NRC newsletter

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Retinal Imaging as Proxy for CT Brain Imaging in Acute Stroke Care

Luca Giancardo, PhD & Amanda Jagolino-Cole, MD

Giancardo

Jagolino-Cole

Abstract: It is an undisputed fact that the faster a stroke is diagnosed and treated, the better the outcome for the patient. "Time is brain," yet in order to intervene with the most appropriate treatment, it is essential to image the patient's brain with a CT scanner. CT scanners are not available in ambulances, with the rare exception of mobile stroke units, and because of their weight, are currently not used in aircraft. Due to the homology between retinal and cerebral vessels, and the ease with which retinal images can be acquired non invasively, we are studying these image modalities to develop a machine learning based-tool for identifying stroke events and stroke types, effectively acting as a proxy for brain imaging.

In the United States alone, more than 700,000 people have a stroke every year. It is one of the leading causes of death and disability in the industrialized world. Out of all strokes, 87% are ischemic (blood flow to the brain is obstructed by a clot), and the other 13% involve hemorrhagic events (blood vessels rupture in the brain). The best tools at our disposal for treating stroke are the ones for the more common ischemic type; these are thrombolytics (drugs that can break up blood clots), and endovascular thrombectomy (a surgical procedure to mechanically remove the blood clot). However, the efficacy of these treatments is directly connected to intervention time and they need to be administered within a few hours from the stroke event - the sooner the better. This poses significant challenges, as patients need to be rushed to stroke centers in order to have their brain imaged with a CT or MRI scanner to diagnose the stroke and stroke type. If we had a way to perform this diagnosis in an ambulance, medical personnel would be able to start to administer drugs that can break up blood clots immediately, with much better outcomes for the patients. This hypothesis has been successfully tested with mobile stroke units, which are ambulances equipped with a CT scanner (Walter et al., *Lancet Neurol*. 11:397, 2012). While effective, this approach is not easily scalable around the country due to the cost and space requirements of a CT scanner.

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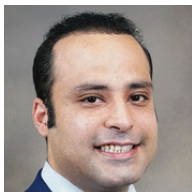
Prediction of Functional Improvement in Stroke Patients During Inpatient Rehabilitation with Machine Learning

Yan Chu, MS & Shayan Shams, PhD

Chu



Shams

Abstract: Stroke is among the leading causes of death worldwide, and it often leads to a severe long-term disability, including both physical and cognitive issues that require continued monitoring and caregiving from families and the community. An accurate prediction of potential functional and cognitive outcomes, provided at the acute stage of stroke, could be a key part of a personalized rehabilitation plan, improving communication among the patient, their family, and clinicians regarding possible outcomes and expectations. With the extraordinary ability of feature extraction and pattern recognition from multidimensional data, state-of-the-art machine learning algorithms empower us to identify patients who will make a significant functional improvement from admission discharge during inpatient rehabilitation. This study aims at developing a framework to predict functional improvement in acute stroke patients using Functional Independence Measure (FIM) and Continuity Assessment Record and Evaluation (CARE). We evaluated and compared both scoring systems for initial functional assessment in the context of predictive modeling. Using Shapley values, we estimated the marginal contribution of each predictor to the final model's prediction of stroke recovery and identified the most influential factors.

Stroke is among the leading causes of death worldwide, taking the lives of 5.5 million in 2016 (Gorelick, *Lancet Neurol*. 18:417, 2019). Despite early treatment, stroke survivors often have a severe long-term disability, including both physical and cognitive issues that require continued monitoring and caregiving from families and the community. Stroke prevalence is projected to rise with the aging of the United States population. By 2030, 3.9% of the U.S. adult population is projected to have had a stroke (Ovbiagele et al., *Stroke* 44:2361, 2013). The significant social impact, economic strain, and personal ramifications of poor patient outcomes justify continued research to improve stroke mortality and survivor quality of life.

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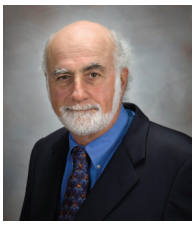
UTHealth | Neuroscience Research Center
The University of Texas Health Science Center at Houston

Director's Column

From the Director, John H. Byrne, PhD



A major component of neuroscience research at The University of Texas Health Science Center at Houston (UTHealth) is housed at the McGovern Medical School—within its Departments of Neurobiology and Anatomy, Neurology, Neurosurgery, Psychiatry and Behavioral Sciences—along with other basic science and clinical departments. Notwithstanding, exciting major neuroscience efforts are also found in the Cizik School of Nursing, School of Dentistry, School of Biomedical Informatics (SBMI), and School of Public Health. In this issue of the *Newsletter*, we are pleased to share some highlights of neuroscience research being conducted at the SBMI. Jiajie Zhang, PhD, SBMI dean and professor, The Glassell Family Foundation Distinguished Chair in Informatics Excellence, and Director of the National Center for Cognitive Informatics and Decision Making (NCCD) observed the following regarding the trends and direction of neuro-related research:

Brain and Neurosciences inspired artificial neural network research, which got an early start in the 1960s, led to a major algorithm breakthrough (the Backpropagation learning algorithm) in the 1980s, and finally contributed to the deep learning revolution in the 2010s. Now, new technologies have a firm basis in neural networks—and, combined with massive data and powerful computing power, neural network research, especially deep learning, is contributing back to brain and neurosciences in many areas, such as the brain imaging of stroke patients; the diagnosis, prognosis, and treatment of neurodegenerative diseases, including Alzheimer's and Parkinson's; and informing combination drug therapies and the genetic basis for psychiatric disorders. SBMI is proud of having a team of top-notch AI researchers who are actively involved in helping drive and shape brain and neurosciences research.

Two research articles from SBMI faculty are featured in this Newsletter. The first article, by Luca Giancardo, PhD, assistant professor at SBMI, and Amanda Jagolino-Cole, MD, assistant professor of neurology at McGovern Medical School, describes a project focused on developing retinal imaging analysis as a proxy for acute stroke CT imaging. Time is of the essence in stroke care, and this technology would enable the creation of lifesaving portable devices that can be used in any ambulance in the country, thereby enabling faster treatment and, ultimately, better patient outcomes. Also working in stroke care, Shayan Shams, PhD, assistant professor at the SBMI, and doctoral student, Yan Chu, MS, have contributed the second research article in this *Newsletter*. Their group is using machine learning to predict rehabilitation outcomes following stroke in order to help clinicians, patients, and their families better determine realistic expectations and achieve the best possible outcomes for patients.

Neuroscience research at SBMI is highly collaborative, with faculty spanning multiple UTHealth institutions and departments, while also involving numerous external partners. Indeed, much of the work discussed in this issue relates to SBMI's collaborative work using machine learning models, with the ultimate goal of contributing toward revolutionizing personalized medicine. For example, in March of 2021, the SBMI hosted its fourth DATATHON event, a healthcare-focused challenge among undergraduate and graduate students from Houston-area and Gulf Coast Consortia institutions. Each highly competitive event features a different theme, and the fourth DATATHON required students to utilize their computational modeling and programming skills, along with their knowledge of machine learning, to build an algorithm that would predict rehabilitation success and outcomes for stroke patients. Again, the ultimate goal of this work is to create a personalized rehabilitation plan that aids in better predicting outcomes, based on changes in cognitive and motor function after stroke. For the theme of the fourth DATATHON, Xiaoqian Jiang, PhD, professor and director of the Center for Secure Artificial intelligence For hEalthcare (SAFE) at SBMI, worked with Shayan Shams, PhD and Yejin Kim, PhD, assistant professor at SBMI, as well as Sean Savitz, MD, professor of neurology and Director of the UTHealth Institute for Stroke and Cerebrovascular Disease. The first DATATHON, held in September of 2019, asked the student participants to develop models that would predict the risk of sudden unexpected death in epilepsy through the use of EEG features after epileptic seizures. The second DATATHON directed students to build algorithms that predicted and ranked promising drugs in given cancer cell lines (February, 2020); in the third DATATHON, students were asked to predict COVID-19 infection and mortality trends in Greater Houston (August, 2020). Each machine learning DATATHON has resulted in a number of interesting and potentially viable solutions to real-world problems—by bridging the gap between science and medicine, encouraging new data scientists to sharpen their skills, and building collaborations between UTHealth departments and local institutions.

In addition to their work on DATATHON events, both Dr. Jiang and Dr. Kim develop machine learning models to integrate clinical and/or biological data with practical applications and novel treatments. Dr. Jiang focuses on healthcare privacy, data mining, and computational phenotyping. He and his group work on projects that range from drug repurposing to identify potential new COVID-19 treatments, to collaborating with the UTHealth Stroke Institute in using big data to study new drug combinations for the treatment of Alzheimer's disease (AD). Dr. Kim develops innovative algorithms for computational phenotyping and sequential decision making models for use in clinical practice. Recently, she collaborated with Mya Schiess, MD, professor of neurology, on novel Parkinson's disease treatment regimens, as well as with Paul Schulz, MD, professor of neurology, on AD multimodal phenotyping.

Also using big data to advance precision medicine, Degui Zhi, PhD, an associate professor and one of the founding members of the SBMI Center for Precision Health, is currently collaborating with Myriam Fornage, PhD (Professor at the Institute of Molecular Medicine Center for Human Genetics) and Shuiwang Ji, PhD

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(Texas A&M University) on a new project that aims to create AD imaging endophenotypes using deep learning methods. This emerging area of machine learning research, combined with advanced neuroimaging and whole-genome sequencing data, will hopefully lead to the discovery of new genes relevant to AD, a better understanding of the molecular basis of the disease, and potential new treatments. Dr. Zhi's research also includes development of the RaPID method for analysis of large genotyped cohorts, as well as the use of deep learning methods for the analysis of electronic health records (EHRs).

Hua Xu, PhD, an SBMI professor and Associate Dean for Innovation, has also focused his attention on advancing AD treatment through two unique projects utilizing extant data. In collaboration with Dr. Cui Tao, professor and Director of the Center for Biomedical Semantics and Data Intelligence, Dr. Xu seeks to develop novel natural language processing (NLP) and ontology approaches to extract detailed clinical information of patients from their EHRs. Using NLP and ontology methods allows for a much more rapid extraction of relevant patient data—inclusive of information on diagnosis, prognosis, treatment, and response—to support clinical studies. In addition, a collaboration with Yonghui Wu, PhD (University of Florida) aims to detect drugs that can be repurposed for AD treatment using data derived from EHRs. By discovering new uses for existing drugs, the protracted FDA approval process for new drugs can be circumvented, attendant clinical trials using repurposed drugs can be rapidly designed and implemented by scientists and physicians, and the time required to bring effective new treatment modalities to patients can be greatly reduced.
Amy Franklin, PhD, an associate professor, Associate Dean for Student, Faculty, and Community Affairs at SBMI, and an NRC Executive Committee member, merges her background in psychology and linguistics with bioinformatics and technology to study decision making in the emergency department through her work to characterize communication and information-seeking strategies among medical staff in critical care environments. Dr. Franklin's research expands to online and mobile platforms as well; in this regard, she utilizes mobile health technologies to monitor stress management and identify methods for adapting educational content for mobile platforms. Most recently, she has been focused on the use of machine learning and linguistics-based text analysis to identify behavioral changes in tobacco cessation among users of an online platform.

Due to space constraints, I am unfortunately only able to provide details for a few existing and emerging projects from SBMI, but I would invite you to continue exploring their wide-reaching work and learning about their exceptional faculty and programs at https://sbmi.uth.edu. In subsequent issues we will highlight neuroscience research in the other schools of UTHealth.

At this writing, it appears that NRC activities will be returning to near-normal in the fall. We look forward to seeing you (hopefully in-person) at one of our many programs this next academic year. Information about the annual Neurobiology of Disease course held in the fall and the Neuroscience Poster Session held in December will be added to our website throughout the coming months.

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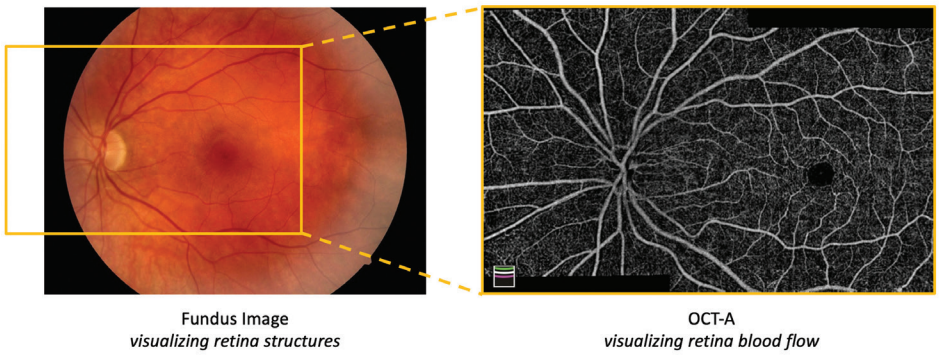

Figure 1. Example of two retinal imaging modalities.

On the left, an example of a fundus image of a healthy retina. On the right, an example of the 2-dimensional projection of an OCT-A image of the same retina. The yellow box indicates the shared field of view of the two modalities.

Due to the homology between retinal and cerebral vessels, retinal images have been studied as markers for cerebrovascular events. Fundus images provide a structural view of the retina vasculature and optic disc shape (see Figure 1). Previous studies have already identified retinal vascular abnormalities in patients who have had strokes in their medical history, such as arteriolar narrowing and reduced vessel fractal dimension (a measure of vasculature "complexity"), which are used as imaging biomarkers associated with the risk of stroke (Wu et al., *Ophthalmol*. 10:109, 2017). However, these have never been studied in the acute phases of stroke. Recent advances in optical coherence tomography angiography (OCT-A) gives us the ability to measure retinal blood flow directly, which is affected by alterations in systemic circulation. Both OCT-A and fundus images are non-invasive imaging modalities that do not require injection of contrast agents or dilation of the pupil. In addition, the optics required for their acquisition can, in principle, be miniatured in a device not larger than a shoebox, with components orders of magnitude cheaper than the those of a CT scanner. These characteristics make them the ideal candidate for a device that can potentially be used in any ambulance.

However, the exact retinal changes that occur during an acute stroke are still not known. Nor is it known whether we can

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grants&awards

The 2021 Champions of Clinical Learning Environment awards were presented by NRC member **Vineeth John, MD,** professor of psychiatry and behavioral sciences and one of the directors of Learning Environment at McGovern Medical School. Recipients of the award included NRC members from the Department of Psychiatry and Behavioral Sciences: **Chase Findley, MD,** associate professor, **Gregory Hestla, MD,** assistant professor, and **Hanjing Emily Wu, MD, PhD,** assistant professor; the Department of Neurology: **Pedro Mancias, MD,** professor, and **Shivika Chandra, MD,** assistant professor; and the Department of Neurosurgery: **Jay-Jiguang Zhu, MD, PhD,** professor and director of neuro-oncology.

Two members of the Department of Neurobiology and Anatomy, **Valentin Dragoi, PhD,** the Rochelle and Max Levit Distinguished Professor in the Neurosciences, and **Andrea K.H. Stavoe, PhD,** assistant professor, received the Faculty Science and Technology Acquisition and Retention (STARs) award from the University of Texas System's Board of Regents.

Holger Eltzschig, MD, PhD, professor and chair of the Department of Anesthesiology, John P. and Kathrine G. Distinguished University Chair, and associate vice president for Translational Research and Perioperative Programs, was virtually inducted into the Association of American Physicians (AAP) in April.

Gabriel Fries, PhD, assistant professor of psychiatry and behavioral sciences, was awarded the Young Investigator Grant from the American Foundation for Suicide Prevention (AFSP) that will assist him in his research focusing on the biology of suicide and bipolar disorder.

Ruth Heidelberger, MD, PhD, professor of neurobiology and anatomy and Frederic B. Asche Chair in Ophthalmology, received a competitive renewal of an NIH/National Eye Institute grant, "Mechanisms of Neurotransmission in Vertebrate Retina," now in its 21st year of funding. The research program examines the activity-dependent post-translational modification of a synaptic protein and its roles in the regulation of membrane fusion, neurotransmitter release, and the transmission of visual information in the mammalian retina.

Claire E. Hulsebosch, PhD, professor of neurobiology and anatomy, received the 2021 John H. Freeman Award for Faculty Teaching. Chosen by the senior class at McGovern Medical School, this award recognizes the most outstanding basic science faculty member.

Bhavani Iyer, OD, associate professor of ophthalmology and visual science and director of the Dan Arnold Center for Vision Rehabilitation, received grants from the Houston Delta Gamma Foundation and Houston Sports Lions Club for a grant titled, "Vision rehabilitation therapy services grant." This will help fund vision rehabilitation therapy services and orientation and mobility services for the underserved population. Dr. Iyer also received an award of Diplomate in Low Vision, a peer administered, highest level of certification in the field of low vision and vision rehabilitation from the American Academy of Optometry.

Radha Korupolu, MD, assistant professor of physical medicine and rehabilitation, received a grant from the UTHealth Center for Clinical and Translational Sciences (CCTS) for a project titled, "Comparison of mechanical ventilation with low and high tidal volumes in acute spinal cord injury: A pilot randomized comparative effectiveness trial."

Samden Lhatoo, MD, John P and Kathrine G McGovern Distinguished University Professor of Neurology, and Executive Vice Chair of Neurology, along with Orrin Devinsky, MD and Daniel Friedman, MD (NYU Grossman School of Medicine), received a research grant from the NIH/Department of Health and Human Services to review multi-center data collected from Sudden Unexpected Death in Epilepsy (SUDEP) patients and control patients and analyze ictal and postictal electroclinical features of seizure severity, including postictal generalized EEG suppression, decerebrate, and decorticate posturing, postictal bradycardia with or without asystole, and post convulsive central apnea. The grant is titled, "Advancing SUDEP Risk Prediction Using Case-control and Big Data Approaches."

Louise D. McCullough, MD, PhD, professor and Roy M. and Phyllis Gough Huffington Distinguished Chair in the Department of Neurology, received the 2020 Paul E. Darlington Mentor Award for GSBS Faculty. This award recognizes a faculty member who has made an exceptional impact as a mentor, on both students and faculty.

Rodrigo Morales, PhD, associate professor of neurology, received an award from the Alzheimer's Association for a project titled, "RAPID supplement on characterization of natural and synthetic Aβ conformational strains." This award is a COVID-19 related supplement provided to current Alzheimer's Association Awardees. The theme of the main project is to analyze the pathological consequences of conformationally different synthetic Aβ aggregates in mouse models, specifically focused on their interactions with the misfolding of tau proteins.

Dr. Morales also received a grant with **Tatiana Barichello, PhD,** assistant professor of psychiatry and behavioral sciences, from the NIH/National Institute of Aging for a grant titled, "Infection-driven mechanisms associated with Alzheimer's disease pathology." This proposal will examine the role of sepsis and meningitis in brain amyloid and tau pathology, associated cognitive decline, and brain inflammation.

Joy Schmitz, PhD, professor of psychiatry and behavioral sciences, was selected as the co-recipient of the 2020 President's Scholar Award for Excellence in Research. Awarded by UTHealth President, Giuseppe N. Colasurdo, MD. Dr. Schmitz was acknowledged for her significant contributions to the field of substance abuse disorders, scientific leadership within the Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, and her mentorship of junior investigators.

Rachael Sirianni, PhD, associate professor of neurosurgery, with Sarah Stabenfeldt, PhD (Arizona State University), received an R01 from the NIH/National Institute of Neurological Disorders and Stroke for a grant titled, "Exploiting sex-dependent brain injury responses for nanoparticle therapeutics injury."

Gary Spiegel, MD, associate professor of neurology, received the Patient Choice Award from the Joe Niekro Foundation, which recognizes a neurological medical professional for their ongoing efforts in the long-term support of patients and families, and is nominated by the foundation's survivor community.

Argyrios Stampas, MD, associate professor of physical medicine and rehabilitation and director of Spinal Cord Injury Medicine Research at TIRR Memorial Hermann, received a grant from the National Science Foundation for a collaborative project titled, "Collaborative research: Assistive robotics and functional electrical stimulation: A synergistic combination to reanimate paralyzed arms." Dr. Stampas is the co-PI, working with Marcia O'Malley (PI; Rice University).

Jin H. Yoon, PhD, assistant professor of psychiatry and behavioral sciences, was awarded a pilot grant from the McGovern Medical School to examine problematic opioid use following traumatic injuries. This proposal will form a collaboration between the Center of Neurobehavioral Research on Addiction (CNRA) in the Faillace Department of Psychiatry and Behavioral Sciences (Joy Schmitz, PhD) and the Center for Translational Injury Research (CeTIR) in the Department of Surgery (John Harvin, MD).

Jay-Jiguang Zhu, MD, professor of neurosurgery and director of neuro-oncology, received a Cancer Prevention & Research Institute of Texas (CPRIT) grant entitled, "Development of artificial intelligence framework for assessment of responses to treatment and automated tumor volume measurement in glioblastoma."

Graduate Students & Postdoctoral Fellows

Camila Lima, PhD, a postdoctoral fellow in the Faillace Department of Psychiatry and Behavioral Sciences, mentored by **Gabriel Fries, PhD,** and **João de Quevedo, MD, PhD,** was presented with the prestigious and highly competitive Samuel Gershon Junior Investigator Award at the 23rd Annual Conference of the International Society for Bipolar Disorders. This award recognizes the next generation of leaders in the bipolar disorder field.

Russell Milton, a graduate student in the laboratory of **Valentin Dragoi, PhD,** the Rochelle and Max Levit Distinguished Professor in the Neurosciences, received the Dean's Research Award and presented his work, "Leveraging wireless neuro-technologies to investigate state-of-mind in freely-moving monkeys," at the Student Research Symposium and the Dean's Research Award Ceremony.

Khush Patel, MD, Tanjida Kabir, Jie Liang, Yaobin Ling, and Shikha Tripathi received 3rd place in the fourth overall UTHealth SBMI DATATHOM held in March 2021 for graduate students and postdoctoral fellows. These individuals utilized their programming skills and knowledge of machine learning to build an algorithm to predict stroke patient rehabilitation scores.

Nabina Paudyal, a graduate student in the laboratory of **Vasanthi Jayaraman, PhD,** professor of biochemistry and molecular biology, received the Dean's Research Award and presented her work, "Kainate receptors (KARS): Pre-synaptic and post-synaptic membrane in the mammalian central nervous system," at the Student Research Symposium and the Dean's Research Award Ceremony.

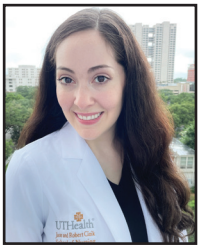
Congratulations to the NRC Faculty Members, from 12 different departments, that received the 2021 Dean's Teaching Excellence Award. For a complete list, please visit our website.

2021 DISTINGUISHED MEDICAL STUDENT IN THE NEUROSCIENCES AWARD

Hannah Uhlig-Reche, a recent graduate of the MD/MPH program, was extraordinarily productive during her graduate career, publishing multiple papers investigating topics from "nutrition in stroke" to "mechanical ventilation in spinal cord injury." She will begin her residency training in Physical Medicine and Rehabilitation at the University of Texas Health Science Center at San Antonio, with the goal of working in neurorehabilitation in an academic setting.

Vijay Dharmajar, a recent MD graduate with a Scholarly Concentration in Neurosciences, performed outstanding research in the area of spatial and functional neurocartography, an emerging field of high-resolution brain mapping. He will continue his research as he begins his residency program in Surgery at Baylor College of Medicine.

2021 GRADUATE STUDENT BRAIN AWARENESS OUTREACH AWARD



Andrea Ancer-Leal, a graduate student at the UTHealth Cizik School of Nursing, has exhibited remarkable dedication to brain awareness activities in the community by developing a Spanish stroke awareness tool – RÁPIDO, to help bridge the gap in access to stroke literacy for Spanish speakers. In addition, she helped create a National Alliance on Mental Illness (NAMI) student chapter at the Cizik School of Nursing.

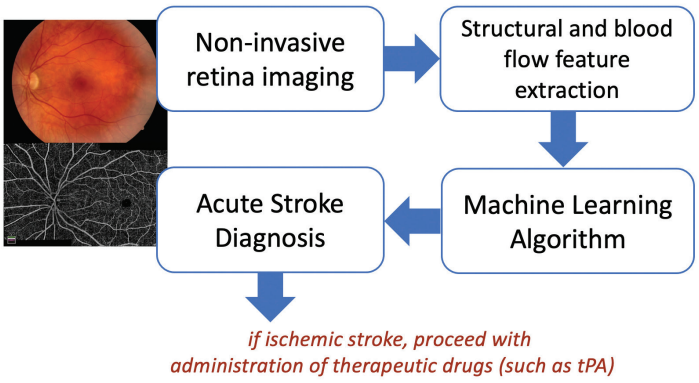


Figure 2. Flow chart of our envisioned system.

A portable retina imaging device acquires the data non-invasively, which is then pre-processed to extract structural and blood flow features. Finally, a machine learning approach would output a stroke diagnosis which would enable the prompt administration of life-saving drugs.

automate their detection using an imaging-based machine learning algorithm integrated in the cameras, nor whether this would be sensitive and specific enough to act as a proxy for brain imaging. Because of this, our team at the School of Biomedical Informatics (Luca Giancardo, PhD, Ivan Coronado, and Juntao Yan), McGovern Medical School (Amanda Jagolino-Cole, MD, Sunil Sheth, MD, Rania Abdelkhaleq, Charles Green, PhD, and Sergio Salazar Marioni), Institute for Stroke and Cerebrovascular Diseases, and in collaboration with the University of Wisconsin (Roomasa Channa, MD), implemented a project to answer exactly these questions, made possible due to a grant from the NASA Translational Research Institute for Space Medicine (NNX16A069A).

This type of technology is of particular interest for space medicine because of the documented increased risk of cerebrovascular disease associated with prolonged exposure to ionizing radiation in space, greatly increasing the risk of stroke during deep space missions. During space missions, a precise diagnosis of acute ischemic stroke is not possible due to the lack of CT or MRI brain imaging aboard the spacecraft.

In our preliminary results, we were able to train a simple machine learning approach to distinguish controls from acute stroke subjects within four days from the stroke event using OCT-A images. The discriminative ability of the algorithm was good as the probability that a subject with stroke receives a score higher than given to a control was 86%. These results are very encouraging, within the limitations of a small sample size using 65 retinal images.

The algorithm was trained using a strategy to encourage its generalizability to unseen data while using vasculature density features at retinal layers ranging from the internal limiting membrane to the outer plexiform layer on macula-centered 3x3 mm images. Each retina included 36 statistical measurements done on a 3D version of the OCT-A image shown in Figure 1. These measurements capture the distribution of blood flow at different layers around the fovea. We excluded patient images if the OCT-A vasculature density features could not be computed.

While retinal perfusion changes that mirror an acute stroke have been measured in laboratory animals with specialized cameras, to our knowledge, this is the first time that OCT-A images have been used to detect acute stroke in humans. As shown in Figure 2, our vision is a portable system that can diagnose stroke and stroke type everywhere from ambulances to deep space missions with minimal operator intervention.

If NRC newsletter readers would like to would like to help us, we are always looking for healthy control volunteers. The whole data acquisition requires around 30 minutes, it is noninvasive, and does not involve any pupil dilation. Please contact our study coordinators Rania Abdelkhaleq (Rania.Abdelkhaleq@uth.tmc.edu) and Juntao Yan (Juntao.Yan@uth.tmc.edu) if interested.

About the Authors

Luca Giancardo, PhD *is an assistant professor at the UTHealth School of Biomedical Informatics Center for Precision Health, with co-appointments in the Diagnostic and Interventional Imaging Department at McGovern Medical School, as well as the Institute for Stroke and Cerebrovascular Diseases. He received his Master of Science degree in Computer Vision and Robotics from Heriot-Watt University, Edinburgh (UK), Universitat de Girona (Spain) and Université de Bourgogne (France), and his PhD in Computational Image Analysis from Oak Ridge National Laboratory and Université de Bourgogne (France). Dr. Giancardo has extensive experience in biomedical image/signal analysis and machine learning method development. His work has been applied to a number of biomedical applications, such as stroke diagnosis, diabetic retinopathy screening or neurodegenerative disease tracking and successfully translated to industry with two startups based on his methods.*

Amanda Jagolino-Cole, MD *is an assistant professor of neurology at the McGovern Medical School at UTHealth. She completed her Vascular Neurology training, also at McGovern, and now serves as the Program Director of the same fellowship. Prior to this, she served as co-chief resident at the Miller School of Medicine, after graduating from Jefferson Medical College in Philadelphia. She decided to pursue medicine after competing service as a Peace Corps volunteer in Ukraine, where she discovered my interest in health education. As faculty at UTHealth, she is dedicated to cultivating teleneurology and telestroke education for residents and fellows, with a personal focus on improving the quality of stroke care provided via telestroke, in acute and follow-up inpatient settings, and also on mobile stroke units, regarding incorporation of telestroke and also pre-hospital thrombectomy assessment.*

news&information

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

John H. "Jack" Byrne, PhD, director of the NRC, associate dean for research at McGovern Medical School, professor and June and Virgil Waggoner Chair in the Department of Neurobiology and Anatomy, was recently named chair of the Learning, Memory, and Decision Neuroscience Study Section, Center for Scientific Review, by the National Institutes of Health. The committee includes studies focused on cellular and molecular changes, circuitry, and neural coding and integration that underlie learning, memory, decision-making, and cognition.

The 8th annual Neuro ICU Symposium, "Envisioning the Future of Neurocritical Care," a virtual course held in July, educated physicians, surgeons, nurses, respiratory therapists, and other health care professionals on how to optimally manage patients using a team approach and evidence-based medicine. **Tiffany R. Chang, MD,** associate professor of neurosurgery and neurology, served as the course director. The course co-directors were **Ryan Kitagawa, MD,** associate professor of neurosurgery, and **George Williams III, MD,** associate professor of anesthesiology.

The Stroke Busters Podcast, presented by the UTHealth Stroke Institute, recently launched its third podcast episode. Each episode, hosted by Barbra Ovuegbe, UTHealth Marketing Coordinator, is co-hosted by a member of the UTHealth Stroke Institute and invites faculty guests to discuss stroke and cerebrovascular disease with a focus on evolutionary research and care. To date, guests have included **James C. Grotta, MD,** director of Stroke Research at the Clinical Institute for Research and Innovation at Memorial Hermann – TMC and director of the Mobile Stroke Unit Consortium, **Louise D. McCullough, MD, PhD,** professor, chair and Huffington Distinguished Chair in Neurology, and **Sunil Sheth, MD,** associate professor and co-director of the Vascular Neurology Fellowship at McGovern Medical School. New episodes are posted to https://anchor.fm/uthealthstroke.

In June, the George McMillan Fleming Center for Healthcare Management at UTHealth School of Public Health hosted a panel on "Mental Health: An Imperative for Diversity, Equity, and Inclusion," which was moderated by Gordon Shen, PhD, assistant professor at UTHealth School of Public Health.

Angela M. Heads, PhD, associate professor of psychiatry and behavioral sciences, was recently elected to the board of directors for the College on Problems of Drug Dependence, a professional society for addiction scientists.

Vasanthi Jayaraman, PhD, professor of biochemistry and molecular biology, has been named the editor-in-chief of the *Biophysical Journal*, the main publication of the Biophysical Society. Dr. Jayaraman's five-year term will begin January 2022. She has been serving as an associate editor for the Channels and Transporters Section of the journal since 2019.

The Mind, Mood & Microbes conference was held virtually in May. **Cameron Jeter, PhD,** NRC Executive Committee Member and Associate Professor at the School of Dentistry, gave a talk and served on the conference Program Committee.

In March, the UTHealth SBMI hosted its fourth DATATHON event, a healthcare-focused challenge among undergraduate and graduate students from Houston-area and Gulf Coast Consortia institutions. Each highly competitive event features a different theme, and the fourth DATATHON required 26 student participants to build an algorithm that would predict rehabilitation success and outcomes for stroke patients. **Xiaoqian Jiang, PhD,** professor and director of Center for Secure Artificial intelligence For hEalthcare (SAFE) at the SBMI, who oversees SBMI's DATATHON events, partnered with **Sean Savitz, MD,** director of UTHealth's Institute for Stroke and Cerebrovascular Disease, and SBMI assistant professors, **Yejin Kim, PhD,** and **Shayan Shams, PhD.**

Eunhee Kim, PhD, assistant professor of neurosurgery, recently had their research featured as the May cover of the journal, *Annals of Neurology*. The paper is titled, "Selective endothelial hyperactivation of oncogenic KRAS induces bAVMs in mice." Authors included **Peng Chen, MD,** professor of neurosurgery, **Pramod K. Dash, PhD,** chair of the Department of Neurobiology and Anatomy and Nina & Michael Zilkha Distinguished Chair in Neurodegenerative Disease Research, **Balveen Kaur, PhD,** professor and John P. and Kathrine G. McGovern Endowed Chair and Vice Chair of Research in Neurosurgery, **Tae Jin Lee, PhD,** assistant professor of neurosurgery, **Ji Young Yoo, PhD,** assistant professor of neurosurgery, and **Shuning Huang, PhD,** instructor of diagnostic and interventional imaging.

João L. de Quevedo, MD, PhD, professor and director of the translational psychiatry program, was appointed as associate editor for the journal, *Translational Psychiatry*, the highest-ranked open access journal in psychiatry.

The John S. Dunn Behavioral Sciences Center has been established at UTHealth by the Dunn Foundation. This Center will be used to address gaps in mental health care services in the community with innovative behavioral health research, education, and patient care through the Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, UT Physicians clinics, Harris Health outpatient clinics, and Harris Health's Lyndon B. Johnson Hospital.

The Department of Psychiatry and Behavioral Sciences hosted the 2021 Benjamin J. Geigerman Lecture series in April with the theme, "Neurodiversity and the Changing World of Work." The lecture focused on the importance of recognizing neurodiversity in corporate hiring practices to better address the struggles many people with Autism Spectrum Disorder face while finding and maintaining employment.

In*the*Spotlight

UTHealth NRC Distinguished Lecture in the Neurosciences

Edward S. Boyden

On May 26th, the NRC virtually hosted Edward S. Boyden, PhD, the Y. Eva Tan Professor in Neurotechnology, and Professor in the Departments of Media Arts and Sciences, and Biological Engineering and Brain and Cognitive Sciences at the Massachusetts Institute of Technology (MIT). He is also the Co-Director of MIT's Center for Neurobiological Engineering and an Investigator at the Howard Hughes Medical Institute. In addition to a formal lecture, Dr. Boyden met individually with multiple UTHealth faculty throughout the day via WebEx.

Public Forum

The annual NRC Public Forum event titled, "Advances in Brain Stimulation for Treatment-resistant Depression," was held virtually on Saturday, April 24, 2021. The event was led by **João de Quevedo, MD, PhD**, Professor and Vice Chair for Faculty Development & Outreach, Director of the Translational Psychiatry Program, and Director of the Treatment-Resistant Depression Clinic in the Department of Psychiatry and Behavioral Sciences. An esteemed group of panelists included **Jair C. Soares, MD, PhD, Bobby Nix, MD, Salih Selek, MD and Marsal Sanches, MD, PhD.**

Brain Awareness Video Contest

Shane Reader

Jing Cai

Rachel Van Drunen

Due to COVID-19-related restrictions, our annual Brain Awareness event, Brain Night for Kids at The Health Museum, had to be canceled. However, the NRC wanted to do more to promote brain awareness in our community. This spring, in lieu of the event, the NRC hosted a Brain Awareness Video Contest for graduate students and postdoctoral fellows. Two outstanding submissions received awards for their 5-minute videos, available for viewing on our website. Shane Reader won 1st place for his video titled, "Brains! Form and Function," and Jing Cai and Rachel Van Drunen won 2nd place for their video titled, "Rodzilla vs. Cones."

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Rehabilitation is essential to stroke recovery and begins soon after the injury, typically 24 hours after a stroke, when the brain is especially receptive to processes that can enhance repair. As varied an event as a stroke can be, exacting predictors of recovery, their time-sensitivity, and strength, have not yet been studied in sufficient detail. Insight into these predictors and their importance can impact healthcare treatment plans by informing early rehabilitation strategies and long-term disease management.

By maintaining the ability to learn the relationships from data without strong prior knowledge directly, machine learning serves as a promising tool to process noisy and heterogeneous data in healthcare research. Several prior studies using traditional statistical modeling have evaluated predictors of recovery or functional gains during inpatient rehabilitation, such as age and Functional Independence Measure (FIM) at admission, which assist in identifying the patients' disability level (Scrutinio et al., *Stroke* 48:3308, 2017). But they encounter collinearity issues and do not consider the highly inter-dependent relationships of the different variables such as severity and comorbidities. As a result of the limitations of traditional statistical approaches, we still do not have a clear understanding of the impact of severity, comorbidities, duration of rehabilitation, or type of stroke on predicted recovery during inpatient rehabilitation.

In collaboration with Xiaoqian Jiang, PhD (professor and director of the Center for Secure Artificial intelligence For hEalthcare (SAFE)), Sean Savitz, MD (professor and Frank M. Yatsu, MD Chair in Neurology) and the Memorial Hermann Health System (MHHS), a retrospective review of clinical factors and outcomes of patients admitted to an inpatient stroke rehabilitation unit was conducted. We collected data from patients who had been hospitalized with acute ischemic stroke or intracerebral hemorrhage between March 1, 2017, and August 31, 2019, followed by inpatient rehabilitation within MHHS. (Ischemic stroke occurs when blood vessels to the brain become clogged, whereas intracerebral hemorrhage (ICH) occurs when bleeding interferes with the brain's ability to function.) We excluded those patients whose rehabilitation was interrupted due to acute hospital readmission. The database includes 421 men and 382 women, with a racial breakdown of 45% Caucasian, 17.8% African American, 2.2% Asian, 2.1% Hispanics. The median age was 69. Right and left laterality was nearly equal, with bilateral stroke noted in 81 patients. One-quarter of patients had an ICH, and three-quarters had an ischemic stroke.

The variables used as predictors (n=138), including demographics, presenting condition, risk factors, treatment, and clinical notes, were extracted from Electronic Health Record (EHR) data. They were categorized into numerical, categorical, and clinical notes (unstructured variables). All the numerical variables are normalized, and Kruskal-Wallis tests were performed to examine for heterogeneity and determine if there were statistical differences in the mean, median, and proportion estimates, respectively. The missing values for continuous variables were iteratively imputed using a multivariate Bayesian regression model. In addition, categorical variables are encoded to a unique integer for each class, and heterogeneity for categorical variables was tested using chi-square testing. Moreover, unstructured clinical notes including "initial symptoms presentation," "past medical history," "infarct etiology," and "complications" were extracted from EHR notes and processed by Natural Language Processing (NLP) techniques to vectorize the free text for these variables. To solve the problem with sparsity and arbitrary encoding, we utilized the Word2Vec technique, where the embedding value for each word is learned through training instead of encoding the words manually. Therefore, arbitrary words are converted into a harmonized latent space, in which cosine distances can directly measure their semantic similarity.

To capture the patient's functional independence at admission, we used two different functional assessment scores, FIM and Continuity Assessment Record and Evaluation (CARE). The FIM is among the most widely used standardized scales for assessing a patient's disability level. It involves 18 items, under 6 categories, including eating, grooming, bathing, upper and lower body dressing, toileting, bladder and bowel control, bed transfer, shower transfer, and walking. These items are scored from 1 to 7, with higher scores indicating greater independence. The CARE Item Set is an emerging standardized patient assessment tool that competes with FIM as a clinical outcome measure and it can be employed in acute and post-acute care settings, which include inpatient rehabilitation, skilled nursing facilities, long term care, and home health services. In this tool, there are 22 items for patient evaluation categorized as self-care and mobility, such as eating, chair transferring, lying to sitting, and walking. Each item is scored on a 6 point scale, with higher scores indicating greater independence. The primary outcome sought in the training, validation, and test cohorts is a functional improvement, which is defined as an increase by a minimum of 2 points in at least 5 FIM subcategories. Using both assessment criteria for the same cohort to predict functional improvement allows us to compare these two scoring systems and determine which score provides a better initial assessment of the patient and better captures the information needed for recovery prediction.

Outcomes of our predictions are meausured using the area under receiver operating characteristic curve (AUROC); a performance metric used to evaluate model performance regarding prediction accuracy. The AUROC number determines a model's ability to correctly assign an outcome to a specific patient, where 1.00 is perfect prediction. In this study, we used the CatBoost model, which is a fast gradient boosting framework leveraging categorical variables using random permutations and ordered boosting to overcome overfitting issues. With CatBoost, the model achieved an AUROC of 0.89 using CARE admission scores and an AUROC of 0.79 using FIM admission scores. Furthermore, in Table 1, we compared the CatBoost models with the performance of other commonly used models, including zero-truncated negative binomial model (Grogger & Carson, *J. Appl. Econ.* 6:225, 1991), random forest (Svetnik et al., *J. Chem. Inform. Comput. Sci.* 43:1947, 2003), Elastic Net (Zou & Hastie, *J. R. Stat. Soc. Series B. Stat. Methodol.* 67:301, 2005), XGBoost (Chen & Guestrin, *Proceedings of the 22nd ACM SIGKDD*, 785, 2016), Logistic Regression (Menard, *Applied Logistic Regression Analysis*, 2002), and a state-of-the-art learning model TabNet (Arik & Pfister, *arXiv* 1908.07442, 2019). In addition, due to the non-linearity and complexity of our models, it is non-trivial to interpret the results explicitly. We used SHAP (SHapley

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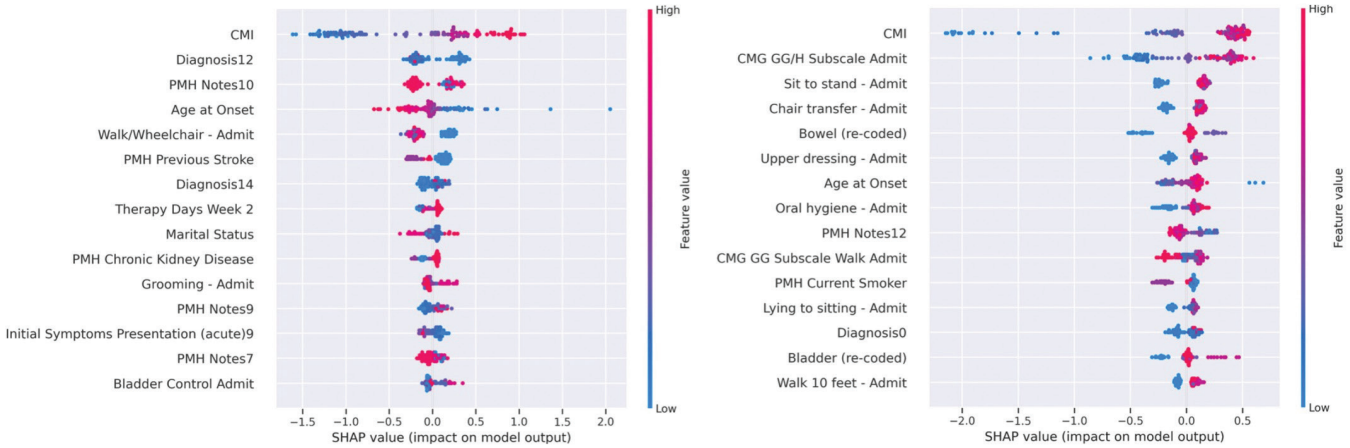

Figure 1. SHAP summary plot for functional improvement prediction after inpatient rehabilitation using Care Tool dataset (right) and FIM dataset (left). The summary plot combines feature importance. Each point on the plot is a Shapley value for a feature in one observation in the test set. The plot illustrates the significance of CMI, clinical notes (Diagnosis, PMH Notes), admission FIM/CARE subcategories assessment scores, and age to predict functional improvement after inpatient rehabilitation.

Model	AUROC (FIM)	AUROC (CT)
Model Baseline Binary Classification	0.50	0.50
Extra Trees Classifier w/ Imputer	0.67	0.79
Zero-Truncated Negative Binomial Model	0.69	0.71
Elastic Net Classifier w/ Imputer	0.53	0.50
Random Forest	0.67	0.81
Logistic Regression Classifier	0.66	0.72
TabNet	0.61	0.77
XGBoost	0.74	0.87
CatBoost	**0.79**	**0.89**
Abbreviations: FIM, Functional Independence Measure, CT, CARETools.		

Table 1. Model's performance using FIM and CARE (CT) admission scores. Best performance entries are highlighted in bold fonts. The area under receiver operating characteristic curve (AUROC) is utilized to evaluate model performance regarding prediction accuracy.

Additive exPlanations) (Lundberg et al., *Nat. Mach. Intell*. 2:56, 2020; Lundberg & Lee, *NIPS*, 30:4765, 2017), which combines feature importance with feature effects, to estimate the average marginal contributions of each variable across all permutations and to quantify variable importance (Figure 1), which provides some explanations into the model's predictions.

Our findings showed that functional assessment scores and age at admission are among the most significant variables (compatible with previous studies). The most significant variable for both models is the individual Case Mix Index (CMI) and the CMI value lower than average has a negative impact (left side of impact axis) on the functional improvement during inpatient rehabilitation. In the SHAP plot, the marginal contribution of the variables to the final prediction decreases from top to bottom. It is not surprising then that the CMI, which captures both the functional and medical needs of patients by considering each patient's risk factors, following acute stroke has been highly predictive in this model, as it reflects multiple variables. It is available prior to the finalization of planning for the rehab treatment, so this study highlights the fact that CMI should be carefully considered by clinicians planning discharge disposition. An element of past medical history that is included among top predictive variables for both SHAP summary plot views of outcome predictors is chronic kidney disease (CKD). While the prior history of hypertension or stroke and chronic pulmonary disease diagnoses or personal habits such as smoking are more commonly considered, this study points to a need for larger prospective studies on the prevalence of CKD in this population and its impact on outcomes. Similarly, hypothyroidism was identified as a predictive variable in this study. While further study is needed, a strength of the model presented is that it may be applied to both ischemic and hemorrhagic stroke types. It predicts functional improvement across many subscales, not limiting the outcome to motor or cognitive.

As illustrated in Table 1, models consistently reached higher AUROC when using CARE admission scores as predictors, as opposed to using FIM admission scores. The best model achieved an AUROC of 0.89 using CARE admission scores, while it reached an AUROC of 0.79 using FIM admission scores. Because all other predictors and hyperparameters are kept consistent for the model, this 10% higher AUROC can be attributed to the CARE scoring system's more detailed initial assessment of functional impairment with 22 items, ranging from bathing and grooming, to chair transferring. It also illustrates that the proposed final model is superior in capturing the information needed for recovery prediction in acute stroke patients compared to traditional statistical modeling.

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The models presented here can help clinicians predict functional score improvement for rehabilitation patients at the admission stage and optimize discharge planning. They also contribute to optimally assigning medical resources to achieve more efficient and effective delivery of healthcare. In our future work, we will validate our model on a larger dataset to ensure its prediction accuracy and validate the identified influential variables in a larger cohort of patients.

About the Authors

Yan Chu, MSc *is a doctoral student at the UTHealth School of Biomedical Informatics (SBMI). He holds a Master of Science degree in statistics from the University of Wisconsin - Madison, and a Bachelor of Science in mathematics from Nankai University in China. He's currently applying machine learning to combat fraud, waste, and abuse in the healthcare domain and won the MITRE Healthcare Anti-Fraud Academic Competition in 2020.*

Shayan Shams, PhD *is an assistant professor at the UTHealth SBMI. Dr. Shams received his Master of Engineering in Robotics and Mechatronics from the University of Malaya and his PhD in Computer Science from Louisiana State University. He joined the SBMI in 2019. As an expert in data science and big data, Dr. Shams is interested in the integration of artificial intelligence (AI), high performance computing (HPC) and big data techniques to develop actionable health care models, bringing AI models to edge devices for personalized medicine, telemedicine, and telerehabilitation. His extensive experience and background in deep learning and machine learning has led to the development of AI models in various domains from neurology, radiology, pathology, biology to social sciences.*

Upcoming Events

Current Topics in the Neurobiology of Disease- GS14 1021 Alzheimer's Disease and Related Dementias

Tuesdays, 12:00 p.m. – 1:00 p.m., McGovern Medical School, MSB 7.037

Directors: Tatiana Barichello, PhD, John H. Byrne, PhD, and Paul Schulz, MD

Open to graduate and medical students, postdoctoral fellows, and residents. This course is an integrated approach to neurological diseases, which includes background information as well as the diagnosis, treatment, and biological mechanisms of the disease under study. After completing this course on Alzheimer's disease related dementias (ADRDs), the learner will be able to state their: clinical signs and symptoms, including parameters that differentiate early, middle, and late stages of disease; epidemiologic data, including risk factors and mortality; biomarkers that identify and give insight into processes underlying them, including imaging biomarkers and fluid biomarkers; treatment options, including non-pharmacological and pharmacological; underlying pathophysiologies, including the role of genetics as causative and risk genes, the microbiota-gut-brain axis, the blood-brain barrier, glial cells, and neuroinflammation; pre-clinical models to study them; and, future directions.

28th Annual Neuroscience Poster Session

Saturday, December 4, 2021, 10 a.m. to Noon

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

Participating Institutions:
Baylor College of Medicine
Rice University
UTHealth

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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