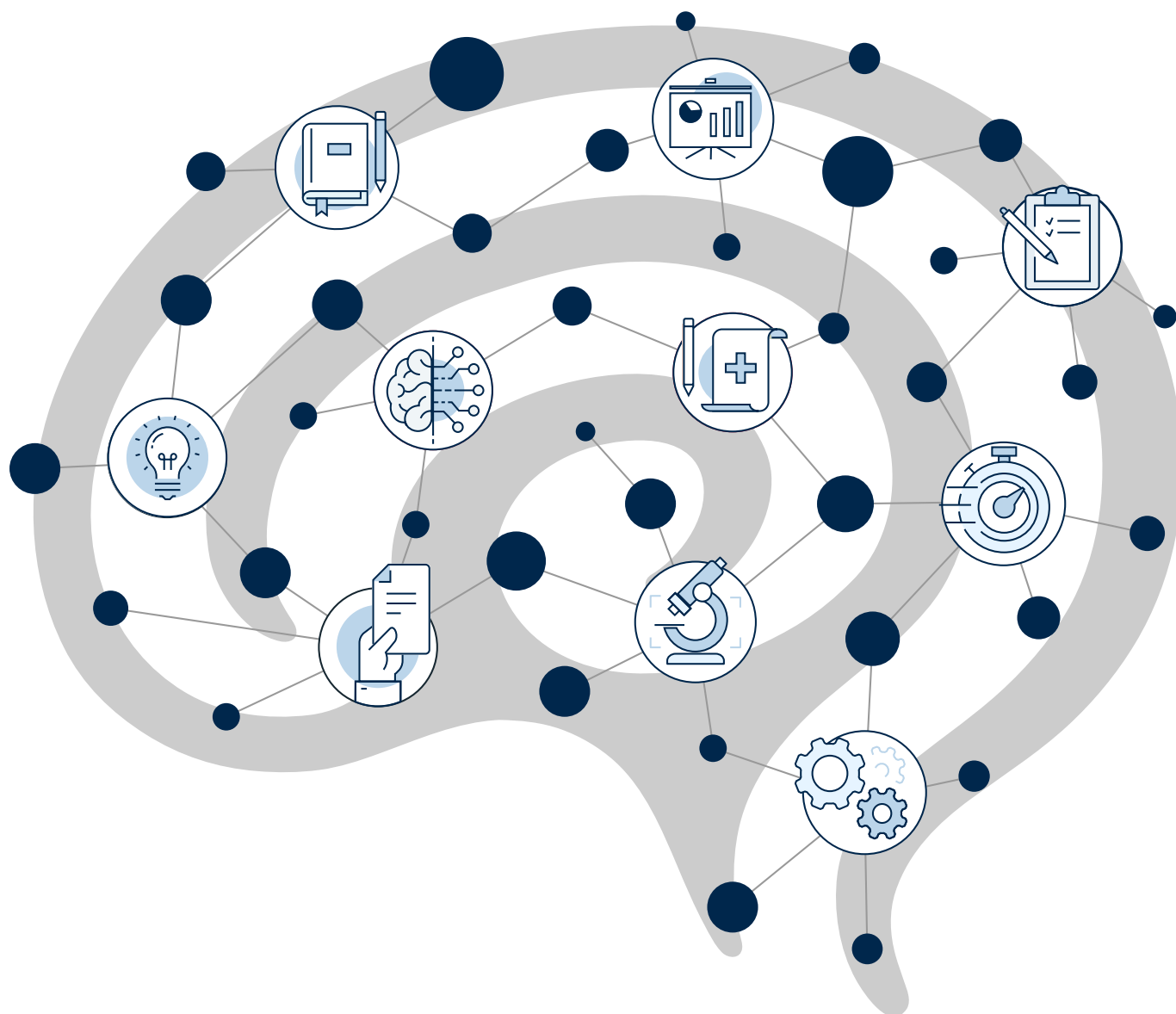


CONTRIBUTING TO FORCE READINESS THROUGH RESEARCH



Research at the National Intrepid Center of Excellence contributes to force readiness by evaluating promising treatments, sharpening our understanding of traumatic brain injury effects on service members and their families, and exporting this knowledge to the Military Health System.



Mission

We improve the lives of patients and families impacted by TBI through excellence and innovation



Vision

To be a global leader in TBI care, research, and education



Guiding Principles

Excellence, Innovation, Compassion, Honor, and Collaboration

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List of Acronyms

CNRM - Center for Neuroscience and Regenerative Medicine, USU, Bethesda, MD

DVBIC - Defense and Veterans Brain Injury Center, Silver Spring, MD

FBCH - Fort Belvoir Community Hospital, Fort Belvoir, VA

NICoE - The National Intrepid Center of Excellence, Bethesda, MD

NIH - National Institutes of Health, Bethesda, MD

USU - Uniformed Services University of the Health Sciences, Bethesda, MD

WAMC - Womack Army Medical Center, Fort Bragg, NC

WRNMMC - Walter Reed National Military Medical Center, Bethesda, MD



Introduction

Treven C. Pickett, Psy.D., ABPP

*Department Chief, Research
National Intrepid Center of Excellence,
Walter Reed National Military Medical Center*



As a Directorate of the Walter Reed National Military Medical Center (WRNMMC), the National Intrepid Center of Excellence (NICoE) is dedicated to improving the lives of patients and families affected by traumatic brain injury (TBI) through excellence and innovation, in a collaborative effort with patients, families, referring providers, and researchers.

Established in 2010 as a center dedicated to advancing our nation's understanding of the "invisible wounds" from the wars in Iraq and Afghanistan, for the past nine years the NICoE has delivered continuous excellence in patient care, innovation, and scientific discoveries. The NICoE plays a pivotal role in the Military Health System (MHS) TBI Pathway of Care through a robust interdisciplinary care program and a research agenda that evaluates TBI diagnostic techniques, treatment methods, and promising discoveries to export those proven effective at contributing to force readiness.

The NICoE's care and research model follows a strategic concept that situates practice and scientific investigations under one roof. Clinicians and researchers work collaboratively and proactively to understand the impact of healthcare offerings in service members' recovery.

The NICoE contributes to cutting-edge research through investigations about the origins, progression, diagnosis, and treatment of TBI. The center partners with leading government agencies, universities, and industry to support these studies.

The NICoE is also part of a traumatic brain injury Intrepid Spirit Center network, a group of specialized, health-focused TBI centers at military treatment facilities across the country. Nested within the MHS TBI Pathway of Care, and in collaboration with the Defense and Veterans Brain Injury Center (DVBIC) and the Uniformed Services University of the Health Sciences (USU), this network utilizes an interdisciplinary care model to provide comprehensive evaluation and treatment for TBI, while contributing to clinical best practices, standardization of clinical and research data management, and a research mission that will advance the science of TBI care.

These strategic partnerships result in a combined scientific workforce and cutting-edge technology, allowing the NICoE to access a broad range of resources and expertise.

A critical piece of the NICoE's research efforts involves advanced technology and imaging equipment, including:

- 3-Tesla Magnetic Resonance Imaging (3T MRI)
- Positron Emission Tomography-Computed Tomography (PET/CT)
- Magnetoencephalography (MEG)
- Computer-Assisted Rehabilitation Environment (CAREN)
- Transcranial Magnetic Stimulation (TMS) treatment technology

These capabilities are located under one roof at the NICoE, and they allow researchers to gather measurements of brain structure and function to identify consequences of injury and persistent symptoms.

The body of research highlighted in this booklet represents the NICoE's current portfolio of actively-recruiting studies, which are making significant impact in advancing the understanding of TBI and, therefore, contributing to warfighter readiness.



A Randomized, Sham-Controlled, Blinded Study of Bilateral Prefrontal Individual Connectome-Targeted Repetitive Transcranial Magnetic Stimulation (ICT-rTMS) to Treat the Symptoms of Depression Associated with Concussive TBI

David Brody, M.D., Ph.D., Principal Investigator

Director of Center for Neuroscience and Regenerative Medicine (CNRM), USU



RESEARCH HIGHLIGHT

This multi-site study sponsored by the Center for Neuroscience and Regenerative Medicine at the USU investigates the efficacy and tolerability of individual connectome-targeted repetitive transcranial magnetic stimulation (ICT-rTMS) treatment to improve symptoms of depression that are often associated with concussive traumatic brain injury (TBI).

Up to ninety subjects will be block randomized to active ICT-rTMS or sham treatment. Subjects will receive 20 sessions of ICT-rTMS over approximately five weeks. Treatment sessions will consist of high-frequency left dorsolateral prefrontal cortex (DLPFC) stimulation for 3,000 pulses followed by low-frequency right DLPFC stimulation for 1,000 pulses for a total stimulation time of approximately one hour per session. The primary outcome will be change in depression severity from baseline to post-treatment.

This study aims to develop a novel, effective treatment for depressive symptoms associated with concussive TBI. Depression after TBI also increases the risk for developing other neuropsychiatric problems that may contribute to morbidity and functional disability after TBI, including increased suicidality, cognitive dysfunction, and aggressive behavior. Posttraumatic depression also interferes with physical and cognitive rehabilitation, making depressive symptoms one of the strongest correlates of poor recovery and quality of life after injury.

STUDY IMPACT

If successful, findings from this study will speed the development of a novel, nonpharmacologic treatment for depression for service members with a history of concussion.

KEY STUDY TEAM

Lindsay Oberman, Ph.D. (CNRM, USU)

Charline Simon, M.A. (CNRM, USU)

Diana Nora, C.N.A. (WRNMMC)

Nancy de Almeida, R.N. (WRNMMC)

Nicholas Heredia, B.A. (FBCH)

FUNDING

Center for Neuroscience and Regenerative Medicine

STUDY SITE(S)

- WRNMMC, Bethesda, MD
- FBCH, Fort Belvoir, VA

SELECTED PUBLICATION

1. Siddiqi, S. H., Trapp, N. T., Hacker, C. D., Laumann, T. O., Kandala, S., Hong, X., ... & Brody, D. L. (2019). Repetitive Transcranial Magnetic Stimulation with Resting-State Network Targeting for Treatment-Resistant Depression in Traumatic Brain Injury: A Randomized, Controlled, Double-Blinded Pilot Study. *Journal of neurotrauma*, 36(8), 1361-1374.

FIND OUT MORE: <https://clinicaltrials.gov/ct2/show/NCT03523507>



Rehabilitation of Acquired Auditory Processing Disorders – Low-Gain Hearing Aids

Douglas S. Brungart, Ph.D., Principal Investigator

Chief Scientist, National Military Audiology and Speech Center, WRNMMC

Chief Scientist and Associate Director, Research Coordination Branch, Hearing Center of Excellence

RESEARCH HIGHLIGHT

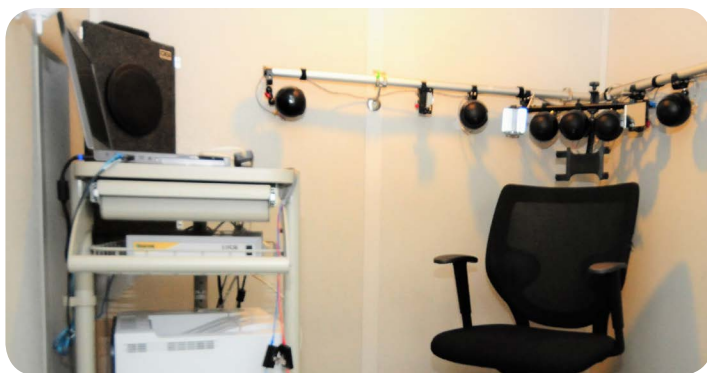
Adult patients diagnosed with acquired auditory processing deficits (APD) are often offered low-gain hearing aids (LGHAs) as a treatment option despite the presence of normal-to-near-normal hearing thresholds (NHT). This treatment, which is arguably becoming standard of care in the private sector and military medical system, is based primarily on anecdotal patient reports with minimal published research.

While peripheral hearing loss remains a pervasive problem among service members, injury to the peripheral and central auditory system within the military is increasingly related to traumatic brain injury (TBI) and blast exposure. The functional communication and hearing deficits subjectively reported by these individuals often occur in the absence of elevated pure-tone thresholds and have therefore been identified as APD. While these service members often receive treatment in the form of LGHAs, there exists a lack of systematic evaluation of treatment efficacy, despite common reports of subjective benefit.

The aim of this work is to examine the efficacy of LGHAs in an active-duty military population with a history of mild TBI and blast exposure who have been diagnosed with APD in the presence of NHT. This research addresses the lack of evidence to support fitting LGHAs in this population by comparing aided and unaided outcomes using both subjective and objective measures. In addition, the potential “hidden” peripheral damage associated with the functional presentation of these deficits, in spite of NHTs, will be examined as it relates to subjective and objective outcomes.

STUDY IMPACT

Results from this study will influence the standard of care received by adult TBI patients diagnosed with APD in the presence of NHT, thus improving the ability to treat and limit associated functional impairments.



KEY STUDY TEAM

Associate Investigators:

Melissa Kokx-Ryan, Au.D. (NICoE, WRNMMC)

Shoshannah Russell, Au.D. (WRNMMC)

Mary Barrett, Au.D. (WRNMMC)

FUNDING

Congressionally Directed Medical Research Program
Research Development Testing and Evaluation funds

STUDY SITE(S)

- WRNMMC, Bethesda, MD

SELECTED PRESENTATION

1. Kokx-Ryan, M. (2017, April) Low-gain hearing aids as a treatment option for patients with normal-hearing thresholds who exhibit auditory processing deficits. Oral Presentation, eAudiology Web Seminar.



Assessing the Impact of mTBI on Multi-Sensory Integration While Maneuvering on Foot

Douglas S. Brungart, Ph.D., Principal Investigator

Chief Scientist, National Military Audiology and Speech Center, WRNMMC

Chief Scientist and Associate Director, Research Coordination Branch, Hearing Center of Excellence

RESEARCH HIGHLIGHT

Service members' success in combat operations is largely dependent on their ability to shoot, move, and communicate on the battlefield. These critical tasks require the execution of numerous complex subtasks that involve processing simultaneous inputs from the auditory, visual, vestibular, tactile, and proprioceptive senses.

This project uses an aurally-aided visual search (AAVS) paradigm to examine the impact that unimodal and multi-sensory deficits have on the functional performance of sensory-impaired service members. Experiments are conducted using the Computer Assisted Rehabilitation Environment (CAREN), which was modified for this study to include a 64-speaker audio array. The CAREN makes it possible to measure how well participants perform audio-visual integration tasks while standing still or maneuvering on foot over simulated terrain.

Two groups of participants are currently being recruited: 1) healthy controls and 2) those with blast-related mild traumatic brain injury (mTBI). Preliminary results show that the mTBI group responds about 15% slower in the AAVS task and that both groups respond faster while walking without any reduction in accuracy. With further testing, the researchers hope to validate whether the AAVS paradigm is sensitive enough to detect subtle multimodal integration problems that are not apparent in more traditional unimodal sensory tasks.

STUDY IMPACT

Information obtained from this study will have near- and long-term positive impacts, both in defining return-to-duty standards for brain-injured personnel, and in helping to develop rehabilitation strategies for impaired patients.



KEY STUDY TEAM

Associate Investigator:
Sarah E. Kruger, M.S.

STUDY SITE(S)

- NICOE, WRNMMC, Bethesda, MD
- National Military Audiology and Speech Center, WRNMMC, Bethesda, MD

FUNDING

U.S. Army Medical Research
and Materiel Command

SELECTED PUBLICATIONS

1. Brungart, D., Kruger, S., Kwiatkowski, T., Heil, T., Highland, K. B., Cohen, J., ... & Zion, D. (2019). The Effects of Blast-Related Neurotrauma on Aurally Aided Visual Search While Standing and Walking. *Journal of neurotrauma*.
2. Brungart, D. S., Kruger, S. E., Kwiatkowski, T., Heil, T., & Cohen, J. (2019). The effect of walking on auditory localization, visual discrimination, and aurally aided visual search. *Human factors*, 0018720819831092.



Rehabilitation of Acquired Auditory Processing Deficits – Mobile Application-Based Computerized Auditory Training

Douglas S. Brungart, Ph.D., Principal Investigator

RESEARCH HIGHLIGHT

The auditory system is among the most frequently damaged in modern warfare, second only to the musculoskeletal system. While sensorineural hearing loss from noise exposure continues to be a pervasive problem in the military force, recent evidence suggests that blast and/or noise exposure without permanent hearing loss can have significant negative ramifications previously undetected.

Despite the significant prevalence of patients with auditory processing deficits (APD) in the presence of normal hearing thresholds, professionals do not agree on the course of treatment. Management can range from receiving diagnosis of normal hearing with no additional follow-up to implementation of auditory training, counseling strategies, or management of acoustic conditions including hearing aids or frequency modulated system, or a combination of these strategies.

While there is ample research that supports the use of auditory training via software-based training programs, compliance with software-based auditory training is low. Furthermore, the efficacy of auditory training in service members with history of significant noise exposure, blast injury, and/or traumatic brain injury (TBI) has not been evaluated.

The specific aim of this study is to provide evidence regarding the effectiveness of computerized auditory training as a treatment option for adults with normal-to-near-normal hearing thresholds and APD, who have a history of blast exposure and/or TBI.

STUDY IMPACT

Analysis from this data may influence the standard of care that service members impacted by TBI receive, in order to improve our ability to treat functional hearing problems, which directly correlate to their quality of life.



KEY STUDY TEAM

Shoshannah Russell, Au.D. (WRNMMC)
Mary Barrett, Au.D. (WRNMMC)
Melissa Kokx-Ryan, Au.D. (NICoE)
Shannon Auxier, M.S. (NICoE)

FUNDING

Congressionally Directed Medical Research Program
Research Development Testing and Evaluation funds

STUDY SITE(S)

- WRNMMC, Bethesda, MD



Integration of Image and Clinical Measurements of TBI Patients Using Machine Learning Techniques

Jesus J. Caban, Ph.D., Principal Investigator

Chief for Clinical and Research Informatics, NICoE, WRNMMC



RESEARCH HIGHLIGHT

The traumatic brain injury (TBI) military patient population is a high-risk group with more than 60% of active-duty service members diagnosed with a TBI showing signs of depression and other behavioral health conditions within a year following their first brain injury. Currently, across the Military Health System, providers don't have the tools to quickly identify patients at risk of developing mental health conditions or the capabilities to model different clinical trajectories a patient can follow.

This retrospective study uses a large longitudinal clinical dataset of more than 100,000 mild traumatic brain injury (mTBI) patients to create machine learning and artificial intelligence models that can be used to automatically identify clinical trajectories, sub-categories of mTBI, and risk factors associated with the onset of mental health conditions. Through this study, a number of advanced predictive models have been developed, including models to estimate the probability of a patient returning to active duty, forecast models for retention post-injury, machine-learning models to identify the likelihood of developing clinical conditions, and predictors of healthcare utilization post-injury.

KEY STUDY TEAM

Associate Investigators:

Gerard Riedy, M.D., Ph.D.

Joseph Bleiberg, Ph.D.

Thomas DeGraba, M.D.

Donna Neuges, R.N.

STUDY SITE(S)

- NICoE, WRNMMC,
Bethesda, MD

STUDY IMPACT

The use of machine learning and artificial intelligence with large longitudinal retrospective clinical datasets will allow us to model the progression of mTBI, impacting our understanding of the short- and long-term effects of traumatic brain injuries.

SELECTED PUBLICATIONS

1. Dabek, F., Hoover, P., & Caban, J. (2018, December). DeepDx: A Deep Learning Approach for Predicting the Likelihood and Severity of Symptoms Post Concussion. In International Conference on Brain Informatics (pp. 381-391). Springer, Cham.
2. Dabek, F., Hoover, P., & Caban, J. (2018, December). Evaluating Mental Health Encounters in mTBI: Identifying Patient Subgroups and Recommending Personalized Treatments. In International Conference on Brain Informatics (pp. 370-380). Springer, Cham.
3. Dabek, F. J., & Caban, J. J. (2016). A k-reversible approach to model clinical trajectories. In AMIA Annual Symposium Proceedings (Vol. 2016, p. 460). American Medical Informatics Association.
4. Dabek, F., & Caban, J. J. (2015). Leveraging big data to model the likelihood of developing psychological conditions after a concussion. *Procedia Computer Science*, 53, 265-273.



A Retrospective Study of the Natural History of Traumatic Brain Injury and Psychological Health Outcomes in Military Personnel Through Analysis of the NICoE Clinical Research Database

Thomas J. DeGraba, M.D., Principal Investigator

Chief Innovations Officer, NICoE, WRNMMC



STUDY IMPACT

This systematic approach to collecting information on TBI and other psychological health conditions will advance the ability to evaluate, diagnose, and treat these conditions in both military and civilian populations. Additionally, this study is designed to provide information to enhance clinical practice guidelines, leveraging evidence-based analysis to identify best treatment practices for complex patient subpopulations cared for within the MHS.

KEY STUDY TEAM

Dr. Louis French
Dr. Chandler Rhodes
Dr. Treven Pickett
Donna Neuges
Caroline Tuman

STUDY SITE(S)

- NICoE, WRNMMC, Bethesda, MD

RESEARCH HIGHLIGHT

A central strategy to the national research action plan is to develop a more precise staging and criteria for clinical subpopulations with combat-related traumatic brain injury (TBI) and comorbid psychological health conditions. This improved characterization of the heterogeneous injury state will lead to more rapid and earlier identification of brain disturbances and more accurate selection of targeted treatment strategies.

This protocol is designed to leverage nine years of comprehensive data collected in the NICoE's Intensive Outpatient Program (IOP) for service members with TBI and associated comorbidities. Synchronized collection of clinical data from this integrative program provides an opportunity to identify patterns of symptom clusters and corresponding neural network disruption to understand which treatment modalities are successful in specific subgroups of patient populations.

Preliminary data obtained from patients' self-report scales revealed a significant improvement in posttraumatic stress, anxiety, depression, sleep disturbances, and satisfaction in life from admission to discharge, with improvements lasting at least six months after participation in the program.

Continuing research aims to identify specific treatment strategies in the 17 different disciplines utilized in the NICoE IOP. Future goals include the ability to share information with other Military Health System (MHS) TBI treatment facilities, such as the Intrepid Spirit Centers, to standardize best practices across the spectrum of injury severity.



Genomic Determinants Pre- and Post-NICoE Skills-Based Training: Measuring Relaxation Response in Service Members with Post-Traumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI)

Thomas J. DeGraba, M.D., Principal Investigator

Chief Innovations Officer, NICoE, WRNMMC



RESEARCH HIGHLIGHT

The need for effective treatments and reliable outcome measures for post-traumatic stress disorders (PTSD) and traumatic brain injury (TBI) is a top priority for the Military Health System.

The goal of the study is to measure quantifiable biological and clinical responses to integrative and conventional medicine treatments used in NICoE's four-week Intensive Outpatient Program (IOP), which targets service members recovering from TBI and behavioral health comorbidities.

Preliminary outcomes indicate that time spent in the creative arts, in particular art therapy, is associated with a reduction of posttraumatic stress symptoms, as well as anxiety. Additionally, implementation of integrative medicine that includes mind-body treatments correlated with a reduction in anxiety and the improvement of autonomic function and cerebral blood flow.

Furthermore, initial analysis of genomic expression reveals a reduction of inflammatory gene activation during the four-week period. By the third and fourth weeks of the IOP, activation of genes involved in neuronal repair were noted to be up-regulated and closely-correlated with time spent in art therapy.

Ongoing recruitment for this study aims to validate initial findings. The study is a partnership with Harvard Medical School/Beth Israel Deaconess Medical Center for blood specimen analysis of genomic expression and the National Institutes of Health for protein marker identification.

STUDY IMPACT

The goal of this study is to develop definitive diagnostic biomarkers for TBI and comorbid PTSD and associated psychological health conditions.

KEY STUDY TEAM

Donna Neuges
Caroline Tuman
Manoj Bhasin
Herbert Benson

STUDY SITE(S)

- NICoE, WRNMMC, Bethesda, MD

FUNDING

With support from Operation Support Our Troops



Expanding Our Understanding of Computer-Based Cognitive Rehabilitation in the Military Population – a Longitudinal Brain Fitness Center Database

Louis M. French, Psy.D., Principal Investigator

Deputy Director for Operations, NICoE, WRNMMC

Site Director, DVBIC

Associate Professor of Neurology and Rehabilitation, USU



RESEARCH HIGHLIGHT

Cognitive dysfunction can occur from a variety of brain insults, including traumatic brain injury. These deficits can have a significant impact on service members' functioning and quality of life. Unfortunately, there is a limited range of treatment options to address these concerns. Technology provides additional methods of treatment that can also increase access to rehabilitation for those with limited options. While computer-based cognitive rehabilitation is heavily marketed commercially, understanding of its efficacy, applicability in sub-populations, and other treatment characteristics is limited.

The purpose of this study is to improve understanding of the efficacy of computer-based cognitive rehabilitation tools and their utilization in the Brain Fitness Center (BFC) by developing a data repository.

The data repository consists of retrospective and prospective data, such as demographic information, objective cognitive assessments, self-report questionnaires, and participation data from individuals who use the computer-based cognitive rehabilitation tools in the BFC at Walter Reed National Military Medical Center and Fort Belvoir Community Hospital.

STUDY IMPACT

This study will improve the understanding of the population, the utilization, and the efficacy of the Brain Fitness Center through retrospectively analyzing data from a pre-existing and pre-approved data collection protocol.

KEY STUDY TEAM

Associate Investigator:
Katherine W. Sullivan, M.S.

FUNDING

Defense and Veterans Brain Injury Center (DVBIC)

STUDY SITE(S)

- WRNMMC, Bethesda, MD
- FBCH, Fort Belvoir, VA

SELECTED PUBLICATIONS

1. Sullivan, K. W., Solomon, N. P., Pramuka, M., Quinn, J. E., Teixeira, K. A., & French, L. M. (2015). Computer-based cognitive rehabilitation research in a military treatment facility: Recruitment, compliance, and lessons learned. *Work*, 50(1), 131-142.
2. Sullivan, K. W., Quinn, J. E., Pramuka, M., Sharkey, L. A., & French, L. M. (2012). Outcomes from a pilot study using computer-based rehabilitative tools in a military population. *Studies in health technology and informatics*, 181, 71-77.



The 15-Year Studies

Louis M. French, Psy.D., Principal Investigator

Deputy Director for Operations, NICoE, WRNMMC

Site Director, DVBIC

Associate Professor of Neurology and Rehabilitation, USU



RESEARCH HIGHLIGHT

Walter Reed National Military Medical Center serves as the core site for this multi-site, longitudinal study into the long-term implications of traumatic brain injury (TBI) in military service members. This Defense and Veterans Brain Injury Center supported study was developed to respond to a congressional mandate (Sec721 NDAA FY07). It has two components:

1. The Natural History Study, which employs a host of clinical, behavioral, cognitive, sensory-motor, blood biomarker, and imaging assessments to identify issues that may make TBI recovery more difficult.
2. The Caregiver Study, which examines caregiver outcomes such as physical and mental health, employment, finances, family functioning, relationship satisfaction, and quality of life, as well as the impact on the health and behavior of the caregiver and service member's children.

STUDY IMPACT

These studies focus on the long-term physical and mental health outcomes and the effects on service members and their families following TBI with the goal of improving treatments and services for those affected.

KEY STUDY TEAM

Associate Investigators:

Rael T. Lange, Ph.D. (DVBIC)

Tracey A. Brickell, Psy.D. (DVBIC)

FUNDING

Defense and Veterans Brain Injury Center (DVBIC)

STUDY SITE(S)

- WRNMMC, Bethesda, MD
- FBCH, Fort Belvoir, VA

SELECTED PUBLICATIONS

1. Lange, R. T., Lippa, S. M., French, L. M., Bailie, J. M., Gartner, R. L., Driscoll, A. E., ... & Holzinger, J. B. (2019). Long-term neurobehavioural symptom reporting following mild, moderate, severe, and penetrating traumatic brain injury in US military service members. *Neuropsychological rehabilitation*, 1-24.
2. Lippa, S. M., Yeh, P. H., Gill, J., French, L. M., Brickell, T. A., & Lange, R. T. (2019). Plasma tau and amyloid are not reliably related to injury characteristics, neuropsychological performance, or white matter integrity in service members with a history of traumatic brain injury. *Journal of neurotrauma*.



NICoE TBI Magnetoencephalography (MEG) Core Project

John D. Hughes, M.D., Principal Investigator

Behavioral Biology Branch, Walter Reed Army Institute of Research (WRAIR)



KEY STUDY TEAM

Associate Investigators:

Mihai Popescu, Ph.D.

Anda Popescu, Ph.D.

Thomas DeGraba, M.D.

Jaqueline Dyer (Study Coordinator)

Andrew Bryant (Technologist)

COLLABORATING SITE(S)

- WRAIR, Silver Spring, MD
- Washington DC VA Medical Center, Washington, DC
- USU, Bethesda, MD

STUDY SITE(S)

- WRNMMC, Bethesda, MD
- Washington DC VA Medical Center, Washington, DC
- USU, Bethesda, MD

RESEARCH HIGHLIGHT

Brain function is determined by the coordinated activity of ensembles of neurons bound together by virtue of neuronal oscillations (brainwaves) of various frequencies at various spatial scales (local, global). Brain dysfunction can be conceptualized fundamentally as an alteration of these oscillations and disorganization of these neuronal networks. Such alterations can only be assessed by methodologies, such as MEG, which record brain activity at a time scale of milliseconds.

This research is providing neurophysiological data that will help in understanding the neurobiology of traumatic brain injury (TBI) and psychological health conditions, such as post-traumatic stress disorders and depression. Our researcher scientists are mapping brain activity by noninvasively recording the magnetic fields produced when brain cells communicate with one another while participants are at rest or performing cognitive tasks.

By understanding the associations between functional impairments, such as memory problems and alterations in oscillatory brain activity, this study aims to further inform and evaluate treatment strategies to improve cognitive and emotional functioning in those affected by TBI and associated psychological health conditions.

STUDY IMPACT

This study hopes to advance the understanding of the relationship between specific symptoms that affect those with traumatic brain injury and the brain activity changes that underlie them. The physiologic changes that are associated with these symptoms may provide increased insight to tailor specific therapies and treatments for TBI and psychological health concerns.

SELECTED PUBLICATIONS

1. Popescu, M., Popescu, E. A., DeGraba, T. J., Fernandez-Fidalgo, D. J., Riedy, G., & Hughes, J. D. (2019). Post-traumatic stress disorder is associated with altered modulation of prefrontal alpha band oscillations during working memory. *Clinical Neurophysiology*.
2. Popescu, M., Hughes, J. D., Popescu, E. A., Mikola, J., Merrifield, W., DeGraba, M., ... & DeGraba, T. J. (2017). Activation of dominant hemisphere association cortex during naming as a function of cognitive performance in mild traumatic brain injury: Insights into mechanisms of lexical access. *NeuroImage: Clinical*, 15, 741-752.
3. Popescu, M., Hughes, J. D., Popescu, E. A., Riedy, G., & DeGraba, T. J. (2016). Reduced prefrontal MEG alpha-band power in mild traumatic brain injury with associated posttraumatic stress disorder symptoms. *Clinical neurophysiology*, 127(9), 3075-3085.



Nutrition for Post-Traumatic Headache Study

Kimbra Kenney, M.D., Principal Investigator

*Service Chief, Research Operations, NICOE, WRNMMC
Associate Professor, Neurology, USU*



RESEARCH HIGHLIGHT

This is a multi-site randomized control trial (RCT) of a dietary intervention funded by the U.S. Department of Defense. The goal of the study is to examine whether targeting certain fats in the diet can minimize or eliminate headache pain and decrease medication use.

Post-traumatic headache (PTH), which is prevalent in active-duty military and veteran populations, is an important and understudied cause of impaired quality of life and disability, with substantial societal costs and adverse impact on force readiness.

Existing pharmacologic and behavioral therapies are of some benefit, but many patients are refractory to these therapies, which often carry serious adverse effects. This study investigates a novel strategy for PTH treatment and evaluates novel biomarkers of therapeutic response, which can be modified by diet.

STUDY IMPACT

The proposed intervention, if shown to be effective for post-traumatic headache, is easily implemented, cost-efficient, and no more than minimal risk to combatants.

PRINCIPAL INVESTIGATORS

Melissa Guerra, M.D. (FBCH)
Wes Cole, Ph.D. (WAMC)
Kim Faurot, Ph.D. & J. Doug Mann, M.D. (UNC)
Christopher Ramsden, M.D. (NIH)

KEY STUDY TEAM

Cora Davis
Rebecca Sandlain
Brittney Roberson

STUDY SITE(S)

- WRNMMC, Bethesda, MD
- FBCH, Fort Belvoir, VA
- Womack Army Medical Center (WAMC), Fort Bragg, NC
- National Institutes of Health (NIH), Bethesda, MD
- University of North Carolina (UNC), Chapel Hill, NC

FIND OUT MORE: <https://clinicaltrials.gov/ct2/show/NCT03272399>



Oculomotor Assessment of Traumatic Brain Injury

John E. King, Ph.D., Principal Investigator

Audiologist, NICoE, WRNMMC



RESEARCH HIGHLIGHT

Oculomotor testing, a subcomponent of vestibular testing, is a broad term for a number of tests that evaluate a patient's eye movements with specialized camera systems. Historically, oculomotor testing is used to rule out central vestibular disorders that contribute to dizziness or imbalance; however, it is reasonable to expect that functional deficits in the oculomotor system are sensitive indicators of insult in traumatic brain injury (TBI).

The purpose of the study is to compare the sensitivity and specificity of three oculomotor testing devices. Data from each device will undergo area-under-the-curve analysis to determine the ability of each to correctly identify control subjects versus subjects with confirmed history of TBI.

The study is designed as a prospective research project in which a group of 120 normal controls without a history of TBI will be compared to another group of 120 participants who have a confirmed history of TBI. Each participant (total of 240) will complete the TBI assessment protocol for all three aforementioned devices.

STUDY IMPACT

Results from this study will be utilized by the military for further development of a deployable system for use in theater.

KEY STUDY TEAM

Louis French, Psy.D.

Saafan Malik, M.D.

STUDY SITE(S)

- Intrepid Spirit Center, FBCH, Fort Belvoir, VA
- Robinson Clinic, Womack Army Medical Center (WAMC), Fort Bragg, NC

Devices provided by the United States Army Medical Research and Materiel Command

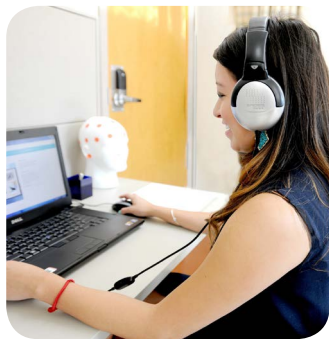
FIND OUT MORE: <https://clinicaltrials.gov/ct2/show/NCT03156010>



Comparison of Visual and Auditory Technologies in Large Scale and Mobile Virtual Reality Systems

Sarah E. Kruger, M.S., Principal Investigator

Biomedical Engineer, NICoE, WRNMMC



STUDY IMPACT

This study seeks to validate a mobile system that combines visual and audio technologies and has the potential to improve the current standard of care. This advancement to the field of TBI research may benefit service members who experience persistent sensory systems injury.

RESEARCH HIGHLIGHT

The Military Health System (MHS) has made substantial investments into the development of sophisticated multimodal virtual reality (VR) systems to address the unique challenges faced by service members suffering from vestibular and sensory issues related to mild traumatic brain injury (mTBI). One VR-based system used therapeutically within the MHS is the Computer Assisted Rehabilitation Environment (CAREN).

Although there are benefits to using the CAREN, the systems are fixed, large in size, and expensive to install and maintain. These constraints can severely limit the number of patients who have access to them. However, with recent advances in head-mounted display technology, in conjunction with 3D spatial audio ("virtual audio"), alternatives to larger scale VR-based systems like the CAREN may be possible.

The purpose of this study is to replicate CAREN-based VR therapy by leveraging new technologies, combining visual and auditory inputs into a mobile rehabilitation system that can be used in a variety of settings. It is expected that the mobile system will have sufficient detail and function as to provide similar feedback to participants, comparable to those received while utilizing the CAREN. Additionally, participant performance outcomes should be similar between the two systems.

This is a multi-site study in collaboration with the Naval Health Research Center (NHRC) in San Diego. Up to 60 participants (40 healthy, 20 mTBI) will be recruited at both sites.

KEY STUDY TEAM

Associate Investigator:

Dr. Douglas S. Brungart (WRNMMC)

Lead Principle Investigator:

Dr. Pinata H. Sessoms (NHRC)

FUNDING

U.S. Army Medical
Research and Materiel
Command

STUDY SITE(S)

- NICoE, WRNMMC, Bethesda, MD
- NHRC, San Diego, CA
- Naval Medical Center San Diego, San Diego, CA



NICoE Traumatic Brain Injury Neuroimaging Core Project

John Ollinger, Ph.D., Principal Investigator

Biomedical Engineer, NICoE, WRNMMC



RESEARCH HIGHLIGHT

Despite ongoing research, there remains a critical knowledge gap of the relationship between blood-based and exosome biomarkers and neuroimaging biomarkers in chronic traumatic brain injury (TBI).

The goal of this study is to develop a database of advanced neuroimaging measurements, along with relevant blood-based biomarkers, to clarify these relationships.

This project is being done in collaboration with scientists at the National Institutes of Health (NIH) and the Center for Neuroscience and Regenerative Medicine. Structural, resting-state, and multi-shell diffusion images are being collected at the NICoE, along with clinical variables and detailed injury information. Blood data will be analyzed at the NIH for biomarkers reflecting axonal, neuronal, and vascular injury as well as astrogliosis/neuroinflammation and synaptic activity. Finally, these data will be analyzed jointly using advanced statistical methods.

STUDY IMPACT

Findings from this study will be used to develop neuroimaging and blood biomarkers that can provide objective evidence of TBI and differentiate them from psychological health issues.

FUNDING

This project was originally funded by the U.S. Army Medical Research and Materiel Command but is currently unfunded.

STUDY SITE(S)

- NICoE, WRNMMC, Bethesda, MD

KEY STUDY TEAM

Ping-Hong Yeh, Ph.D.
Andy Srikanthana, Ph.D.
Wei Liu, Ph.D.
Chihwa Song, Ph.D.
Kimbra Kenney, M.D.
Jessica Gill, Ph.D.
Pashtun Shahim, Ph.D.

SELECTED PUBLICATIONS

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3. Tchopev, Z. N., Yeh, P. H., Morgan, G. W., Meyer, E., Wolf, J. M., Ollinger, J. M., ... & Young, L. C. (2018). Acquired sleep-related hypermotor epilepsy with disrupted white matter tracts assessed by multishell diffusion magnetic resonance imaging. *Frontiers in neurology*, 9, 6.
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Treating mTBI and PTSD with Bilateral Prefrontal Transcranial Magnetic Stimulation (TMS)

Paul F. Pasquina, M.D., Principal Investigator

Chair of Physical Medicine and Rehabilitation, USU



STUDY IMPACT

Results from this study may shed light on the ability of Transcranial Magnetic Stimulation (TMS) to reduce the symptoms associated with post-traumatic stress disorder (PTSD) for individuals with traumatic brain injury (TBI), to hopefully improve their overall quality of life.

RESEARCH HIGHLIGHT

Numerous reports have shown a high association between war-related post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI). The NICoE, in collaboration with the Center for Rehabilitation Sciences Research (CRSR) at the USU, has set out to assess the efficacy of using repetitive Transcranial Magnetic Stimulation (rTMS) to treat the symptoms associated with PTSD in patients who have experienced a traumatic brain injury.

TMS is a non-invasive way to safely stimulate specific regions of the brain that is widely used to treat depression and other behavioral health conditions, and it may be a safe alternative to many patients who currently suffer from posttraumatic stress and PTSD.

This study seeks to determine the efficacy and tolerability of TMS as a treatment for mTBI with PTSD symptoms and correlate treatment response with anatomical and biological factors unique to each service member. Exploratory work will be done to look at the neuronal and biological changes that may occur over the course of TMS treatment.

KEY STUDY TEAM

Dr. Louis French
Dr. Navneet Atwal
Jared Garland
Emilia-Marie Jaskot
Jerika Taylor

FUNDING

Center for Rehabilitation Sciences Research

STUDY SITE(S)

- WRNMMC, Bethesda, MD

FIND OUT MORE: <https://clinicaltrials.gov/ct2/show/NCT02458521>



Biopsychosocial Effect of Service Dog Training on Post-Traumatic Stress (PTS) and Post Concussive Symptoms

Paul F. Pasquina, M.D., Principal Investigator

RESEARCH HIGHLIGHT

Preliminary anecdotal evidence suggests that service members with posttraumatic stress (PTS) report improved physical, social, and psychological symptoms after participation in the NICoE's Service Dog Training Program (SDTP).

The SDTP entails teaching service members how to train dogs to become service dogs that can then be paired with veterans with mobility impairments and mood disorders. The purpose of the program is to help service members develop skills that are translatable to other social settings, such as effective communication and emotion regulation. This research study prospectively evaluates the efficacy of the SDTP by scientifically assessing a variety of biological, psychological, and sociological outcomes. Participation in the study is available to those enrolled in the NICoE four-week Intensive Outpatient Program.

Up to 104 participants will be recruited. Half of these participants will be randomized to participate in the SDTP, while the other half will serve as a control group. Participants randomized to the SDTP group will work with professional service dog trainers for one hour, twice a week, for three weeks to help train service dogs that will eventually be given to a veteran once fully trained. Each group will continue to receive the same standard of care. Self-reported measures of behavioral symptoms will be completed weekly throughout participation in the study. Biological measures such as blood draws, heart rate, and blood pressure will be collected at the baseline, during the three-week post-training visit, and during an optional three-month follow-up.

Participation in this program may help injured service members develop skills, such as effective communication and emotion regulation, that are needed to successfully shape the dog's behavior and are translated to other social settings. Additionally, by volunteering to help train service animals for veterans, the program may help participants develop a restructured commitment to service post-injury.

STUDY IMPACT

Findings from this study will inform the efficacy of implementing the SDTP as a complementary program for service members undergoing treatment for symptoms of PTS and traumatic brain injury. If the results of this study are positive, it could lead to more service members and veterans being offered access to the SDTP to augment their ongoing care.

KEY STUDY TEAM

Dr. Louis French
Jerika Taylor
Kiara H. Buccellato
Michelle J. Nordstrom
Will Roddy

FUNDING

Congressionally Reprogrammed
Research Development Testing and
Evaluation Funds

STUDY SITE(S)

- WRNMMC, Bethesda, MD

FIND OUT MORE: <https://clinicaltrials.gov/ct2/show/NCT03907254>



Clinical Trial of 3MDR to Treat PTSD After mTBI, With and Without Eye Movement

Michael J. Roy, M.D., M.P.H., Principal Investigator

Recruitment Core, CNRM, USU

Director, Division of Military Internal Medicine, Department of Medicine, USU

Staff Internist, Internal Medicine, WRNMMC

RESEARCH HIGHLIGHT

Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are persistent and frequently comorbid complications of recent combat. There is no proven treatment for mTBI, and standard treatments for PTSD frequently achieve only transient, modest impact.

Motion-assisted, Multi-modular Memory Desensitization and Reconsolidation (3MDR) is a novel treatment for PTSD combining aspects of virtual reality exposure therapy and eye movement desensitization and reprocessing treatment within the Computer Assisted Rehabilitation Environment (CAREN). The purpose of this pilot study is to 1) obtain an initial estimate of the efficacy of 3MDR in service members with comorbid PTSD and mTBI and 2) determine the impact of eye movement on treatment response.

Up to 20 participants with comorbid PTSD and mTBI receive 10 sessions (three preparatory, six 3MDR treatment, and one conclusion). In preparatory sessions, the therapist helps each participant select songs and pictures to be used in treatment sessions. During 3MDR treatment, participants walk on the CAREN's embedded treadmill through an immersive virtual environment, first listening to a musical piece to bring them back to the time of their traumatic experience, and subsequently, facing and actively walking toward a series of emotionally-evocative images that are displayed directly in front of them on the CAREN's curved screen.

STUDY IMPACT

Findings from this study may support the use of 3MDR in the Computer Assisted Rehabilitation Environment (CAREN) as an enhanced therapy to significantly impact the care of individuals with PTSD and mTBI and improve quality of life.



KEY STUDY TEAM

Sarah E. Kruger

Paula G. Bellini

Charline E. Simon

STUDY SITE(S)

- NCoE, WRNMMC, Bethesda, MD

- CNRM, USU, Bethesda, MD

FIND OUT MORE: <https://clinicaltrials.gov/ct2/show/NCT03796936>





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For more information on the NICoE, please visit our website:

<https://www.wrnmmc.capmed.mil/NICoE>

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