



Neurorehabilitation: Neurons *to* Networks

Traumatic Brain Injury Center of Excellence

About Us

The Neurorehabilitation: Neurons to Networks (N:N2N) Traumatic Brain Injury (TBI) Center of Excellence (COE) was established in 2009 when the Michael E. DeBakey VA Medical Center (MEDVAMC) was awarded a five-year grant by VA Office of Research and Development. The TBI COE is led by its Scientific Director, Harvey Levin, PhD.

Brain injury is the signature wound of wars in Iraq and Afghanistan. About 20% of returning Veterans have sustained at least one TBI. Most of the TBIs are mild and due to exposure to blasts. Some people who had a TBI report problems with headaches, memory, attention and concentration, mood swings, and sleep. Some of these symptoms may also be related to posttraumatic stress disorder (PTSD). In many cases, these symptoms result from a combination of TBI and PTSD. Some individuals may recover fully; but others have longer lasting problems that can interfere with their ability to work or to get along with their friends and family.

Researchers at the N: N2N TBI COE are evaluating the Service Members and Veterans who were deployed to Iraq and Afghanistan since 2001 to better understand how brain injury and other deployment-related conditions affect their lives. The researchers want to help to improve Veterans' reintegration into civilian life, develop new tools and treatments for TBI-related symptoms and other deployment-related conditions, and improve diagnosis of TBI.

The TBI COE Evaluation. All eligible participants are invited to complete the Behavioral Assessment Core evaluation. The evaluation includes: computer and paper and pencil based tests of thinking skills; an interview to understand the severity and impact of TBI; a thorough assessment of other deployment-related conditions; and measures of community participation and quality of life. There is an optional blood draw, which researchers in the Genetics Core will use to identify genes that may be related to adaptability and coping skills following deployment.

The TBI COE has seven established cores led by their directors: Recruitment and Retention (Dr. B. Miller), Behavioral Assessment (Dr. N. Pastorek), Neuroimaging (Drs. R. Scheibel, E. Wilde, and B. Taylor), Genetics (Dr. D. Nielsen), Statistical (Dr. N. Petersen), Research Support (Dr. M. Troyanskaya), and Administrative (Ms. R. O'Donovan). Recently two new cores were added: the Rehabilitation and Translational Research cores. The main goal of the cores is to provide a wide range of support for all projects conducted within the COE and to ensure that there is a close connection between research and everyday clinical care.

Several of the ongoing projects include brain imaging. The Neuroimaging Core provides assistance with the acquisition and analysis of the structural magnetic resonance imaging (MRI), task-related functional MRI (fMRI), diffuse tensor imaging (DTI), functional

connectivity magnetic resonance imaging (fcMRI), magnetic resonance spectroscopy (MRS), arterial spin labeling (ASL), and susceptibility-weighted imaging (SWI).

How to Contact Us

Anyone who was deployed to a combat theater in support of OEF/OIF/OND is invited to participate in our research studies. Please see sections below for the additional studies available through the COE. Also, VA health care providers, undergraduate and graduate students, and post-docs are welcomed to contact us. To learn more about the TBI COE, available research projects, and internship and volunteer opportunities, please call us at 832-316-6336, 713-794-7493, or toll-free 1-866-838-2778. You can also email us at TBICOErecruitment@va.gov. Our mailing address is: Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd, TBI-153, Houston, TX 77030.

Pilot Funding and Fellowship

N:N2N Sponsored Research and VA Advanced Fellowship Program in Polytrauma & TBI Rehabilitation. The N:N2N encourages investigator-initiated research within the theme and mission of the N:N2N. Each year the TBI COE awards several **12-month seed/feasibility projects** in the amount of \$2,000-\$50,000. In addition to financial support, investigators will benefit from the presence of the cores and the N:N2N staff to provide guidance, support, and limited manpower to implement ideas. These awards should be used to gather pilot data that will ultimately result in externally funded awards (e.g. VA Pilot, VA Merit, R03, R21, R01). Requests for applications will be distributed through the MEDVAMC Research & Development newsletter and will be posted on this site each July with an application due date of September 1st. Please see sections below for the ongoing pilot projects. The COE is offering a **two year fellowship program** in polytrauma, TBI, and related neuroscience fields. This program is funded through the Office of Academic Affairs and is intended to develop clinicians and scientists with vision, knowledge, and commitment to lead polytrauma and TBI efforts throughout VA, the nation, and the world. For further details and eligibility requirements please contact Ms. Rhonda O'Donovan (Rhonda.Odonovan@va.gov).

Ongoing Pilot Projects Funded by the TBI COE N:N2N

The TBI COE supports several ongoing pilot studies. These studies aim to collect initial data and apply to receive independent funding.

Atypical Performance on Memory Tests and TBI (PI: Dr. R. Scheibel): Traumatic brain injury can be associated with a variety of different memory complaints. Individuals are assessed with tests that are designed to study their memory strategies and identify different types of memory difficulties. Additional tests are administered to identify related problems with attention and other complications that can make it difficult to remember information.

Stability of cognitive control activation and functional connectivity after TBI (PI: Dr. M. Newsome): Quantifying changes in patterns of brain activation over time in Veterans without a history of TBI could suggest a range of variability which could identify Veterans (with TBI) whose patterns of activation are not reliable. Early identification of the degree of stability of recruitment patterns could, therefore, be key in providing interventions aimed to increase pattern

stability, potentially including increasing fluency with which the task is performed. The overall goal of this project is to analyze imaging data that have already been previously collected to investigate the stability of neuronal reorganization associated with cognitive control after TBI in OEF/OIF/OND Veterans by comparing fMRI results between scans acquired 2-24 months apart.

Modeling TBI susceptibility with human induced pluripotent stem cell-derived neurons.

(PI: Dr. P. Moretti): Military personnel are at risk of the acute and chronic effects of TBI, including chronic traumatic encephalopathy (CTE). Considerable variability exists in functional outcome after TBI. Clinical data suggest the existence of biological differences influencing susceptibility to the acute or chronic effects of trauma, or the ability to recover from it. This pilot study uses induced pluripotent stem cell technology to develop a cell culture system to study the response of human neurons to trauma. In preliminary studies we generated and validated a control human iPSC line, we used this line to differentiate neurons in culture, and we performed selected axonal stretch injury experiments using rodent primary neurons.

Independent projects leveraging N:N2N resources

A longitudinal study of chronic TBI in OEF/OIF/OND Veterans and Service Members

(PIs: Drs. R. Scheibel and E. Wilde): Repetitive TBI is of great significance in view of recent reports of CTE resulting from repetitive sports concussions and, most recently, from trauma experienced during combat. CTE is a progressive neurodegenerative disease that has an insidious clinical presentation, including the development of cognitive and emotional symptoms, and in some cases, other neurological symptoms. This study uses neurocognitive and behavioral assessments, multimodality brain imaging, and genetics to study the long-term effects of deployment-related TBI, including blast and non-blast mechanisms and co-morbidities in Veterans and service members and to elucidate underlying neural mechanisms of these changes. The overall goal of this project is to characterize the long-term effects of TBI on cognition, neuroimaging, and functional outcome in post-deployed OEF/OIF/OND Veterans and service members and perform multiple assessments to track recovery and decline.

An fMRI Study of TBI Associated with Blast Injury (PI: Dr. H. Levin). To elucidate the neural mechanisms mediating cognitive deficit after deployment-related TBI, researchers perform multimodality brain imaging and administer cognitive, behavioral and health related quality of life outcome measures in OEF/OIF/OND Veterans and service members. The multimodal imaging data which include the fMRI, fcMRI, and DTI have been analyzed adjusting for co-morbid PTSD and depression symptoms. With this design, researchers plan to evaluate the effects of deployment-related TBI on brain function in relation to indices of brain structural integrity and co-morbidities of injury.

Brain Plasticity-based Cognitive Remediation Available to Veterans with TBI (BRAVE)

trial (PIs: Drs. H. Levin and M. Newsome). The TBI COE is one of five sites for the Brain Plasticity-based Cognitive Remediation Available to VEterans with mild TBI (BRAVE) trial. The overall objective of this study is to evaluate the efficacy of a novel plasticity-based adaptive cognitive remediation program in patients with persistent post-concussive symptoms following TBI. Deployment to a war zone is strongly associated with neuropsychological difficulties on tasks of sustained attention, verbal-learning, and visual-spatial memory. Some form of attention

is involved in virtually all cognitive domains, except when task performance has become habitual or automatic. The BRAVE trial employs visual and auditory sensory, attentional, and memory tasks with the aim of improving global cognitive function.

Identifying Biomarkers for TBI Recovery with fMRI and Behavioral Tests (PI: Dr. D. Graham). This Career Development Award is a four-year cross-sectional study simultaneously examining functional neuroimaging, genetic polymorphisms, and neuropsychological tests for biologic markers associated with good versus poor social recovery from blast-related TBI in returning OEF/OIF/OND Veterans. Once this study identifies potential biomarkers, the next step of investigation will be to evaluate the potential utility of the identified biomarkers in improving the linkage of Veteran's with TBI to the clinical and psychological treatments most likely to show each individual a positive outcome.

Neuroimaging Group Based Exposure Therapy's (GBET) Impact on Veterans with mild TBI and PTSD (PI: Dr. M. Newsome). GBET significantly reduces PTSD symptoms and these improvements have been found to remain three months after therapy cessation. However, this therapy has not yet been extended to OEF/OIF/OND Veterans and, since co-morbidity with TBI was not examined, it is unknown whether brain pathology associated with TBI may affect treatment. Given that there are different, as well as overlapping, brain regions involved in the two conditions, this investigation may help discern whether neural pathways involved in successful treatment of these disorders are similar or different.

Completed TBI COE Pilot studies that are in a process of obtaining external funding and publishing the results

Virtual Reality Treatment (PIs: Drs. P. Bordnick/ R. De La Garza). Alcohol craving and excessive drinking is a problem among Veterans, particularly if they have TBI and/or PTSD. Such conditions are often associated with delayed recovery, increased disability, and worse treatment outcomes. Using advanced virtual-reality technology in conjunction with cognitive-behavioral therapy, Veterans received virtual-reality based relapse prevention. Veterans were taught coping and relapse prevention skills during one-on-one sessions with a trained therapist. Researchers evaluated the efficacy of cognitive-behavioral therapy (CBT) in conjunction with virtual-reality (VR) based relapse prevention on alcohol consumption and craving among treatment-seeking Veterans with TBI and/or PTSD. The observed improvements in drinking and craving indicated that CBT in conjunction with VR shows great promise as a potential treatment for this population. Data from this study has been used for a submission for new funding from NIH R01.

Substance Abuse and TBI Pilot (PIs: Drs. E. Wilde and S. McCauley). The Women's Inpatient Specialty Environment of Recovery (WISER) and Returning OEF/OIF Veteran's Environment of Recovery (ROVER) units of the MEDVAMC offered a novel treatment approach for TBI, PTSD, and other deployment-related conditions that is not available at other VA hospitals. Researchers at the MEDVAMC conducted a study to demonstrate improvements in cognitive (thinking) abilities, emotional functioning, and structural brain changes that occur as a result of this treatment program. This project had two primary aims: 1) investigate treatment effects on emotion, cognition, addiction, and global function in previously-deployed

OEF/OIF/OND Veterans and Service Members with disorders including mild TBI, PTSD, and alcohol abuse disorders (ETOH), and 2) investigate treatment-related neuroimaging effects in these Veterans. Findings from this pilot were used for a submission for new RR&D funding to investigate the short-term (3 months) durability of treatment-related gains.

Brain Imaging and Cognitive Control (PI: Dr. H. Levin). It is believed that the individuals with a deployment-related TBI have a different pattern of brain activity when performing memory functions. While participants did memory tasks inside an MRI scanner, researchers used special brain imaging techniques to look for signs of damaged connections in the brain. This pilot project demonstrated possible disruption of at least three networks associated with verbal working memory and interference resolution that are not limited to surface cortical regions, indicating that disruption of neural processing may be quite extensive. Understanding the extent of neural disruption suggests that follow-up remediation programs target multiple brain regions. Because these effects were found in novice meditators and occurred after a short period of time, a meditation intervention may be particularly efficacious for Veterans. In addition, PTSD was associated with greater activation. Dr. Levin is planning to use data from this pilot for a submission for new RR&D funding.

Temporal Perception (PI: Dr. D. Eagleman): The perception of time depends on a complex collaboration of many brain areas. Some findings indicate that damage to the brain compromises performance on simple timing tasks. Therefore, simple timing tasks have the potential to highlight damage quickly and with no human administrator. Our aim was to validate an automated software battery developed in our laboratory that rapidly assesses six different aspects of brain function in the time domain. Task 1, the “Temporal Eye Chart”, measures the speed at which participants can distinguish alternating images. Most of the TBI participants performed in the normal range; however, several outlying individuals called for further examination in relation to the data from the other cores and pilots. Task 2, known as the “proliferation effect”, uses flickering images to measure temporal response to novelty. We found that TBI patients showed significantly higher numerosity than controls, indicating a longer window of integration for visual stimuli. In Task 3, which measures how people recalibrate timing expectations between motor acts and sensory feedback, we found that several TBI participants behaved abnormally.

Community Reintegration in Service Members (CRIS) Instrument – A pilot project to detect differences attributable to mild TBI (PI: Drs. D. Helmer and L. Resnik)

Diagnosing mild TBI in returning service members can be challenging. Clinicians, researchers, and policy makers focus on the level of functioning in one’s life, or “community reintegration,” to determine the need for and success of treatments. The CRIS instrument evaluated how well service members were adjusting to civilian life and assessed participation in community and social activities. Specific aims of this project were to: 1) Examine the face validity of the CRIS through focus groups of OEF/OIF Veterans with mild TBI and family members with expertise in mild TBI. 2) Field the CRIS in OEF/OIF Veterans undergoing evaluation for possible mild TBI and compare CRIS results between those with and without mild TBI and by severity of TBI. 3) Describe mediating and moderating factors of the association between mild TBI and performance on the CRIS. Findings from this pilot will be used for a submission for new RR&D funding.