Cramer et al., *JAMA Neurol.* 76:1079, 2019) and cognitive functional gains to those who received face-to-face rehabilitation (Lawson et al., *J. Int. Neuropsychol. Soc.* 26:58, 2020). Virtual reality (VR) has been shown to be beneficial for stroke rehabilitation in the clinical setting, but the VR systems used in prior studies are expensive (minimum of \$1000) and/

or are not commercially available. We received the IoT (Internet of Things) and Aging in Place Joint Seed Grant Program from the Cizik School of Nursing and UTHealth Consortium in Aging to study the Oculus VR headset as it may be a cost-effective way at \$400 to deliver stroke rehabilitation in the home setting without the presence of a rehabilitation therapist. The Oculus VR allows the stroke patient to be fully immersed in a 3-D gaming environment that simulates activities of daily living. Combining motor and cognitive rehabilitation, known as dual tasking, may promote neuroplasticity, the brain's ability to develop new neural connections and may lead to improved functional recovery. Because the Oculus VR is highly interactive, it may prove to be more effective than telerehabilitation, where the therapist provides rehabilitation over a video link, as this can lead to a lack of motivation and patient satisfaction over time. The Oculus VR may not be an appropriate intervention in stroke patients who cannot hold the controller with their affected hand or who have a history of vertigo or motion sickness. Our study protocol was developed by highly experienced investigators

and experts in stroke rehabilitation and will determine the feasibility, usability, and acceptability of the Oculus VR to chronic stroke patients (>6 months to 2 years post-stroke) and their caregivers for remote stroke rehabilitation.

There remains a paucity of interventions for either post-stroke pain or cognition, two related patient factors each with a large impact on a patient's ability to participate in rehabilitation and recover function. Post-stroke pain remains an under examined and poorly understood sequelae of stroke. Our future research directions are aimed at providing important and timely evidence that advances pain assessment and interventions in stroke survivors and enables participation in critical rehabilitation. Cognitive decline is also a detrimental complication after stroke needing further investigation. Interventions that are targeted for post-stroke pain (e.g., qEEG) may also prove to be beneficial for PSCI. However, randomized controlled trials are needed to determine the effectiveness of these interventions in stroke survivors.

About the Authors

Seema Aggarwal, PhD, APRN, AGNP-C, is an Assistant Professor at the Cizik School of Nursing and is the Director of the Vascular Cognitive Impairment research program at the Institute for Stroke and Cerebrovascular Disease, UTHealth Houston. Dr. Aggarwal's research focus is on vascular predictors of cognitive decline and dementia and includes MarkVCID, DISCOVERY and the Cameron County Hispanic Cohort study in collaboration with the UTHealth School of Public Health at Brownsville, Texas.

Deniz Dishman, PhD, CRNA is an Assistant Professor at the Cizik School of Nursing and Director of the Post-stroke Pain research program at the Institute for Stroke and Cerebrovascular Disease, both of UTHealth Houston. Dr. Dishman's research focus is on post-stroke pain management, specifically to dually develop effective treatments for post-stroke pain and remove the barriers to intensive rehabilitation. Dr. Dishman's current pilot study, "Biomarkers Illuminating Post-Stroke Pain (BIPAS)" is funded through the generosity of the Partners Nursing Research Award.

news & information

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

UTHealth Houston President Giuseppe Colasurdo, MD, recently made several position announcements regarding UTHealth faculty. John Hancock, MA, MB, BChir, PhD, ScD, has been appointed as executive dean of McGovern Medical School. **Carmen Dessauer, PhD**, will serve as chair ad interim of the Department of Integrative Biology and Pharmacology. LaTanya Love, MD, will be the permanent dean of education, and **Richard Andrassy, MD**, will join the President's Office in the role of senior vice president for clinical and faculty affairs.

Erin Furr-Stimming, MD, professor of neurology, and William G. Ondo, MD, Director of the Movement Disorder Clinic at Houston Methodist Hospital, recently published the book, "Movement Disorders in Psychiatry," through Oxford University Press. This book provides an overview of the clinical definitions and pathophysiology of movement disorders, and discusses movement disorders associated with drugs of abuse and psychotropic medications, movement disorders seen in primary psychiatric disorders, and diseases with concurrent movement disorder and behavioral symptoms. T

Diane Santa Maria, DrPH, MSN, RN, dean of Cizik School of Nursing at UTHealth Houston, spoke at the UTHealth Houston's Diversity and Equity Speaker Series in October, highlighting increased rates of homelessness, suicide, and mental health issues

facing sexual- and gender-minority youth, compared to their heterosexual and cisgender peers.

The 2022 UTHealth Houston Mood Disorders Conference, "From Neurobiology and Diagnosis to Improved Therapeutics," was held in October. Directed by **Jair Soares, MD, PhD**, and **Rodrigo Machado-Vieira, MD, PhD**, the conference highlighted the public health significance of bipolar disorder and explored the development of early intervention strategies, and recent advances in recognition and treatment of these co-occurring disorders.

The 5th Annual UTHealth Neurology Update Symposium was held in November. This event focused on new migraine medications, thalamic neuromodulation for the treatment of epilepsy, novel deep brain stimulation technologies for movement disorders, recent advances in the management and treatment of Multiple Sclerosis, and provided an update on stroke prevention,

UTHealth Houston is co-hosting the "Artificial Intelligence in Epilepsy and Neurological Disorders" first international conference March 7-10, 2023, in Breckenridge, Colorado. The conference's primary objective is to highlight the latest algorithms, machine learning, deep learning, and artificial intelligence advancements in epilepsy and neurological disorder clinical care.

hypoactive delirium. Agitated delirium is the easiest subtype to detect; it exacts a high energy-consumption toll on patients with compromised pathophysiological reserves, and it is the most difficult for family and healthcare staff to witness.

The prevalence of delirium is variable by patient population and setting, but is highest in intensive care unit (ICU) patients (pooled prevalence = 32%, Krewulak et al., *Crit. Care Med.* 46:2029, 2018) and inpatient palliative care units (pooled prevalence = 35%, Watt et al., *Palliat. Med.* 33:865, 2019). The estimated rates approach 70% in mechanically ventilated adults in the ICU (Almeida et al., *PLoS ONE* 9:e85332, 2014) and 88% in palliative care patients within days of end of life (Duff et al., *BMC Psych.* 20:182, 2020).

The first author first encountered agitated delirium in the 1970s in ICU patients 48-72 hours after cardiac surgery. Patients suddenly developed hallucinations and delusions; agitated movements; and heightened autonomic nervous system manifestations of tachycardia (a heart rate over 100 beats a minute), hypertension, tremors, and diaphoresis (extensive sweating). Their voices, facial expressions, and postures connoted extreme fear, which no amount of reassurance quelled. Interviews with these patients and their loved ones after transfer to the general floor, and again at their 6-week post-operative visit in the clinic, consistently showed persistence of the hallucinations and delusions, but abatement of agitated movements, autonomic overload, and extreme fear across the time of follow-up.

At that time, and for decades later, psychiatrists posited that delirium in ICU patients was due to sleep fragmentation and paradoxical sensory deprivation in the high-tech environment, and recommended such strategies to maintain patient orientation as calendars and clocks at the bedside; frequent reorientation to place, person, and time; windows in ICU patient rooms; liberal family visitation; and bundled nursing care that leaves uninterrupted time for sleep. Despite implementation of the strategies, delirium persists in significant numbers of patients in the ICU.

Delirium is seen also in palliative and hospice care settings: the first author's most recent experience with agitated delirium occurred when she was the primary caregiver for her husband who had widespread metastasis of cancer and was enrolled in at-home hospice care. Her husband developed agitated delirium 5 days before his death. Despite severe cachexia and having been unable to take food for weeks and water for days due to a comatose state, he suddenly exhibited agitated delirium with unimaginable strength, tachycardia, expressions and behaviors that suggested stark terror, and the indomitable goal of getting out of bed.

Patients in the ICU and near end-of-life share commonalities: frailty, high severity of illness, physiological and psychological

stress, and reduced mobility, and the treatment for delirium is similar across these clinical settings. Nonpharmacological management reflects the strategies advocated in the 1970s, but there is little evidence that such strategies prevent or ameliorate agitated delirium. Thus, pharmacological management is initiated with antipsychotic and/or sedative drugs. Such drugs mute the cognitive and behavioral disturbances to varying degrees, but likely do not address the mechanism(s) of delirium.

The pathogenesis of delirium in ICU and end-of-life care settings is not at all clear, perhaps in part because delirium occurs in patients with pathological conditions that confound possible underlying mechanisms. A heightened stress response and inflammatory state precipitate and/or accompany delirium in ICU and acute palliative care patients. Multiple studies in the field of psychoneuroimmunology have provided evidence that the duration and intensity of stress are related to the breadth and magnitude of changes in inflammatory biomarkers (Khan et al., *Crit. Care Med.* 48:353, 2020; Kiecolt-Glaser et al., *J. Consult. & Clin. Psych.* 76:537, 2002).

Neuroinflammation is a hypothesized mechanism (**Figure 1**) that has stimulated the search for inflammatory biomarkers of delirium. Circulating pro-inflammatory cytokines (e.g., interleukin [IL]-1 β and IL-6 and tumor necrosis factor-alpha [TNF- α]) disrupt the blood-brain-barrier, allowing peripheral immune cells to enter the brain, and activate cerebral mediators of inflammation.

The investigation of biomarkers may shed light on the pathological mechanism(s) of delirium, which then can inform treatment. Cytokines, signaling molecules that mediate an inflammatory response, are expressed in several types of tissues, including neurons. The most studied cytokines in stress states include the pro-inflammatory IL-1 β , IL-8, and TNF- α ; the anti-inflammatory IL-10; and IL-6, which has both pro- and anti-inflammatory properties. Inflammation also contributes to the pathogenesis of advanced cancer and its clinical manifestations. In a recent systematic review (Amgarth-Duff et al., *BMC Psych.* 20:182, 2020) of the literature with overlap of putative biomarkers in delirium and advanced cancer, 41 biomarkers were found to be common in both delirium and advanced cancer. The most studied biomarkers in these 41 studies included the inflammatory mediators of IL-6, IL-8, IL-10, and TNF- α .

We are conducting a double-blind, double-dummy, multi-site, randomized clinical trial (David Hui, PI; ClinicalTrials.gov NCT03743649) to compare treatment effects of various combinations of the antipsychotic haloperidol, the benzodiazepine lorazepam, and placebo in acute palliative care unit patients with cancer and persistent agitated delirium despite treatment of reversible causes, standard non-pharmacologic therapies, and low-dose haloperidol. Secondary objectives of this study include exploring (a) baseline levels of the cytokines IL-6, IL-8, and IL-10, and S100B, a calcium-binding protein that acts as a neurotrophic factor during

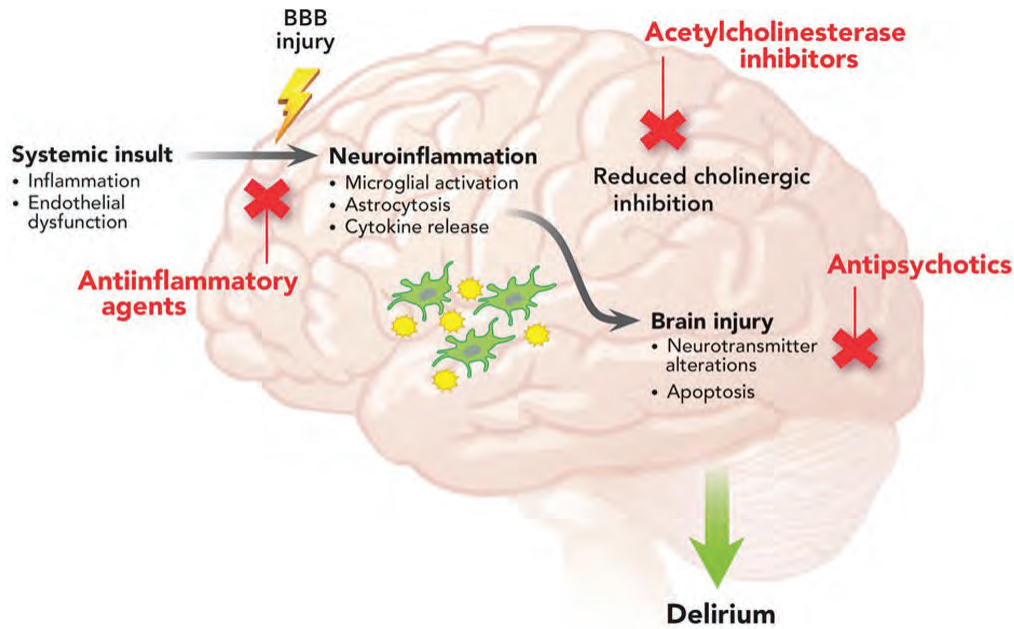


Figure 1. Proposed mechanisms of delirium and its treatment. We hypothesize that neuroinflammation is a mechanism of agitated delirium in patients at the end of life. Peripheral immune cells may cross the blood-brain barrier and the brain's immune cells (microglia) may be activated by pro-inflammatory cytokines that cross the blood-brain barrier.

nervous system development, but as an indicator of brain damage in the adult; and (b) the extent to which the biomarkers predict treatment response. Blood specimens are drawn at the onset of agitated delirium and within 24 hours of treatment with the randomized therapy.

We could not locate published studies of predictors of treatment response to neuroleptics or benzodiazepines in patients with advanced cancer at end of life with agitated delirium. van den Boogaard and colleagues found that levels of the stress hormone cortisol, IL-6, IL-8, IL-10, and TNF- α , but not S100B, were significantly higher in delirious than non-delirious ICU patients (van den Boogaard et al., *Crit. Care* 15:R297, 2011). These data suggest neuroinflammation, as opposed to structural neuronal injury, as a possible mechanism for agitated delirium.

The sequelae of delirium are consequential, and include prolonged hospital stay and cognitive decline, neuronal injury, and progression of preexisting dementia. Beyond patient consequences, delirium is associated with financial and emotional burdens. In the U.S., delirium is responsible for up to \$152 billion in health care costs annually and precipitates feelings of worry and fear among patients, family caregivers, and healthcare professionals. Whether viewed as an outcome statistic or as the sight of a patient in distress, multiple studies underscore delirium's association with both acute and long-term adverse consequences. The search for the underlying mechanism(s) of agitated delirium to guide rational and effective treatment is imperative on behalf of the large numbers of patients in the ICU, acute palliative care, and hospice care units who are terrorized by the experience.

About the Authors

Sandra K. Hanneman, PhD, RN, FAAN, is the Jerold B. Katz Distinguished Professor for Nursing Research and tenured professor in the Research Department at the UTHealth Houston Cizik School of Nursing. Before entering academia, she practiced for many years as an ICU nurse and pulmonary critical care clinical nurse specialist.

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David Hui, MD, MSc, is associate professor and clinician investigator, Department of Palliative, Rehabilitation and Integrative Medicine, Division of Cancer Medicine, The University of Texas M. D. Anderson Cancer Center.

In the Spotlight

28th Annual Neuroscience Poster Session Saturday, December 3, 2022 - UTHealth Cooley University Life Center

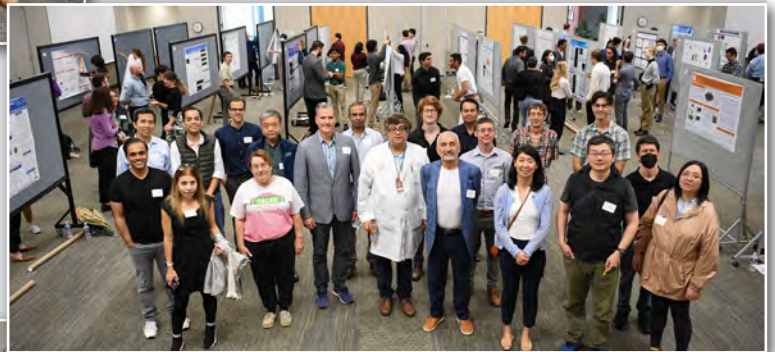
The NRC hosted the 28th Annual Neuroscience Poster Session on Saturday December 3, 2022. Faculty, postdoctoral fellows, graduate and medical students, as well as undergraduate students, from four Houston institutions gathered to present and discuss their neuroscience research. The large group included the Departments of BioSciences, Psychology, and Electrical and Computer Engineering at Rice University, the Department of Neuroscience at Baylor College of Medicine, the UTHealth Neuroscience Research Center, and for the first time, the University of Houston.

Seventy-five research posters were presented to faculty judges from each institution and prizes were awarded for the best poster presentations in each category. For a complete list of winners, please visit our website. Congratulations to all of the winners from the 28th Annual Neuroscience Poster Session!



Winners from the 28th Annual Neuroscience Poster Session.

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



Undergraduate, graduate, and medical students, as well as postdoctoral fellows and research scientists, presented their recent findings at the Poster Session.



UTHealth Houston Poster Session Winners: University of Texas MD Anderson Cancer Center UTHealth Houston Graduate School of Biomedical Sciences students, Xu Zhang (1st Place), Melissa Franch (2nd Place), and Cana Quave (3rd Place), pose with their ribbons after receiving prizes for the Dee S. and Patricia Osborne Endowed Scholarship in the Neurosciences.



In the Spotlight

Scenes from the UTHealth Houston Neuroscience Research Center's annual reception at the Society for Neuroscience Meeting, held on November 15, 2022 at the San Diego Wine and Culinary Center.



Upcoming Events


Brain Night for KIDS



2023 BRAIN AWARENESS WEEK
TheHealthMuseum

Thursday March 16th
Free Event
Open to the Public


DISTINGUISHED LECTURE
in the
Neurosciences

ANN GRAYBIEL, PHD
INSTITUTE PROFESSOR,
MASSACHUSETTS
INSTITUTE OF TECHNOLOGY
INVESTIGATOR AT THE MCGOVERN
INSTITUTE

MAY 11, 2023

***PLEASE CHECK WEBSITE
FOR MORE INFORMATION**

**Annual Public Forum
Free Event**



**Post-COVID
Brain Health**

**April 15, 2023
10:30am to Noon**

**Cooley University
Life Center**
7440 Cambridge St
Houston, TX 77054

Moderated by
Antonio Teixeira, MD, PhD
Professor and Director of the
Neuropsychiatry Program

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



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The Neuroscience Research Center Newsletter

Editor: Anne Hart, PhD

Design: Brad Slack, ImageSet

The Neuroscience Research Center is a component of
The University of Texas Health Science Center at Houston.

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