

# Appendix A: Fiscal Year 2017 Research Narrative

## Behavioral Science Division

The Behavioral Science Division in Boston, Massachusetts, conducts research on adjustment after military deployment, assessment methods, genomic and neuroscience mechanisms linked to psychopathology, and innovative approaches to clinical intervention and treatment delivery.

### Prospective Cohort Studies

Division researchers are working on two large prospective cohort studies that collect information from strategically selected groups of people over time. The first, [Project VALOR \(Veterans After-Discharge Longitudinal Registry\)](#), is working with a registry of 1,649 male and female combat Veterans who became users of Department of Veterans Affairs (VA) services after 2002. The project collects data about health outcomes associated with posttraumatic stress disorder (PTSD), supplemented by clinical information from VA electronic medical records. Data collection for the fourth sampling wave is now complete, with 1,205 participants (73% of the initial cohort); examination of PTSD symptom trajectories and predictors of those trajectories are in process. The next phase of the project involves collecting saliva samples from participants for future genomic analyses.

The second large investigation, the [Neurocognition Deployment Health Study \(NDHS\)](#), began data collection at the outset of the Iraq War in 2003. Military personnel were assessed before deployment and at several intervals afterward—making it the first prospective, longitudinal study to address the psychological impact of war zone stress. The study design allows examination of long-term emotional and neuropsychological outcomes, as well as health-related quality of life and occupational functioning. Initial papers have described PTSD outcomes; longitudinal neuropsychological outcomes; and relationships among PTSD, traumatic brain injury (TBI), and neuropsychological outcomes. Data preparation and analysis are underway for an associated study that examines the adjustment of both partners and children of the Servicemembers and Veterans in the cohort.

### Biomarkers

Biomarker (measurable biological factors) research at the Division includes a rapidly growing portfolio of genetic and neuroimaging studies, working with collaborators such as the [Translational Research Center for TBI and Stress Disorders \(TRACTS\)](#) Center of Excellence, the [National PTSD Brain](#)

[Bank](#), the Psychiatric Genomics Consortium (PGC), and the [Enhancing Neuroimaging Genetics through Meta-Analysis \(ENIGMA\) PTSD Working Group](#). During FY 2017, Division investigators contributed to the largest neuroimaging study of PTSD conducted to date (see Duncan et al., 2017). They also found evidence in both blood and brain tissue that suggests a role for inflammation in the pathophysiology of PTSD; and they published findings consistent with the accelerated-aging hypothesis that addresses the biological impact of PTSD.

Other Division investigators are examining biomarkers of PTSD and blast-related TBI in Veterans of Iraq and Afghanistan war zones. Through this research, investigators aim to clarify the relative contribution of mild TBI and psychiatric conditions to various deficits experienced by military personnel with blast injury, as well as long-term negative consequences such as neurodegenerative disease. The biomarkers are drawn from structural and functional neuroimaging, epigenetic indicators, candidate genes, and examination of polygenic risk.

Recent published work has identified genes that moderate hippocampal volume in mild TBI and PTSD. Other published and in-progress work has examined how risk for Alzheimer's disease and Parkinson's disease moderates cortical thickness and volume following mild TBI. Future work will examine blood-based biomarkers such as those associated with neuronal injury and inflammation.

Division investigators are using functional and structural magnetic resonance imaging (MRI) to identify neural circuitry involved in PTSD. Structural MRI data point to specific hippocampal subfield volumes that are negative correlates of PTSD and that may play a role in the persistence of PTSD symptoms. Additional work is being conducted to examine the relationship between hippocampal subfield volume and overgeneralization of memory in PTSD. Data from functional MRI projects also suggest reduced function in specific brain regions within the prefrontal cortex during attempts at memory suppression. This finding identifies a possible

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mechanism for intrusive thoughts in PTSD that might be targeted in treatment.

### Treatment Research

The Division continues to conduct pioneering research on treatments for PTSD, with the key aims of overcoming barriers to seeking care, reducing dropout, and increasing efficiency of care delivery. A prime example is the internet-based treatment [VetChange](#), designed for Iraq and Afghanistan combat Veterans who report risky use of alcohol and PTSD-related distress. The initial clinical trial produced evidence that VetChange was effective in reducing both drinking and PTSD symptoms.

The research version of VetChange was subsequently modified to include a mobile-friendly public website. This version, which is applicable to Veterans of all eras, is now under evaluation. A [mobile app](#) that has key VetChange features was recently developed in conjunction with the Dissemination and Training Division and will soon begin a pilot test phase. In addition, a major extension of the VetChange web intervention is underway to directly integrate with clinical care delivered by VA providers and to evaluate its effectiveness in VA clinics.

Other Division efforts include developing and testing efficient, therapist-delivered interventions or treatment extenders, with the goal of finding approaches that require less professional staff time and that are easier for patients to complete. A prime example is a five-session Prolonged Exposure (PE)-based treatment for PTSD that has shown strong effects with non-Veteran patients. Current and planned studies are testing whether this brief intervention is as effective as Cognitive Processing Therapy (CPT), and whether it can be implemented successfully with Veterans and active-duty Servicemembers.

Research on factors that link PTSD with aggression toward intimate partners has led to the development and evaluation of interventions that reduce or prevent aggression within at-risk military families. Positive clinical trials have been published; and the interventions are being implemented at multiple sites in the VA health care system and on one military installation. A new pilot study is planned that will adapt and test one of these programs for use in an underserved urban civilian setting.

In the area of complementary interventions, a five-year study has begun examining the impact of two active 12-week treatments on chronic pain in Gulf War Illness. In this project, Tai Chi, a mind-body exercise associated with both physical and mental health benefits, is compared with a wellness promotion group that is based on VA's Whole Health approach. Manuals for both group treatments have been developed, and the first cohort of Veterans has begun the interventions.

Division investigators are also examining a phenomenon termed later-adulthood trauma reengagement (LATR),

in which older combat Veterans actively reengage with wartime memories in an effort to build coherence and/or to find meaning in the experience. It is theorized that the LATR process may either lead to growth and positive outcomes or result in negative outcomes such as increased symptomatology. A current study of LATR is examining the utility of a 10-week psychosocial discussion group for older combat Veterans who report experiences consistent with the LATR process. Three cohorts are complete, and recruitment for the fourth cohort will begin in early 2018.

Lastly, Division investigators are evaluating evidence-based psychotherapy programs operating under the VA Boston PTSD Clinic. Recent findings demonstrated that changes in clinic intake procedures are associated with increased rates of retention in evidence-based psychotherapies.

### Assessment

Data collection is underway on a study designed to validate a cutoff score for PTSD status based on the most recent version of the [Primary Care Screen for PTSD for DSM-5 \(PC-PTSD-5\)](#) for the *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5)*. The study is part of a larger effort to validate DSM-5 versions of measures that have been developed by National Center investigators. The project recruits Veterans from VA primary care locations and uses the [Clinician-Administered PTSD Scale for DSM-5 \(CAPS-5\)](#) as the criterion index. The study will also explore the extent to which the optimal PC-PTSD-5 cutoff score varies across subgroups of Veterans and will provide initial information about the acceptability of the screening measure for these patients.

A recent study evaluated Restructured Form scales from the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) as predictors of PTSD-related outcomes. One paper based on this work demonstrates that the MMPI-2 Restructured Form scales can differentiate high PTSD symptom severity alone from high severity accompanied by dissociation—a difference that has implications for treatment decisions. A second paper provides formal psychometric support for the utility of the [Dissociative Subtype of PTSD Scale \(DSPS\)](#) in a clinical sample of Veterans. Data collection is also underway for an investigation into the utility of the MMPI-2 Restructured Form scales in relation to chronic pain and treatment outcomes for Veterans who receive care in a VA pain clinic.

Division investigators are collaborating with research teams from the MITRE Corporation and MIT Lincoln Laboratory to develop a nonintrusive method of PTSD detection that utilizes voice analysis. This work uses neurocomputational modeling to identify vocal markers based on timing and coordination of speech to determine the presence and severity of PTSD. The nonintrusive nature of this approach increases its potential for real-world application.

Another ongoing project is designed to inform postmortem donor classification for the [VA National PTSD Brain Bank](#). Data are being collected from living elderly Veterans to determine their status for PTSD and comorbid disorders; this criterion information is then used to evaluate the predictive potential of information obtained from an informant interview and medical record review. The goals are to determine the best predictors from indirect sources and to provide an assessment template for use by the PTSD Brain Bank.

### Epidemiology and Risk/Resilience

A collaborative project with investigators from VA Boston Healthcare System takes a lifespan, multidisciplinary approach to studying the impact of military service. This effort has facilitated research and advanced the traumatic stress field through creation of a website that provides information about military service variables found in a large number of publicly accessible longitudinal data sets. Research facilitated by this effort is reported in the forthcoming book *Long-Term Outcomes of Military Service: The Health and Well-Being of Aging Veterans*.

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## Clinical Neurosciences Division

The Clinical Neurosciences Division in West Haven, Connecticut, focuses on research designed to uncover biomarkers (measurable biological factors) of disease mechanisms, as well as on clinical research that investigates paradigms of risk and resilience. The Clinical Neurosciences Division utilizes an interdisciplinary approach that includes neuroimaging, treatment, genetics, and epidemiological studies targeted at translating discoveries from the lab into interventions for treating posttraumatic stress disorder (PTSD) and comorbid conditions.

### Neuroimaging Studies

Clinical Neurosciences Division investigators are working to characterize biochemical, structural, and functional abnormalities underlying PTSD. This body of work suggests connections between how the nervous system and brain, in particular, respond to extreme stress. Investigators are also working on the integration of neuroimaging and genomics to understand how genetic and environmental influences come together to create unique phenotypes of PTSD. Other work includes projects using advanced machine-learning methods and artificial intelligence (AI) to investigate disruptions in brain network circuitry.

#### *Neurochemical & Molecular Brain Imaging*

A recent body of research, conducted by Clinical Neurosciences Division researchers and Department of Veterans Affairs ([VA's National Posttraumatic Stress Disorder Brain Bank \(PTSD Brain Bank\)](#)), strongly points to alterations in the glutamatergic and glucocorticoid (cortisol) systems that underlie brain network impairment and dysfunction in PTSD. Research using positron emission tomography (PET) technology has shown that mGluR5 (metabotropic glutamatergic receptors) may be a promising treatment target in depression and PTSD, as it plays a role in the modulation of glutamate neurotransmission.

Studies have shown that mGluR5 is present in higher levels in trauma survivors with PTSD compared to those without PTSD; mGluR5 density is highest in the hippocampus and putamen, two brain regions that hold specific relevance for PTSD. Additional pilot data found that mGluR5 is even higher in PTSD patients with comorbid suicidal ideation. Investigators have also demonstrated that mGluR5 availability is related to glutamate levels in stress-related psychopathology as well as to changes following drug administration, suggesting

that normalization of glutamate neurotransmission by modulating mGluR5 may be an important component of successful treatment. Investigators are building on findings from animal work showing that glucocorticoids can modulate the glutamatergic system; these efforts could increase understanding of the neurobiology of PTSD and provide novel targets for treatment development.

Investigators continue to study neuroinflammatory processes in PTSD using PET technology. Prior work has indicated a link between immune alterations and PTSD following trauma exposure; and investigators are now studying whether activation of microglial cells contributes to PTSD pathogenesis. Preliminary data have been collected to evaluate the role of activated microglia in mediating PTSD expression. Other work aims to study the relationship between peripheral inflammatory markers such as TNF- $\alpha$  (tumor necrosis factor alpha) and trauma-related symptoms. By characterizing the type and extent of neuroinflammation in PTSD, it may be possible to uncover new targets for treatment with anti-inflammatory agents; findings may also inform new research evaluating long-term effects of increased inflammation that occur in response to chronic stress. Additionally, pilot data collected in a second project of PTSD and arterial inflammation is currently undergoing analysis, and may contribute to efforts to reduce cardiac mortality in PTSD patients.

Additionally, investigators are conducting preclinical and clinical studies to measure synaptic density alterations in PTSD and in other trauma- and stress-related disorders. They are using a PET tracer for SV2A (synaptic vesicle glycoprotein 2A), which is a likely biological marker of brain synaptic plasticity (the ability of the brain to reorganize synaptic connections in response to learning or from injury). The SV2A tracer is an extremely valuable tool, as stress-related

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synaptic loss is believed to be an essential contributor to PTSD pathophysiology, treatment failure, and functional impairment. The next phase of this work will include a clinical study with nonhuman primates, as well as clinical participants with depression and PTSD, to evaluate changes to synaptic density following the administration of ketamine, a medication that affects the glutamate system. This study is building on prior preclinical work showing that damage to synaptic connections caused by chronic stress is rapidly reversed by ketamine.

### *Structural and Functional Brain Imaging*

Sophisticated functional and structural neuroimaging are important tools used to study brain metabolism and brain circuitry in PTSD. Recent findings from this work have shown that global brain connectivity is a potential marker for stress-related dysfunction and a possible target for treatment. Studies have also found that disruptions between neural pathways in the anterior hippocampus—an area involved in forming, organizing, and storing memories—is associated with higher PTSD severity.

Data from projects that characterize brain circuitry using EEG (electroencephalography) testing and fMRI (functional magnetic resonance imaging) have shown that decreased hippocampal volume in patients with PTSD is associated with reduced functional connectivity in other areas of the brain. Additional imaging research includes the study of neuroanatomical correlates of abnormal fear regulation, information processing, and decision-making in the context of ambiguity and risk in patients with PTSD.

### *Morphometric Brain Imaging*

The Clinical Neurosciences Division continued its collaboration with [PGC-ENIGMA \(Psychiatric Genomics Consortium-Enhancing Neuroimaging Genetics Through Meta-Analysis\)](#), a large-scale coalition partnering in the analysis of neuroimaging and genetic data. Investigators recently replicated the finding that the volumes of the hippocampus and amygdala are smaller in Veterans with PTSD. Although the literature has been largely concentrated on studies of overall volume of these brain regions, recent studies by Clinical Neurosciences Division researchers have utilized novel morphometric and subfield approaches to localize PTSD-related atrophy within specific regions within the hippocampus and amygdala. Further work is using high-resolution MRI to study the association between cortical thickness and suicidal ideation in combat-exposed Veterans. Preliminary analyses suggest that suicidal ideation may be associated with altered cortical thickness in brain areas key to the neurobiology of PTSD, and may serve as a potential biomarker for increased risk of suicidality.

### **Treatment Research**

Investigators have previously shown that ketamine has rapid antidepressant effects that are associated with changes

in the brain's functional connectivity, thus improving neuroplasticity. Researchers are now testing the therapeutic effects of ketamine in a PTSD population over longer periods of time to study the durability of treatment response in PTSD. Data from this study is also examining ketamine's potential procognitive and anti-suicidal effects in PTSD. Additional work includes a study to evaluate ketamine's potential to augment the treatment effects of Prolonged Exposure (PE) therapy to determine whether improved neuroplasticity can positively affect fear inhibition and memory reconsolidation.

Researchers continue to explore intervention strategies that might improve fear extinction among trauma survivors who do not respond to standard treatment approaches. One such avenue of work includes the use of real-time fMRI neurofeedback. Resting-state functional connectivity (that is, regional changes in brain activity when the brain is not involved in a task) data from an fMRI neurofeedback project revealed that neurofeedback led to changes in brain connectivity during traumatic memory recall that were consistent with clinical improvement. Investigators will continue to study the clinical utility of this emerging technique in the treatment of PTSD.

Other pharmacotherapeutic agents currently under study include riluzole, a glutamate modulating agent; the immunosuppressant rapamycin; and neuropeptide Y, an endogenous neuropeptide.

### **Genetic and Molecular Studies**

The Clinical Neurosciences Division is a major contributor to the field of genetics, utilizing neurogenomics to explore interactions among genotypes, phenotypes, and the environment via a range of bioinformatic approaches. Using tissue from the PTSD Brain Bank, investigators have shown that a specific gene—SGK1 (serum and glucocorticoid-regulated kinase 1)—that is expressed at lower levels in people with PTSD, was also lower in stressed animals, and that overexpressing this gene in animals made them more resilient to stress. Ongoing efforts include studying SGK1 as a potential marker for PTSD and investigating strategies for raising SGK1 levels in the brain as a potential new treatment. Several other genes of interest—including FKBP5 (FK506 binding protein 5) and NPAS4 (neuronal PAS domain protein 4)—have also been targeted in reverse transcription polymerase chain reaction analysis, a technique used to detect Ribonucleic Acid (RNA) expression.

Researchers have recently teamed with experts in high-level computational analyses to examine thousands of gene expression changes and DNA methylation in hundreds of subjects. This combined effort has led to identification of major networks of gene expression in PTSD patients—as compared with patients who have major depressive disorder and with control subjects—as well as alterations in single genes of interest in individuals with PTSD. Further bioinformatics

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studies are expected to result in identification of key network and hub genes that contribute to PTSD pathophysiology.

Clinical Neurosciences Division investigators continue to participate in the ongoing [Million Veteran Program \(MVP\)](#). Investigators recently completed a genome-wide association study (GWAS) in approximately 150,000 subjects, evaluating how genetic and environmental influences (phenotypes) come together to affect symptom reexperiencing. Work was also conducted on an epigenome-wide association study (EWAS) of PTSD in 1,135 Veterans—including both dimensional and categorical measures of PTSD as well as subphenotypes of reexperiencing, avoidance, numbing, and dysphoric and anxious arousal. Once finalized, this project will be the largest EWAS of PTSD conducted to date. Preliminary results suggest that the UPS48 (ubiquitin-proteasome system 48) gene, which is involved in the regulation of NF- $\kappa$ B-activation (nuclear factor kappa-light-chain-enhancer of activated B cells), plays

an important role. NF- $\kappa$ B-activation is a key regulator of inflammation, which is also implicated in synaptic plasticity and memory.

### Epidemiological Studies

Investigators are continuing to study the link between the neurobiology and epidemiology of PTSD. Several new studies were conducted in FY 2017 using data from the [National Health and Resilience in Veterans Study \(NHRVS\)](#) and the World Trade Center (WTC) Health Program. Recently published reports have examined questions on public health relevant to Veterans including factors that protect against the development of suicidal thinking, the role of attachment style in moderating effects of FKBP5 polymorphisms and childhood abuse in predicting PTSD symptoms, a comparison of International Classification of Diseases 11 (ICD-11) and *DSM-5* criteria for PTSD, and trajectories of posttraumatic growth.

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## Dissemination and Training Division

The Dissemination and Training Division in Palo Alto, California, conducts research on patient needs and preferences, implementation science, the development of novel and adapted treatments that attend to patient preferences, and the development and testing of treatments that employ the potential benefits of technology-based delivery of services.

### Patient Needs and Preferences

Several projects are aimed at developing and evaluating strategies to quickly identify patient needs, patients at risk, and patient preferences. A Health Services Research & Development Service study is developing a brief measure of patient characteristics associated with effective engagement in care. The measure is expected to guide identification of the type and amount of service resources needed to engage Veterans into care.

A second study related to patient needs will develop and cross-validate a risk-screening tool that identifies patients at risk for subsequent mental health problems. The study will focus on racial and ethnic minority patients who have been found to experience disparities in trauma exposure and mental health care.

Dissemination and Training Division investigators, working with collaborators at the Women's Health Sciences Division, completed research and evaluation work on screening and treatment for military sexual trauma (MST). The Dissemination and Training Division is also participating with the Executive Division to validate the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5).

### Implementation Research

A new study is evaluating how to simplify assessment of the quality of delivery of cognitive-behavioral therapy (CBT) for PTSD, depression, and anxiety disorders. A second ongoing study on Cognitive Processing Therapy (CPT) is evaluating

competing strategies intended to enhance and sustain the delivery of a PTSD treatment: one strategy emphasizes fidelity to the protocol through expert consultation and online resources, and the other focuses on using continuous quality improvement strategies to improve fit and to address barriers to treatment delivery. Investigators involved in evaluating the national rollout for Prolonged Exposure (PE) are investigating the effectiveness of different training models on trainee delivery of PE.

In collaboration with the Minneapolis Department of Veterans Affairs (VA) Medical Center, investigators completed a study identifying organizational factors that differentiate whether VA PTSD clinics have high or low usage of evidence-based psychotherapies. This project led to a new study that will take place in FY 2018, led by Minneapolis VA with co-investigators at two National Center Divisions, to test an implementation toolkit in VA PTSD clinics. The project also led to approval of a new multisite study to test whether a tailored set of implementation strategies increases the use of PE within the military health system, above and beyond the impact of standard provider training. This mixed-methods study will engage stakeholders at various levels and then match implementation strategies to site-specific barriers and facilitators.

New efforts are underway to improve patient access to care, including reduced patient wait times, by using participatory systems dynamics: a collaborative stakeholder model in which specific system problems are identified, changes are proposed,

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and the impact of the change on the outcome of interest is predicted in a data-driven fashion. The team is hoping to secure funding to assess the cost-effectiveness of this approach and to test its mechanisms of action.

A long-term project is the development of a practitioner network across both VA and Department of Defense (DoD) that can test strategies for implementing best practices. The network is currently engaged in quality improvement projects, but can also become a resource for implementation science research in the future. Lastly, a study that focuses on assessing and increasing implementation of many core elements of the [VA/DoD Clinical Practice Guideline for PTSD](#) in all three service delivery sectors (VA, DoD, and the general community) is nearing completion.

### Treatment Research

Dissemination and Training Division investigators are conducting several trials that evaluate patient outcomes in treatments adapted for use in a variety of settings and under a variety of delivery methods. A hybrid effectiveness and implementation study will compare two non-trauma-focused treatments delivered to women Veterans in their homes via video teleconference: Skills Training in Affective and Interpersonal Regulation (STAIR), which is an 8-session individual treatment for a variety of patients with PTSD, and Present-Centered Therapy (PCT), which is a non-trauma-focused therapy that focuses on current life problems related to PTSD. The goals of the study are to assess the relative effectiveness of these treatments, and to identify barriers and facilitators for using video to deliver treatment.

The efficacy of a web version of PE (Web-PE) in reducing symptoms of PTSD in military personnel and Veterans is being tested. Web-PE is delivered online with therapist oversight and facilitation, and could have significant potential to increase the reach of PE to those who cannot otherwise access traditional face-to-face care.

A large multisite clinical trial is now evaluating the effectiveness of flexibly delivered STAIR plus PE among civilian

public sector women, and will examine how variations in delivery affect patient outcomes. Lastly, investigators are evaluating adaptive changes in cardiac autonomic status, physical activity, social cognition, and social interaction in real time among Veterans participating in VA's Service Animal Training Intervention program.

### Technology-Based Treatments and Treatment Delivery

Several ongoing studies are assessing the benefits of phone- and web-based technologies to increase Veteran access to mental health care and to enhance outcomes. Following two successful pilot studies of the [PTSD Coach mobile app](#), a new project will assess the efficacy of PTSD Coach compared with traditional treatment for reducing PTSD symptoms in Veterans utilizing primary care service. Several pilot studies of mobile phone apps are underway including a pilot study of app-based personalized and semiautomated coaching integrated into PTSD Coach; a pilot study of a couples-based intervention using mobile apps; and two ongoing trials of the [Mindfulness Coach app](#) in Veterans with PTSD and as an adjunct for Veterans receiving other types of medical care.

A mobile cognitive-control training for the treatment of alcohol use and PTSD will determine the efficacy of a novel neurocognitive intervention for improving recovery outcomes. The first investigation of [Moving Forward](#) (an online problem-solving intervention for Veterans that teaches skills for overcoming stressful problems and helps them meet their goals) has been completed, with Veterans reporting less avoidance of problem solving as well as greater satisfaction with the online course when helped by a peer mentor.

In collaboration with investigators from the Minneapolis VA, the Dissemination and Training Division is conducting a study to test a web-based intervention to help National Guard families encourage their loved ones to seek mental health care. Key questions concerning the methods and the extent to which social networks can be utilized to increase treatment engagement, and to improve mental and physical health outcomes, is being investigated in a study of another highly stressed population: cancer survivors.

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## Evaluation Division

The Evaluation Division in West Haven, Connecticut, supports the National Center's mission through a programmatic link with Department of Veterans Affairs (VA)'s [Northeast Program Evaluation Center \(NEPEC\)](#). NEPEC has broad responsibilities within the VA Office of Mental Health and Suicide Prevention (OMHSP) to evaluate their programs including those for specialized treatment of posttraumatic stress disorder (PTSD).

### Program Monitoring and Evaluation

NEPEC has continued to monitor and assess PTSD treatment at VA. The monitoring includes both residential and outpatient specialty treatment programs, as well as PTSD treatment by trained providers not working within one of the PTSD specialty programs. The Evaluation Division via NEPEC also monitors

efforts to improve psychotropic medication prescribing practices at the Veterans Health Administration (VHA). Two of the measures in this initiative are the use of antipsychotics to treat PTSD and the use of benzodiazepines without an appropriate diagnosis or medical indication. Although NEPEC is primarily engaged in evaluation research, it also works on

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independent research projects related to the treatment of PTSD.

### Prospective Cohort Studies

Recruitment has finished for the Survey of Returning Veterans (SERV) study, which is a repeated panel study of gender differences in psychiatric status and functioning among OEF/OIF/OND (Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn) Veterans. SERV recruited 850 participants who were interviewed at three-month intervals for at least a year; a sizeable subset continued interviewing for up to three years. Over 40% of the sample is women. Follow-up rates are 80–85%. Analyses have begun, and the Evaluation Division is looking for investigators interested in analyzing the SERV data, or in leveraging the SERV sample in add-on or other primary data collection studies. Papers have been published on military sexual trauma (MST) and PTSD as they relate to unit cohesion, gender differences in prevalence rates of disorders over time, and characteristics of Veterans endorsing sex addiction items. Other papers and presentations are in progress on insomnia and PTSD symptoms, suicidal ideation and behaviors, and behavioral addictions. SERV data and an add-on study have been used to develop a pornography addiction scale that is currently in testing for psychometric properties; results in international samples are positive.

### Treatment Research

The Evaluation Division continues research on PTSD health service research, pain management, and the role of pain in the treatment of PTSD, as well as on sex differences in the health of returning Veterans. Data collection for a study of the implementation of two evidence-based treatments (EBTs)—Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT)—in 38 VA residential treatment programs (RTPs) for PTSD has been completed. Findings continue to be published on provider perspectives on perceived effective residential treatment ingredients, provider perceptions of dissuading factors to the use of PE and CPT, and changes in implementation of PE and CPT over time.

The Evaluation Division has a number of investigators using administrative data to explore treatment patterns and outcomes of PTSD care. Studies have been published on medication used for the treatment of PTSD, as well as on correlates of self-reported PTSD symptom severity scores over time. During FY 2018, the Evaluation Division will further examine the role of pain in specialized PTSD treatment and in the treatment of comorbid disorder, and will continue publishing results from the SERV interviews. The national Psychotropic Drug Safety Initiative (PDSI) has entered its fourth year and has been tracking data on changes in practice in prescribing for PTSD. The Evaluation Division continues its work with technical advisors at the PTSD Mentoring Program and at the OMHSP to provide technical assistance, and continues to respond to requests from specialized programs and staff in the field on policy, operations, handbook implementation, and the provision of evidence-based practices (EBPs).

The Measurement-Based Care (MBC) in Mental Health Initiative, which was formally launched by OMHSP in June 2016, completed its first year of work; and 58 facilities and 179 mental health clinics were enrolled as Champion Sites for implementing MBC. Two Evaluation Division staff are supporting the initial pilot program evaluation; members of the Executive Division and the Dissemination and Training Division are involved in the senior leadership of the Initiative. Additional investigators from within the Center are closely involved in the evaluation study itself, as well as in the Communications, Education and Training, and Coaching work groups. The National Center investigators from the Dissemination and Training Division have secured a contract with the RAND Corporation to perform in-depth interviews with MBC project directors, frontline provider-Veteran dyads, and individual providers to better understand their experiences with MBC. As the Initiative moves into its second year, NCPTSD members will continue to be active participants as investigators and as Initiative leaders.

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## Executive Division

The Executive Division, in White River Junction, Vermont, provides leadership, directs program planning, and promotes collaboration to facilitate optimal functioning of the other Divisions both individually and collectively. The Executive Division specializes in the development and evaluation of innovative and authoritative educational resources, in programs that disseminate and implement best management and clinical practices, and in the use of technologies to reach a broad range of audiences. The Executive Division also oversees the administration of Department of Veterans Affairs (VA)'s National Posttraumatic Stress Disorder (PTSD) Brain Bank.

### Treatment Research

The Executive Division has a long history of participation in VA's Cooperative Studies Program (CSP). During FY 2017, enrollment continued for CSP #591, a groundbreaking study

comparing Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT). The study is expected to reach the enrollment goal of 900 Veterans at 17 sites across the country in early 2018. Findings will help VA leadership, clinicians, and Veterans

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make informed choices about the delivery of PTSD care in VA, and will also be broadly relevant to the scientific and clinical communities outside VA.

In collaboration with the Behavioral Science Division, the Executive Division is leading a study to provide further validation of the *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5)* version of the [Primary Care PTSD Screen for DSM-5 \(PC-PTSD-5\)](#), which is currently used across VA for mandatory PTSD screening. Although initial validation has been completed, the ongoing study, which uses the [Clinician-Administered PTSD Scale for DSM-5 \(CAPS-5\)](#) as the criterion index, will provide more definitive information regarding the most appropriate cutoff scores and will allow investigation of the screen's ability to detect PTSD in key subgroups such as women.

Investigators continue to focus on issues that frequently co-occur with PTSD. Follow-up assessments have been completed for a trial looking at cognitive-behavioral therapy (CBT) along with usual outpatient addiction care compared with usual care alone for Veterans with PTSD and substance use disorders; analyses are underway. Data collection for a second trial comparing two psychotherapies for comorbid alcohol use disorder and PTSD (PE and Seeking Safety) will be completed during winter 2018. A new trial evaluating the combination of topiramate and PE for co-occurring PTSD and alcohol use disorder has been funded; recruitment launched in November 2017. Investigators continue collaborations with the PTSD specialty clinics and with the residential PTSD/substance use treatment program at the San Diego VA to develop ways to use clinical data for research. An ongoing pilot study is investigating the safety and efficacy of a novel form of synchronized transcranial magnetic stimulation (sTMS) for PTSD with comorbid depression. Lastly, a trial to evaluate a brief protocol to reduce guilt and shame related to a traumatic event among Veterans of Iraq and Afghanistan is midway through recruitment.

Investigators completed a pilot study that evaluated Veterans' reactions to [AboutFace](#), a web-based video gallery of Veterans with PTSD who share their personal stories about PTSD and how treatment has turned their lives around. Veterans assigned to AboutFace had positive attitudes toward the program and improved attitudes toward mental illness from baseline to the two-week follow-up, as compared with those in a control group.

### Implementation Research

The Executive Division continues work on several initiatives aimed at assessing models of care and at improving evidence-based practice. Investigators continue to analyze data and to publish results from a national survey that assessed the treatment needs and preferences of Veterans and non-Veterans with PTSD symptoms. Results of this survey also informed the development of the first publicly available

online treatment decision aid for PTSD, which was released to the National Center website in March 2017. The [PTSD Treatment Decision Aid](#) is interactive and enables users to identify preferences among treatment options and print that information to share with their providers.

An initiative funded by the Office of Rural Health (ORH) will examine the impact of facilitation and an academic detailing model, in which pharmacists reach out directly to clinicians to improve PTSD treatment practices in rural clinics throughout VISN 1 (VA New England Healthcare System). A published manuscript that focused on the impact of a multifaceted academic detailing program noted improvements in PTSD care consistent with clinical practice guidelines, as well as reductions in prescribing of benzodiazepines, antipsychotics, and prazosin during the educational intervention. These findings suggest that academic detailing and other educational programming can effectively address gaps in quality PTSD care.

In addition to projects aimed at improving clinical practices, investigators are continuing to assess the state of VA care for PTSD. Work is ongoing on a project that applies novel informatics and operational methods to medical and administrative data in order to understand multiple dimensions of quality of PTSD care within VA. As investigators have gained more skills and experience in retrospective data analysis, new projects have been created to understand and compare the effectiveness of evidence-based treatments (EBTs) for PTSD in routine clinical practice.

### VA's National PTSD Brain Bank

Dr. Matthew Friedman, Senior Advisor to the National Center, continued to coordinate the operations of VA's first [National PTSD Brain Bank](#). The PTSD Brain Bank supports the Presidential Executive Order of August 2012 on deployment health by enabling VA to lead the nation in unique research that will facilitate deeper understanding of the causes and consequences of PTSD, as well as furthering assessment and treatment techniques.

Enrollment of potential postmortem donors began in May 2015 with the launch of the PTSD Brain Bank website. Initially, the Brain Bank was a five-part consortium; it has subsequently grown to seven parts, with facilities at six VA Medical Centers (Miami, Florida; Durham, North Carolina; Boston, Massachusetts; San Antonio, Texas; West Haven, Connecticut; and White River Junction, Vermont) and the Uniformed Services University of the Health Sciences (USUHS). The PTSD Brain Bank currently has 168 brains, including 56 PTSD brains, and has received commitments of more than 100 additional brains by the end of 2018. Currently, 64 prospective donors (called *antemortem donors*) have volunteered to be followed over their lifetimes.



## Pacific Islands Division

The Pacific Islands Division in Honolulu, Hawaii, was created to advance posttraumatic stress disorder (PTSD) work in the Pacific Rim; to focus on improving access to care by increasing understanding of cultural attitudes and the bases of racial and ethnic disparities in treatment; and to evaluate the use of advanced technology, such as telemedicine, to reach out to Veterans who are otherwise unable to access adequate care.

### Treatment Research

Three major projects are aimed at evaluating different methods of delivering PTSD treatment. Investigators are in the dissemination phase of a large trial that examines Veterans' preferences for and the clinical efficacy of three modalities for the provision of Prolonged Exposure (PE): two involving technology and one involving in-home visits to Veterans. A second trial that compares different treatments for in-home delivery of a couples-based intervention for PTSD was recently launched; this study examines the clinical efficacy of Cognitive-Behavioral Conjoint Therapy (CBCT) for PTSD, and compares home-based care to traditional office-based care. Lastly, a new trial in collaboration with the Dissemination and Training Division is looking at home-based Skills Training in Affect and Interpersonal Regulation (STAIR) treatment for women Veterans who have experienced military sexual trauma (MST).

### Specific Populations

Several ongoing studies examine the prevalence of PTSD, response to treatment, and presence of related mental health comorbidities in ethnic minority populations. The studies

identify unique risk and resilience correlates of PTSD among ethnically and racially diverse Veterans, and the effects of those correlates on Veterans' response to evidence-based PTSD treatments.

In FY 2017, researchers initiated a study using data from the Honolulu Asian-Aging project, looking at the effects of military service combat exposure in particular on late-life dementia, as well as on marital and family structures, mental health, and physical health among Japanese-American men. Another ongoing project examines sociocultural and community influences on mental health decision-making among male and female African American, Latino, and white Veterans who are starting PTSD care in a Department of Veterans Affairs (VA) mental health clinic; the study is looking at social network influences, individual perceptions of mental health issues, provider expectations and experiences, and treatment preferences. Analyses of a longitudinal cohort study in which patient-reported PTSD symptoms and mental health quality of life were evaluated six months after receipt of a PTSD diagnosis were also completed this year; also examined were racial and ethnic disparities in those clinical outcomes.

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## Women's Health Sciences Division

The Women's Health Sciences Division in Boston, Massachusetts, specializes in the study of women Veterans and non-Veterans, with a particular focus on understanding gender differences in trauma exposure and post-trauma psychopathology.

### Biomarkers

Work at the Women's Health Sciences Division includes studies aimed at explaining the basic biological processes underlying posttraumatic stress disorder (PTSD) with particular relevance to women: a study examining the role of neurobiological and psychosocial factors that impact negative pregnancy outcomes among women with PTSD; data analysis on a study of sex hormones and derivatives associated with decreased retention of extinction learning across the menstrual cycle in women with PTSD; a study of GABAergic (gamma-aminobutyric acid-ergic) neuroprotective steroids in men and in women across the menstrual cycle; and a series of studies of the gene-environment interplay in the comorbidity of PTSD and eating disorders.

Another biomarker effort is a study of the role of stress-modulating biological factors in reducing symptoms of withdrawal and negative mood during smoking cessation in trauma-exposed individuals with and without PTSD. The Women's Health Sciences Division is also working on two

studies investigating the role of progressive exercise training to determine whether it affects participants' capacity for releasing shared neurohormones to help reduce or better manage chronic pain (including fibromyalgia) and PTSD symptoms.

### Treatment Research

Several intervention studies are examining more efficient treatment formats for Cognitive Processing Therapy (CPT). With support from the [South Texas Research Organizational Network Guiding Studies on Trauma and Resilience \(STRONG STAR\)](#) Consortium, investigators are continuing analysis on data from a recently completed study comparing the relative effectiveness of CPT delivered in an individual format with that delivered in a group format. Also through STRONG STAR, staff are investigating a variable-length CPT protocol testing the efficacy of the intervention when treatment end is determined by patient progress. Another trial will test the efficacy of CPT delivered in an intensive outpatient format with active duty military Servicemembers.

## Appendix A: Fiscal Year 2017 Research Narrative

In related studies, Women's Health Sciences Division investigators are working to improve adherence to existing PTSD treatments. A current study is exploring Veteran and provider perspectives on reasons for dropout from both CPT and Prolonged Exposure (PE) to develop an intervention aimed at increasing rates of completion for these treatments.

Other intervention studies focused on traumatized populations include an open trial to test the effectiveness of a therapist-assisted self-management intervention intended to increase self-efficacy and facilitate greater community engagement following a successful course of PTSD treatment. Analyses are ongoing on two trials examining therapist fidelity and client variables as contributors to changes in PTSD across administrations of CPT, and the role of sleep improvement in aiding recovery from PTSD and depression among survivors of interpersonal violence. Another ongoing intervention examines the effectiveness and fit of a transdiagnostic treatment, the Unified Protocol (UP), for trauma-exposed Veterans with co-occurring diagnoses.

The Women's Health Sciences Division is also focused on intervention research among those who have not necessarily been diagnosed with PTSD, including the development of a national network of peer-facilitated psychoeducation and support groups for women Veterans who want to improve their well-being. Additionally, filming has begun on a brief mindfulness-based training video that will be used to assist Servicemembers coping with post-deployment intrusive thoughts.

### Gender Differences

The Women's Health Sciences Division continues its major focus on understanding gender differences in stress, trauma, and related psychiatric outcomes. The Longitudinal Investigation of Gender, Health, and Trauma (LIGHT) study is a national survey of Veterans that is just getting underway, focusing on the impact of trauma and community violence on mental, physical, and reproductive health. The [Veterans Metric Initiative \(TVMI\)](#) is a large-scale longitudinal study—supported through a public-private partnership among Department of Veterans Affairs (VA), DoD, academia, and industry—that is investigating the reintegration experiences and program use of male and female post-9/11 Veterans.

Investigators also continue to analyze data from a study of the effects of deployment stressors and resulting mental health conditions on the occupational and family quality of life over time of female and male post-9/11 Veterans. In a separate large sample of Veterans who had deployed to in Iraq and Afghanistan, investigators recently conducted a

gender-stratified examination of suicidal ideation risk models, and found critical gender differences in pathways to suicidal ideation among this cohort.

Work on gender differences also extends to important non-Veteran samples including community members and law enforcement officers exposed to community violence. One prospective study examines gender differences in positive and negative health outcomes within the context of socioeconomic status, racial identity, and prior trauma history. In another series of studies, investigators are establishing a population trauma cohort using the Danish national health and social registries, with a projected sample size of 70,000. Gender differences in longitudinal psychopathology and resilience will be examined, using latent class analyses and machine-learning methodologies.

The health of older women Veterans is another area of focus. One study is examining the impact of military and other lifetime stress exposures and mental health results, with a focus on effects of PTSD on later life health and functioning in Vietnam-era women Veterans. In collaboration with investigators in the Behavioral Science Division, a follow-up study of female and male Vietnam-era Veterans is examining predictors of mortality, as well as changes in physical and mental health-related well-being over time.

### Military Sexual Trauma and Intimate Partner Violence

Exposure to interpersonal violence is a key issue of study at the Women's Health Sciences Division. Research specifically related to military sexual trauma (MST) includes two studies: a qualitative investigation aimed at identifying unique factors associated with sexual trauma that occur within a military context, and a mixed-methods investigation of Veterans' experiences with and preferences for the universal MST screening program at the Veterans Health Administration (VHA).

The Women's Health Sciences Division is also studying intimate partner violence (IPV), another important issue among female Veterans. Investigators are examining best practices for IPV identification, assessment, treatment, and the targeting of health services within the VHA context. One study will refine and evaluate the effectiveness of a patient-centered brief counseling intervention for women who experience IPV. This study incorporates hybrid methodology to inform expansion of the intervention throughout VA. A new pilot study is identifying best clinical practices for IPV screening programs within VA primary care settings, with the ultimate goal of disseminating these practices to all VA primary care clinics.