Alzheimer's and Related Diseases Research Award Fund

2020-2021 FINAL PROJECT REPORT SUMMARIES

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 and is administered by the Virginia Center on Aging at Virginia Commonwealth University. The summary of a delayed final project report submitted by an investigative team funded during the 2020-2021 round of competition is given below. To receive the full report, please contact the investigators or the ARDRAF administrator, Dr. Constance Coogle (ccoogle@vcu.edu).

Hunter Holmes McGuire VAMC

Kathryn Holloway, MD, and Mark Baron, MD*

Deep Brain Stimulation of the Nucleus Basalis of Meynert: Using electricity to regenerate and restore cognitive function in dementia rodent model

There is a network of cholinergic neurons at the base of the frontal lobes that arises from the nucleus basalis of Meynert (NBM), and orchestrates learning, memory and other higher-level cognitive processes. This circuit is destroyed in both Alzheimer's disease and Parkinson's disease with dementia, through a progressive degenerative process. Electrical stimulation of the NBM can overcome some of the deficiencies in that circuit, with resultant symptom improvement. However, differences in stimulation parameters between animal and human studies may be a critical factor in the relative lack of response in the clinical trials. Consequently, this study evaluated the effect of burst stimulation modeled on normal brain oscillatory patterns. The effect of stimulation duration on learning ability and cholinergic neuron viability were documented. Results were consistent with the hypothesis that stimulation throughout the sleep-wake cycle might have mixed effects due to interference with sleep. The preliminary evidence gathered in this study resulted in a successful R03 proposal to study this aspect further by comparing stimulation only when the rat is awake to continuous stimulation. ***(Dr. Holloway may be contacted at 804-828-9465, kathryn.holloway@vcuhealth.org; Dr. Baron may be contacted at 804-828-9350, mark.baron@vcuhealth.org)***

UVA

Meghan Mattos, PhD, Justin Mutter, MD, MSc, and N. Aaron Yao, PhD

Interprofessional Home-Based Medical Care and Education Program Serving Rural Adults Living with Dementia

Virginia at Home (VaH) is an innovative program for homebound older persons with dementia (PWDs) that brings together an interprofessional VaH team partnering with the patients' primary care providers, home health agencies, and caregivers to optimize care in the home through regular house calls, telehealth visits, caregiver support, and advanced care planning. The program aims to support PWD and their caregivers through the provision of home-based primary care (HBPC). This mixed methods study was intended to examine the impact of VaH on the overall care and outcomes of homebound patients with dementia and their families. We compared clinical outcomes at baseline and six months, and conducted phone interviews at baseline and six months with PWD and caregivers to understand facilitators and barriers to the new HBPC program. Thirty PWD-caregiver dyads enrolled in the study. Seventeen dyads completed baseline and six-month clinical visits. Of the 17 dyads who completed both visits, PWD's physical function and caregiver burden decreased significantly over time. There was also a significant improvement in PWD's behavioral symptoms over the six-month period. In dyad interviews, four themes emerged: 1) participants established trusting relationships with the VaH team, 2) VaH supported family caregivers in their caregiving responsibilities, 3) participants met their pre-program goals through increased healthcare access, and 4) perceptions of the impact of VaH on health. Findings suggest that VaH improved care satisfaction and healthcare access and alleviated caregiver burden. Future studies should consider introducing HBPC programs in this hard-to-reach population to decrease health care utilization and costs while improving care satisfaction and quality. ***(Dr. Mattos can be contacted at 434-243-3936, ms2bv@virginia.edu; Dr. Mutter can be contacted at 434-982-6282; Dr. Yao can be contacted at 434-243-4874, ayao@virginia.edu)***

UVA **Maureen Metzger, RN, PhD, Ishan Williams, PhD, FGSA, and Emaad Abdel-Rahman, MD, PhD**

A Study Describing the Unique Needs of Caregivers of Patients with Both End-Stage Kidney Disease and Cognitive Impairment

Despite recommendations, routine screening of cognitive function in patients with end stage renal disease (ESRD) rarely happens, leading to inaccurate estimates of the prevalence of cognitive impairment (CI), limited understanding of the unique needs of caregivers of patients with both CI and ESRD, and a dearth of interventions to support patients and their caregivers. The purpose of this descriptive study was to identify potential barriers to routine screening for CI, estimate the prevalence of cognitive impairment in a sample of dialysis patients, and describe the unique and most pressing needs of caregivers of patients with ESRD and CI. A total of 100 patients, age 50 years and older (48% female, 49% Black/African American) from 7 hemodialysis centers in central Virginia were screened using both the Montreal Cognitive Assessment (MoCA) and the Geriatric Depression Scale (GDS). To ascertain patients' perceptions of screening, they participated in structured interviews. To better understand caregiver experience, 46 caregiver participants (87% female, 61% White/Caucasian, mean age 54±15 years), also completed the Caregiver Reaction Assessment and Patient Health Questionnaire. Of those screened, 32 had scores indicating normal cognitive function, 56 mild CI, and 12 moderate CI. Participants with scores indicating mild or moderate CI evaluated screening less favorably than those with normal MoCA scores. Most caregivers reported that caregiving adversely affects their health and finances. Younger, non-spouse, non-White caregivers reported greater burden. Preliminary analysis of interview data indicated caregivers may benefit from practical support, such as educational resources and transportation assistance. These findings should inform the development of interventions targeting the most significant barriers to screening and the most pressing needs of this vulnerable population. ***(Dr. Metzger can be contacted at 434-924-0112, mjm9cd@virginia.edu; Dr. Williams can be contacted at 434-924-0480, icw8t@virginia.edu; Dr. Abdel-Rahman can be contacted at 434-924-1984, ea6n@hscmail.mcc.virginia.edu)***

VCU **Dong Sun, MD, PhD, Xiang-Yang Wang, PhD, and Shijun Zhang, PhD**

TBI-induced immune/inflammatory response to the development of Alzheimer's disease

Epidemiological evidence strongly indicate that traumatic brain injury (TBI) accelerates the development of Alzheimer's disease (AD), however, the underlying mechanisms connecting TBI to AD are unclear. Recent studies have identified that NLRP3 inflammasome (a multiprotein complex regulating innate immune response and production of pro-inflammatory cytokines) is critical for the onset of AD, whereas TBI induces its activation in the brain. Based on these observations, the investigators hypothesize that neuroinflammation, triggered by TBI activated NLRP3 inflammasome, is the key connecting factor of TBI to AD. To test this hypothesis, they generated a novel transgenic AD mice line with NLRP3 gene-knock down at the background of 3xTg AD mice, which express human APP/PS1/Tau genes. They then evaluated TBI-induced immune responses by assessing immune cell phenotypes and cytokine expression profiles in the brain of 3xTg AD mice with or without the NLRP3 gene at different times following TBI. Results indicated that: 1) TBI significantly alters immune cell response in AD mice, and there are sex-related differences in immune and cytokine profiling correlating to clinically observed sex difference in TBI and AD. 2) NLRP3 inflammasome is important in mediating this TBI-induced immune/inflammatory changes at the acute stage following injury. 3) Blockage of NLRP3 inflammasome significantly reduces tau pathology in the 3xTg AD mice. Collectively, thee findings strongly indicate the critical role of NLRP3 in TBI-induced changes of immune/inflammatory response in the development of AD**. *(Dr. Sun can be contacted at 804-828-1318, dong.sun@vcuhealth.org; Dr. Wang can be contacted at 804-628-2679, xiang-yang.wang@vcuhealth.org; Dr. Zhang can be contacted at 804-628-8266, szhang2@vcu.edu)***