The Chronic Effects of Neurotrauma Consortium (CENC) multi-centre observational study: Description of study and characteristics of early participants


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Abstract

Primary objectives: To establish and comprehensively evaluate a large cohort of US veterans who served in recent military conflicts in order to better understand possible chronic and late-life effects of mild traumatic brain injury (mTBI), including those that may stem from neurodegeneration.

Research design: Cross-sectional and prospective longitudinal.

Methods and procedures: Inclusion criteria are prior combat exposure and deployment(s) in Operation Enduring Freedom, Operation Iraqi Freedom or one of their follow-on conflicts (collectively OEF/OIF). Effects of mTBI will be assessed by enrolling participants across the entire spectrum of mTBI, from entirely negative to many mTBIs. Longitudinal assessments consist of in-person comprehensive testing at least every 5 years, with interval annual telephonic testing. The primary outcome is the composite score on the NIH Toolbox neuropsychological test battery. Assessments also include structured interviews, questionnaires, traditional neuropsychological testing, motor, sensory and vestibular functions, neuroimaging, electrophysiology, genotypes and biomarkers.

Main outcomes and results: The authors fully describe the study methods and measures and report demographic and exposure characteristics from the early portion of the cohort of OEF/OIF veterans.

Conclusions: This centrepiece observational study of the Chronic Effects of Neurotrauma Consortium (CENC) is successfully launched and, within several years, should provide fertile data to begin investigating its aims.

Introduction

Overview

In August 2012, President Obama issued an Executive Order to develop a National Research Action Plan (NRAP) on traumatic brain injury (TBI) as well as post-traumatic stress disorder (PTSD) and other mental health conditions, for improved prevention, diagnosis and treatment. An area of particular concern was the very high prevalence of mild TBI (mTBI) among veterans of recent US military conflicts, including Operation Enduring Freedom (OEF, Afghanistan), Operation Iraqi Freedom (OIF, Iraq) and their follow-on conflicts like Operation New Dawn (collectively OEF/OIF) [1,2]. The potential link to early dementia, an increasingly grave concern for OEF/OIF era veterans and their families, has important service utilization consequences for military and veterans’ healthcare systems. These factors led to the establishment of two large combined Department of Defense (DoD) and Veterans Affairs (VA) competitive consortium grants, one of which was focused on military mTBI and was termed the Chronic Effects of Neurotrauma Consortium (CENC). In 2013 Virginia Commonwealth University (VCU) received the $62.3 million CENC award to comprehensively study mTBI in veterans and service members (SMs). For a complete description of the overarching VCU-led CENC and its infrastructure please see https://cenc.rti.org/. The centrepiece of CENC is a government steering committee (GSC) approved large, multi-centre, observational longitudinal study. This paper describes this study’s objectives and methods and reports the characteristics of the first group of participants enrolled.

Background

TBI, long recognized as an important source of morbidity in the general population, has a recently escalated prevalence in the
military sector and is considered the signature wound of OEF/ OIF [3]. Nearly 20% of the more than 2.5 million deployed SMs deployed to these conflicts since 2003 are identified as TBI survivors [4]. Greater use of explosive weaponry by insurgents in OEF/OIF compared to prior conflicts stoked this rise in prevalence and created a new endemic of blast-related TBI [1,2]. Like the civilian sector, the vast majority of combat TBIs are graded as mTBI or concussion [5], an acute condition for which late effects are questioned and poorly understood [6]. Although distressing long-term physical, emotional and/or cognitive symptoms are common among OEF/OIF era SMs and veterans [7–10], the relatedness to mTBI remains unclear [6,11]. The late effects from these deployments on recovery from combat and trauma-related comorbidities and on long-term brain functioning are also unknown [12]. Furthermore, despite laboratory pathophysiologic differences between blast TBI and blunt TBI, clinical differences have not been identified [13,14].

Perhaps the most disturbing potential mTBI complication is chronic traumatic encephalopathy (CTE), a type of neurodegeneration that may cause progressive dementia [15]. Post-mortem pathologic findings attributed to CTE include cerebral atrophy, cavum septi pellucidi with fenestrations, shrinkage of the mammillary bodies, dense tau immunoreactive inclusions (neurofibrillary tangles, glial tangles and neuropil neurites) and sometimes a TDP-43 proteinopathy [15]. Retrospectively, these findings have been associated with disordered memory and executive functioning, behavioural and personality disturbances (e.g. apathy, depression, irritability, impulsiveness, suicidality), Parkinsonism and, occasionally, motor neuron disease [15]. An increasing media and scientific focus is being placed on the risk of CTE in relation to mTBI history in both civilian and military populations, while its pathogenesis remains poorly understood [12]. If CTE does exist outside of the extreme examples (i.e. hundreds of untreated concussions over a 20 year career) found among professional athletes, it is further unclear whether a single TBI may be enough to begin a degenerative cascade in select individuals or whether a critical number (dose threshold) of TBIs are needed to ‘prime’ the central nervous system for degeneration. Given the absence of case-control studies or existing large, prospective longitudinal datasets, the association between mTBI and early or abnormal neurodegeneration is merely theoretical and the actual risk factors and rate/extent of physiologic and clinical decline over time are unknown [12].

Existing literature limitations

Limitations in the existing scientific literature have prevented firm conclusions about the role of mTBI in long-term health. One crucial and pervasive limitation is the operational definition of mTBI [16]. Existing mTBI studies within military populations (and even many civilian studies) usually rely on retrospective identification of injury and have not adequately addressed the design challenge of valid retrospective mTBI identification. Documentation from early clinical evaluations is often not available and, as Powell et al. [17] demonstrated, even when available, it has poor diagnostic accuracy for mTBI. Military mTBI studies have commonly relied on self-classified concussion or screening instruments [18], such as those mentioned by Hoge et al. [19], which are influenced by other symptoms [20] and have unproven diagnostic accuracy for mTBI. Screening instruments of any type cannot be relied upon without additional diagnostic steps following positive screens. For example, it has been shown that individuals often report illogical or even frankly contradictory responses to alteration of consciousness (AOC) items on TBI screening questionnaires, such as endorsing LOC but denying a memory gap [21]. Unstructured interviews, which could discredit such responses, are limited by the degree of examiner thoroughness, experience, expertise and bias in question formatting and response interpretation. In research settings, using an unstructured interview to diagnose mTBI has the further problems of reproducibility and questionable inter-rater reliability.

The literature commonly assumes that mTBI is a homogeneous condition, but emerging research indicates there is a spectrum of mTBI, with variability of severity and brain areas implicated [22,23]. When studies have addressed mTBI sub-classification, the most common scheme is dichotomizing mTBI into loss of consciousness (LOC) vs no LOC [19,24]. However, LOC is typically defined using self report without considering witness verification, which is the only valid construct for identifying a state that cannot be personally remembered. Additionally, prospective evidence from the athletic concussion population indicates the presence vs absence of post-traumatic amnesia (PTA) is a more important severity demarcation, providing better prediction of short-term deficits on neuropsychological testing [25]. Yet, very few mTBI studies in either military or civilian settings have analysed and reported their data with respect to the presence or absence or duration of PTA.

A range of additional limitations have been noted across the many types of studies addressing the question of late effects of mTBI. Recent systematic reviews of this literature have cited small sample sizes, retrospective design, inadequate comparison groups and/or biased sample selection among existing studies [26]. Additionally, important confounding variables, such as pre-morbid or co-morbid conditions including substance use, alcohol misuse, chronic pain and psychological/emotional problems are not well-controlled [27]. The present CENC multi-centre, prospective observational longitudinal study was designed with the intention of meeting these challenges wherever possible.

Study overall objectives

This CENC longitudinal study of former OEF/OIF combatants aims to establish a comprehensive database to provide needed empirical information on the chronic and late-life effects of mTBI including those that may stem from neurodegeneration. Furthermore, this research aims to identify predictors and pre-clinical evidence of neurodegeneration to assist in prognostication and in the development of neuroprotective therapy. To that end, a comprehensive array of known and hypothesized covariates which may contribute to or mediate mTBI outcomes was proposed and considered for inclusion by the investigative team. This study also solicited and received recommendations on study measures and procedures from several Defense Centres of Excellence (DCOEs) including vision, hearing, epilepsy and pain. In the vetting process for final measures
available resources were considered as well as participant burden, which the authors strove to minimize in order to facilitate enrolment and retention. Thus, efficiency was highly valued and a balance was sought between participant burden, costs and scientific merit.

Study-specific aims

Aim 1
Establish a large cohort of former OEF/OIF combatants and study them longitudinally and comprehensively to evaluate the potential late outcomes of combat-related mTBI including evidence of neurodegeneration with a focus on neurocognitive decline.

Aim 2
Determine whether the mTBI exposed group differs from the unexposed group in outcomes and determine the effects of single vs multiple mTBIs, blast vs blunt TBI and high-grade vs low grade mTBI at baseline (enrollment) and over time.

Aim 3
Identify sub-groups with different levels or patterns of behavioural decline over time suggestive of neurodegeneration, especially that consistent with CTE (Stage 1: poor concentration and headaches; Stage 2: memory problems, depression, poor impulse control and emotional instability; Stage 3: executive dysfunction, cognitive impairment; Stage 4: language difficulties, aggression, and dementia) [28].

Aim 4
Identify biologic variables (e.g. APO E4 carrier, other genotype, cortical thickness changes, disrupted white matter integrity, white matter hyperintensities, altered cerebral blood flow, disrupted functional connectivity, neuroendocrine abnormality, presence or absence of pathology) associated with Aim 3 behavioural patterns to provide converging evidence for neurodegeneration.

Aim 5 (Exploratory, not all sites conducting)
Seek additional electrophysiological evidence of neurodegeneration via association to Aim 3 patterns, clarify functional significance of changes in neurobiological variables through real-time measurement of neural co-ordination and characterize the neurocognitive mechanisms of any impairments demonstrated on performance tasks.

Methods

Participants
The intended population is OEF/OIF era service members and veterans who experienced combat situation(s) and have a spectrum of exposure to mTBI, from none to many. A broad representation from this population is desired, so eligibility criteria (see Table 1) are kept to a minimum and recruitment efforts are expansive. Target sample size is 1100 individuals; ~ 880 participants (80%) with at least one prior mTBI (mTBI exposed) and ~ 220 participants (20%) without any prior mTBI (unexposed).

The sites currently engaged in recruiting and enrolling participants are McGuire VA Medical Center (VAMC) in Richmond, VA, James Haley VAMC in Tampa, FL, South Texas Veterans Health Care System in San Antonio, TX, and Michael DeBakey VAMC in Houston, TX. The first military site approved by the GSC, Fort Belvoir National Intrepid Center of Excellence (NICOE), is scheduled to begin enrolling in the fall of 2016. At each recruitment site, potentially eligible participants are identified by phone contact from persons responding to letters or flyers, clinician or peer referral or in-person contact at veteran/military-centric clinics or gatherings. Such individuals are pre-screened and, if meeting preliminary eligibility, invited to undergo the consent process. Participants, unless on duty hours, receive modest monetary compensation for their travel, time and inconvenience. Procedures are in place and under continued development to promote participant retention throughout the duration of the study.

Longitudinal assessments
Longitudinal assessments occur annually and are of two types, comprehensive in-person evaluations and brief telephone-based evaluations. Comprehensive assessments require ~ 8 hours of participant time and with the option of completing one full day or two half-days. These occur at baseline and, assuming continued funding, on the following anniversaries of the index date (derived from injury or deployment dates; see diagnosis section below): Year 1, 3, 5, 10, 15, 20, 25, etc., every 5 years. Brief telephone assessments require 30–45 minutes of participant time and occur at baseline and all years intervening comprehensive evaluations (i.e. Year 2, 4, 6, 7, 8, 9, 11, 12, 13, 14, 16, etc.). Additionally, a brain donation system is being set-up to allow post-mortem tissue assessment upon death.

Potential concussive events mapping and TBI diagnoses
The accurate determination of each participant’s mTBI exposure history is a cornerstone of this study. The in-depth structured interview process entails identifying all potential lifetime concussive events (PCEs), i.e. PCE mapping, and then assessing each PCE for an mTBI diagnosis. PCE
identification is done using a modification of the Ohio State University TBI Identification (OSU TBI-ID) screening instrument, starting with combat deployment period(s) and then again for all other periods of life. When a PCE is identified, the event immediately is explored through a detailed structured diagnostic TBI interview, the Virginia Commonwealth University retrospective concussion diagnosis interview (VCU rCDI) [29]. The VCU rCDI is based on the DoD/VA common definition of mTBI [30] and a fully structured diagnostic algorithm derived from it has been validated against a consensus rating of five TBI physicians [29]. Versions are being used which are specific to blast [VCU rCDI-blast version (VCU rCDI-B)] and non-blast events [VCU rCDI-general version (VCU rCDI-G)]. Thus, the interview process is layered with CDIs interspersed during PCE mapping and made user-friendly via a web-based data collection application. The programmed diagnostic algorithm derives a preliminary mTBI diagnosis for each CDI.

In addition to the interviews, a comprehensive review of all available medical records takes place. For each CDI, the structured interview data and preliminary algorithm diagnosis are reviewed by a study clinician and vetted against the unstructured free text portion of the interview and against any found medical documents recorded in proximity to the event (i.e. first responder, emergency department or in-theatre documentation). The site PI either confirms the preliminary rating, changes it based on overwhelming evidence to the contrary or refers the event to a central diagnosis committee for review. If baseline evaluation finds any historical TBI that is moderate or severe, the participant is excluded from the study and unenrolled. Barring that, this process which is collectively termed ‘PCE mapping’ results in a definitive mTBI diagnosis labelling (no mTBI vs mTBI (without PTA vs with PTA; blast vs non-blast) for each PCE. The ‘index’ date from which all study re-evaluations are timed longitudinally is also identified through the PCE mapping process. Because the focus of this study is military TBI, the longitudinal index date is the worst mTBI incurred during combat deployment. Alternatively, if deployment-related TBI history is entirely negative, then a pre-defined ‘sham’ index date is identified (self-identified ‘worst’ PCE during combat deployment; if none then midpoint of deployment dates). Figure 1 shows how TBI exposure type is categorized and index date is selected.

**Primary outcome measure and power calculations**

The NIH Toolbox was developed by the NIH Blue Print Initiative for Neuroscience Research to accelerate scientific knowledge by providing a standard set of well validated and non-proprietary measures that represent common currency for use across different health conditions from ages 3–85 [31]. The Toolbox Cognition Battery was designed to capture important cognitive constructs sensitive to the effects of TBI. Test domains are vocabulary and reading (Picture
Vocabulary), executive functions and cognitive flexibility (Dimensional Change Card Sort), inhibitory control and attention (Flanker Inhibitory Control and Attention test), episodic memory (Picture Sequence Memory Test), working memory (List Sorting) and Processing Speed (Pattern Comparisons). This highly efficient computerized assessment battery takes 30 minutes to administer [32]. Of note, a secondary aim of the present study is to cross-validate the Toolbox cognitive domains vs traditional gold-standard neuropsychological tests.

A composite score from the NIH Toolbox Cognition battery was chosen as the primary outcome for the present study because it is more reliable and sensitive than the individual tests. It is continuous with a mean of 100 and standard deviation of 15 and reductions indicate reduced cognitive performance. For power analyses, a clinically meaningful difference was defined as at least 5 points on the composite score (e.g. a 5% difference from the mean of 100 or an effect size of 0.33 on Z-scale).

The planned analyses include a variety of univariate, covariate adjusted and multivariate approaches intended to assess the potential causal effect of mTBI exposure on the various study outcomes; and separately to develop prediction models for neurodegeneration based on mTBI exposure and other covariates. Because limited information is available on the complex relationships of these measures, estimates of power were calculated via t-tests on the primary outcome either between various sub-groups of interest in baseline data (e.g. unexposed vs exposed, exposed to 1 mTBI vs ≥4 mTBIs, ≤5 years since index date vs 10+ years) or among mTBI participants over the anticipated average 2-year follow-up from baseline. Assumptions on the characteristics of the sample were derived from the participating sites’ collective mTBI clinical and research experiences. Specifically, throughout the enrollment period the distribution of mTBI exposures among participants would be: (1) 20% without exposure to any lifetime TBI vs 80% with exposure; (2) of those exposed, 20% with only one mTBI, 50% with 2–3 mTBIs, vs 30% with ≥4 mTBIs; and (3) 33% enrolled within 5 years of index date, 33% between 5–10 years from index date vs 33% over 10 years ago. Lastly, a 10% dropout rate was assumed for longitudinal calculations.

To address all pre-defined study aims, multiple separate power calculations were performed using a 5% level of significance and power of at least 80%. These calculations yielded a sample size of 1100 participants necessary to meet all pre-defined study aims. With a final sample size of 1100 and if assumptions are met, there will be ≥90% (via a two-sided t-test) power to detect a clinically meaningful difference in cognitive performance between unexposed participants and those with at least one mTBI, and at least 80% to detect differences of similar magnitude for the planned sub-group comparisons. Finally, at the 5% level of significance and a within-person correlation of 0.5, one will have over 90% power (via a two-sided paired t-test) to detect clinically meaningful changes in cognitive performance for the anticipated average 2-year follow-up of mTBI participants.

Secondary outcome measures and covariates
A wide array of questionnaires and neuropsychological tests was selected to sample various cognitive and psychological domains. The number of covariates and outcome measures are extensive. In addition to focusing on evidence of CTE, final outcome measures are meant to capture all known and suspected long-term effects of TBI. Given space limitations these measures are presented in concise table format; covariates in Table II and secondary outcome measures in Table III. Most included measures are part of the TBI Common Data Elements (TBI CDEs), to which the reader is referred for further information including references [33]. References are provided within the tables for measures which are not TBI CDEs.

Detailed information on the neuroimaging acquisition protocol and analytic techniques was too lengthy for this manuscript. Briefly, the CENC standard operating procedures and acquisition parameters are intentionally aligned with those utilized by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) studies and other large consortia efforts in TBI (e.g. Transforming Research and Clinical Knowledge in TBI; TRACK-TBI-2) using 3T magnetic resonance imaging (MRI) scanners and sequence parameters designed to be relatively comparable across scanner platforms. Sequences conventionally used for clinical interpretation in TBI and which are consistent with DVBIC recommendations and International TBI CDEs, including 3D T1-weighted, 3D T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences for analysis of volumetrics and quantitative white matter hyperintensity measures, respectively, as well as diffusion tensor imaging (DTI), resting state functional MRI (functional connectivity; fcMRI) and arterial spin labeling (ASL) are collected.

Abnormalities in eye movements (saccades and smooth pursuits)
Tracking of eye position in response to specific visual target movements is done with the Eyelink II, a non-invasive head-mounted eye tracking human–machine interface system [34]. In a recent pilot study, several CENC investigators showed differences between SMs with chronic mTBI and unexposed participants using this system [34]. For this study, an 8 minute EyeLink II protocol was devised with 10 different stimulus tests including challenging sequences to minimize false positive findings due to fatigue/boredom in under-challenged individuals. These tests include horizontal/vertical step changes of amplitudes between 0.3–12.0° and random time spacing, smooth pursuit eye movement (SPEM) tests that include one-dimensional horizontal/vertical sinusoidal tracks (amplitude 10°, 0.25 Hz, 1.0 Hz), circular tracks (10°, 0.3 Hz, 0.5 Hz), figure 8 tracks (x/y = (0.25, 0.5 Hz), (0.5 Hz, 1.0 Hz), (0.75 Hz, 1.5 Hz)) and random two-dimensional SPEMS (slow, fast), memory-guided tasks (repeating a presented stimulus pattern from memory), anti-saccades (performing the opposite movement of the stimulus relative to a vertical centre line) and self-paced saccades (alternating gaze between two stationary targets as fast and as often as possible). Measures being extracted include standard assessment measures used to
Table II. Synopsis of study independent measures and covariates.

| Domain Measure | Health Condition of Interest: PCE and mTBI History and Indexing: OSU-TBI-ID modified x x VCU-tCDI (B & G versions) x – Supplement with DoD or other injury reports if available x n/a Personal Fixed Factor: Demographic: CDC Behavioural Risk x n/a Factor Surveillance System (BRFSS) [43] x Environmental Factor: Educational history: TBI Model Systems Form 1 modified excerpt [38] x n/a Past health history: BRFSS [43] x n/a Genotypes: phlebotomy; TBD testing x x n/a Environmental Factor: Ethnicity: BRFSS [43] x n/a Military branch and length of service: x n/a DVBIC 15 year study [39] x Combat exposure: Deployment Risk and Resiliency Inventory, Version 2, Section D: Combat Experiences (DRRI-2-D) x Social support: DRRI-2-Section O, Post-deployment Social Support Scale (DRRI-2-O) x Disability compensation: VA records and self-report x n/a Modifiable Factor: Alcohol use: Alcohol Use Disorders Test-Consumption (AUDIT-C) x x Substance abuse: Drug Abuse Screening Test 10 item version (DAST10) [44] Effort: Medical Symptom Validity Test (MSVT) x x Symptom exaggeration: mild brain injury atypical symptoms scale (mBIAS) [45] x x Resiliency: TBI Quality-of-Life (TBI-QOL) Resiliency module x x Self-Efficacy: General Self Efficacy (GSE) Scale [46] x n/a Tobacco use: BRFSS [43] x n/a Exercise: BRFSS [43] x n/a Comorbidities: PTSD diagnosis: Mini-International Neuropsychiatric Interview DSM5 version x x PTSD module (MINI) [47] x x PTSD symptom severity: PTSD Checklist for DSM5 (PCL5) [48] x x Depression: Patient Health Questionnaire Depression Scale (PHQ-9) x x Pain: Toolbox numerical scale, TBI-QOL pain interference module x x Headache: Headache Impact Test Short Form (HIT-6) x x Sleep disorder: Pittsburg Sleep Quality Index (PSQI) [49] x n/a Sleep apnea: STOP-BANG questionnaire [50] x n/a Medical conditions (HTN, DM, etc.): BRFSS x n/a Biometrics (BP, HR, Wt) x n/a

TBI CDE, NINDS TBI Common Data Element.

Table III. Secondary outcome measures.

| Domain Description/Measure | Health Condition of Interest: PCE and mTBI History and Indexing: OSU-TBI-ID modified x x VCU-tCDI (B & G versions) x – Supplement with DoD or other injury reports if available x n/a Personal Fixed Factor: Demographic: CDC Behavioural Risk x n/a Factor Surveillance System (BRFSS) [43] x Environmental Factor: Educational history: TBI Model Systems Form 1 modified excerpt [38] x n/a Past health history: BRFSS [43] x n/a Genotypes: phlebotomy; TBD testing x x n/a Environmental Factor: Ethnicity: BRFSS [43] x n/a Military branch and length of service: x n/a DVBIC 15 year study [39] x Combat exposure: Deployment Risk and Resiliency Inventory, Version 2, Section D: Combat Experiences (DRRI-2-D) x Social support: DRRI-2-Section O, Post-deployment Social Support Scale (DRRI-2-O) x Disability compensation: VA records and self-report x n/a Modifiable Factor: Alcohol use: Alcohol Use Disorders Test-Consumption (AUDIT-C) x x Substance abuse: Drug Abuse Screening Test 10 item version (DAST10) [44] Effort: Medical Symptom Validity Test (MSVT) x x Symptom exaggeration: mild brain injury atypical symptoms scale (mBIAS) [45] x x Resiliency: TBI Quality-of-Life (TBI-QOL) Resiliency module x x Self-Efficacy: General Self Efficacy (GSE) Scale [46] x n/a Tobacco use: BRFSS [43] x n/a Exercise: BRFSS [43] x n/a Comorbidities: PTSD diagnosis: Mini-International Neuropsychiatric Interview DSM5 version x x PTSD module (MINI) [47] x x PTSD symptom severity: PTSD Checklist for DSM5 (PCL5) [48] x x Depression: Patient Health Questionnaire Depression Scale (PHQ-9) x x Pain: Toolbox numerical scale, TBI-QOL pain interference module x x Headache: Headache Impact Test Short Form (HIT-6) x x Sleep disorder: Pittsburg Sleep Quality Index (PSQI) [49] x n/a Sleep apnea: STOP-BANG questionnaire [50] x n/a Medical conditions (HTN, DM, etc.): BRFSS x n/a Biometrics (BP, HR, Wt) x n/a

TBI CDE, NINDS TBI Common Data Element.

(Continued)
parameterize eye tracking accuracy as well as generalized quantification approaches of the overlap of target motion and eye movement.

**Electroencephalographic (EEG) measures**

Routine resting EEG is collected for evaluation of potential seizure or other abnormal activity and to assess resting state EEG spectra and connectivity measures for which there is a growing body of literature in mTBI [35]. In addition, event-related potentials (ERPs) will be used to probe neural coordination in real time. Several cross-sectional controlled studies have demonstrated ERP abnormalities in concussed athletes and a series of longitudinal studies of ERPs have identified several components that are abnormal in mild cognitive impairment (MCI) [36]. Because of the sensitivity of ERPs to cognitive decline in dementia and to mTBI, even after symptom resolution, examination of ERPs is likely to provide significant insights into the longitudinal neurocognitive patterns after mTBI and to the functional significance of neurobiological changes. The testing paradigm will measure well-studied ERPs, including the auditory and visual early cortical potentials and P300 (Oddball task) and the N400 and P600 (Semantic memory task) [37].

**Information security and data transfer**

Given the scope and complexity of the data collection requirements and the personal nature of many of the study measures, it is essential to provide a secure and efficient informatics platform. Figure 2 gives an overview of the enrolment process in the context of the informatics and data collection systems used to conduct the study.

Enrolment is initiated using a custom web-application known as the Study Management System (SMS) to record consent status, basic demographics, the Deployment Risk and Resilience Inventory-2 (DRRI-2) Combat Exposure measure and the PCE mapping. The PCE mapping instrument is a custom programmed web-based interview that guides the interviewer and the participant through a series of questions with automated navigation for branch points. Once determined eligible and assigned an exposure category, the system creates participant records in a number of supporting systems, including the NIH assessment centre and the clinical electronic data capture (EDC) system.

Once a participant is determined eligible, the remaining clinical measures are collected using a combination of case report forms, the Assessment Center (a web-based data collection tool for NIH toolbox and related measures) and a series of physiological devices (including electroencephalogram, subjective visual vertical test, computerized dynamic posturography and Eyelink II eye-tracking). Data from these devices are securely uploaded into the CENC data repository where they are tracked and ultimately incorporated into analysis datasets. The collection of biospecimens and completion of the neuroimaging sequence is also tracked within the EDC system and a neuroimaging clinical read is performed using a custom MRI viewer. Common data elements from the MRI review are collected using a web-based instrument in the SMS.

**Data quality and sharing**

A number of complementary techniques are used to ensure the quality of the data. For data entered directly into the web-based systems and for data imported from the physiological devices, real-time validation checks are applied at the time of entry. An overarching tracking system is used to monitor data completeness. Key facets of the data collection process can be monitored in real time using a series of web-based study dashboards. Figure 3 is an example of an interactive dashboard used to monitor the overall recruitment rate, enrolment by site and exposure breakdown. Similar dashboards and reports are used to monitor data completeness and to support the ongoing activities of the data quality committee. The data quality committee includes staff from multiple areas of expertise, including physicians, neuropsychologists, statisticians and data managers. The committee is charged with closely reviewing the data for
errors or inconsistencies, identifying trends and providing feedback to site staff to vet flagged entries and address operational or logistical issues. Feedback from this group informs system updates and adjustments to the overall data collection process.

In concert with data cleaning and quality control activities, data elements are also processed for inclusion in the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. Those based on the NINDS CDEs are already defined within FITBIR. For those instruments and variables that are not yet defined, a further data mapping and processing step will be applied prior to uploading the data into FITBIR on a quarterly basis.

Data security and site logistics

Individual site logistics and data security requirements presented a number of challenges given the complexity of the data collection process and the combination of direct participant data entry (NIH Toolbox), site staff data entry and data transmission from multiple additional devices. Security concerns were addressed both centrally and at a local level and security standards were set to meet the requirements of the most restrictive institution. A detailed security review was conducted on each system. All electronic communication between the systems enforced the latest encryption and transmission protocols. Direct identifiers are not collected for transfer between systems and a detailed risk assessment was completed to determine the risk of re-identification from the non-direct identifiers collected in the data. A site capability assessment was completed by each participating site and used to guide the resolution of logistical issues, which included access to non-VA internet connections, use of appropriate server certificates and data transfer processes.

Results

Because enrolment is incomplete and ongoing, the results presented are limited to a description of the participants enrolled through 1 December 2015 that have been determined eligible and have provided complete data for the demographic and baseline characteristics summarized. To that date, 226 participants consented; of whom 195 have been confirmed as fully eligible and provided sufficient data for summary. Enrolment was discontinued for nine participants because of ineligibility or failure to follow through with the baseline evaluations. One additional participant withdrew after completion of baseline assessments. The remaining 216 participants are still actively enrolled in the study. Screening and enrolment numbers and flow are further depicted in Figure 4.

The demographic characteristics of those actively enrolled at present (as of 1 December 2015) and completed interviews are shown in Table IV, along with a breakdown by mTBI groups of interest. Deployment, PCE and mTBI characteris-
tics are shown in Table V. Overall the median age of the study population is 38 years, 90% of the study population is male, 20% are Hispanic and 22% are African American. Sixty-nine per cent of the study population serve or served in the Army and 89% were enlisted at their last reported rank. Across all study groups, the median years since last deployment and index date are 8 and 9, respectively, median reported PCEs is 5, and median total lifetime mTBIs is 2.

Discusssion

The CENC is a co-ordinated, multi-centre collaboration linking premier basic science, translational, and clinical neuroscience researchers from the VA, military and academia to systematically address the sequelae of mTBI as well as its diagnosis and treatment. While the CENC encompasses multiple distinct studies, this multi-centre, longitudinal, observational study is its centerpiece and was designed to answer questions about the potential long-term effects of mTBI.

The final protocol design of the CENC observational study was influenced by its uniquely large size, its combined VA R&D and DoD funding and the related high level of oversight. There was a desire to harmonize and leverage study methods with existing large federally funded longitudinal TBI epidemiologic studies. Accordingly, the study team worked

<table>
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<th>Non-combat mTBI (only)</th>
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<td>43 (78%)</td>
<td>24 (83%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic or Latino</td>
<td>39 (20%)</td>
<td>19 (20%)</td>
<td>12 (22%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know/Not sure</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Race</td>
<td>African American</td>
<td>42 (22%)</td>
<td>20 (21%)</td>
<td>14 (25%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>125 (64%)</td>
<td>62 (66%)</td>
<td>30 (55%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>28 (14%)</td>
<td>12 (13%)</td>
<td>11 (20%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>126 (65%)</td>
<td>65 (69%)</td>
<td>33 (60%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td></td>
<td>Single/Divorced/Other</td>
<td>69 (35%)</td>
<td>29 (31%)</td>
<td>22 (40%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>Service branch</td>
<td>Air Force</td>
<td>12 (6%)</td>
<td>2 (2%)</td>
<td>3 (5%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td></td>
<td>Army</td>
<td>135 (69%)</td>
<td>65 (69%)</td>
<td>40 (73%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td></td>
<td>Marines</td>
<td>36 (18%)</td>
<td>20 (21%)</td>
<td>11 (20%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td></td>
<td>Navy</td>
<td>12 (6%)</td>
<td>7 (7%)</td>
<td>1 (2%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Last rank</td>
<td>Enlisted</td>
<td>174 (89%)</td>
<td>86 (91%)</td>
<td>50 (91%)</td>
<td>24 (83%)</td>
</tr>
<tr>
<td></td>
<td>Officer</td>
<td>21 (11%)</td>
<td>8 (9%)</td>
<td>5 (9%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Highest education</td>
<td>≤ HS</td>
<td>32 (16%)</td>
<td>19 (20%)</td>
<td>9 (16%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td></td>
<td>&gt; HS</td>
<td>163 (84%)</td>
<td>75 (80%)</td>
<td>46 (84%)</td>
<td>26 (90%)</td>
</tr>
</tbody>
</table>

Table V. Combat history and mTBI exposures across mTBI groups (Median [IQR]).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 195)</th>
<th>Combat + Non-combat mTBI (n = 94)</th>
<th>Combat mTBI (n = 55)</th>
<th>Non-combat mTBI (n = 29)</th>
<th>No TBI (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combat deployment</td>
<td>2 [1,3]</td>
<td>2 [1,3]</td>
<td>2 [1,2]</td>
<td>2 [1,2]</td>
<td>2 [1,3]</td>
</tr>
<tr>
<td>Years since last deployment</td>
<td>8 [5,10]</td>
<td>7 [5,10]</td>
<td>8 [5,9]</td>
<td>9 [6,11]</td>
<td>7 [6,9]</td>
</tr>
<tr>
<td>Non-combat PCE</td>
<td>2 [1,4]</td>
<td>3 [2,4]</td>
<td>1 [0,2]</td>
<td>3 [2,4]</td>
<td>1 [1,2]</td>
</tr>
<tr>
<td>Deployed controlled detonations</td>
<td>5 [0,30]</td>
<td>6 [1,50]</td>
<td>5 [0,17]</td>
<td>3 [0,20]</td>
<td>10 [0,30]</td>
</tr>
<tr>
<td>Non-deployed controlled detonations</td>
<td>0 [0,10]</td>
<td>3 [0,40]</td>
<td>0 [0,10]</td>
<td>0 [0,6]</td>
<td>1 [0,10]</td>
</tr>
<tr>
<td>Total mTBI</td>
<td>2 [1,3]</td>
<td>3 [3,4]</td>
<td>1 [1,2]</td>
<td>2 [1,2]</td>
<td>0 [0,0]</td>
</tr>
<tr>
<td>Blast mTBI</td>
<td>1 [0,1]</td>
<td>1 [0,2]</td>
<td>1 [1,1]</td>
<td>0 [0,0]</td>
<td>0 [0,0]</td>
</tr>
<tr>
<td>Non-blast mTBI</td>
<td>2 [0,3]</td>
<td>2 [2,3]</td>
<td>0 [0,1]</td>
<td>2 [1,2]</td>
<td>0 [0,0]</td>
</tr>
<tr>
<td>mTBI w/PTA</td>
<td>1 [1,2]</td>
<td>2 [1,3]</td>
<td>1 [1,1]</td>
<td>1 [1,2]</td>
<td>0 [0,0]</td>
</tr>
<tr>
<td>mTBI w/o PTA</td>
<td>1 [0,2]</td>
<td>2 [1,2]</td>
<td>1 [0,1]</td>
<td>1 [0,1]</td>
<td>0 [0,0]</td>
</tr>
</tbody>
</table>
closely with NIDILRR TBI Model Systems [38], the Defense and Veterans Brain Injury Centre (DVBIC)'s 15 year mTBI Study [39] and the existing VA and DoD PTSD consortiums to match measures and study procedures when possible. Because specific study aims and target populations differ across these federal research programmes, full concordance was not possible. Some unique measures were chosen, some common measures were modified and some were excluded entirely or replaced with an alternative if of questionable value to the main study aims and/or added excessive participant burden. Another stipulation was the migration of study data into the fairly new Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system for later scientific analyses by non-consortium investigators [40]. Thus, the team placed an emphasis on use of NIH TBI CDEs [33] which would facilitate FITBIR compatibility.

As noted earlier, prior studies have been limited by imprecise and varied methods of identifying and quantifying PCEs and actual mTBI diagnoses. Thus, in a final protocol a fairly large portion of participant time and effort is spent on comprehensive interview of lifetime PCEs and mTBI history. Additionally, because neurocognitive impairment is considered the key outcome, a very large proportion of evaluation time is devoted to neuropsychological testing. This comprehensive battery has some redundancy, specifically the battery of traditional neuropsychological tests vis-à-vis the domains tested in the NIH Toolbox Cognition battery. This redundancy is intentional given the secondary aim of cross validating the Toolbox. Relatedly, as the study progresses the plan is plan to eliminate traditional tests that correlate highly and have high diagnostic accuracy against corresponding Toolbox domains which will reduce longitudinal participant burden and further facilitate retention.

With four geographically diverse enrolment sites, standardization of all procedures was paramount. Extensive time and effort has been expended in this area, including extensive scripts, operational definitions and manualized operational procedures. This has been reinforced with in-person training, a certification process for test administrators, site visits from the lead centre (VCU) and data/co-ordinating centre (RTI), as well as ongoing audits and weekly conference calls. To maximize standardization of the most important independent variable, mTBI, this study is utilizing a recently published highly structured retrospective mTBI diagnostic interview. The VCU rCDI-B is a combination unstructured and fully structured interview designed to affirm the presence of a blast-associated mTBI, either with or without PTA [29]. Using this tool in addition to a prognostic classification of ‘with PTA’ vs ‘without PTA’, several CENC investigators have recently demonstrated measureable persisting cognitive (Under Review) and postural balance [41] deficits 7–9 months on average after ‘blast-mTBI with PTA’ in comparison to blast exposure with no mTBI and/or mTBI without PTA.

During the CENC observational study beta phase of early enrolments, the initial lifetime PCE and associated TBI diagnostic interview were found cumbersome for study staff and exhausting for some participants. Thus, this process was shortened and revised to improve scripts and flow while retaining all necessary elements for the diagnosis algorithm. This change was well received by staff and better tolerated by participants with very minimal compromise of depth of information obtained. These and other minor protocol and process revisions facilitated traction in study enrolment which has been proceeding smoothly since.

Recruitment efforts during the beta phase centred on the VA Polytrauma clinic population using a combination of direct in-person recruitment by research staff present in the clinic area, clinician referrals and advertising materials in the clinic. This produced good early enrolment volume as can be seen by the current sample size less than 1 year into study procedures, but led to a lower than intended proportion of unexposed participants with an entirely negative lifetime history of mTBI (9% actual vs 20% desired). This was in large part because, among the 46 participants without exposure to combat mTBI, most (n = 29, 63%) were positive for mTBI outside of deployment. At an overall rate of 65%, the prevalence of non-combat mTBI(s) so far in this study was higher than expected. Accordingly, recruitment efforts have been adjusted with greater emphasis on outreach beyond the clinic population and into the intended broader population of current and past military personnel who were deployed in OEF/OIF and exposed to combat situations. As of 1 December 2015, this was a work in progress, with tempo dictated by IRB approvals and staffing adjustments. Two sites have instituted letter mailings to all persons registered at their local VAMC and designated as having deployed in OEF/OIF and have gotten a good initial response including unexposed individuals. The study team is seeking Institutional Review Board (IRB) approval to institute this approach at the other sites. All sites are at various stages of indirect recruiting with in-services and brochures at non-Polytrauma clinics such as Primary Care as well as various military service organizations and college campuses, as well as general social media avenues.

Participant retention is equally important because inadequate retention will not only limit the power of future longitudinal analyses but also add another layer of potential sample selection bias. An early commitment was made to include reimbursement for participant time and effort into the budgets. While many of the research participants are primarily altruistic volunteers (e.g. to help military comrades), financial incentives are known to improve longitudinal study retention rates [42]. This study collaborated with IRBs to identify monetary amounts that are fair but not coercive, and travel expenses up to a maximum are being reimbursed. The authors are still in the process of developing other general retention strategies. To date, token logo gifts have been acquired to be mailed out with holiday cards and birthday card, and a participant newsletter has been designed that will be mailed out semi-annually. In concert with retention best practices literature, additional strategies are being developed with near-term implementation likely. Regardless, the plan is to continuously monitor attrition and adjust the enrolment goal upward if an early trajectory that threatens the long-term 90% retention goal is seen.
Conclusion
The CENC Observational Study Team is well underway in enrolling participants into this large scale, multi-centre, longitudinal study that aims to comprehensively assess mTBI outcomes, outcome mediators and potential complications including CTE. This study appears to be on track to reach the target of at least 1100 participants by 2019. The early enrollment group of 195 participants included 24% who were negative for combat mTBI and 9% with an entirely negative lifetime history of mTBI. Recruitment efforts have been adjusted with greater emphasis on outreach beyond the clinic population. While some exploratory analyses will be conducted over the next few years, complete cross-sectional analyses will take place upon closure of enrolments. Some preliminary longitudinal analyses will be done by 2019, but complete longitudinal analyses will be deferred to more remote future dates (consistent with the concept of ‘late effects’) and will depend on continued funding.

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Declaration of interest
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References