NRC newsletter

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Hard to Swallow: Oral bacteria as a biomarker of dysphagia in Parkinson's disease

Cameron Jeter, PhD, Natalia Rozas, PhD

Jeter

Rozas

Abstract: Among neurological disorders, Parkinson's disease is the fastest growing in prevalence, disability and deaths. In addition to loss of control over bodily movements, many patients also suffer unique oral health concerns as a result of decreased oromuscular functions like swallowing. Restriction of oral movement alters clearance of food and saliva, initiating a shift of oral bacteria to dysbiosis. Using the contents of the oral microbiome as a biomarker, we may be able to identify dysphagia preemptively and avert aspiration pneumonia, the leading cause of death in Parkinson's disease.

Parkinson's disease robs our adult population of control over their movements. Patients also exhibit non-motor symptoms like constipation, sleep problems, slowed thinking, dementia and impulsivity. The public easily recognizes the motor symptoms of Parkinson's disease such as stooping, shuffling and tremor. Tragically, though, few see the covert, but equally intrusive oral consequences of difficulties in speaking, swallowing and salivating. These ravage patients of the ability to maintain oral health, eat and communicate that so many of us take for granted (Rozas et al., *Parkinsonism Relat Disord*. 43:9, 2017).

Because Parkinson's disease is progressive, both motor and non-motor symptoms advance in number and severity over time. Approximately 80% of patients with Parkinson's disease demonstrate alterations in swallowing. Whereas dysphagia stealthily begins shortly after disease onset, patients usually only complain of this symptom around ten years later. Disturbingly, the average survival time after onset of reported dysphagia is only two years.

Normal swallowing involves complex coordination of contraction and relaxation in muscles of the lips, tongue, larynx, pharynx and esophagus. Dysphagia, then, is the result of one or more difficulties causing defective closure of the lips, alteration

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Gut matters – in context of Alzheimer's diseases and other neurodegenerative diseases

Bhanu Priya Ganesh, PhD

Ganesh

Abstract: The gut-brain axis (GBA) is a bilateral communication network between the gastrointestinal (GI) tract and the central nervous system (CNS) and is a key player in the pathogenesis of neurodegenerative diseases (NDD), most notably in Alzheimer's disease (AD). AD is a brain disorder, but it is increasingly recognized that peripheral factors can alter the onset and/or progression of diseases that affect the brain. Our recent findings provide evidence that gut dysfunction occurs in AD and may contribute to its etiology. We found that the pathogenesis of cerebral amyloid β (Aβ) has a caudo-rostral gradient of dysfunction that begins as a dysregulation of intestinal epithelial barrier (IEB) and peripheral inflammation. This peripheral disturbance might then spread centrally, leading to cerebral Aβ pathology.

Alzheimer's disease (AD) is a common, progressive and devastating neurodegenerative disease (NDD) characterized by memory impairment and cognitive decline. The most prominent pathological hallmarks of the disease are the extracellular accumulation of amyloid β (Aβ) peptides in the form of plaques and the intracellular accumulation of hyper-phosphorylated tau (ptau) proteins as neurofibrillary tangles (NFTs). AD is the sixth leading cause of death in the US and an estimated 5.8 million Americans were living with AD in 2019. According to the Alzheimer's Association, Alzheimer's and other dementias cost the nation $290 billion in direct health care expenses in 2019, and by 2050 these costs may rise as high as $1.1 trillion.

Numerous studies indicate that microbial communities are an essential factor for many physiological processes including nutrition, inflammation, protection against pathogens and the development of the nervous system. The microbial community is largely composed of bacteria that colonize all mucosal surfaces, with the highest bacterial densities found in the gastrointestinal tract. Microbes are known to influence the host by production of secretory metabolites (essential vitamins, short chain fatty acids (SCFA), bioamines, neurotransmitters) or bacterial components (biofilms, lipopolysaccharides (LPS), peptidoglycan, DNA fragments). This influence is one component of the "gut-brain

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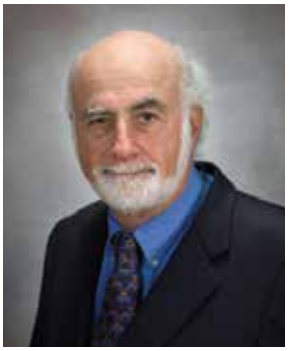
UTHealth | Neuroscience Research Center
The University of Texas Health Science Center at Houston

Director's Column

From the Director, John. H. Byrne, PhD



The UTHealth NRC is glad to be moving forward with great hope and anticipation for what 2021 will bring for us all. Even through the difficulties we have experienced this past year, our Center has remained steadfast in delivering services and programs to benefit our community. We plan to complete the academic year with virtual programs, but are encouraged that in-person programs will return again this fall.

Without a doubt, the highlight of the year was our incredibly successful seminar course, the Neurobiology of Disease. This annual graduate-level course is an integrated approach to brain disorders, which includes the diagnosis, treatment, and biological mechanisms of the disorder under study. The theme and course director change every year, and this year brought additional changes as our course was held virtually for the first time. Dr. Cameron Jeter, UTHealth NRC Executive Committee Member and Associate Professor of Diagnostic and Biomedical Sciences at the UTHealth School of Dentistry, led our course, "The Microbiome and the Brain." This year's course brought together our most diverse group of speakers and attendees, with steady, record-breaking attendance each week. This course explored how dynamic changes in the microorganisms living within the body, the microbiota, can alter brain physiology and behavior. Content experts from UTHealth's McGovern Medical School, School of Biomedical Informatics and School of Dentistry, as well as Baylor College of Medicine, University of Houston, and Houston Methodist Research Institute, delivered widely appealing lectures, which resulted in cross-institutional, inter-departmental discussions. I personally enjoyed learning about the role of the microbiome in aging-related neurological diseases, neurodevelopmental disorders, traumatic brain injury, stroke, multiple sclerosis, and substance abuse disorders. Our final lecture topic was very fitting for the year and was on the neurological complications of respiratory viruses including COVID-19.

The hugely popular topic of this course was the inspiration behind the theme of this Newsletter. This issue, we are excited to feature the research of two speakers from this course, Cameron Jeter, PhD, and Priya Ganesh, PhD. In their articles, Dr. Jeter describes the newly discovered connection between the oral microbiome and Parkinson's disease, while Dr. Ganesh highlights her recent findings, further supporting a connection between gut disfunction and the etiology of Alzheimer's disease. Both articles will give you a brief insight into this emerging field in neuroscience research.

One of our favorite events at the NRC is our annual reception at the Society for Neuroscience meeting. Held every fall, this event allows current and former members of the UTHealth NRC community to gather in person, share updates on recent research progress, and reminisce over shared memories which span the decades. While the Society for Neuroscience meeting has moved to a modified virtual platform, we will have to wait to convene again in the fall of 2021. Until then, I hope you will enjoy photos from our past receptions highlighted in this edition of the Newsletter.

Another casualty of the pandemic is our large, in-person, multi-institutional, Neuroscience Poster Session. Located in the largest medical center in the world, networking across institutions is one of our biggest advantages here in Houston. Our annual event which brings together three leading neuroscience institutions, UTHealth, Baylor College of Medicine, and Rice University, had to be cancelled due to concerns over virus spread. This event awards multiple scholarships and financial awards for graduate students and postdoctoral fellows and allows for networking opportunities not otherwise available. Until we can meet again in person this December, each institution is independently identifying ways to still provide scholarship opportunities for their students and postdocs.

Here at the NRC, we decided to host a smaller, virtual Neuroscience Poster Session for our UTHealth community. Our first ever virtual poster session was a great success and very uplifting for our university. The top three abstracts submitted by neuroscience graduate students and postdoctoral fellows, and judged by UTHealth faculty, were presented virtually the week of January 25th. Details of the event are highlighted in the Newsletter, and all submitted abstracts have been published online on our website. I encourage you to visit our site to learn more about our exciting research findings from this past year.

We look forward to continued steps towards our return to regular programming, with high hopes of seeing many of you again later this year.

Please visit our "Neurofax Calendar" for neuro-related events in the Houston area.

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.

grants&awards

Jennifer Beauchamp, PhD, RN, associate professor of research at the Cizik School of Nursing, received a IoT and Aging in Place Joint Seed Grant for a project titled, "Facial and Motion Technology to Detect Psychosocial Distress in Stroke Survivors and Informal Caregivers Living at Home." The primary objectives are to customize facial expression and body motion technology, and examine the acceptability of the technology, through a study of stroke survivors and their informal caregivers within a simulated home environment.

Patricia M. Butler, MD, professor of psychiatry and behavioral sciences and vice dean for Educational Programs at McGovern Medical School, received the 2019 President's Scholar Award for Teaching. This top honor presented by UTHealth President, Giuseppe N. Colasurdo, MD, is awarded annually to four individuals who have demonstrated a longstanding excellence in the areas of teaching, research, and clinical care.

John H. Byrne, PhD, director of the UTHealth NRC and professor of neurobiology and anatomy, was awarded a multi PI grant from the National Institutes of Health (NIH) BRAIN Initiative for a project titled, "A Novel Approach to Analyzing Functional Connectomics and Combinatorial Control in a Tractable Small-Brain Closed-Loop System." This research will provide insight into how neurons work in conjunction to contribute to the regulation of behavior. The research team includes scientists from The University of Michigan, Case Western Reserve University, Mount Sinai Medical School, and Bar Ilan University in Israel.

Carmen W. Dessauer, PhD, vice chair and professor of integrative biology and pharmacology, and **Edgar T. Walters, PhD**, professor of integrative biology and pharmacology, received an R01 grant from the NIH/National Institute of Neurological Disorders and Stroke (NINDS) for a project titled, "Mechanisms of cAMP Signaling that Drive Spontaneous Activity in Nociceptors." This joint project will define mechanistic changes that occur in sensory neurons that contribute to chronic pain after spinal cord injury.

Albert J. Fenoy, MD, director of the Deep Brain Stimulation Program and associate professor of neurosurgery, received an R01 grant from the NIH/NINDS for a project titled, "Elucidating the Temporality of Structural and Functional Connectivity Changes in Essential Tremor After Successful Deep Brain Stimulation to the Dentato-Rubro-Thalamic Tract (DRTt)." The purpose of this study is to see how the brain functions in people undergoing deep brain stimulation surgery for treatment of essential tumors. The overall objective is to use individual connectivity to optimize DRTt stimulation for a successful clinical response. Co-investigators are **Mya Schiess, MD**, professor of neurology and director of Movement Disorders and Neurodegenerative Diseases, and **Nitin Tandon, MD**, vice chair and professor of neurosurgery.

Myriam Fornage, PhD, professor of genetics at the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, is co-principle investigator on a large grant co-sponsored by NIH/NINDS and NIH/National Institute on Aging (NIA) to study the role of white matter lesions in dementia. The study is led by Charles DeCarli, MD, at University of California Davis School of Medicine and part of the NIH's Vascular Contributions to Cognitive Impairment and Dementia (VCID) research program.

Gabriel R. Fries, PhD, assistant professor of psychiatry and behavioral sciences, received a NIH/ National Institute of Mental Health (NIMH) K01 Mentored Research Scientist Career Development Award for a project titled, "Deciphering the Role of Neuronal and Peripheral DNA Methylation in Suicide and Bipolar Disorder."

Jeffrey A. Frost, PhD, professor of integrative biology and pharmacology, was recently named one of the 27 recipients of The University of Texas System Board of Regents' Outstanding Teaching Award (ROTA) for 2020. This high honor recognizes faculty members at UT System institutions who have demonstrated dedication to innovation and advancing excellence.

Georgene W. Hergenroeder, PhD, associate professor of neurosurgery, received the Mission Connect Jerry Johnson Andrew Award for Spinal Cord Injury Research from the TIRR Foundation. She received this award for her research focused on restoration of function in persons with spinal cord injury.

Melba Hernandez-Tejada, PhD, DHA, associate professor of psychiatry and behavioral sciences in the UTHealth Trauma and Resilience Center, received funding through the Victims of Crime Act grant fund managed by the Office of the Governor of Texas. This support will allow her team to address a need of older adults with evidence-based mental health treatments combined with community-based support to treat negative psychological outcomes of abuse.

Tae Jin Lee, PhD, assistant professor of neurosurgery, received a Cancer Prevention & Research Institute of Texas (CPRIT) High-Impact/High-Risk Research Award for a project titled, "Small RNA Nanovector Based Targeted Immunotherapy for Glioblastoma."

Jun Li, PhD, associate professor of neurology and director of Basic Stroke Research, and **Louise D. McCullough, MD, PhD**, UTHealth NRC Executive Committee Member and chair and professor of neurology, received a RF1 grant from the NIA for a project titled, "Stroke Disordered Breathing and its Impact on Cognitive Decline in Aging, Alzheimer's Disease and Cerebral Amyloid Angiopathy."

Devin W. McBride, PhD, assistant professor of neurosurgery, was awarded a grant from the Brain Aneurysm Foundation for a project titled, "Are Neutrophil Extracellular Traps a Biomarker of Delayed Deficits After Subarachnoid Hemorrhage?" Dr. McBride also received a Pilot Award from Celense, Inc. for a project titled, "Infiltrating Immune Cells Lead to Delayed Deficits after Subarachnoid Hemorrhage in Mice."

Sheryl A. McCurdy, PhD, associate professor of health promotion and behavioral sciences, and **Eric C. Jones, PhD**, assistant professor of epidemiology, human genetics and environmental sciences, both at the School of Public Health, recently received a grant from the National Science Foundation (NSF) Social, Behavioral and Economic Sciences, Cultural Anthropology Program for a project titled, "Addiction, Mutual Aid, and the Navigation of Care Networks." The goal is to describe the types of caring and caring networks that people who use heroin interface with and build as they navigate changing relationships and opportunities during different stages of their drug use and recovery.

Dr. McCurdy also earned a contract with the Texas Health and Human Services Commission, along with **J. Michael Wilkerson, PhD**, assistant professor of health promotion and behavioral sciences at the School of Public Health, for Project HOMES (Housing for Opioid MAT Expanded Services). This project provides housing and a supportive environment for opioid recovery to men and women using medically assisted therapy in 13 homes across Texas.

Rodrigo F. Morales, PhD, associate professor of neurology, received two grants from the USDA Animal and Plant Health Inspection Service (APHIS). The first grant titled, "Assessment of PMCA and RT-QuIC for CWD Diagnosis in Animal and Environmental Samples," is a collaborative project with the Texas Parks and Wildlife Department. The second grant titled, "Detection of Infectious Prions in Tissues of Feral Swine Collected in Texas," will analyze biological samples from wild boars for their content of CWD prions. In addition, Dr. Morales received a grant from the NIH/NIA for a project titled, "Role of Circulating Abeta Seeds and Peripheral Tissue Damage in Alzheimer's Disease Pathogenesis."

Hope Northrup, MD, professor of pediatrics and director of the Division of Medical Genetics, won the Excellence in Clinical Science award at the McGovern Medical School at UTHealth Women's Faculty Forum. **Amanda Jagolino-Cole, MD**, assistant professor of neurology and co-director of the Vascular Neurology Fellowship Program, also earned a Rising Star award at the event.

John O'Brien, PhD, professor of ophthalmology and visual science, was recently awarded a new BRAIN Initiative multi-PI grant titled, "Transgenic Tools for Revealing the Contributions of Electrical Synapses to Neural Circuits." The other PIs are Alberto Pereda, MD, PhD, from Albert Einstein College of Medicine, and Adam Miller, PhD, from the University of Oregon. The goals of this project are to develop novel transgenic zebrafish to enable comprehensive mapping of expression of all of the electrical synapse (connexin) genes throughout the central nervous system, to analyze development and functional organization of several microcircuits in which they reside, and to evaluate functional properties of electrical synapses in several example microcircuits.

Through a collaborative effort between UT Physicians and UTHealth, **Sudhakar Selvaraj, MD, PhD**, psychiatrist with UT Physicians and assistant professor of psychiatry and behavioral sciences, will lead an emergency program funded by the Substance Abuse and Mental Health Services Administration. This COVID-19 Emergency Response for Suicide grant will focus on helping to prevent suicide and provide support for victims of domestic violence.

Nitin Tandon, MD, UTHealth NRC Executive Committee Member, vice chair and professor of neurosurgery, received a grant from the NIH/NINDS BRAIN Initiative for a project titled, "Network Based Neuro-Modulation for Mesial Temporal Lobe Epilepsy." Dr. Tandon also received a R25 award from the NIH/NINDS for Research Training for Neurosurgery and Neurology Residents & Fellows to develop a mentored training program at UTHealth for neurosurgery/neurology residents, which will create the next generation of leaders in academic clinical neurosciences. In addition, Dr. Tandon received the UT System Translational STARs Award to create a synergistic approach to the development of scientific and technological advancements in the care of patients with language impairments.

Ying Liu, MD, PhD, associate professor of neurosurgery, and Claudio Soto, PhD, professor of neurology, are co-investigators on a new project led by Wenbo Li, PhD, assistant professor of biochemistry and molecular biology, which will examine the pathological basis of Down syndrome as part of the NIH Common Fund 4D Nucleome program. Erez Lieberman Aiden, PhD, from Baylor College of Medicine, is also a co-investigator.

Postdoctoral Fellows and Graduate Student Awards:

Laís Bhering Martins, PhD, a postdoctoral fellow under mentorship of **Antonio Teixeira, MD, PhD**, professor of psychiatry and behavioral sciences, recently won the Frontiers in Headache Research award, offered by the American Headache Society (AHS).

Valeria Cuellar, MD, recently won the best poster award at the National Network of Depression Centers' 12th annual conference. The poster, "Deep Brain Stimulation in the Medial Forebrain Bundle for Treatment Resistant Depression: An Open-Label, Long-Term Study," highlighted early results from a study by a team of investigators including **Jair C. Soares, MD, PhD**, NRC Executive Committee Member and professor and chairman of psychiatry and behavioral sciences.

Constanza de Dios, PhD, a postdoctoral fellow at the UTHealth Center for Neurobehavioral Research on Addiction, under mentorship of **Joy M. Schmitz, PhD**, won first place at the MD Anderson Annual Postdoctoral Science Symposium in an oral presentation titled, "Identifying Predictors of Opioid Misuse in Adult Trauma Patients Using a Bayesian Data Science Approach." **Angela Medvedeva, PhD**, a postdoctoral fellow in the laboratory of **Nitin Tandon, MD**, received a Postdoctoral Fellowship from the Gulf Coast Consortia/Keck Center's National Library of Medicine (NLM) Training Program in Biomedical Informatics & Data Science. Her project is titled, "Decoding Speech from Neural Activity by Developing Novel Speech Production Models."

Alexandre Paim Diaz, MD, PhD, a postdoctoral research fellow with mentor, **Jair C. Soares, MD, PhD**, recently received the 2020 Brain & Behavioral Research Foundation (BBRF) Young Investigator Grant. This two-year grant will investigate the feasibility and acceptability of home-based transcranial direct-current stimulation (tDCS) to reduce the risk of suicidal ideation relapse in adult patients after psychiatric hospitalization.

Heather Soder, PhD, a postdoctoral fellow with mentors **Scott D. Lane, PhD**, and **Joy M. Schmitz, PhD**, won second place at the MD Anderson Annual Postdoctoral Science Symposium. The poster she presented was titled, "Brain Reactivity and Attentional Bias to Drug Cues in Cocaine Users."

Tina Thomas, MD, a fourth-year psychiatry resident, received a grant from the American Psychiatric Association Foundation to investigate the feasibility of using mobile technology to gather data from people who are homeless during COVID-19. This grant proposal was developed with her mentor, **Jane Hamilton, PhD, MPH**, assistant professor of psychiatry and behavioral sciences, as well as **Ronald Acierno, PhD**, and **Scott Lane, PhD**.

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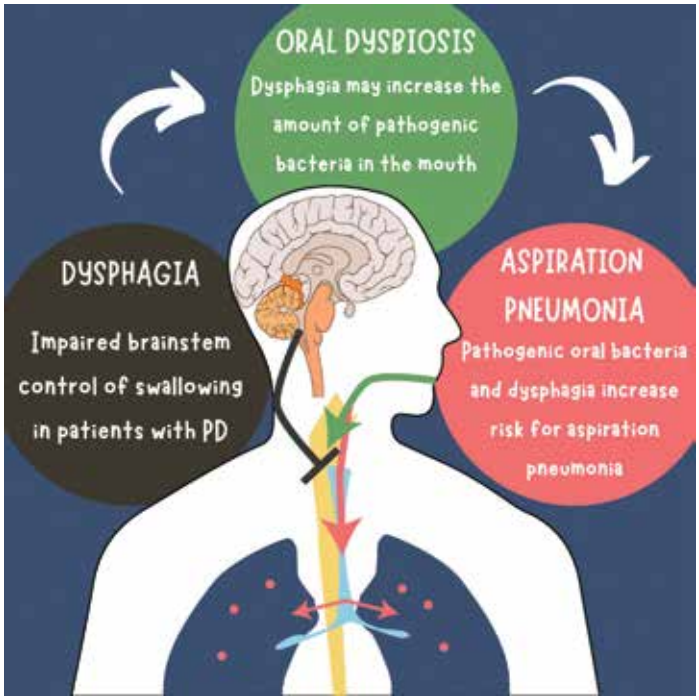


Figure 1. Link between dysphagia, oral dysbiosis, and aspritation pneumonia.

in the propulsion of food by the tongue, delay in the initiation of swallowing, and disruption of the tracheo-esophageal transit of food. These dysfunctions can result in entrance of food, drink or saliva into the air passages rather than into the stomach. If aspiration leads to bacterial infection of the lungs or large airways, aspiration pneumonia can result (Figure 1). Indeed, aspiration pneumonia afflicts half of patients with Parkinson's disease (10 times the incidence in age-matched controls) and is their leading cause of mortality, accounting for up to 70% of deaths.

Oral movement serves to move food and debris from the mouth and is the body's natural defense mechanism against oral infections and tooth decay. Restriction of oral movement in persons with movement disorders leaves them highly prone to accumulation of oral pathogens, infection and inflammation (Jeter et al., *MedEdPORTAL*, 14:10699, 2018). Microorganisms grow as biofilms on both the hard tissues (teeth) and soft tissues (tongue, gums, inner cheek) of the oral cavity. Even just 1 mm^3 of dental plaque (a mature biofilm) contains more than 10^6 bacteria of 300 different species. You can feel (healthy) slimy biofilm on your teeth several hours after toothbrushing. These communities, known collectively as the oral microbiota, are complex communities whose bacterial composition differ by oral location (niche). Whereas the species of bacteria in oral biofilms during health are commensal and symbiotic with the host, they can shift to opportunistic and hostile depending on the virulence of the bacteria, host immunological response and environmental factors like smoking or frequency of oral hygiene.

The prevalence and severity of dysphagia in Parkinson's disease is a clear motivator for active screening. When asked, only 35% of patients with Parkinson's disease subjectively report trouble swallowing. The prevalence of dysphagia increases to 82% when objective swallowing tests like fiberoptic endoscopic evaluation of swallowing (FEES) are performed. Patients' subjective report of dysphagia remains low in part due to their unconscious adjustment to their slow progression in swallowing difficulty. Though it may seem prudent to order swallowing tests as an early diagnostic measure, repeated screening with invasive and radiologic methods is not feasible or safe. Therefore, early identification of patients at risk of dysphagia represents a significant problem.

Unlike traditional tests of swallowing, measurements of the oral microbiome can be repeated easily and safely. Oral pathogens directly cause oral diseases like caries (cavities) and periodontitis (gum disease) and are linked with respiratory disease. My laboratory at the UTHealth School of Dentistry hypothesized that oral health status and oral microbiome composition would correlate with dysphagia severity in Parkinson's disease. Understanding shifts in the oral microbiome may lead to the development of diagnostic biomarkers for debilitating oropharyngeal symptoms and disease progression. If identified early, patients at risk of dysphagia can be taught techniques to encourage safe swallowing.

In collaboration with the UT MOVE clinic of UT Physicians, we characterized the oral microbiome of patients with Parkinson's

disease. Alpha and beta diversity of bacterial species were compared to factors of the disease, oral health, and diet to explain any difference from that of age- and gender-matched controls (Rozas, Tribble and Jeter, under review). Alpha diversity is an estimation of the number of bacterial species (i.e., species richness) and their evenness (i.e., equal abundance) in a single sample. Beta diversity includes measures of the presence/absence and abundance of bacterial species across samples. Thus, in our study, alpha diversity measures variation of microbes in a single person, whereas beta diversity measures variation of microbial communities among people.

Two oral swabs were collected from each participant, the first from hard tissues (teeth) and the second from oral soft tissues (tongue and inner cheek). The swab samples were processed for bacterial whole DNA. The DNA reads were compared to a curated database of >300,000 16S rRNA gene sequences called operational taxonomic units (OTUs) to determine the identity of the organism from which each sequence was generated.

Alpha diversity measures did not reveal significant differences in community richness between patients with Parkinson's disease and controls. Beta diversity significantly differed between hard and soft tissues both among patients with Parkinson's disease and among control subjects. These results suggest that the oral environment in Parkinson's disease supports a microbial community that is normal in overall diversity and community abundance, and the distinctions between hard and soft tissue sites as niches are maintained.

Our results, and that of previous studies, show that patients with Parkinson's disease have worse oral health than age, gender and education-matched controls. Thus, we expected overall hard tissue community abundance (beta diversity) to differ between the groups but found that it was comparable. Interestingly, oral hygiene habits also were similar in frequency and effectiveness between the two groups. This supports the hypothesis that poor oral health in Parkinson's disease is not due to poor oral hygiene as a result of their movement disorder, but rather other disease-specific factors that produce increased abundance of OTUs known to incite oral disease.

In contrast to hard tissue, soft tissue beta diversity is significantly different between Parkinson's disease and control groups. Analysis of individual OTUs demonstrates that patients with Parkinson's disease had higher abundance of species associated with opportunistic oral and respiratory disease. *Streptococcus pneumoniae* is found more commonly in our Parkinson's disease subjects, particularly those with dysphagia, and is a common pathogen in aspiration pneumonia. This places patients with dysphagia at a multiplicative risk of aspiration pneumonia by not only having difficulty swallowing safely, but also harboring respiratory pathogens in the oral cavity.

The next phase is to compare objective measures of swallowing (e.g., FEES) to the diagnostic accuracy of the oral microbiome for dysphagia in patients with Parkinson's disease. When this relationship is established for patients across stages of disease and dysphagia severity, the oral microbiome may serve as the missing noninvasive measure of dysphagia, even before subjective onset. This advancement would enable early intervention to protect patients with Parkinson's disease from poor quality of life and demise due to aspiration pneumonia.

About the Authors

Cameron Jeter, PhD is an associate professor in the Department of Diagnostic and Biomedical Sciences at the UTHealth School of Dentistry. She is also a faculty member of the neuroscience program at her alma mater, the MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences. She serves as an Executive Committee member of the Neuroscience Research Center. Her research has focused on the role of oral biomarkers in revealing the bidirectional relationship of oral health and neurodegenerative diseases. Recent projects have expanded her research scope to examine the oral cavity as an entry to the microbiome-gut-brain axis that is implicated in the etiology of Parkinson's disease and Alzheimer's disease.

Natalia Rozas, PhD is a research scientist in the Department of Diagnostic and Biomedical Sciences at the UTHealth School of Dentistry. Dr. Rozas has research training in the molecular mechanisms of learning and memory and extensive experience in clinical and translational research in both Alzheimer's disease and Parkinson's disease. She has co-developed and executed multiple observational clinical trials, including the identification of oral microbiome biomarkers for disease state and rate of progression.

Continued from page 1; Ganesh

axis" (GBA), the bidirectional communication axis between the gut and the brain. Given recent studies showing that the gut microbiota (the mixed community of microorganisms, mainly bacteria) and its secreted microbial metabolites change with age and alter host immunity, our BRAINS research laboratory at McGovern Medical School at UTHealth is using established animal models to uncover how the gut microbiota contribute to age-related diseases, including AD. Our work has focused primarily on understanding the communication within the microbiota-gut-brain axis. Our emerging data strongly suggest that changes in gut physiology, including its microbiota composition, might modulate the secretory metabolites that these microorganisms produce, which can then influence the neuronal health status of the host.

Interestingly, a growing body of evidence suggests that intestinal bacteria produce amyloid-like proteins that form biofilms in the gut. These proteins may contribute to neurological disease progression from the gut to the brain. In our recent work, we have used immunohistological analysis and two-photon microscopy to show that the gut mucosa stains positive for Aβ and was co-localized with blood endothelial marker prior to brain Aβ detection in the pre-symptomatic AD mouse model (Figure 1). In association with the presence of Aβ, we documented a significant increase in the gut barrier breakdown as well as an elevated antigen invasion in the lumen. Interestingly, an interleukin, IL-9, known to reduce epithelial repair, was elevated in these pre-symptomatic mice. Overall, we found that gut dysfunction occurs before development of Aβ pathology in the brain using a transgenic AD mouse model.

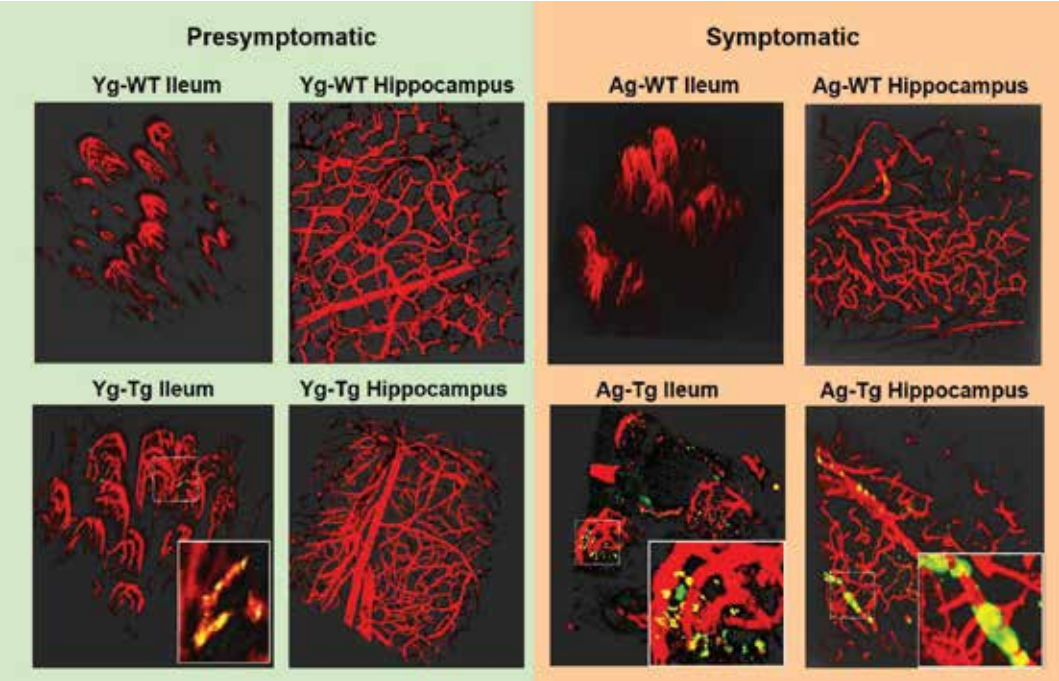


Figure 1.

Two-photon imaging of intestinal tissue shows detectible levels of Aβ accumulation with ileal vasculature in the gut but not in the hippocampus of the brain at the presymptomatic time point (Yg-Tg) compared to the samples showing strong Aβ plaques co-localized with ileal-gut and hippocampus-cerebral vasculature at the symptomatic time point in Tg2576 mice (Ag-Tg), whereas WT littermate non-AD controls shows negative co-localization. Red, vasculature; Green, amyloid β plaque.

In addition to changes in the gut physiology, we found drastic changes in the gut microbiome at the symptomatic time in these animal models. We examined the gut microbiome compositional changes by performing 16S rRNA sequencing followed by qPCR from the intestinal contents. One major change is in the diversity of gut microbiota, which is defined by the ratio of its two largest bacterial subgroups, Firmicutes and Bacteroidetes (F:B ratio). This ratio represents gut dysbiosis (abnormal alternation in gut microbiome). Comparing the percentage abundance of F:B ratio, we found that the F:B ratio was significantly higher in the symptomatic AD mice when compared to the age-matched wild-type (WT) littermates control mice. When we looked at the alpha-diversity, or within-sample diversity, we found no difference at the pre-symptomatic time point, compared to WT littermates. However, upon visualization of bacterial beta-diversity (between-samples diversity) using weighted UniFrac distances (a metric used for comparing biological communities) by principal coordinate analysis (PCoA), a significant clustering effect emerged along one principal component axis at the symptomatic time point, which was not observed at the pre-symptomatic time point in AD mice. Examination of 16S data at the genus level showed a significant reduction of *Ruminiclostridium* genus (volatile fatty acid producer) in the pre-symptomatic AD mice, which also persisted in the symptomatic AD mice. Interestingly, we also found a significant increase in *Lactobacillus* abundance in the symptomatic AD mice. Our 16S data show that significant bacterial compositional differences exist in the symptomatic AD mice gut microbiota, which are not present in pre-symptomatic AD mice, when compared to normal littermate controls.

Based on our current data set we believe that "gut" physiology and its ecosystem, especially bacterial composition, play a major role in modulating the immune responses that then trigger the Aβ pathology-associated cascade in the brain. Recently, other labs around the world have started to look at the impact of gut and its microbiota on Aβ pathogenesis. Interestingly, a recent article showed that bacteria produces proteins that share sequence identity with alpha-synuclein aggregates which cause Parkinson's disease (Challis et al., *Nat Neurosci.* 23:327, 2020). My lab is working on understanding and characterizing the bacterial derived metabolites and bacterial secretory proteins that initiate the downstream cascade in Aβ pathogenesis. We believe that "gut matters" in AD progression. Slowing AD progression by manipulating peripheral factors early in life before disease progression in the brain has high translational potential for clinical treatments of patients with mild cognitive impairment (MCI). Understanding the AD microbiome and its composition in detail may even serve as an early predictive biomarker for AD onset.

About the Author

Bhanu Priya Ganesh, PhD is an assistant professor in the Department of Neurology at McGovern Medical School of UTHealth. She received her PhD in Gastrointestinal Microbiology from the German Institute of Human Nutrition Potsdam-Rehbruecke, Leibniz Institute. Dr. Ganesh completed her postdoctoral training at Baylor College of Medicine in the Department of Pathology and Immunology and was recruited as a senior postdoctoral fellow in the Department of Neurology of McGovern Medical School in 2017. One year later, she was promoted to her current position of assistant professor. Dr. Ganesh works closely with other faculty in the BRAINS research lab, with her Biome group primarily focusing on identifying the molecular mechanisms involved in the communication between the gut-brain axis with a specific interest on aging-associated diseases.

In*the*Spotlight

Virtual UTHealth Neuroscience Poster Session

Out of an abundance of caution related to COVID-19, the in-person, multi-institutional 27th Annual Neuroscience Poster Session event was cancelled. To continue the UTHealth NRC's commitment to scholarship through awards at this annual event, we held an independent, first-ever, virtual Neuroscience Poster Session. The top 3 abstracts from each category were presented and judged at virtual meetings. Please visit our website for a full list of submitted abstracts from UTHealth medical students, graduate students, and postdoctoral fellows.

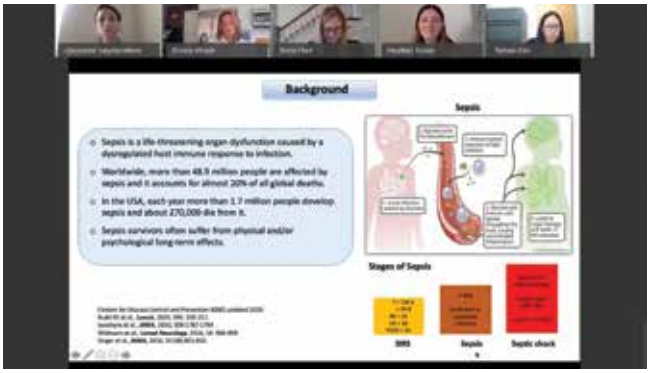
Congratulations to the winners of the virtual UTHealth Neuroscience Poster Session!

Graduate Student Awards

Dee S. and Patricia Osborne Endowed Scholarship in the Neurosciences: Melissa Franch
Second place: Eyad Shihabeddin Third place: Alexis Mobley

Postdoctoral Fellows Awards

First place: Heather Webber and Vijayasree Vayalanellore Giridharan
Second place: Sehee Kim



Vijayasree Vayalanellore Giridharan presenting her research at the virtual Postdoctoral Fellow Neuroscience Poster Session

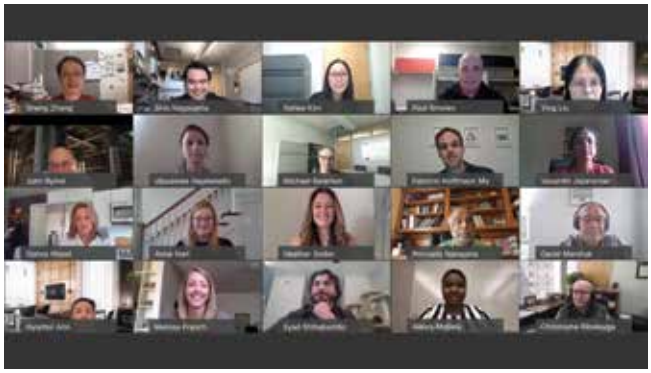
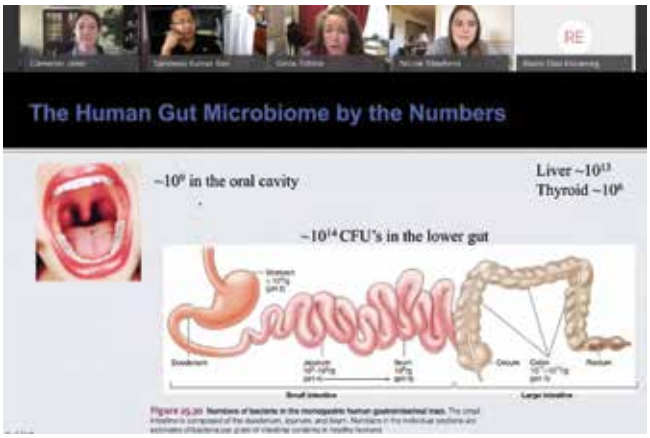
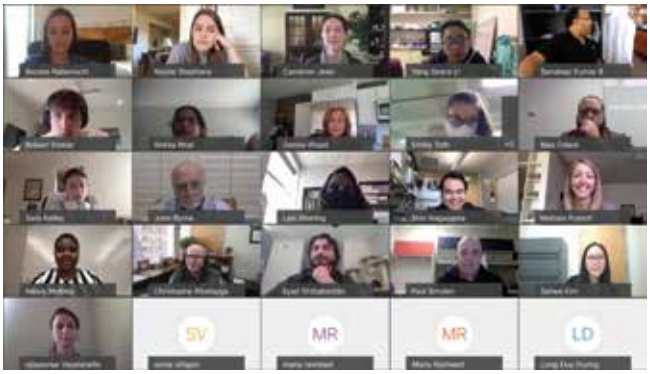


Photo from the virtual Postdoctoral Fellow Neuroscience Poster Session

2020 Neurobiology of Disease Course - The Microbiome of the Brain

Held virtually this year, our annual graduate level course had record levels of attendance. Many thanks to our course lecturers and Course Director and Executive Committee member, **Cameron Jeter, PhD.**





Photos from the virtual Neurobiology of Disease course.

In*the*Spotlight

A Look Back at Former UTHealth NRC Receptions at the Annual Meeting of the Society for Neuroscience.

Since we could not be together in 2020, we hope you enjoy this visit down memory lane. We look forward to being together again at the next annual meeting of the Society of Neuroscience. Until then, we encourage you to reconnect with current and former colleagues, as we would have traditionally done this past fall.

news&information

A recent list of publications from UTHealth NRC Faculty Members is available on our website and in the digital copy of our Newsletter.

Through the Texas Child Health Access Through Telemedicine (TCHATT) program, which is part of the Texas Child Mental Health Care Consortium, UTHealth has partnered with several local schools to provide virtually mental health care to children during the COVID-19 pandemic. This new program connects students experiencing an emotional or behavioral crisis with sustainable care at UTHealth. School districts participating in the program are Alief ISD, Aldine ISD, Fort Bend ISD, Huffman ISD, Humble ISD, Lamar Consolidated ISD, and YES Prep.

The Houston 2020 Mood Disorders Conference sponsored by The Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences was a great success. This year's two-day, virtual program "Bipolar Disorder: Advances in Diagnosis and Management" was held in October, and featured keynote speakers from UTHealth and Baylor College of Medicine.

Hyochol "Brian" Ahn, PhD, ANP-BC, associate professor at the Cizik School of Nursing, has been named assistant dean for Research and the Isla Carroll Turner Chair in Gerontological Nursing for the Cizik School of Nursing.

Elaheh Ashtari, PsyD, assistant professor of psychiatry and behavioral sciences, and Nicole R. Gonzales, MD, professor of neurology, have been appointed vice chairs for Diversity and Inclusion in their respective McGovern Medical School departments. Eight faculty were appointed as part of an initiative to facilitate cultural awareness, and to provide leadership for diversity and inclusion across each departments' clinical, research, and teaching sites.

April Crawford, PhD, and **Tricia Zucker, PhD**, associate professors in the Department of Pediatrics, have been have been named co-directors of the Children's Learning Institute (CLI) at UTHealth. **Susan Landry, PhD**, the founding director of the CLI, recently stepped down from her position. She continues her role as a developmental psychologist, Albert & Margaret Alkek Distinguished Chair in Early Childhood Development, and the Michael Matthew Knight Memorial Professor in the Department of Pediatrics.

A new program, HEARTS@UTHealth, has been developed by **Angela Heads, PhD**, associate professor of psychiatry and behavioral sciences, and will focus on substance use as well as HIV and Hepatitis C prevention services in minority communities. HEARTS, which stands for HIV Education, Awareness, Referral, and Treatment for Substance use disorders, is funded by the Substance Abuse and Mental Health Services Administration of the U.S. Department of Health and Human Services. Evidence-based treatments will include motivational interviewing and goal-setting, cognitive behavioral therapy (CBT), Seeking Safety treatment, and medication-assisted treatment.

Nominated by The Harris County Medical Society, **Eddie L. Patton, Jr, MD, MBA, MS**, clinical assistant professor at UTHealth Neurosciences, has been selected as one of the alternate delegates to the American Medical Association (AMA), by the Texas Medical Association House of Delegates at its 2020 TMA House of Delegates virtual session.

Marsal Sanches, MD, PhD, associate professor of psychiatry and behavioral sciences, has started a specialty bipolar disorder outpatient clinic as part of the UTHealth Center of Excellence on Mood Disorders. The clinic will focus on state-of-the-art pharmacological treatments and psychotherapy, with a goal of facilitating clinical research studies to address novel treatment strategies for bipolar disorder.

Diane M. Santa Maria, DrPH, MSN, RN, FAAN, has been appointed dean of the Cizik School of Nursing at UTHealth. In this role, Dr. Santa Maria will serve as the Jane and Robert Cizik Distinguished Chair and the Huffington Foundation Endowed Chair in Nursing Education Leadership.

Guo-Qiang Zhang, PhD, professor in the Department of Neurology and co-director of the Texas Institute for Restorative Neurotechnologies at UTHealth, has been appointed vice president and chief data scientist in the newly created Office of Data Science at UTHealth. This office will work directly with physician scientists and clinical researchers to create digital ecosystems that are specific to particular diseases and specialties.

Jiajie Zhang, PhD, dean and The Glassell Family Foundation Distinguished Chair in Informatics Excellence at UTHealth School of Biomedical Informatics, was recently named a 2020 fellow to the International Academy of Health Sciences Informatics (IAHSI), established by the International Medical Informatics Association (IMIA). Membership is considered one of the highest distinctions and honors in the field of biomedical and health informatics.

As part of UTHealth guidelines, Rong-Yu Liu, PhD, assistant professor of research in the Department of Neurobiology and Anatomy, wears a face mask to perform all experiments.

Upcoming Events

Brain Awareness Week

Our annual event, Brain Night for Kids at The Health Museum, has been postponed due to COVID-19-related concerns. We are still bringing brain awareness to our community - virtually! Please visit our website for a list of resources and brain awareness educational videos.

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

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

Virtual Event via WebEx

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

UTHealth NRC 2021 Distinguished Lecture in the Neurosciences

Ed Boyden, PhD
Y. Eva Tan, Professor in Neurotechnology
Massachusetts Institution of Technology

May 26, 2021, 4:00 p.m.

Virtual Event via WebEx

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

publications

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