# Design of "Neuropsychological and Mental Health Outcomes of Operation Iraqi Freedom: A Longitudinal Cohort Study"

*Mihaela Aslan, PhD,*† John Concato, MD, MS, MPH,*† Peter N. Peduzzi, PhD,‡ Susan P. Proctor, DSc,§||¶ Paula P. Schnurr, PhD,**†† Brian P. Marx, PhD,‡‡§§ Miles McFall, PhD,||||¶¶ Theresa Gleason, PhD,*** Grant D. Huang, PhD,*** and Jennifer J. Vasterling, PhD‡‡§§*

**Objective:** This study aimed to describe methodological challenges encountered in designing a follow-up assessment of US Army Soldiers who served in Operation Iraqi Freedom.

**Study Design and Setting:** The Neurocognition Deployment Health Study (NDHS) enrolled 1595 soldiers at 2 military installations, starting in 2003. Prior work compared predeployment and postdeployment assessments among Iraq-deployed and nondeployed soldiers. The current phase, as VA Cooperative Studies Program #566, is collecting follow-up data on participants who were deployed to Iraq or Afghanistan. Specific aims include evaluating the prevalence and course of posttraumatic stress disorder (PTSD), the persistence of previously observed neuropsychological changes, and the relationship of these changes—and traumatic brain injury—to subsequent PTSD. The target sample size is 817 participants, with 200 participants also receiving performance-based neuropsychological assessments.

**Results:** We describe 6 methodological challenges and their implications for longitudinal research among a "closed," young, mobile study population: transitioning from cluster-based (battalion) sampling to individual-level sampling; overcoming practical barriers (such as location searches); selecting exposure and outcome measures that combine previously collected and current study data; accounting for loss of an exposed (deployed) versus (nonexposed) nondeployed comparison; determining timing of assessments; and developing a complex statistical analysis plan. Enrollment is ongoing.

**Conclusions:** The study provides unique insights regarding elements of study design and analysis that are relevant to longitudinal research. In particular, the dynamic "real-life" context of military deployment provides a basis for applying observational methodology to characterize mental health disorders associated with exposure to war-zone deployment and other contexts associated with exposure to extreme stress.

**Key Words:** posttraumatic stress disorders, brain injuries, traumatic, neuropsychological tests, closed cohort studies, methods

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Since 2001, more than 2 million US troops have been involved in operational military deployments to Iraq or Afghanistan.[1] Advances in battlefield medicine have improved survival among soldiers injured in these recent conflicts, but high rates of nonfatal injuries are seen among returning war-zone survivors, including traumatic orthopedic injury and traumatic brain injury (TBI).[2] Whereas physical injuries are readily apparent, psychiatric symptoms have been referred to as the "invisible injuries of war."[3] In particular, neuropsychological impairment (eg, attention and memory deficits) may negatively affect day-to-day functioning and general well-being, and functional impairment could potentially increase if symptoms become more chronic. These health-related impacts, as seen in the aftermath of previous wars,[4] constitute a significant public health problem if prevalent and persistent, and not addressed. Unfortunately, efforts to understand such effects are limited by the ability to obtain adequate baseline data before exposures.

Although mental health and, to a lesser extent, neuropsychological functioning have commonly been evaluated after war-zone deployment, assessing the status of military veterans in relation to their own predeployment functioning is more challenging but potentially more informative. Identifying specific outcomes of military deployment that could negatively impact occupational and psychosocial functioning—especially in a predominantly young population transitioning from active military duty to civilian life—is of particular relevance to informing healthcare needs and policy.

As an interagency collaboration between the Departments of Defense and Veterans Affairs (VA), the Neurocognition Deployment Health Study (NDHS) previously examined[5] performance-based neuropsychological and subjective psychological outcomes of Army Soldiers deployed in support of Operation Iraqi Freedom (OIF). An initial phase of the NDHS, launched in April 2003, collected data on soldiers prospectively during both predeployment (baseline) as well as short-term postdeployment to Iraq (typically within 2 to 6 months after return from the war) periods. As an additional design feature, the NDHS had a comparison sample of soldiers who had not (yet) deployed overseas, but had military characteristics similar to those deployed and were assessed in sessions timed as close as possible to those deployed. A smaller, secondary component of the NDHS assessed Iraq-deployed participants again 1-year after their short-term postdeployment assessment.

From the *Clinical Epidemiology Research Center, VA Connecticut Healthcare System, West Haven; †Department of Medicine, Yale University School of Medicine; ‡Yale Center for Analytical Sciences and Yale School of Public Health, Yale University, New Haven, CT; §Department of Environmental Health, Boston University School of Public Health; ||Research Service, VA Boston Healthcare System, Boston; ¶United States Army Research Institute of Environmental Medicine, Natick, MA; **Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, NH; ††VA National Center for Post-Traumatic Stress Disorder (PTSD), White River Junction VA Medical Center, White River Junction, VT; ‡‡Department of Psychiatry, Boston University School of Medicine; §§Psychology Service and National Center for PTSD, VA Boston Healthcare System, Boston, MA; ||||Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine; ¶¶VA Puget Sound Healthcare System, Seattle, WA; ***Office of Research & Development, U.S. Department of Veterans Affairs, NW, Washington, DC.

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Reprints: Mihaela Aslan, PhD, Clinical Epidemiology Research Center, VA Connecticut Healthcare System, 950 Campbell Ave, Mailcode 151B, West Haven, CT 06516. E-mail: mihaela.aslan@va.gov.

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"VA Cooperative Study Program (CSP) Study #566: Neuropsychological and Mental Health Outcomes of Operation Iraqi Freedom: A Longitudinal Cohort Study" is the current phase of the NDHS,[6] designed to examine long-term, war-related, mental health, and neuropsychological function, taking into account data yielded by prior assessments, including pre-deployment evaluation of the same participants. Whereas longitudinal studies often face difficulties related to recruitment and follow-up, this particular study also faced additional methodological challenges related to a population that is young and mobile, and has an occupational priority that may limit availability for research participation.

The study is collecting new data at least 5 years after each soldier's return from their first OIF deployment; these data will be analyzed with previously collected NDHS data. Figure 1 summarizes the conceptual model underlying the study. It shows the potential influence of war-zone psychological trauma and other risk and protective factors (eg,, subsequent life stress and social support) on the course of stress-related emotional symptoms, and also emphasizes neuropsychological alterations associated with prolonged psychobiological responses to life threats.

The overarching goal of the current study is to use longitudinal methods to examine long-term mental health, in particular posttraumatic stress disorder (PTSD) and neuropsychological outcomes—taking into account previous levels of functioning, including those observed before war-zone deployment, as well as a range of risk and resilience factors. Unlike other longitudinal cohort studies, the present study is distinctive in the mobility and occupational characteristics that define membership in the study population. In applying a longitudinal framework designed around deployment, CSP #566 is characterized by a novel combination of 3 methodological features: (1) incorporation of archived data from initial assessments timed to occur before and after a specific referent deployment, which for most of the participants was their very first; (2) the administration of performance-based neuropsychological tests and structured psychiatric interviews in the context of a relatively large, epidemiological sample; and (3) the inclusion of participants who served in regular active duty and activated national guard capacities.

This report describes the design of the ongoing study, and discusses specific methodological challenges encountered, and corresponding decisions made, during its planning.

## MATERIALS AND METHODS

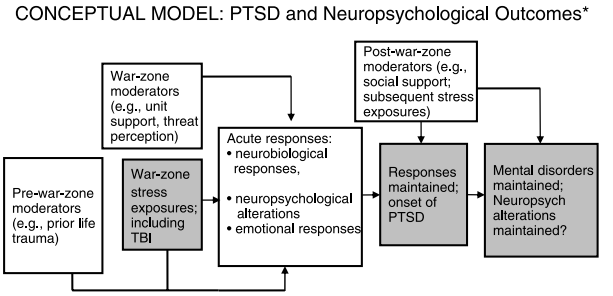
In recognition of a nationally dispersed but "closed cohort" sample, the current study is being conducted at 2 geographically distant VA Healthcare Systems (Boston and Puget Sound) to facilitate broader temporal availability of participant appointments. In addition, selected aspects of the study are conducted within the participants' communities by a "travel team" (described subsequently).

Developing a protocol for the current study involved conceptualizing a basic study design, while also developing a sampling strategy, anticipating participant recruitment, selecting measures and instruments, and refining an analytic plan that had to account for unique characteristics of the sample. As the study protocol evolved, specific methodological and pragmatic challenges were encountered; these issues represent fundamental considerations to be addressed using principles of clinical epidemiology and biostatistics. Considering both science and feasibility, decisions were made regarding how to transition from a cluster-sampling strategy to an individual-sampling strategy, maximize enrollment of the source population, address the reality that any nondeployed soldiers would likely have characteristics affecting cause-effect associations of interest, reconcile timing of assessments with important nonmilitary life events, and provide a framework for analyses (including power calculations). These considerations are described in more detail in subsequent sections, under selected headings, and are listed in Table 1.

### Participants

The current project has a priori eligibility criteria limited to only those NDHS participants who had an occupation-specific experience involving deployment at least once to Iraq and who gave permission to be contacted for subsequent research. Two modes of assessment are used, namely, phone-based interviews and written survey-based assessment of all eligible participants; and in-person, performance-based, neuropsychological assessment of a smaller, randomly selected subset of these participants.

Among the 1595 participants enrolled previously in the NDHS, 1321 surviving participants had consented to be contacted for follow-up studies; an additional participant who had not given such permission later provided consent after hearing about the current study. On the basis of tracking data from the Defense Manpower Data Center, we estimated that 1149 (87%) soldiers would likely have been deployed to Iraq at the initiation of the current study. Using prior experience and the existing literature regarding locating, contacting, and enrolling participants, we projected that approximately 70% of those deployed (n = 817 participants), as a full sample receiving the core assessment battery, would be contacted and agree to




*The model does not reflect all pertinent outcomes, nor specify the full set of variables that may moderate the relationship between war-zone stress exposure and emotional outcomes.

Shaded boxes depict the war-zone exposures and the primary outcomes of interest (PTSD and neuropsychological functioning).

PTSD = posttraumatic stress disorder; TBI = traumatic brain injury.

**FIGURE 1.** Conceptual model showing PTSD, mental health disorders, and neuropsychological outcomes.

**TABLE 1.** Methodological Challenges, Organized According to General Categories of Patient-Oriented Research (in Order of Discussion in the Text)

| |
|---|
| Participants |
| • Transitioning from cluster-based (battalion) sampling to individual-level sampling |
| • Overcoming barriers related to: location searches, preliminary contact, assessment of eligibility and willingness to participate, scheduling, and study participation |
| Exposure and outcome |
| • Selecting appropriate exposure and outcome measures, considering both previously collected data and current study objectives |
| Modified study design |
| • Conceptualizing hypotheses and analytic plans that account for the loss of an exposed (deployed) versus (nonexposed) nondeployed comparison |
| • Determining the timing of assessments relative to important life events, including deployments subsequent to the index deployment |
| Analysis |
| • Developing a statistical analysis plan that accounts for substantial complexity of the project |

receive phone-administered structured clinical interviews and mail-administered (paper-and-pencil) psychometric instruments. We also planned to enroll a subsample of 200 of these participants to receive face-to-face, individually administered, performance-based neuropsychological testing and relevant health variables.

The NDHS was designed originally to include both regular active duty and activated Army National Guard Soldiers, whether male or female, who were "combat ready" to deploy to Iraq and who served in military units representing a range of operationalfunctions, including combat arms (eg, infantry and artillery), combat support (eg, transport and equipment maintenance), and combat service support (eg, supply and medical support). For the current study, NDHS participants with sensory-motor loss sufficiently profound to preclude meaningful participation in the study are excluded. In addition, NDHS participants who did not deploy to Iraq are excluded, given that nondeployment within the timeframe of the study may reflect factors (eg, active physical or mental health issues) that would possibly influence measured outcomes. Two additional exclusion criteria are applied to participants in the neuropsychological subsample: participants who did not complete both predeployment and short-term postdeployment neuropsychological assessment components; and participants who scored below a previously established cut-off criterion for error on a cognitive effort test (during prior NDHS assessments or during the proposed neuropsychological subsample assessment session).[7]

Given that approximately 5 years have elapsed already since the end of the initial NDHS phase, many of the surviving 1321 participants will likely have moved, as soldiers often change duty stations and some would have transitioned into veteran status. Accordingly, as *a first methodological challenge, the current study represents a transition from a cluster-sampling strategy, based on selection of participants according to their military unit assignments in the initial phase of NDHS, to individual-level sampling*. Specifically, attempts are being made to contact all surviving participants, in sequential waves of up to 200 (with 7 total waves), by selecting individuals through a stratified random sampling mechanism based on initial battalion-level strata. Statistical analyses, to be discussed, will account for battalion level, time-interval from original NDHS deployment, and military operation specialty (MOS). As a prominent methodological feature of the study, many soldiers were deployed more than once, either to Afghanistan (in Operation Enduring Freedom [OEF]) or Iraq (in OIF or in Operation New Dawn [OND]). Accordingly, a detailed military history is being obtained for inclusion in analyses.

In parallel with a general approach to sampling, the *practical aspect of location searches, preliminary contact, assessment of eligibility and willingness to participate, scheduling, and actual study participation represent a second methodological challenge*. To promote a steady-state workload for enrollment, potential participants are contacted in sequential waves of several months each. Because of uncertainty regarding actual recruitment and eligibility rates, all participants in the first several waves are being offered enrollment in the neuropsychological subsample. Random selection will be used for sampling in later waves, if recruitment appears to be substantially over-enrolling participants in the substudy.

Eligible potential participants (who gave prior permission to be recontacted) are contacted to determine their willingness to participate in the current study. Regarding the full sample, the study obtained a waiver of documentation of written informed consent from the VA Central Institutional Review Board that allows for a verbal consent process to participate in the study. After obtaining informed consent via telephone, each participant receives a self-report questionnaire by mail to be completed (taking an estimated 2 to 3 hours) and returned by mail.

Neuropsychological subsample eligible participants are further scheduled for a session involving a face-to-face interview and neuropsychological assessment (estimated 2 to 3 hours). Written informed consent is obtained in person at the time of the face-to-face interview. As a practical and cost-effective aspect of the study, a travel team—consisting of research staff based at either the Boston or Seattle site locations—was organized to visit communities close to participants' homes to conduct the face-to-face portion of the protocol, if travel to Boston or Seattle was not desired by the participant.

Participants are compensated for their time and effort $200 after participating in the full sample, and an additional $200 after participating in the subsample. The amounts of compensation were selected to account for "opportunity costs" associated with a relatively young participant sample.

Summary results (only) of the study will be made available to participants after publication of the primary manuscript describing the project. Individual results of both the psychosocial assessment and neuropsychological testing may be releasable at that time, if requested by a participant. Results would be provided in the form of individual summary test scores and normative information (as available), and will be guided by a study staff member to minimize the possibility of misinterpretation.

Another challenge for the current study is the fixed number of soldiers with predeployment data. Although recruiting from a "closed cohort" is not novel, NDHS participants were predominantly young and highly mobile regular active duty and activated reservist soldiers, many of whom subsequently became highly mobile veterans. Accordingly, success in locating potential participants is a key element of study feasibility. Several tiers of information to locate participants are being used, such as existing NDHS locator information, credit bureau database searches contracted through a professional survey corporation, and federal database information contracted through the Veterans Health Administration. For current military service members, we are also using the Defense Manpower Data Center

unit identification codes, Army databases, and Army Knowledge Online telephone and email information.

In prior engagement of participants in earlier phases of the NDHS, all NDHS participants would have previously received a study newsletter. As part of the current study, new (annual) newsletters are developed to keep participants informed and engaged, and possibly enhance enrollment by word-of-mouth to other eligible participants. During the proposed funding period, greeting cards are being sent annually to participants on Veterans Day and Memorial Day. Also, a small token of appreciation (eg, pen) with the NDHS logo is mailed to potential participants during the recruitment process, to acknowledge their previous contributions to the NDHS. T-shirts and leatherette tumblers with the study logo are also provided to participants after they complete the questionnaires/interviews and neuropsychological substudy, respectively.

## Exposure and Outcome Variables

Table 2 describes exposure and outcome measures in the study, including PTSD measures, neuropsychological measures, potential TBI exposures, and assessments of depression, anxiety, and functional as well as occupational activities. Additional measures focus on deployment stress exposure, postdeployment stress exposure, and modifiable risk or protective factors. As

**TABLE 2.** Study Exposure and Outcome Measures

| Measure | Construct | Administration |
|---|---|---|
| PTSD measures | | |
| CAPS | PTSD diagnosis | Phone interview |
| PCL | PTSD symptom severity; clinical threshold | Self-report survey |
| NES3-CPT | Attention | Face-to-face, computer-assisted |
| ANAM Simple RT | Behavioral responsivity (reaction time) | Face-to-face, computer-assisted |
| WMS VR | Visual memory | Face-to-face, performance-based |
| WMS-III VPA | Verbal learning | Face-to-face performance-based |
| Head injury exposure | | |
| TBI from baseline to short-term postdeployment | Deployment TBI | Interview* |
| Depression | | |
| MINI Mood Disorders Modules | Major depressive disorder | Phone interview |
| CES-D | Depression severity | Self-report survey |
| Anxiety | | |
| MINI Panic Disorder Module | Panic disorder | Phone interview |
| DASS | Anxiety severity | Self-report survey |
| Functional activities | | |
| VR12 | Health-related functioning | Self-report survey |
| MOS-CF | Cognitive functional impact | Self-report survey |
| Occupational | | |
| HPQ Work Appraisal | Occupational functioning | Self-report survey |
| Employment Status | Objective index of occupational functioning | Self-report survey |
| HPQ Relative Absenteeism (modified) | Objective index of occupational functioning | Self-report |
| Stress exposures | | |
| DRRI Early Life Events | Pre-war-zone exposure to stressful life events | Self-report survey |
| DRRI Combat Experiences | War-zone combat exposure during deployment | Self-report* |
| DRRI Post-Battle Experiences | War-zone events other than direct combat during deployment | Self-report* |
| DRRI Deployment Concerns | Perceived war-zone threat during deployment | Self-report* |
| DRRI Life and Family Concerns | Homefront stressors while deployment | Self-report* |
| DRRI Post-Life Events | Postdeployment exposure to stressful life events | Self-report |
| DRRI Postdeployment Support | Postdeployment social support | Self-report |
| DRRI Unit Support | Perceived unit cohesion | Self-report |

*Will only be administered if participant has been deployed subsequently to the initial deployment or if exposure data were not gathered previously as part of the NDHS.

ANAM indicates Automated Neuropsychological Assessment Metric; CES-D, Center for Epidemiological Studies Depression Inventory; CPT, Continuous Performance Test; DASS, Depression Anxiety Stress Scales; MCS, Mental Component Score; MDD, major depressive disorder; MINI, Mini-International Neuropsychiatric Interview; MOS-CF, Medical Outcomes Study, Cognitive Functioning; NES3, Neurobehavioral Evaluation System, third ed; PCS, physical component score; RT, reaction time; SF-12v, Short-Form Health Survey, Veterans Version; VR, visual reproductions; VPA, Verbal Paired Associates; WMS, Wechsler Memory Scale; WMS-III, Wechsler Memory Scale, third rev; baseline, NDHS predeployment assessment (for participants who were in military units that did not deploy between the first 2 unit-based assessments in the NDHS, the first assessment will serve as baseline); short-term postdeployment, short-term NDHS postdeployment assessment (typically within 90 days post-return from initial Iraq deployment) for original "deployed" sample; long-term postdeployment, proposed new CSP #566 long-term follow-up assessment (more than 5 years post-return from initial Iraq deployment) for original "nondeployed sample" (for participants with multiple Iraq deployments, this assessment follows the first Iraq deployment).

*a third methodological challenge, selecting appropriate exposure and outcome measures—balancing previously collected data with current needs—involved using clinical and methodological judgment*.

Much remains unknown about the longer-term course of war-related mental disorders, including the relative proportions of war-zone veterans who remain healthy, the proportion of those who develop chronic or recurrent mental disorders, and how many develop emotional symptoms but subsequently recover. Prior NDHS work[7] reports that a sizable subset (approximately 10%) of military personnel reported significant predeployment, stress-related symptoms, as measured by the PTSD symptom severity checklist (PCL), civilian version.[8] As such, analyses incorporating NDHS predeployment data, and examining clinically significant PTSD as an outcome, will use the PCL as a screening measure of clinically significant PTSD due to its availability at predeployment. In addition, PTSD diagnosis will be derived from diagnostic summary scores from the Clinician Administered PTSD Scale (CAPS).[9,10] Ideally, the CAPS would be used for such analyses, but because of severe constraints on assessment time and the scientific focus of the earlier stages of the NDHS on neuropsychological functioning, administering the CAPS was not feasible before deployment. Because of their frequent co-occurrence (comorbidity) with PTSD and their relevance to appropriate clinical management, major depressive disorder, panic disorder, dysthymia, agoraphobia, and generalized anxiety disorder will also be screened using appropriate modules of the Mini-International Neuropsychiatric Interview.[11] Depression severity will also be assessed using the Center for Epidemiological Studies Depression Inventory self-report survey,[12,13] whereas anxiety severity will be assessed using the Depression Anxiety Stress Scales self-report survey.[14]

Scientific findings from preliminary NDHS work[7] show that Iraq deployment was associated with a pattern of neuropsychological outcomes (eg, reaction time, sustained attention, verbal learning, and visual-spatial memory) distinct from those associated with nondeployment. Thus for the current study, we selected neuropsychological variables for which the initial predeployment and postdeployment NDHS analyses demonstrated particular sensitivity to deployment. These variables include the Neurobehavioral Evaluation System, third revision (NES3[15]) Continuous Performance Test, total errors (attention), the Automated Neuropsychological Assessment Metric (ANAM[16]) Simple Reaction Time (RT) throughput scores (behavioral responsivity), the Wechsler Memory Scale (WMS[17]) Visual Reproductions (VR) percent retention (visual-spatial memory), and the Wechsler Memory Scale, third revision (WMS-III[18]) Verbal Paired Associates total correct (verbal-auditory learning).

Objective indicators of early mental compromise are important tools in identifying returning war-zone veterans at elevated risk for subsequent mental health problems. A particular risk of contemporary war-zone participation is brain compromise, whether from direct exogenous insult (eg, TBI) or associated with a neurobiological stress response. Thus, history of TBI will be captured with interview-based data available from postdeployment NDHS data collection. We will code any head injury that was self-reported to occur between predeployment and short-term postdeployment and that was also associated with alteration or loss of consciousness. The TBI interview questions were derived from those used by the Defense and Veterans Brain Injury Center. These basic questions will be supplemented by detailed questions (eg, injury-related symptoms and duration) in the current study inquiring about (up to) 5 significant head injuries in subsequent deployments. Both the original questionnaire and the modifications reflect current classification standards[19] and empirically derived indicators (eg, duration of posttraumatic amnesia) of brain injury severity.[20,21]

Although associations between functional outcomes and disorders of extreme stress (eg, those related to military combat) have been documented, limited knowledge exists regarding the long-term impact of stress-related emotional disorders (eg, neuropsychological and PTSD outcomes) on occupational and health functioning. Occupational functioning outcomes will be measured with a self-appraisal measure, the 10-part item from the World Health Organization Health and Work Performance Questionnaire (HPQ[22]), as well as measures of current employment status and absenteeism during the past month, queried through survey questions and HPQ absenteeism questions, respectively. The self-appraised impact of somatic, emotional, and cognitive problems on basic components of day-to-day functioning (eg, "accomplishing less than usual") relevant to occupational performance will be measured with the Veterans RAND 12-item Health Survey (VR12[23]), adapted for use in military Veterans (SF 12-V), and the Medical Outcomes Study Cognitive Scale (MOS-CF[24]).

Stress exposures ranging from one's early (pre–war-zone) life events, the impact of distressing or uncomfortable living conditions, perceptions of threat in the war zone and combat-related experiences from contemporary wars, to concerns about life and family disruptions and postdeployment life events, as well as modifiable protective factors such as predeployment unit cohesion and postdeployment social support may have implications for veterans' long-term well-being. Stress exposures will be measured with the Deployment Risk and Resilience Inventory (DRRI[25]), a modular inventory with strong psychometric properties that was developed after the 1991 Gulf War to capture events common to contemporary war-zone deployment and with demonstrated implications for veterans' long-term health. DRRI modules include Early Life Events, Combat and Post-battle Experiences, Deployment Concerns and Life and Family Concerns, Post-Deployment Life Events, Unit Support, and Post-Deployment Support.

Although data were collected for a subset of NDHS participants who remained within the same military unit 1-year after the original postdeployment assessment—representing a follow-up for the original study—a decision was made not to include such data as part of the main protocol, given incomplete sampling of the larger population. The data are available, however, for checks of consistency regarding self-report responses relevant to invariant factors (eg, certain demographic and historical information), as applicable.

## Links to Prior NDHS Design

Components from both the initial and current (CSP #566) phases of the NDHS are depicted in Figure 2; ongoing data collection for the current study is shaded. A new framework was adopted to describe the sequence of encounters for each participant: predeployment; within 90-day postdeployment; and at least 5-year postdeployment. (As mentioned previously, a 1-year follow-up in the original NDHS is not included in the main study design.)

During the planning process for the current study, it was evident that most "original" (initial phase) NDHS participants had been deployed already to Iraq. As suggested by preliminary analyses of available archived data from the NDHS, many soldiers who did not deploy could be hypothesized to differ on critical health-related characteristics from those who did (ie, the "healthy warrior effect"). Accordingly, for the purposes of the

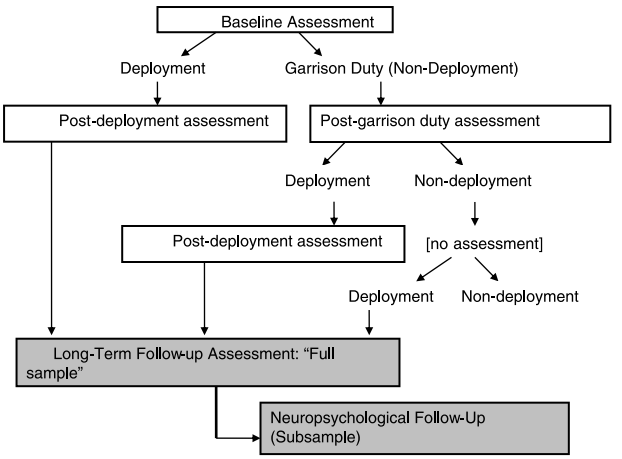



**FIGURE 2.** Overview of study design, including available and current data elements.

current study, we excluded all "Garrison Duty (Non-Deployment)" soldiers who never deployed to Iraq. Although we considered retaining these NDHS participants as a nondeployed comparison, we were concerned that their nondeployment status would not be random, and would instead reflect other factors such as potential physical or psychosocial issues precluding deployment. Thus, *a fourth methodological challenge involved identifying and refining aims (and hypotheses) of interest, and also conceptualizing an analytic plan that accounts for the loss of a deployed versus nondeployed comparison*.

In this general context, the study has 4 aims grouped into 2 primary and 2 secondary objectives. The 2 primary objectives are to determine the prevalence and course of PTSD more than 5 years after return from initial Iraq deployment (aim 1), and to assess the persistence of previously observed predeployment to short-term postdeployment neuropsychological changes, while evaluating the relationship of these changes—as well as TBI—with subsequent (current) PTSD (aim 2). The 2 secondary objectives are to examine the association of risk and resilience factors (eg, exposures to stressors experienced before, during, and after war-zone participation, social support constructs measured at various time points) with the outcomes of PTSD, major depressive disorder, dysthymia, and selected anxiety or alcohol-use disorders (aim 3), and to determine whether predeployment to long-term postdeployment changes in PTSD symptoms or neuropsychological function are associated with subsequent (ie, current) day-to-day functioning, including health-related functional activities and occupational functioning (aim 4). Administration of dimensional measures of PTSD, depression, and anxiety symptom severity further allow sensitivity analyses related to the outcomes of central interest.

The current study recognizes an opportunity to determine the prevalence and severity of PTSD among combat veterans, with the added benefit of information regarding baseline (predeployment) health status. Comparisons of the prevalence of PTSD to prior military conflicts, and to the US population in general, can also be explored. In addition, the clinical course (trajectories) of PTSD, as an understudied phenomenon, can be determined by making use of the available data over time (ie, acquired before deployment, soon after return from Iraq, and 5 or more years later).

Aim 1 represents a descriptive component of the study. We expect that PTSD prevalence at long-term follow-up will be increased when compared to the prevalence among participants at predeployment. We also hypothesize that specific trajectories of PTSD (eg, none, persistent, recovered, and late onset) can be identified from predeployment to long-term follow-up. With regard to aim 2, alterations (both advantageous and disadvantageous) in neuropsychological function, observed from baseline to short-term postdeployment, may or may not persist from short-term postdeployment to long-term follow-up.

Individual trajectories of PTSD symptoms for the projected 817 participants in aim 1, and individual growth curves for each neuropsychological measure in the subsample of 200 participants in aim 2, will be examined based on the original status of participants as deployed or nondeployed. Specifically, the change in PTSD symptoms or neuropsychological functioning from predeployment to short-term postdeployment—observed previously in the NDHS study[7] among the initially deployed participants—will be compared with corresponding changes from short-term postdeployment to long-term follow-up, among originally nondeployed participants, but after their subsequent deployment.

If the changes for these 2 groups are similar, based on their similar yet "staggered" deployment experience, then evidence of PTSD or neuropsychological impairment attributable to OIF would be strengthened. Conversely, the changes in PTSD symptoms or neuropsychological testing from short-term postdeployment to long-term follow-up for the original nondeployed group, after their subsequent (first) deployment, may not replicate the prior association.

The *timing of assessments relative to important life events, especially subsequent deployments, represents a fifth methodological challenge*. Accounting for the complexity in timing of study-related assessments, in relation to both military and civilian periods for each participant, was difficult. These issues are particularly relevant for secondary objectives focusing on risk and resilience factors, including the impact of war-zone stressors on mental health outcomes (aim 3), and the association of primary outcomes with day-to-day functioning, including health-related functioning and occupational functioning (aim 4).

## Statistical Analyses

When issues related to participants, exposures and outcomes, and study design are considered in their entirety, *developing a statistical analysis plan that adequately considers multiple complex factors of study design represents a sixth methodological challenge*. For aims 1 and 2, the effect of deployment experience on PTSD symptoms and/or neuropsychological changes will be tested in mixed-effects longitudinal regression models. To determine the most parsimonious model, we will consider mixed-effect models with random intercepts, linear, and quadratic terms,[26,27] and the initial covariance structure will include 3 sources of variation: random effects, serial correlation, and measurement error. Before conducting any analyses, the patterns of missing data will be examined and multiple imputation methods (eg, the multiple imputation procedure of Rubin[28]) will be considered, as appropriate. Most missing data within NDHS occur at the short-term postdeployment time point and are due to changes in military unit assignment and separation from the service, suggesting a missing-data mechanism that is reasonably ignorable, or missing at random (MAR). Longitudinal analyses will be based on likelihood methods assuming MAR. Variables that are predictive of missingness will be included in the MAR longitudinal analyses. If the missing data are not ignorable, sensitivity analyses will be conducted, such as the fitting of pattern mixture and selection models.[27]

The projected full sample of 817 participants provide 95% confidence intervals shown in Table 3 for estimating a range of

**TABLE 3.** Confidence Intervals for n = 817 and Range of Prevalence for PTSD (see Aim 1)

| Aim | Outcome Measure | Prevalence, % | 95% Confidence Interval, % |
|---|---|---|---|
| Prevalence and trajectory of PTSD | CAPS at long-term postdeployment | 8 | 6.1–9.9 |
| | | 10 | 8.0–12.0 |
| | | 12 | 9.8–14.2 |
| | | 14 | 11.6–16.4 |
| | | 16 | 13.5–18.5 |
| | | 18 | 15.4–20.6 |

Long-term postdeployment, proposed new CSP #566 long-term follow-up assessment (more than 5 years post-return from initial Iraq deployment).

likely prevalence rates for PTSD at long-term follow-up for primary aim 1. The McNemar $\chi^2$ test and paired *t* tests will be used to compare long-term follow-up to predeployment differences in the prevalence of PTSD based on the PCL as a discrete and continuous measure, respectively. Clinically relevant trajectories of PTSD symptoms over the 3 time points will be determined; for example, a predeployment negative (ie, PCL at baseline ≤50), short-term postdeployment negative (ie, PCL at short-term postdeployment ≤50), long-term follow-up negative (ie, PCL at long-term follow-up ≤50) combination will be categorized as "never" having been diagnosed with PTSD; a predeployment negative, short-term postdeployment positive, long-term follow-up positive combination represents a new and "persistent" diagnosis.

Primary aim 2 also involves several hypotheses based on participants in the full sample at long-term follow-up. First, deployment-related alterations in neuropsychological function observed between baseline and short-term postdeployment will be associated with PTSD diagnosis and higher levels of PTSD symptoms at long-term follow-up. Second, TBI incurred between baseline and short-term postdeployment will be associated with PTSD diagnosis and higher levels of PTSD symptoms at long-term follow-up. Third, a significant interaction exists between early (baseline to short-term postdeployment) deployment-related neuropsychological alterations, TBI (incurred between baseline to short-term postdeployment), and PTSD. Specifically, participants with alterations in neuropsychological functioning and TBI will have an increased probability of PTSD diagnosis and manifest more severe PTSD symptoms at long-term follow-up, compared with other participants.

Separate multiple logistic regressions and multiple linear regressions will be used to assess the association between changes in the 4 neuropsychological measures and TBI, respectively, between baseline and short-term postdeployment, with PTSD at long-term postdeployment, adjusting for age, gender, education, number of deployments, and durations of (baseline to short-term postdeployment) and (short-term to long-term postdeployment) intervals. Models will also be assessed accounting for the effect of the pairwise interaction terms for the 4 neuropsychological measures and TBI on PTSD. A global test of interaction will be constructed based on the likelihood ratio statistic, by comparing the models with and without the interaction terms. The fit of all models to the data will be assessed using standard measures of determining goodness of fit (residual plots, $r^2$, etc).

The sample of 817 participants can detect odds ratios in the range of 1.4 to 1.6, with 80% power at the 5% level of significance, for the association between early neuropsychological changes and development of PTSD. Specifically, the method uses a logistic regression model to assess differences between the probability of a PTSD diagnosis at the mean value of all 4 neuropsychological measures, and the probability of a PTSD diagnosis when 1 of the 4 continuous measures is increased to 1 standard deviation above the mean, whereas all other measures are held equal to their mean values. The calculations adjust for a range of multiple correlations, from $R^2$ of 0.15 to 0.30, for other covariates included in the model. Data were limited to calculate power for the effect of the interaction between TBI and neuropsychological measures on PTSD development. Power will be greater to detect effects for the continuous PCL measure of PTSD symptoms using a multivariate linear regression model.

Aim 3 includes 3 hypotheses. First, stress exposures during early life, the initial ("index") deployment period, and subsequent military deployments, will increase—and protective factors (eg, unit cohesion and postdeployment social support) will decrease—the risk of PTSD, major depressive disorder, and panic disorder diagnoses, when assessed at long-term follow-up. Second, deployment and postdeployment exposures, compared with early life events, will be more strongly associated with an increased risk of PTSD and with PTSD symptom severity, when using data at long-term follow-up. Third, dose-dependent relationships will exist between these stress exposures and PTSD symptoms, depression, and anxiety symptom severity at long-term follow-up.

Aim 3 provides data to understand more fully the contribution of deployment stressors (both war-zone and home-front) on the development of PTSD, depression, and anxiety disorders. To provide information that might be directly translated into interventions, the aim also targets examination of the impact of 2 potentially modifiable protective factors (unit cohesion and post-war social support) on mental health outcomes. This aim includes a focus on dimensional (continuous) values for exposure and outcome variables, to examine the full range of responses, including subclinical manifestations, as a potential preventive target. Similarly, the inclusion of depression and anxiety disorders is an important element of this objective because of their frequent co-occurrence (comorbidity) with PTSD and their relevance to appropriate clinical management. The results may have implications for healthcare regarding how therapeutic interventions (eg, exposure-based therapies) could be tailored to individual patients, both in content (eg, trauma focus) and clinical presentation (eg, associated depressive symptoms).

Aim 4 targets functioning, and allows exploration of associations between war-related mental health outcomes and day-to-day functioning, thereby providing better understanding of the full scope of problems and societal costs associated with PTSD and neuropsychological dysfunction. We hypothesize that increased PTSD symptoms from predeployment to long-term follow-up will be associated with lower levels of functioning, including occupational measures and physical health-related, psychological health-related, and cognitive health-related self-reported functional activities. We also hypothesize alterations in

neuropsychological performance, from predeployment to long-term follow-up, will be associated with lower levels of functioning, including occupational measures and cognitive-related self-reported functional activities.

Details of statistical analyses for secondary aims (3 and 4) are not discussed herein; insufficient data were available when the study was in planning phase to calculate power for secondary outcome measures. An additional study limitation is casewise missing data due to unit changes/separation from service at postdeployment, but based on the initial NDHS experience we expect little missing outcome data within individual participants at long-term follow-up. Measures will also be instituted to reduce the amount of missing data at long-term follow-up, such as extensive assessor training and redundant error checking.

## RESULTS

Prominent methodological challenges encountered in designing the study, as presented in Table 1, include transitioning from a cluster-sampling strategy to individual-level sampling; practical problems of location searches, preliminary contact, assessment of eligibility and willingness to participate, scheduling, and study participation; selecting appropriate exposure and outcome measures, while balancing previously collected data with current needs; identifying and refining specific aims, and conceptualizing an analytic approach that accounts for the loss of a deployed versus nondeployed comparison; incorporating the timing of assessments relative to important life events, including multiple deployments; and developing a statistical analysis plan that accounts for the overall complexity of the project. Enrollment into the current study is ongoing and is scheduled to be completed in 2014.

## DISCUSSION

The study has the potential to enhance understanding of the course and predictors of war-related emotional function, better identify objective indicators of mental functioning that can influence long-term mental health outcomes, and provide evidence regarding functional consequences related to operational military deployment to Iraq or Afghanistan. Prevalence estimates of PTSD diagnoses, and a description of their time course in this study population, can help calculate the need for, and optimal timing of, therapeutic interventions. The focus on PTSD symptom severity, in addition to a formal diagnosis, provides data on a comparable scale at 3 points separated in time.

The study also offers a unique scientific opportunity to determine whether objectively measured neuropsychological changes—observed in completed work[7] for the first time with a comparison to predeployment functioning—persist or have resolved at long-term follow-up. The study specifically evaluates the association of an increasingly common Iraq War exposure thought to affect neural integrity, that is, TBI, with PTSD and posttraumatic stress symptoms at long-term follow-up.

The results of the study may help to inform clinical and health policy decisions regarding the infrastructure needed for the delivery of health care, determining optimal "windows" for therapeutic interventions, and improving individual and societal outcomes related to mental health. The methodological lessons learned from this longitudinal study of an at-risk, dynamic population can be applied more generally to other military samples, as well as civilian samples at risk for trauma exposure.

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