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14. ABSTRACT
The complex of multiple symptoms known as Gulf War Illness (GWI) continues to affect a substantial number of veterans who served in the 1990-1991 Gulf War. Despite considerable research, the biological processes underlying veterans' symptoms have not been clearly elucidated. In order to develop useful diagnostic tests and optimize the search for effective GWI treatments, it is imperative to establish a more definitive and integrated understanding of the pathophysiology of this problem. This study utilizes a case-control design to evaluate diverse biological measures in a single, well-characterized sample of 130 Gulf War veterans. Eighty veterans with GWI are compared to 50 healthy veteran controls in a protocol that includes physical and neuropsychological evaluations, neuroimaging (MRI, fMRI, DTI), adrenal function tests, and diverse immune, inflammatory, and coagulation measures. Statistical analyses will determine which objective measures significantly distinguish GWI cases from controls, and explore the extent to which biological findings are interrelated or are associated with identifiable veteran subgroups. Data collection has not yet begun, as we finalize the process of obtaining regulatory approvals. When complete, the study is expected to clarify many of the ambiguities currently associated with GWI and improve understanding of the biological processes that underlie veterans' symptoms. This will facilitate efforts to identify useful diagnostic tests and promising treatments.

15. SUBJECT TERMS
Gulf War illness, neuroimaging, neuropsychological testing, immune function, hypothalamic-pituitary-adrenal testing

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Assessment of Diverse Biological Indicators in Gulf War Illness:
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Introduction

A substantial proportion of military veterans who served in the 1990-1991 Persian Gulf War continue to suffer from a serious, often debilitating illness that is not explained by established medical or psychiatric diagnoses. This symptomatic illness is commonly known as Gulf War illness (GWI), and is characterized by a profile of concurrent symptoms that typically includes persistent headaches, memory and cognitive difficulties, widespread pain, unexplained fatigue, gastrointestinal problems, and other difficulties. Studies consistently indicate that GWI is not a psychiatric disorder and is not the result of combat stress (Institute of Medicine 2010; Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) 2008). Longitudinal studies indicate that few veterans who developed GWI during and after the 1991 Gulf War have recovered, or even substantially improved, with time (RAC 2008, Wolfe 2002, Kang 2008, Hotopf 2003).

Despite considerable research related to GWI, the pathophysiological underpinnings of veterans' symptoms have not yet been clearly elucidated. Studies have identified diverse biological differences between groups of GWI cases and healthy controls associated with neurological, endocrine, immune, and hematological measures. Most results, however, have been "one-off" findings. That is, most objective findings related to GWI have come from individual studies that have evaluated different questions, sometimes with limited samples or methodologies. Even studies evaluating abnormalities in the same biological system have used diverse methods and outcome measures, making comparison of results difficult or impossible. There are relatively few examples of specific GWI-related biological findings that have been replicated by a second team of investigators. There are also few instances in which measures related to different biological systems, for example, measures of brain function and immune function, have been evaluated in a single group of Gulf War veterans. It is therefore not possible to know whether findings in different biological systems occur in the same individuals, or in discrete subsets of ill veterans. And for many of the biological differences identified thus far, there is no clear rationale to explain why or how they relate to symptoms characteristic of GWI.

As a result, a relatively large body of suggestive evidence has accumulated that provides preliminary indications of biological processes that underlie veterans' symptoms. But the lack of replicated findings, the difficulty of comparing results from different groups, and the lack of information about the co-occurrence of findings in different systems presents an enormous barrier to developing a clear understanding of the biological nature of GWI. This limited understanding has slowed efforts to identify promising avenues for diagnostic tests and treatments.

The present study utilizes a case-control design to evaluate diverse biological measures in a well-characterized and population-based sample of 130 veterans, proactively recruited from among 1991 Gulf War veterans who currently reside in Central Texas. Eighty veterans with GWI, defined by Kansas GWI criteria, will be compared to 50 healthy Gulf War veteran controls in a protocol that includes physical examinations, neuroimaging (MRI volumetric assessments, fMRI, diffusion tensor imaging), neuropsychological evaluations, assessment of hypothalamic-pituitary-adrenal function, standard diagnostic laboratory tests, and blood tests to evaluate immune,

inflammatory, and coagulation parameters. Statistical analyses will determine which measures significantly distinguish GWI cases from controls, and will explore the extent to which findings are interrelated and/or are associated with subgroups of ill veterans distinguished by biological measures, deployment experiences/exposures, or illness severity and characteristics.

This multidisciplinary study is being conducted by investigators at Baylor University in conjunction with collaborators at the Scott & White Healthcare System, the Center of Excellence for Returning War Veterans at the Central Texas VA, Texas A&M Health Sciences Center, Columbia University School of Public Health, and the Minneapolis (MN) VA. Veterans will be evaluated over two consecutive mornings using a protocol designed to address multiple questions at once in the most rigorous, comprehensive, and efficient way possible. This protocol emphasizes the use of testing methods that, if found to successfully distinguish sick from healthy veterans, can most readily be developed for clinical application in the near term.

Body

Task 1. Prepare and Submit Documents to Obtain Regulatory Approvals

This multi-institutional project requires review and approval by six Institutional Review Boards (IRBs) as well as the federal Office of Management and Budget (OMB) before we initiate data collection. In submitting our proposal, we were told by personnel in the DOD Clearance Office that handles Army OMB submissions that the OMB approval process can require up to eight months. The project was therefore designed to allow nine months for the process of regulatory approvals, as indicated in the Statement of Work. Due to a series of startup delays at Baylor, OMB documentation was not provided to the Army for submission to OMB until June 2012. We therefore anticipate that OMB approvals will not be obtained until the end of this calendar year, or early 2013, putting the project several months behind the schedule outlined in the Statement of Work.

Our initial strategy was to prepare and submit documents on the use of human subjects for review by the USAMRMC's Human Research Protection Office (HRPO) in parallel with the OMB process, to ensure all requirements were addressed in parallel with one another. After the award was made, however, our discussions with HRPO staff indicated that they would prefer to review our documents after IRB approvals for the lead institution(s) were obtained. For the six institutions collaborating on the project, we anticipated full IRB reviews from three study sites (Baylor University, Scott & White Healthcare, and Central Texas VA), and expedited IRB reviews (or exemptions) for the three secondary sites (Columbia University, Minneapolis VA, and Texas A&M Health Science Center). We submitted full IRB proposals and all documentation to Baylor, Scott & White, and Central Texas VA, and have now received full approval from the Baylor University IRB, and are currently working out several minor details with the Scott & White IRB for final approval. Protocols, consent forms, and data collection forms have all been designed to incorporate the requirements of all institutions. Once final approval is obtained from Scott & White, we will provide the Baylor/Scott & White-approved protocol and other IRB documents to the Army's HRPO for review. We will also submit the Baylor/Scott & White-approved protocol and documents for IRB review by the three secondary sites. We anticipate that the required approvals will be obtained in a timely manner, allowing us to move forward with data collection at the time OMB approvals are obtained near the end of 2012/early 2013.

Task 2. Identify and Interview Stratified Random Sample of Gulf War era Veterans for Study Participation

Because of the extended time allowed in our initial timeline to obtain OMB approvals for this study, it has always been expected that data collection would not begin until the second year of the project. Therefore, no subject recruitment or data collection activities have yet been initiated and no research results are yet available. Neither have efforts related to sample identification yet been initiated, since obtaining data from the Defense Manpower Data Center (DMDC) for this purpose requires OMB approval.

One activity outlined under Task 2 has been initiated, however. The recruitment process for enrolling study subjects requires veterans to be contacted and screened by trained telephone interviewers working at the Computer Assisted Telephone Interview (CATI) facility at Baylor's Community Center for Research and Development (CCRD). The CATI software requirements for this project are somewhat unique. In addition to the need to program the screening instrument, results from calculations involving a fairly complex algorithm must be presented "live" during the interview to determine if respondents are potential cases or controls, and if they are eligible to participate in the study. The CCRD CATI project directors worked with the PI to determine the optimal software for this purpose, and have initiated CATI programming for the screening interview. This will allow us to test the CATI program extensively and pretest the interview, so that the sampling and recruitment effort can begin as soon as OMB and IRB approvals are in place.

Tasks 3 – 5.

No activities completed or underway at this time.

Key Research Accomplishments

Only regulatory submissions accomplished to date. Study data have not yet been collected.

Reportable Outcomes

There are no manuscripts or other reportable outcomes at this time.

Conclusion

No research results are yet available; no conclusions can be drawn at this time.

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