NRC newsletter

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Determining the Influence of Oral Health, Oral Microbiome and Systemic Inflammation in Alzheimer's Disease

Neha Parikh, MS, PhD

Parikh

Abstract: Alzheimer's disease, characterized by a decline in cognitive function, can interfere with routine activities, including oral health maintenance. Alzheimer's disease, which is often diagnosed in the late stages, has limited treatment options, making early detection vital to prevent its progression. With the goal of building awareness about relationships between Alzheimer's disease and systemic health, as well as its earlier detection, my lab research focuses on identifying the role of oral health, oral microbial dysbiosis, and systemic inflammation in the progression of Alzheimer's disease.

Dementia indicates a decline in cognitive function that interferes with everyday activities. Of the various dementia types that mostly affect the elderly population, neurodegenerative Alzheimer's disease (AD) accounts for 60-80% of dementia cases. Within the last two decades, deaths due to AD have dramatically increased by 145% in the United States. AD is characterized by accumulation of abnormal beta amyloid plaques outside of neurons and phospho-tau protein tangles inside of neurons, ultimately leading to neuronal death and decline in cognitive function. Research shows that the molecular events underlying AD start more than 10-15 years prior to the appearance of clinical symptoms and diagnosis. The continuum of AD spread over years include brain changes with 1) no cognitive impairment (pre-symptomatic for AD); 2) mild cognitive impairment (MCI) with no interference in patients' routine activities; and 3) evident loss of memory and physical disability that interfere with everyday activities (mild/moderate/severe AD). About one third of subjects with MCI develop AD within five years. Throughout different stages of AD, brain changes such as amyloid beta plaques and decreased metabolism of glucose can be measured by imaging techniques such as positron emission tomography (PET) and fluorodeoxyglucose (FDG) PET, respectively. However, these imaging techniques are expensive and often not covered by health insurance. In addition, currently established biomarkers for AD (beta amyloid, tau and phosphor-tau proteins) involve invasive collection of the cerebrospinal fluid

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Interleukin-33, A Critical Player in Neuronal Aging and Aging-related Dementias

Yahuan Lou, PhD

Lou

Abstract: We discovered that brains age suddenly at midlife, which is associated with neuronal damage. The process may evolve to dementia at old age, but the progression may be prevented by interleukin-33.

Cases of elderly dementia, including sporadic Alzheimer's disease (AD), are increasing at an astonishing speed. Approximately 5.8 million Americans aged 65 and older are living with dementia. Researchers have been racing to identify the causes of the disease, and ultimately a cure, but there are still many questions that remain about this elusive disease. The first major victory for researchers was the discovery that dementias, mainly Alzheimer's disease, are associated with the buildup of insoluble substances in the brain called "amyloid" and "tau." Those seemingly toxic substances were, at one time, essential proteins for neurons. However, buildup of those insoluble substances ultimately leads to slow neuronal death.

These initial discoveries have led to several important questions. For example, *how did those proteins become insoluble and build up in individuals with dementia?* There are several possible answers. Initially, researchers aimed to identify a familial genetic link to hereditary Alzheimer's disease by studying genes encoding those proteins, or proteins for processing them. The generation of excessive "sticky" amyloid-β (Aβ) peptide fragments that aggregate into insoluble mass is indeed caused by mutations in the Aβ precursor protein gene (APP), as well as the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes. The aggregates ultimately damage nerve cells and induce hyperphosphorylation of tau, another pathological marker of Alzheimer's disease. Additional genome-wide association studies have identified several other genes that are commonly associated with an increased risk of developing AD, including apolipoprotein E (APOE).

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Director's Column

From the Director, John H. Byrne, PhD

Just as other issues of the UTHealth Houston Neuroscience Research Center *Newsletter* have highlighted research at one of the six schools within the UTHealth Houston system, this issue will feature recent research from the UTHealth Houston School of Dentistry and introduce a new school into the system, the UTHealth Houston School of Behavioral Health Sciences. We will also share information about our upcoming programs that are sure to be of great interest.

Neuroscience research at the UTHealth Houston School of Dentistry has significantly expanded over recent years, as the connections between inflammation, oral health, the microbiome, and brain health grow stronger and more intertwined. Dementia research is especially significant at the School of Dentistry and both research articles in this issue provide important insights into the mechanisms underlying Alzheimer's disease. In the first scientific article, **Neha Parikh, PhD,** Assistant Professor in the Department of Diagnostic and Biomedical Sciences, discusses her lab's efforts to identify the role of oral health, microbial dysbiosis, and systemic inflammation in the progression of Alzheimer's disease. The second article by **Yahuan Lou, PhD,** Professor in the Department of Diagnostic and Biomedical Sciences, highlights his lab's findings which suggest that interleukin-33 is a critical player in neuronal aging and aging-related dementias. Both articles offer great hope for a difficult disease that, despite extensive efforts, remains without a cure.

UTHealth Houston continues to expand its reach in the neurosciences with the addition of the UTHealth Houston School of Behavioral Health Sciences. The new institute, set to be the seventh school in the system and the largest academic behavioral health campus in the country, has recently been approved by the Texas Higher Education Coordinating Board and The University of Texas System Board of Regents. The purpose of the new school is to address a significant need for additional mental health care workers in the state and improve access to mental health care in general. The school will work to provide an anticipated 35 degree or certificate programs for mental health professionals over the next ten years, an impressive goal which reflects the urgent necessity for greater mental health services in our state and beyond. Executive Director of the John S. Dunn Behavioral Sciences Center, **Jair C. Soares, MD, PhD,** shares his vision for the school:

The new UTHealth Houston School of Behavioral Health Sciences is a great development for our community and our state. It is much needed since behavioral health is so underserved. It will be instrumental to develop the workforce needed to keep up with these major needs and gaps in our delivery of mental health services across Texas. We are so excited that our leadership at UTHealth Houston and UT Systems has given us the go ahead to build the new school as the 7th school under UTHealth Houston's umbrella!

The recently built UTHealth Houston John S. Dunn Behavioral Sciences Center is an inspiring state-of-the-art building, and was awarded the 2023 "Development of Distinction Award in the Not-for-Profit category" by the Houston chapter of the Urban Land Institute. The beautiful space, combined with UTHealth Houston's largest academic psychiatric faculty in the state, make this school poised for great success.

The office of the NRC has organized an especially exciting year of events. The fall 2023 Current Topics in the Neurobiology of Disease course had a phenomenal line up of speakers addressing, "Neuromodulation and Brain-Computer Interfaces (BCI)." This course was directed by **John Seymour, PhD,** Associate Professor in the Department of Neurosurgery and Adjunct Associate Professor at Rice University's Department of Electrical & Computer Engineering, and **Heather Webber, PhD,** Assistant Professor in the Faillace Department of Psychiatry and Behavioral Sciences. The course lectures, which were open to all students and faculty, were provided a broad understanding and appreciation for invasive (e.g., electrocorticography (ECoG), stereoelectroencephalography (sEEG), local field potential (LFP), deep brain stimulation (DBS)) and non-invasive (surface EEG, transcranial magnetic stimulation, transcranial current stimulation) recording and stimulation modalities as they relate to brain mapping, neurological/psychiatric diseases and disorders (e.g., stroke, epilepsy, depression, PTSD) as well as the augmentation and/or restoration of certain functions. Importantly, discussion of ethical implications, as well as the future of these emerging technologies, were threaded throughout and specifically addressed. Lectures were given by leading experts in the field from UTHealth Houston, Rice University, and Baylor College of Medicine. For a complete list of lectures, please visit our website or subscribe to our Neurofax calendar of events. Highlights will be shared in the next issue.

In addition, we were delighted to host the annual Neuroscience Poster Session on Saturday, December 2nd at the UTHealth Houston Cooley University Life Center. Participating institutions include UTHealth Houston, Baylor College of Medicine, and Rice University. Highlights will be shared in the next issue. Please visit our website to learn more about this community-building event.

We enjoyed catching up with several of our current and former UTHealth Houston community at the annual meeting of the Society for Neuroscience in Washington, DC. We hosted a lively reception at Hill Country BBQ, located in the heart of the city. Later in the year, we are looking forward to hosting our annual Distinguished Lecture in the Neurosciences, Public Forum, and Brain Night for Kids at the Health Museum. Please check our website and subscribe to our monthly calendar to stay up-to-date on our current program offerings.

grants&awards

The UTHealth Houston John S. Dunn Behavioral Sciences Center was awarded the 2023 UTHealth Houston Department of Facilities, Planning, and Engineering "Development of Distinction Award in the Not-for-Profit category" by the Houston chapter of the Urban Land Institute.

The UTHealth Houston School of Public Health received the 2023 Association of Schools and Programs of Public Health (ASPPH) Harrison C. Spencer Award for Outstanding Community Service. This award recognizes the School's commitment to prioritizing both healthy Texans and a robust Texas economy through the creation of the Texas Epidemic Public Health Institute (TEPHI), a network of public health professionals and resources that ensure the state is at the forefront of pandemic readiness and response.

Michael Beierlein, PhD, associate professor of neurobiology and anatomy, and **Fabricio H. Do Monte, DVM, PhD,** assistant professor of neurobiology and anatomy, received an NIH award for a project titled, "Corticothalamic circuits mediating behavioral adaptations to unexpected reward omission." This study uses a combination of electrophysiology, chemogenetics, and gain/loss-of-function optogenetics in rats to investigate corticothalamic circuits that underlie behavioral adaptations following unexpected omission of reward.

Four NRC faculty members were recognized as 2023 Champions of the Clinical Learning Environment (28 faculty were chosen in total): **Kawal Bir, MD,** assistant professor of psychiatry and behavioral sciences, **Melissa J. Christie, MD,** assistant professor of neurology, **Erin Furr-Stimming, MD,** professor of neurology, and **Brandi Karnes, MD,** assistant professor of psychiatry and behavioral sciences. Awardees were chosen based on the positive impact they had on medical students' third-year clerkship rotations.

John H. Byrne, PhD, Director of the UTHealth Houston NRC and professor of neurobiology and anatomy, and **Fabricio H. Do Monte, DVM, PhD,** assistant professor of neurobiology and anatomy, received an award from the NIH for their project titled, "Modeling the molecular networks that underlie the formation and consolidation of memory." This proposal will use rodent models of associative learning to test the hypothesis that memory can be improved by using computationally designed training protocols that optimize the interactions between kinase cascades and transcription factors involved in the induction of long-term memory.

Several faculty from the Center for Translational Injury Research (CeTIR) received The Focused Program Award from the Department of Defense's Office of Congressionally Directed Medical Research Programs (CDMRP). Funding for their four-year research project aims to address the challenges of treating the hemorrhagic shock-induced exacerbation of traumatic brain injury. These faculty include: **Jessica Cardenas, PhD,** assistant professor of surgery, **Charles S. Cox, PhD,** the George and Cynthia Mitchell Distinguished Chair in Neurosciences, **Charles E. Wade, PhD,** professor and Director of the CeTIR, **Brijesh "Billy" Gill, MD,** professor of surgery, **Jenifer Juranek, PhD,** associate professor of pediatric surgery**. Erin Fox, PhD,** associate professor of surgery and Assistant Director of the CeTIR, leads the Program Core. An additional four-year grant from the CDMRP was also awarded to fund Phase II of a stem cell clinical trial to evaluate whether intravenously infused, adipose-derived mesenchymal stem cells produced by Hope Biosciences reduce the chronic neuroinflammatory response to traumatic brain injury.

Joseph A. Cochran, MD, assistant professor of neurosurgery, was awarded the Patient Choice Award from the Joe Niekro Foundation at the Houston Knuckle Ball in Bloom Gala. Dr. Cochran was nominated by a grateful patient after he successfully treated her brain aneurysm.

Three NRC faculty members were honored as Star Awardees for celebrating 50 years with the university: **Nachum Dafny, PhD,** professor of neurobiology and anatomy, **William Dowhan, PhD,** professor of biochemistry and molecular biology, and **Gary Rosenfeld, PhD,** professor emeritus.

Fernanda Laezza, MD, PhD, professor of pharmacology and toxicology at The University of Texas Medical Branch at Galveston, and co-investigator **Fabricio H. Do Monte, DVM, PhD,** received an NIH award for a project titled, "Probing brain circuit and behavior with protein:protein interaction modulators." In this project, they will use new chemical probes targeting a protein-channel interaction complex that regulates neuronal firing to interrogate the circuitry of the nucleus accumbens and advance the molecular and cellular understanding of reward-seeking and motivated behaviors in rodents, which may have clinical relevance for treating substance abuse and eating disorders.

Khader M. Hasan, PhD, professor of diagnostic and interventional imaging, and **Summer Ott, PsyD,** associate professor of orthopedic surgery and Director of the Concussion Program at Memorial Hermann Rockets Sports Medicine Institute, recently received a Mission Connect grant from the TIRR Foundation. This pilot study titled, "Effects of photobiomodulation (PBM) on clinical recovery from concussion in adolescents," will provide insight on whether the use of wearable PBM technology warrants further examination as a therapy for concussed adolescents.

Amanda Jagolino-Cole, MD, associate professor of neurology, received a Texas Neurological Society Research Grant for a project titled, "Empowering first responders in neurologically-underserved areas through teleneurology," to study the feasibility and effectiveness of first responder neurological education utilizing teleneurology.

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Vineeth John, MD, MBA, professor and Vice Chair for Education in the Faillace Department of Psychiatry and Behavioral Sciences, was selected to The University of Texas Kenneth I. Shine, MD, Academy of Health Science Education. Members of the Shine Academy are recognized as outstanding scholars and leaders in education from across all UT System health science institutions. New members are selected based on their contributions in the areas of direct teaching, curriculum development, mentorship, educational scholarship, and leadership.

Scott D. Lane, PhD, professor of psychiatry and behavioral sciences and Director of Research at the UTHealth Houston Dunn Behavioral Sciences Campus, received an award from the Department of Defense Pharmacotherapies for Alcohol and Substance Use Alliance (PASA) for a project titled, "Development of suvorexant for the treatment of alcohol use disorder and PTSD."

Nuria Lacuey Lecumberri, MD, PhD, assistant professor of neurology, was awarded a five-year NIH National Institute of Neurological Disorders and Stroke (NINDS) grant to study preventive strategies for sudden unexpected death in epilepsy (SUDEP).

David A. Lee, MD, MBA, clinical professor of ophthalmology and visual science, recently received the Life Achievement Honor Award from the American Academy of Ophthalmology. The award symbolizes his longstanding commitment to advancing the profession and for positively impacting patients' eye health.

Sean P. Marrelli, PhD, professor of neurology, was awarded an NIH R01 grant titled, "Modifying endothelial Piezo1 function to improve brain perfusion in Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD)". The five-year grant seeks to determine if enhancing responsiveness of Piezo1, a mechanosensitive ion channel, to shear in brain endothelium can improve brain perfusion in conditions of amyloidosis. In addition, Dr. Marrelli was awarded an NIH R56 grant titled, "Targeting intramural von Willebrand factor (VWF) to improve vasomotor function, enhance brain parenchymal clearance, & delay development of cerebral amyloid angiopathy (CAA) in conditions of amyloidosis." The one-year grant seeks to determine the potential of VWF, when located within the vessel wall, to promote pathological vascular remodeling in conditions of amyloidosis.

David W. Marshak, PhD, professor of neurobiology and anatomy, is the Consortium Principal Investigator on a National Eye Institute research grant (PI, Jay Neitz, PhD, University of Washington) titled, "Linking retinal circuits to perception." The goal of these experiments is to describe the neural circuits that process information from short wavelength-sensitive cones in the primate retina at the level of synapses between identified populations of neurons.

Raja Mehanna, MD, associate professor of neurology and Assistant Director of the Movement Disorder Fellowship, was recently named to both the Texas Super Doctors 2023 list and Texas Top Doctors 2022 list as featured in Texas Monthly magazine, and included in the Best in Texas Magazine Doctor Edition 2022.

Thy Nguyen, MD, associate professor of neurology, was recently named a Texas Super Doctor 2023. In addition, she was invited to join the Academy of Master Educators at UTHealth Houston.

Joy M. Schmitz, PhD, professor and Faillace Chair, Director of the Center for Neurobehavioral Research on Addiction (CNRA), received the 2023 Marian W. Fischman Lectureship Award from the College on Problems of Drug Dependence (CPDD). Established in 2001, this annual award recognizes the contributions of an outstanding woman scientist in drug abuse research. Dr. Schmitz was also named as a member of the 2023 Fellowship class of the Society for Research on Nicotine and Tobacco (SRNT), in recognition of her outstanding contributions to the field of nicotine and tobacco research, and service to the SRNT.

As part of the NIH BRAIN Initiative, **John P. Seymour, PhD,** associate professor of neurosurgery, along with **John C. Mosher, PhD,** professor of neurology, and Charles E. Schroeder, PhD (Columbia University), received an NIH/NINDS grant for a project titled, "Neural recording and simulation tools to address the mesoscale gap."

John P. Seymour, PhD and **Nitin Tandon, MD,** professor of neurosurgery and Co-Director of the Texas Institute of Restorative Neurotechnologies (TIRN) and Vice President of Strategy and Development of UTHealth, received a NIH BRAIN Initiative grant for a project titled, "DIrectional and SCalable (DISC) microelectrode array for speech decoding." This project aims to help reconstruct language patterns in patients with speech impairments caused by stroke or brain injury.

Cesar Soutullo, MD, PhD, professor, Vice Chair, and Chief of Child and Adolescent Psychiatry in the Faillace Department of Psychiatry and Behavioral Sciences, was recently appointed as a member of the American Academy of Child and Adolescent Psychiatry (AACAP) Clinical Essentials Committee.

As part of the NIH BRAIN Initiative, **John Lee Spudich, PhD,** professor of biochemistry and molecular biology, along with Baylor College of Medicine researchers Francois St-Pierre, PhD and Mingshan Xue, PhD, received a grant for their project titled, "Developing an optogenetics technology based on natural potassium-selective channelrhodopsins."

Nitin Tandon, MD, recently received an NIH/NINDS grant for a project titled, "The neural code and dynamics of the reading network." This project aims to identify the specific roles and interactions of the brain areas involved in reading to better understand how humans read fluently and learn to read new words.

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Kelly A. Vaughn, PhD, assistant professor of pediatrics, received funding for a grant from the National Institute of Child Health and Human Development (NICHD) Office of the Director Tackling Acquisition of Language in Kids (TALK) Initiative titled, "Bilingual exposure following preterm birth: toddler language outcomes and cumulative risk factors."

Vijayasree Vayalanellore Giridharan, PharmD, PhD, instructor of psychiatry and behavioral sciences, received a Second Century Implementation Science Award from the American Heart Association (AHA) for her project titled, "Neuropsychiatric consequences on COVID-19 survivors - role of vascular damage and gut microbiome."

Consuelo Walss-Bass, PhD, professor and John S. Dunn Foundation Distinguished Chair in the Faillace Department of Psychiatry and Behavioral Sciences and Director of UTHealth Houston Brain Collection, is part of a team that received an award from the NIH/National Institute of Mental Health (NIMH) for a project titled, "Single cell analysis of epigenetic mechanisms that regulate HIV-1 CNS latency and neuropathogenesis." This is a multiple PI award which includes Andrew P. Rice, PhD and Cristian Coarfa, PhD from Baylor College of Medicine. This study utilizes single cell RNA sequencing technology to examine brain autopsy specimens from individuals who were HIV-1 infected and treated with suppressive antiviral therapy prior to death. The research will focus on epigenetic mechanisms that regulate HIV-1 replication, latency, and neuropathogenesis in the brain. The project will inform therapeutic strategies to tackle the HIV-1 infection of the brain.

Heather Webber, PhD, assistant professor of psychiatry and behavioral sciences, received a K-Award from the National Institute on Drug Abuse (NIDA) for her project, "Identifying electrophysiological targets for transcranial magnetic stimulation in cocaine use disorder."

Graduate Students, Postdoctoral Fellows & Residents

Heather Tsong, a PhD candidate in the laboratory of **Andrea Stavoe, PhD,** assistant professor of neurobiology and anatomy, is the 2023 recipient of the Terry J. Crow, PhD, Scholarship in Neuroscience. Ms. Tsong received the scholarship for her outstanding scholastic achievements. Her research in the field of aging-related brain diseases investigates the molecular mechanisms employed by neurons to regulate autophagy during aging.

A team of residents from the UTHealth Houston Faillace Department of Psychiatry and Behavioral Sciences won first place at the American Psychiatric Association's MindGames competition. The team was put together by **Vineeth John, MD, MBA,** professor and vice chair for education, and consisted of members: Caroline McCool, MD, Hunter Hinman, MD, and Daniel Liaou, MD. This is the fifth time in 11 years that the UTHealth Houston team has won this event.

Camila Nayane de Carvalho Lima, PhD, a postdoctoral fellow in the Faillace Department of Psychiatry and Behavioral Sciences, received a 2022 NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation for her project, "Molecular mechanisms underlying accelerated epigenetic aging in bipolar disorder: a transcriptomic and neuroanatomical study."

Recipients of the NRC 2023 Distinguished Medical Student in the Neurosciences included Alexa Ryder, MD and Michelle Chen, MD (not pictured). Awards were presented by Jack Byrne, PhD, at the NRC Public Forum in April.

Recipients of the NRC 2023 Graduate Student Brain Awareness Outreach Award Pedram Honarpisheh (not pictured, Mentor: Louise McCullough, MD, PhD) and Fiona Shannon Smith (Mentor: Jennifer Beauchamp, PhD, RN). Awards were presented by Jack Byrne, PhD, at the NRC Public Forum in April.

Congratulations to the 2023 winners of the Dean's Teaching Excellence Awards.

(CSF). Due to these challenges and long continuum of disease, most clinical diagnoses occur in the late stages of AD.

Chronic inflammation is implicated as one of the hallmarks of AD. Altered levels of immune system modulators have been detected in the brains of patients with AD that are proposed to drive AD pathology (Kinney et al., *Alzheimers Dement.* (NY) 4:575, 2018; Cuello, *Trends Pharmacol. Sci.* 38:956, 2017; Parachikova et al., *Neurobiol. Aging* 28:1821, 2007). Altered levels of inflammation markers have been reported in both CSF and peripheral blood in patients with AD (Morgan et al., *Alzheimers Dement.* 15:776, 2019; Shen et al., *J. Neurol. Neurosurg. Psychiatry* 90:590, 2019; Leung et al., *PLoS One* 8:e64971, 2013). However, due to data variability likely arising from the variability in cohorts under investigation, collection/storage of biological samples and inherent heterogeneity of the disease itself, there is currently an unmet need to establish an early diagnostic biomarker for AD in more easily accessible biofluids such as plasma or saliva. Recent evidence also suggests an important role of oral health in AD (Aragon et al., *Clin. Oral Investig.* 22:3061, 2018; Delwel et al., *Clin. Oral Invest.* 22:93, 2018). For example, periodontitis, characterized by gingival inflammation and alveolar bone loss, is a microbial biofilm-induced chronic inflammatory disease, shown to be associated with AD (Leira et al., *Neuroepidemiology* 48:21, 2017; Beydoun et al., *J. Alzheimers Dis.* 75:157, 2020). Growing evidence also suggests an infectious etiology of AD, reinforcing the concept of microbial dysbiosis and inflammation resulting in AD progression (Seaks & Wilcock, *PLoS Pathog.* 16:e1008596, 2020; Sochocka et al., *Curr. Neuropharmacol.* 15:996, 2017; Stadlbauer et al., *BMC Geriatr.* 20:248, 2020). The acute inflammatory response to oral pathogens can result in a state of chronic and systemic inflammation, that can exacerbate AD (Teixeira et al., *Front. Aging Neurosci.* 9:327, 2017).

My research focuses on identifying the role of oral health, oral dysbiosis and systemic inflammation in the progression of AD. In an ongoing study in collaboration with Paul E. Schulz, MD at the Neurocognitive Disorders Center, McGovern Medical School, UTHealth Houston, patients in various stages of AD are assessed for oral health through questionnaires recording information such as oral hygiene, dietary habits, and swallowing ability, as well as a visual evaluation of the oral cavity and plaque assessment. Evidence suggests that oral bacteria can spread through the body and influence a number of systemic diseases. Therefore, in collaboration with Gena Tribble, PhD at the UTHealth Houston School of Dentistry and Cameron Jeter, PhD at the Kansas College of Osteopathic Medicine, the role of oral dysbiosis in MCI/AD patients and age matched controls is being investigated through oral microbiome analysis. In addition, the association between systemic inflammation and AD progression is being evaluated in plasma and saliva samples derived from the same cohort of elderly patients with MCI, AD and cognitively intact controls. Our preliminary data, based on a pilot cross-sectional study shows elevated plasma levels of certain inflammatory cytokines in patients with AD, compared to patients with MCI. Patients with AD also show worse oral hygiene habits compared to age-matched cognitively intact healthy controls which is consistent with published literature (Aragon et al., *Clin. Oral Investig.* 22:3061, 2018; Delwel et al., *Clin. Oral Invest.* 22:93, 2018; Leira et al., *Neuroepidemiology* 48:21, 2017; Beydoun et al., *J. Alzheimers Dis.* 75:157, 2020). Future studies would focus on the longitudinal assessment of systemic inflammation and other potential markers in patients with MCI for changes with disease progression.

Leveraging the power of big data in healthcare science, my lab also utilizes a large multi-institutional dataset, called BigMouth Dental Data Repository (Walji et al., *J. Am. Med. Inform. Assoc.* 21:1136, 2014), for correlating the oral and systemic health parameters with dementia diagnoses, using deidentified electronic health records across multiple dental schools in the United States. The dementia diagnoses and medical history reported in the BigMouth Dental Data Repository are currently patient reported. Preliminary data indicate fewer periodontal procedures completed, and poorer periodontal and cardiovascular health in patients with dementia, underscoring the importance of increasing awareness about relationships between dementia and oral/systemic health, and the use of a multi-pronged approach to prevent disease progression in patients with dementia.

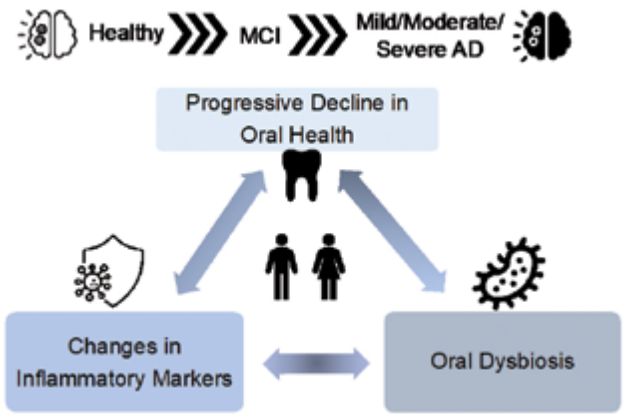

Figure 1. Combinatorial approach of correlating the oral health status, oral microbiome and systemic inflammatory markers in patients with Alzheimer's disease (AD).

According to the American Dental Association, ~100 million Americans fail to see a dentist each year. We hope that our integrated approach will give insights about the critical role of multiple inter-related factors such as oral health, systemic health, microbial dysbiosis, and inflammation in AD progression **(Figure 1)**, potentially leading to simpler and early intervention approaches including improving oral health, anti-inflammatory drugs/peptides, and/or antibiotics for mitigating and slowing AD progression.

About the Author

Neha Parikh, MS, PhD*, is an assistant professor in the Department of Diagnostic and Biomedical Sciences at UTHealth Houston School of Dentistry where she teaches and directs biomedical science courses. Her doctoral research focused on deciphering molecular mechanisms regulating apoptosis. She did her postdoctoral research in aging and cancer biology at Baylor College of Medicine, Houston, TX. In her current role at UTHealth Houston, Dr. Parikh is interested in assessing the progressive role of poor oral health, microbial dysbiosis and systemic inflammation in Alzheimer's disease. Besides scientific and educational research, she enjoys teaching and mentoring dental students.*

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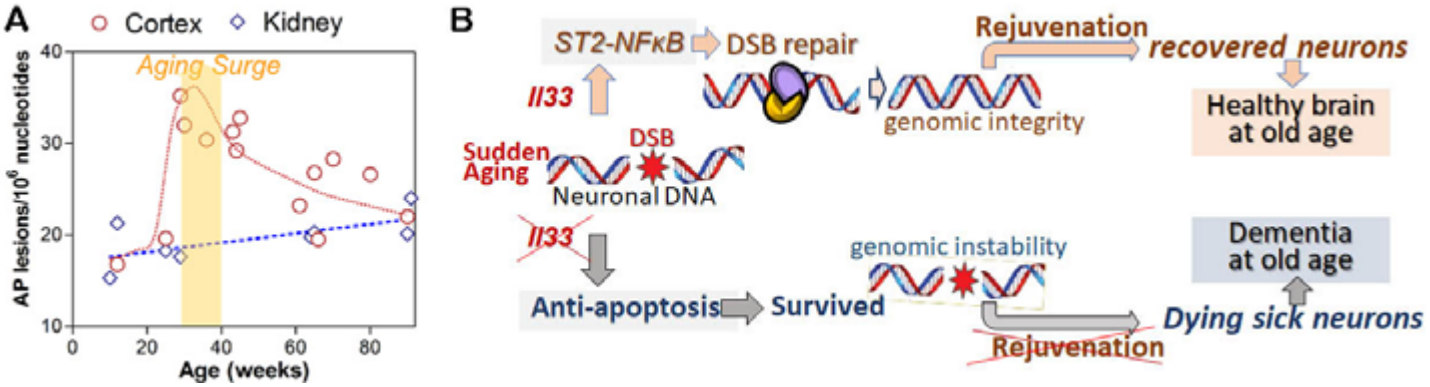

Figure 1. Hypothetical scenario depicts how defects in IL-33 in the brain may cause age-related dementia.

A. Aging in brains at middle age in mice leads to a sudden surge of DNA AP lesions, which cause DNA double strand breaks (DSBs). Note that no such surge exists for other organs, such as the kidney.

B. IL-33 immediately activates the ST2-NFkB pathway in neurons to initiate repair of DSBs to maintain genomic integrity and ensure full rejuvenation of neurons *(upper panel)*. In the case of IL-33 deficiency, DSBs are unrepaired in neurons that may trigger apoptosis. Neurons may use anti-apoptotic mechanisms to avoid their death, but their functions and survivability are gravely compromised. This opens a path to chronic neuronal degeneration and dementia at old age *(lower panel)*.

Interestingly, the genetic component of AD may only account for a small fraction of dementia cases. What does occur in the other cases, in which those genes are perfectly normal? Despite several decades worth of extensive research, it seems there is no single answer. My colleagues and I are currently aiming to identify additional mechanisms underlying dementia to find other potential answers. We started by examining the differences between neurons and other cell types in the body. One major difference is that neurons are long-lived, and are usually not simply replaced by new ones through cell division as seen in many other cells. Nerve cells are relatively proficient at cellular rejuvenation and can protect themselves from oxidative damage, which is part of the aging process for all cells. Because of this, their ability to discard the waste from oxidative stress and damage is especially crucial. Therefore, we decided to explore the impairment of this process as a potential mechanism for dementia.

Oxidative stress is associated with aging. We first discovered a surge of oxidative stress in neurons in mouse brains at middle age (equivalent to 40 years old in humans), which causes damage to vital molecules (Carlock et al., *Transl. Psych.* 7:e1191, 2017). One type of DNA damage called apurinic/apyrimidinic (AP) lesions soared to a level comparable to those in cancer cells (**Figure 1A**). AP lesions cause DNA double-strand breaks (DSBs), leading to an unstable genome. Cells with too many DSBs usually induce programed suicide (apoptosis) of the cell. Yet, neurons in the brain after middle age remain healthy. Therefore, neurons must possess a special ability for repairing or eliminating those damaged molecules, a process we refer to as neuronal rejuvenation. An immediate question for us was *how do neurons rejuvenate themselves, and what will be the result if rejuvenation becomes defective*? Based on our past study on tissue homeostasis (Wu et al., *J. Immunol*. 194:2140, 2015), we suspected that interleukin-33 (IL-33) was involved in neuronal rejuvenation. What is interleukin-33? From the name, it would seem to be a molecule for immunity or inflammation. In contrast, several studies, including our study on ovaries (Carlock et al., *J. Immunol.* 193:161, 2014), have found that it plays an important role in tissue homeostasis, a process to maintain tissue integrity and functionality. IL-33 is first stored in nuclei, and is released as a cytokine by cleavage when needed. It binds to its receptor called ST2 to activate the nuclear factor-κB (NFκB) transcription pathway. In the brain, we unexpectedly observed IL-33 in the nuclei of numerous astrocytes (which are "nurses" for neurons), and further, astrocytes with IL-33 increase with age until early late life (Carlock et al., *Transl. Psych.* 7:e1191, 2017). The brain is an "immune privilege site" and entry of immune cells or molecules is usually blocked. Increased expression of IL-33 in the aging brain suggest its potential roles in neuronal aging or rejuvenation. To test our hypothesis, a mouse strain without the IL-33 gene (IL-33KO) was generated (Wu et al., *J. Immunol.* 194:2140, 2015). Comparing the brains of normal mice and IL-33KO mice, we found that the IL-33KO mice showed defects in at least three rejuvenation mechanisms. First, neurons in IL-33KO mice lost their ability to repair DNA DSBs. Therefore, numerous DSBs accumulated in the nuclei of neurons after middle age, especially in the cerebral cortex and hippocampus. Interestingly, Alzheimer's disease is associated with neuronal damage in those areas. Although those neurons may survive through special mechanisms, they are neither fully functional nor able to rejuvenate themselves. Second, neurons in IL-33KO brains were no longer able to discard damaged molecules through autophagy, a process used to collect cellular waste and further discard it through digestion. Third, IL-33KO brains can no longer effectively remove waste from *around* the neurons, which would be sent to the brain's clearance system called glymphatics (Wu et al., *Mol. Psychiatry*, 26:5912, 2021). It is conceivable that

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defects in the latter two rejuvenation mechanisms would lead to build up of damaged molecules such as amyloid peptide or insoluble tau, and potentially result in Alzheimer's disease.

We next examined the potential consequences of defects in neuronal rejuvenation in IL-33KO mice (Carlock et al., *Transl. Psych.* 7:e1191, 2017). We found that those mice slowly developed dementia, following a similar course and expressing characteristics analogous to sporadic Alzheimer's disease. The first sign of the disease in IL-33KO mice is the loss of neuronal connections, through a loss of such as synapses, axons, or dendrites after middle age (Lou, *Neurosci. Insights,* 16:1, 2021). We also observed an accumulation of insoluble tau at their early late life stage. At old age, the IL-33KO mice start to display changes in behavior, and impairment in cognition and memory. Interestingly, we also noticed that IL-33KO mice lacked amyloid plaque, a hallmark for Alzheimer's disease, as the mouse counterpart of the human protein lacks a structure for aggregation. Currently, we are investigating whether normal human protein responsible for amyloid plaque would have plaques in IL-33KO due to defected waste disposal mechanisms such as autophagy and glymphatics.

Although our findings are just the beginning of a long path of discovery, a scenario for merging potential causes for elderly dementia has been depicted in **Figure 1B**. Oxidative stress in neurons suddenly surges at middle age, causing DNA DSBs and damage in proteins such as tau. "Nurse" astrocytes release IL-33 which activates the NFκB pathway in stressed neurons to initiate DSB repair. Genome integrity is maintained, which ensures full rejuvenation of neurons and proper disposal of damaged molecules. The neurons are able to return to a "young" state. If the IL-33/NFκB pathway is interrupted, neurons cannot repair DSBs. They have to turn on genes important for survival through anti-apoptotic death. However, genomic instability impairs their ability to discard waste. The result is a slow death of sick neurons with an accumulation of waste (such as insoluble tau), leading to dementia at old age. As our next step, we are examining which genes help sick neurons survive, and if they still can be rescued to avoid dementia.

In summary, our study may reveal a novel hypothesis for causing dementia in the elderly, including sporadic Alzheimer's disease. We also believe that the identification of an oxidative stress surge in brains at middle age in humans may be a window for early diagnosis and prevention of dementias at old age.

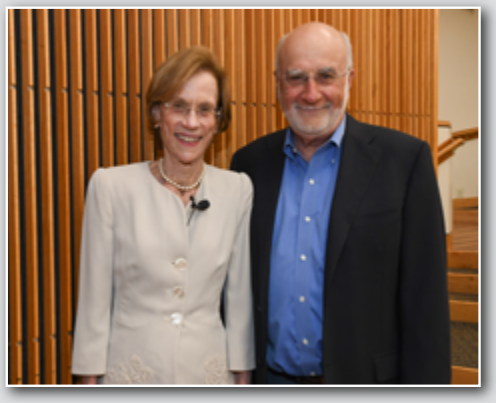
About the Author

Yahuan Lou, PhD, *is a professor in the Department of Diagnostic and Biomedical Sciences at the UTHealth Houston School of Dentistry. In addition, Dr. Lou holds an adjunct position in the Nephrology Division at Baylor College of Medicine. He earned a PhD in biology from Hokkaido University in Japan and completed postdoctoral training at the National Institute for Basic Biology, Japan, and Washington University Medical School at St Louis. His research has been supported by R01 grants from the NIH and other awards for over 20 years. His early research focused on autoimmunity, but has shifted focus to neuronal aging and its role in aging-related dementias after his discovery of a critical role of interleukin-33 in brain aging in 2017.*

In*the*Spotlight

The NRC hosted our annual Public Forum titled, "Post-COVID Brain and Behavioral Health," at the Cooley University Life Center on April 15, 2023. Our panelists are pictured (left to right**): Rodrigo Hasbun, MD, MPH,** Professor, Infectious Diseases, Department of Internal Medicine; **Louise D. McCullough, MD, PhD,** Professor and Chair, Department of Neurology, Roy M. and Phyllis Gough Huffington Distinguished Chair and Co-Director, UTHealth Houston Neurosciences; **Antonio L. Teixeira, MD, PhD,** Professor, Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences and Director, Neuropsychiatry Program; **Leslie K. Taylor, PhD,** Assistant Professor, Louis A. Faillace, MD Department of Psychiatry and Behavioral Sciences and Director, Building Resilience in Youth after Traumatic Experiences (B.R.Y.T.E.) Program.

The NRC hosted our annual **Distinguished Lecture in the Neurosciences** on May 11, 2023 at McGovern Medical School. Our distinguished guest, Ann Graybiel, PhD, Institute Professor at the Massachusetts Institute of Technology and Investigator at the McGovern Institute, held a captive audience during her lecture, "The Basal Ganglia and the Motivation to Act." Dr. Graybiel is pictured here with NRC Director, **Jack Byrne, PhD.**



Brain Night for Kids at The Health Museum

March 16, 2023

In*the*Spotlight

The NRC hosted a reception at the annual meeting of the Society for Neuroscience in Washington, D.C. in November at Hill Country Barbecue Market.

news&information

The fall of 2023 saw the MD Anderson UTHealth Houston Graduate School of Biomedical Sciences (GSBS) celebrating its 60th anniversary.

Leonard J. Cleary, PhD, professor of neurobiology and anatomy, recently transitioned from president-elect to president of the UT System Kenneth I. Shine, MD, Academy of Health Science Educators.

The 2023 UTHealth Houston Mood Disorders Conference titled, "Mood Disorder Challenges: Emerging Systems and Individual Solutions," was held in October and hosted by the Faillace Department of Psychiatry and Behavioral Sciences and the National Network of Depression Centers (NNDC). This conference sought to identify how depression affects various groups of individuals, including children, college students, elderly persons, and overall depression guidelines, as well as focus on treatments for major depressive disorders. Speakers from the Department included: **Joao L. de Quevedo, MD, PhD,** professor and Vice Chair of Faculty Development & Outreach, and **Jair C. Soares, MD, PhD,** professor and chair.

Stuart M. Fraser, MD, assistant professor of pediatrics and Director of the Pediatric Stroke Program at McGovern Medical School, was a recently featured guest on the AVM Alliance Podcast. This podcast was created for parents who are taking care of a medically complex child, including those who have been diagnosed with epilepsy or rare disease. Dr. Fraser appears on the first three episodes of season two.

The 10th annual Pediatric Neuroscience Symposium titled, "Children with Neurological and Neurosurgical Conditions: An Update for Pediatricians," was recently hosted by UTHealth Houston Neurosciences. Speakers for the event from McGovern Medical School included: **Stuart Fraser, MD,** assistant professor of pediatrics, **Brandon A. Miller, MD, PhD,** assistant professor of pediatric neurosurgery, **Shadé Moody, MD,** associate professor of pediatrics, **Shelly Varnado, MD,** assistant professor of pediatrics, **Manish Shah, MD,** associate professor of pediatric surgery, **Michael W. Watkins, MD,** assistant professor of pediatrics, **Jeremy Lankford, MD,** associate professor of pediatrics, **Stephen Fletcher, DO,** professor of pediatric surgery, **Tim Borden, MD,** assistant professor of orthopedic surgery, **Sam Nicholas Russo, MD,** assistant professor of pediatrics, and **David I. Sandberg, MD,** Professor and Chief, Division of Pediatric Neurosurgery.

Under leadership from **Louise D. McCullough, MD, PhD,** Co-Director of UTHealth Houston Neurosciences, the McGovern Medical School Neurohospitalist Fellowship Program has been approved for fellowship accreditation by the Neurohospitalist Society, becoming only the seventh program in the country to receive such distinction. This one-year fellowship program provides additional training for neurologists who have recently completed residency, as well as neurologists who have completed fellowship training in epilepsy or vascular neurology, in the comprehensive care of hospitalized patients with neurologic disorders and diseases.

Curtis Neveu, PhD, senior research scientist in the Department of Neurobiology and Anatomy, recently led a professional development course through the Society for Neuroscience called, "Illustrating Scientific Discoveries with Adobe Illustrator, Part 1 and 2." This course showed participants how to use Adobe Illustrator to create clear and captivating graphics for their scientific posters, presentations, figures, and diagrams. Dr. Neveu is also the creator of LearnBio.org, an interactive website for children to learn neuroscience, and the Adobe Illustrator for Scientists YouTube channel, which provides tutorials on making captivating scientific illustrations and figures.

The UTHealth Houston Addictions Conference titled, "The Kids Aren't Alright: Youth Substance Use Prevention and Treatment," was held in August and organized by The Faillace Department of Psychiatry and Behavioral Sciences, along with **Jair C. Soares, MD, PhD,** professor and chair, and course directors, **Joy M. Schmitz, PhD,** professor, and **Michael Weaver, MD,** professor. The conference provided practitioners with updates on the latest advances in the epidemiology, etiology, prevention and treatment of substance use in youth. Speakers from the department included: **Luis Fernandez, MD,** assistant professor, **Scott Lane, PhD,** professor, **Leslie Taylor, PhD,** assistant professor, **Michael Weaver, MD,** professor, **Luba Yammine, PhD,** associate professor**, Cristian Patrick Zeni, MD, PhD,** associate professor.

Dean **Jiajie Zhang, PhD,** along with faculty, staff, and students, celebrated the newly named D. Bradley McWilliams School of Biomedical Informatics, made possible by a large grant from D. Bradley "Brad" McWilliams. This transformational grant includes an innovation fund established by the McWilliams gift, as well as an endowed D. Bradley McWilliams Research Fund. In addition, funding is included to support endowed faculty appointments, doctoral scholarships, and philanthropic student scholarship support. A portion of this large grant was made possible by over 300 donors.

Upcoming Events

UTHealth Houston
Neuroscience Research Center

Brain Night for KIDS

The Health Museum
1515 Hermann Drive, Houston, TX 77004

Thursday, March 14th, 2024
Free Event
Open to the Public

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

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Questions? Comments?

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This Newsletter is distributed by mail to individuals and groups engaged in neuroscience research within the TMC and worldwide and features research, neuroscience accomplishments and outreach efforts performed at UTHealth. Past issues are available on the NRC website.

If you prefer to receive a digital copy through email, please contact UTHealth.NRC@uth.tmc.edu with your information.

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